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Anesthesiology Clin
26 (2008) xi–xii

Foreword

Lee A. Fleisher, MD
Consulting Editor

As nicely outlined in the preface, thoracic surgery continues to evolve, which requires evolution in the anesthetic management of patients undergoing thoracic surgery. Similar to other surgical procedures, minimally invasive techniques are now commonplace. Technology has also had a major impact on the field, including the development of airway stents and new forms of extracorporeal oxygenation. With these techniques come new challenges. Additionally, postoperative pain management of the thoracic surgical patient has always been considered a key component in achieving optimal outcomes. In this issue of *Anesthesiology Clinics*, a remarkable group of international experts in the field have written outstanding reviews to help all of us provide state-of-the-art care.

In choosing an editor for a thoracic anesthesia issue, it was easy to identify Peter Slinger, MD, as the appropriate individual. Dr. Slinger is currently professor of anesthesia at the University of Toronto and co-editor of four of the major texts in the field. He is currently president of the CVT Section of the Canadian Anesthesiologists Society, associate editor for the *Thoracic Anesthesia* section of the *Journal of Cardiothoracic and Vascular Anesthesia* and a member of the editorial board of *Anesthesia and Analgesia*. He has written

1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.03.009 *anesthesiology.theclinics.com*

and lectured extensively on the issues of one-lung ventilation and thoracic anesthesia, and is, therefore, able to define the key issues for our readers.

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Anesthesiology Clin
26 (2008) xiii–xv

Preface

Peter Slinger, MD, FRCPC
Guest Editor

I would like to thank Dr. Lee Fleisher for the invitation to compile and edit this issue of *Anesthesiology Clinics* on "Thoracic Anesthesia." The volume and complexity of thoracic surgical procedures continues to increase and, coincidentally, the knowledge base for anesthesiologists providing care for these patients needs to grow. This issue is aimed at helping clinicians keep abreast in some of the areas of progress in thoracic anesthesia.

These articles are grouped into four general areas with much overlap. Articles one through five deal with perioperative management issues. In the first article, Dr. Jens Lohser has produced, what I believe is, the most up-to-date summary that I have read on the management of one-lung ventilation. There has been much progress in understanding the physiology of one-lung anesthesia in the past 20 years, but this has remained scattered in many separate clinical studies and has not been well summarized—until now. The physiology is more complex than previously appreciated, but Dr. Lohser provides useful guidelines for ventilation management while stressing that "one size does not fit all." In the next article, Dr. Hilary Grocott considers the possibility of oxygen toxicity as a contributor to acute lung injury after pulmonary resection. This is particularly relevant, as the major causes of perioperative morbidity and mortality in thoracic surgery in the last century (pneumonia and broncho-pleural fistula) are decreasing, and acute lung injury is now assuming a leading role in post-thoracotomy complications. In the third article, Drs. Finlayson and Brodsky discuss

1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.03.008 *anesthesiology.theclinics.com*

the recent advances in airway stenting, both as palliation and definitive therapy for an increasing spectrum of lower airway problems. In the fourth article, Dr. Ju-Mei Ng presents an overview of anesthetic management for esophagectomy. This is probably the common thoracic surgical procedure associated with the highest perioperative complication rate and is also likely the procedure where anesthetic management most affects outcome. This, along with the article by Dr. Gerner comes from the very busy Thoracic Anesthesia group at the Brigham and Women's Hospital in Boston, and I thank the chief of that group, Dr. Phil Hartigan, for his advice and support in assembling this issue. The final article in this section is on anesthesia for patients with anterior mediastinal masses. This subject continues to be a source of anxiety for anesthesiologists, and the topic is well summarized here by Dr. John Gothard, who draws on the large clinical experience of the Royal Brompton Hospital in London, England.

In articles six through eight, the underlying theme is the right side of the heart. In the sixth article, Drs. Heerdt and Park from the Memorial Sloan Kettering Cancer Institute in New York discuss the role that minimally invasive surgery plays in lung resection for elderly patients. Those who began smoking when they were young adults in the 1940s and 1950s (currently in their 80s) are now presenting with lung cancer and form a rapidly increasing portion of our patients. Right ventricular function seems to be the limiting factor in the outcome for many of these patients. Dr. Heerdt is the expert on the response of the right ventricle to lung resection in the elderly. The seventh article by Dr. Amar, from the same institute, examines the problem of perioperative arrhythmias in thoracic surgery and, again, the right heart seems to be the source of much of the problem—fortunately, Dr. Amar is the expert in this area. The eighth article is an overview for anesthesiologists of pulmonary vasodilators by Drs. Granton and Moric from the division of Critical Care here at the Toronto General Hospital. Dr. Granton is a respirologist and intensivist who is responsible for the Pulmonary Hypertension program at this hospital, and as such, this is his area of clinical research.

Articles nine and ten deal with postoperative analgesia in thoracic surgery. The ninth article by Dr. Gerner is an overview of the issues in postthoractomy pain (including acute, chronic, and shoulder pain) and discusses common therapies. The tenth article by Drs. Conlon, Shaw, and Grichnik from Duke University examines the recent resurgence of interest in paravertebral analgesia for thoracic surgery.

The final article by Drs. Meyer, Strüber, and Fischer from Hannover, Germany, is a look at the possible future of respiratory support. They present a new technology for extra-corporeal ventilation. The "Novalung" is similar to previous extra-corporeal membrane oxygenators but can function without an external pump, driven only by the patient's arterial blood pressure. It has a limited capability to increase oxygenation but is very efficient for removal of carbon dioxide. It allows for use of protective ventilation strategies in patients with severe acute lung injuries. We have had good

initial results with this technology in some lung transplant patients, and the authors describe extending the use of this device to other clinical situations of respiratory failure.

I hope this issue of *Anesthesiology Clinics* offers readers a wide-based update on advances in thoracic anesthesia. I have been fortunate in the enthusiasm that the contributing authors have shown for this project and in their willingness to share their knowledge and time in producing this issue.

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Anesthesiology Clin
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Evidence-based Management of One-Lung Ventilation

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The development of lung isolation and one-lung ventilation (OLV) preempted the evolution of thoracic surgery as a subspecialty. Before the description of endotracheal intubation and the cuffed endotracheal tube, only short intrathoracic procedures were feasible. Rapid lung movement and quickly developing respiratory distress caused by the surgical pneumothorax, made all but minimal procedures too difficult and too risky. Selective ventilation of one lung was first described in 1931 by Gale and Waters and quickly led to increasingly complex lung resection surgery, with the first published pneumonectomy for cancer in 1933 [1].

OLV physiology is connected intimately to its effects on ventilation and perfusion matching, which have been reviewed extensively [2–4]. The supine position, induction of anesthesia, and the open hemithorax all affect normal ventilation/perfusion (V/Q) matching, primarily because of their effects on lung compliance. Lung isolation uncouples V/Q matching to the operative lung, which may result in significant hypoxemia if not appropriately managed. To best approach the V/Q disturbance during OLV, the clinician needs to be familiar with the basic principles that govern pulmonary perfusion and ventilation, each of which will be considered separately. After a review of the basic physiology of OLV, focus will be placed on the issue of ventilatory management in regards to lung injury avoidance, as recent studies have indicated a potential role of OLV in the creation of postoperative lung injury.

Pulmonary perfusion

Pulmonary blood flow serves three purposes. First, it delivers oxygen from the alveoli to the body, fueling metabolic oxygen demand. Second, it

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.011 *anesthesiology.theclinics.com*

returns carbon dioxide to the alveoli for removal and exhalation. Third, it provides for left heart preload to support systemic cardiac output. Because of the closed nature of the circulatory system, the entire cardiac output has to pass through the pulmonary circulation. The pulmonary vascular bed is a low resistance conduit and possesses significant recruitable territory. This allows pulmonary pressures to stay low, even when cardiac output is increased to 30 L/min because of exercise [5]. Perfusion is not uniform throughout the lung, as pulmonary arterial (P_a) and venous (P_V) pressures are dependent on the relative elevation above the heart, whereas the extrinsic compressive force of the alveolar distending pressure (P_A) is relatively constant. These effects result in the West Zones (Fig. 1) [6,7]. In zone 1, the most superior aspect of the lung, P_a is lower than P_A because of the elevation above the heart. This results in complete obstruction of flow and creation of dead space ventilation. Moving inferiorly, P_a increases gradually because of the lesser elevation above the heart. Once P_a exceeds P_A (zone 2), flow occurs through the capillaries. The pressure differential between P_a and P_A increases in the more dependent areas of zone 2, resulting in a progressive increase in flow, much like a waterfall. Zone 3 is reached when P_v exceeds P_A, resulting in pulmonary perfusion independent of P_A and only determined by the difference between P_a and P_v. Zone 4 is that portion of lung where interstitial pressure P_{is} is higher than P_v, thus resulting in a reduction in blood flow relative to the pressure differential between P_a and P_{is}. Zone 4 may exist in the most inferior portions of the lung, be created by exhalation to low lung volumes, or be caused by increased interstitial pressures such as in volume overload [6]. Although the gravitational model of the West Zones helps to understand the nature of V/Q mismatch in the lungs, perfusion scanning with tagged albumin microaggregates has shown that it only partially reflects human physiology. Pulmonary perfusion in healthy volunteers exhibits a combination of gravitational distribution and an onion-like layering, with reduced flow at the periphery of the lung and higher flow toward the hilum (see Fig. 1) [8]. Additionally, compressive or distortive forces of the heart and mediastinum in the lateral position cause perfusion of the dependent lung to be lower than expected based simply on gravity distribution [9].

The efficiency of gas exchange depends on matching of perfusion to ventilation. Homeostatic control is exerted through vasoconstriction of poorly ventilated areas, resulting in diversion of blood flow to better-ventilated areas and therefore better V/Q matching. OLV causes an extreme challenge to V/Q matching. Once the operative lung is excluded from the ventilatory circuit, residual oxygen will gradually be absorbed from the nonventilated alveoli until complete absorption atelectasis results. At this point, pulmonary blood flow to the operative lung is wasted perfusion. This right-to-left shunt through the nonventilated lung is in addition to the normal 5% of shunt that exists in the contralateral ventilated lung. As blood flow to each lung is roughly equal (with the right lung receiving more because of its increased size) this mathematically results in a shunt fraction in excess

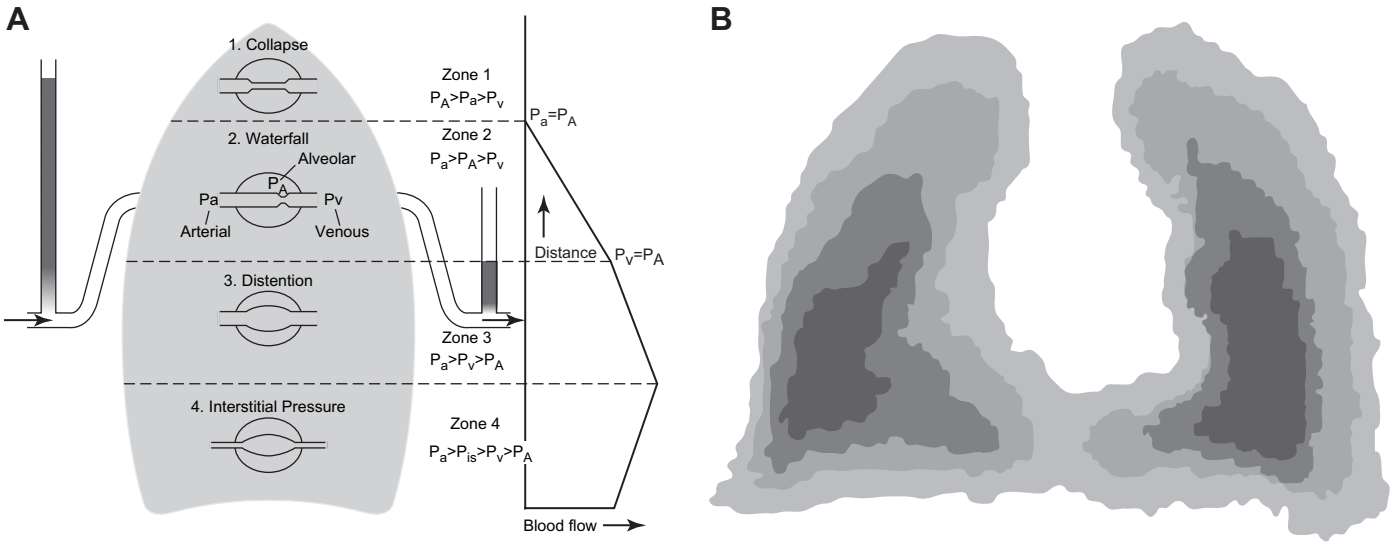

Fig. 1. Pulmonary blood flow distribution relative to the alveolar pressure (P_A), the pulmonary arterial pressure (P_a), the pulmonary venous pressure (P_v), and the interstitial pressure (P_{is}) at various gravitational levels. (*A*) Classic West Zones of blood flow distribution in the upright position. (*Adapted from* West JB. Respiratory physiology: the essentials. 6th edition. Baltimore: Williams and Wilkins; 2000. p. 37; and Hakim TS, Lisbona R, Dean GW. Gravity-independent inequality in pulmonary blood flow in humans. J Appl Physiol 1987;63:1117; with permission.) (*B*) In vivo perfusion scanning illustrating central-to-peripheral, in addition to gravitational blood flow distribution, in the upright position. See text for further details.

of 50%. Observed shunt fractions are fortunately much lower. Both passive and active mechanisms are at play to decrease the blood flow through the operative lung. Surgical manipulation and, in the lateral position, gravity, passively reduce the blood flow to the nonventilated lung. In addition, hypoxic vasoconstriction actively increases vascular resistance in the nonventilated lung, resulting in a gradual decrease in blood flow and shunt fraction.

Hypoxic pulmonary vasoconstriction

Oxygen-sensing mechanisms are active throughout the human body (carotid body, fetal placenta, ductus arteriosus, pulmonary arteries) and have been reviewed in detail [10]. Hypoxic pulmonary vasoconstriction (HPV) of the pulmonary arterial bed is one such mechanism. In the fetal circulation, HPV enables diversion of oxygenated blood away from the pulmonary circulation across the foramen ovale. HPV remains important ex utero as it helps to improve V/Q matching by reducing perfusion of poorly oxygenated lung tissue. HPV is active in the physiologic range (P_AO_2 40 to 100 mm Hg in the adult) and proportional to the severity of the hypoxia. Low partial pressure of oxygen results in inhibition of potassium currents, leading to membrane depolarization and calcium entry through L-type calcium channels (Fig. 2). Extracellular calcium entry, plus calcium release from the sarcoplasmic reticulum, culminates in smooth muscle contraction, primarily in small resistance pulmonary arteries with a diameter less than 500 μm [10]. The primary stimulus for HPV appears to be the alveolar P_AO_2; however, the mixed venous P_vO_2 also is involved. HPV is maximal at normal P_vO_2 levels and is inhibited at high or low levels. Low P_vO_2 (eg, inadequate cardiac output) results in a P_aO_2 decrease in the ventilated lung resulting in competing vasoconstriction, whereas high P_vO_2 (eg, sepsis) decreases the vasoconstrictor response in the nonventilated lung because of the increase in local P_aO_2. Vasoconstriction occurs in seconds and reaches an initial plateau at 15 minutes; however maximal response is only reached at 4 hours secondary to a late response [2,11,12]. HPV reduces the shunt flow through the operative lung by roughly 40%, facilitating the safe conduct of OLV, although its true clinical importance has been questioned [13].

Extremes of HPV may cause harm. Overactivity, particularly during exercise at high altitudes, may result in high-altitude pulmonary edema [12]. The opposite is true in thoracic anesthesia, where inhibition of HPV may result in intraoperative hypoxemia. Many studies thus have attempted to identify agents or interventions that modulate the pulmonary vasoconstrictor response to hypoxia (Table 1). Most data are derived from animal experiments, as interventions are more easily standardized. Selected modifiers that may be of interest in the perioperative period are compiled in Table 1. Only selected studies are included, with special emphasis on human data if available.

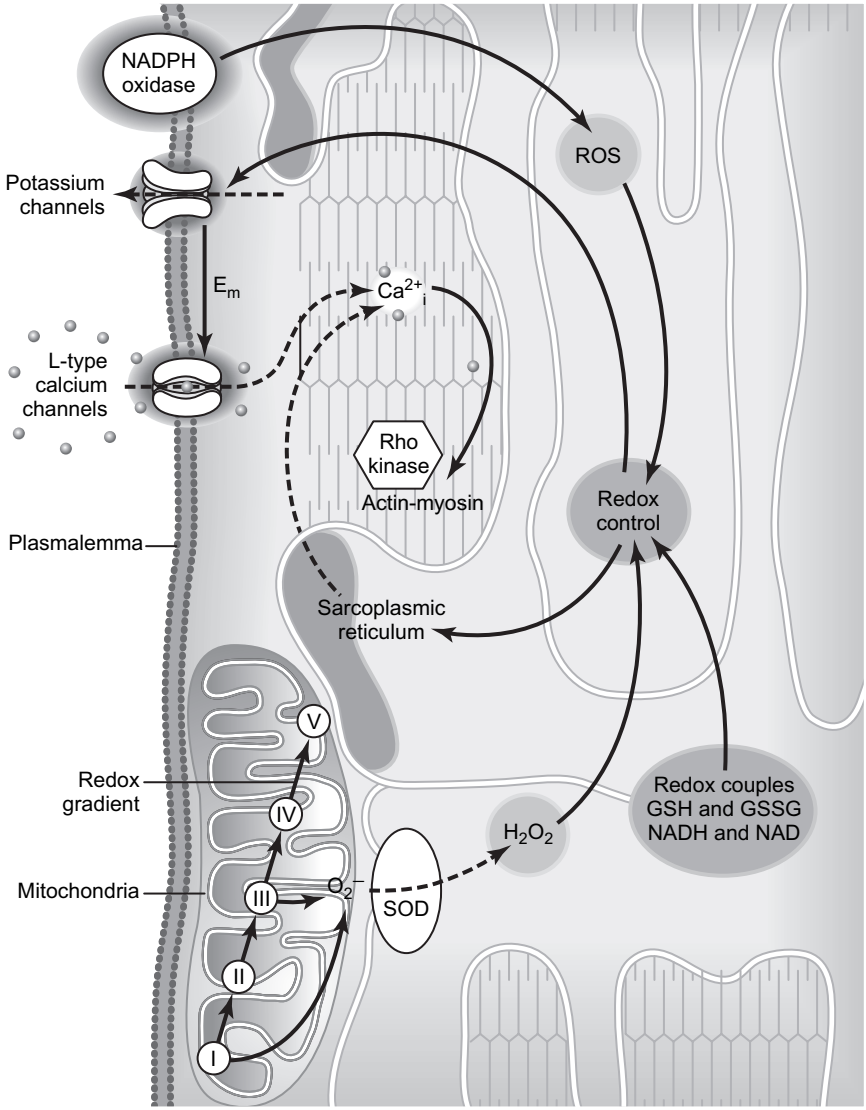

Fig. 2. Proposed redox mechanism for oxygen sensing in specialized tissues. Reactive oxygen species (ROS) from the mitochondria, NADPH oxidase, NADH oxidase, or redox couples may control potassium channel gating and membrane potential (Em) and thus calcium entry. The same redox signaling may control calcium release from the sarcoplasmic reticulum. *Abbreviations:* GSH, glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; SOD, superoxide dismutase. (*From* Weir EK, Lopez-Barneo J, Buckler KJ, et al. Acute oxygen-sensing mechanisms, N Engl J Med 2005;353(19):2050; with permission. Copyright © 2005, Massachusetts Medical Society.)

Table 1
Selected peri-operative modifiers of hypoxic pulmonary vasoconstriction

	Effect on HPV	Reference*
Patient factors		
Chronic obstructive pulmonary disease	−	Peinado 2002 [14]
Cirrhosis	−	Nakos 1993 [15]
Sepsis	−	[a]Reeves 1974 [16]
Pregnancy	−	[a]Moore 1980 in [12]
Female sex	−	[a]Wetzel 1984 [17]
Exercise	−	[a]Favret 2006 [18]
Systemic hypertension	+	Guazzi 1989 [19]
Ethanol	+	[a]Doekel 1978 [20]
Physiologic changes		
Acidosis	+	[a]Brimioulle 1990 in [12]
Alkalosis	−	[a]Brimioulle 1990 in [12]
Hypercapnea	+	Balanos 2003 [11]
Hypocapnia	−	Balanos 2003 [11]
Hyperthermia	+	[a]Benumof 1977 in [12]
Hypothermia	−	[a]Benumof 1977 in [12]
Increased left atrial pressure	−	[a]Benumof 1975 in [12]
Increased PvO_2	−	[a]Marshall 1983 [21]
Decreased PvO_2	+	[a]Marshall 1983 [21]
Perioperative interventions		
Lateral decubitus	+	Bardoczky 2000 [22]
Supine position	0	Bardoczky 2000 [22]
Surgical lung retraction	+	Ishikawa 2003 [23]
Hemodilution	−	Szegedo 2005 [24]
Epidural anesthesia	+	von Dossow 2001 in [12]
Almitrine	+	Moutafis 1997 in [12]
Inhaled Nitric Oxide (NO)	0	Moutafis 1997 in [12]
Pharmacologic agents		
Inhalational anesthetics		
Nitrous Oxide	−	[a]Bindslev 1986 [25]
Halothane	−	Kjaeve 1989 in [12]
Enflurane	0	Carlsson 1987 in [12]
Isoflurane	0	Carlsson 1987 in [12]
Desflurane	0	Kerbaul 2001 [26]
Sevoflurane	0	Pruskowski 2007 [27]
Intravenous anesthetics		
Propofol	+	Nakayama 1999 in [12]
Propofol	0	Pruskowski 2007 [27]
Ketamine	0	[a]Nakayama 1999 in [12]
Opioids	0	[a]Bjertnaes 1980 in [12]
Calcium channel blockers		
Verapamil	−	Kjaeve 1989 in [12]
Diltiazem	0	Clozel 1987 [28]
Adrenergic blockers		
Propranolol	+	[a]Thilenius 1967 [29]
Phenoxybenzamine	−	[a]Thilenius 1967 [29]
Phentolamine	−	Hackett 1992 [30]
Clonidine	+	[a]Luebbe 1991 [31]

(*continued on next page*)

Table 1 (*continued*)

	Effect on HPV	Reference*
Vasodilators		
Hydralazine	−	Hacket 1992 [30]
Nitroglycerin	−	[a]Hales 1978 [32]
Nitroprusside	−	Parsons 1981 [33]
Sildenafil	0	Zhao 2001 [34]
Adrenergic agonists		
Dopamine	0	[a]Marin 1979 [35]
Isoproterenol	−	[a]Silove 1968 [36]
Norepinephrine	−	[a]Silove 1968 [36]
Phenylephrine	+	Doering 1997 [37]
Other		
Losartan	−	Kiely 1995 [38]
Lisinopril	−	Cargill 1996 [39]
Methylprednisolone	0	Leeman 1988 [40]
Indomethacin	+	[a]Hales 1978 [41]
Acetyl-acetic acid	+	[a]Hales 1978 [41]
Prostacyclin	−	Lorente 1992 [42]
Prostaglandin E1	−	[a]Weir 1975 [43]
Salbutamol	+	Pillet 1998 [44]
Ipratropium	+	Pillet 1998 [44]
Lidocaine	+	[a]Bindslev 1986 [25]

* Reference numbers refer to original or citing source.

[a] Animal data.

Anesthetic modifiers of hypoxic pulmonary vasoconstriction

Inhibition of HPV by inhalational anesthesia is well recognized. Ether, halothane and nitrous oxide (N_2O) clearly inhibit HPV in a dose-dependent fashion. Identification of the molecular targets of halothane and their involvement in HPV are beginning to elucidate the mechanisms of this inhibition [45]. The picture becomes somewhat more confusing, however, when one considers the newer inhalation anesthetics isoflurane, desflurane, and sevoflurane. For the most part, they appear to be neutral toward HPV or at least not cause significant depression in clinically relevant doses. Intravenous anesthesia with propofol has been proposed as a means of avoiding HPV modulation, but rarely is used in clinical practice, as the improvement in oxygenation is clinically insignificant except for marginal patients. The traditional thoracic dogma of keeping the patient warm and dry has merit, as hypothermia, hemodilution and increased left atrial pressure inhibit HPV. Almitrine and Nitric Oxide (NO) are commonly discussed as potential avenues to modulate the HPV response. Almitrine, a respiratory stimulant that causes pulmonary vasoconstriction when given intravenously, has been shown to potentiate HPV and improve oxygenation. Endogenous NO causes vasodilation and thereby inhibits HPV; however, if given by the inhalational route to the

ventilated lung during OLV, NO causes localized vasodilation and thereby decreases shunt fraction. The combination of intravenous almitrine with inhaled NO results in synergistic improvement in V/Q matching and oxygenation. Almitrine, however, is not widely available and is associated with the potential for significant toxicity. Although clearly efficacious, the focus on HPV manipulation with potentially dangerous agents such as almitrine has been called a distraction from more common reasons for desaturation, such as hypoventilation of the dependent lung [13].

Other modifiers of hypoxic pulmonary vasoconstriction

Surgical retraction may aid HPV by increasing pulmonary vascular resistance (PVR) in the operative lung [23]; however, release of vasoactive substances secondary to the manipulation also may result in inhibition of HPV [3]. Ligation of pulmonary vessels during lung resection results in the permanent exclusion of vascular territory and thereby a reduction in shunt flow [3]. The side of surgery influences the extent of shunt flow, as the right lung receives a 10% higher portion of cardiac output than the left lung because of its larger size. Positioning is important, as the lateral decubitus position allows for gravity-induced reductions in shunt flow to the nondependent lung. Procedures that call for supine positioning, on the other hand, are hampered by higher shunt flow to the nondependent lung and may have higher rates of intraoperative desaturations [22].

Ventilation

In the awake patient, ventilation favors the dependent lung, as dependent alveoli are on the steeper portion of the compliance curve than alveoli in upper, nondependent regions (Fig. 3). This relationship is maintained on assuming the supine or lateral position. In the spontaneously breathing patient in the lateral decubitus position, ventilation therefore will favor the lower, dependent lung, aided by the cephalad displacement of the diaphragm by increased abdominal pressure, which results in more effective diaphragmatic muscle contraction. Addition of anesthesia, paralysis, positive pressure ventilation (PPV), and the surgical pneumothorax causes ventilation to increasingly favor the upper, nondependent lung. Anesthesia causes a decrease in the functional residual capacity (FRC) of the dependent lung and an improvement in nondependent lung FRC, resulting in preferential ventilation of the upper lung. Muscle relaxation and institution of positive pressure ventilation cause a further shift toward upper lung predominance in ventilation. Static displacement of the relaxed diaphragm by abdominal contents and the gravity force of the mediastinum restrict the lower lung, resulting in additional decreases in its compliance. Opening of the chest further deteriorates lower lung ventilation, as the loss of negative

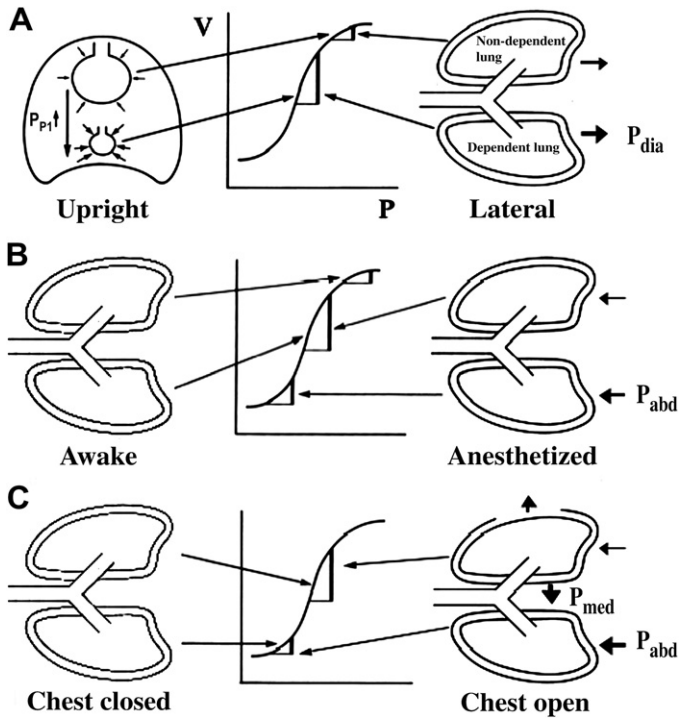

Fig. 3. Positional changes of ventilation as they relate to the pressure–volume curve. Transitions from upright to lateral (*A*), from lateral awake to anesthetized (*B*) and from lateral, anesthetized with chest closed to open (*C*) are illustrated. (*Adapted from* Benumof JL. Anesthesia for thoracic surgery. 2nd edition. Philadelphia: WB Saunders; 1995. p. 127–9; with permission.)

intrapleural pressure releases the mediastinal weight onto the lower lung. All these changes result in progressive uncoupling of V/Q matching, as perfusion continues to favor the dependent lung. On initiation of OLV, the upper, nondependent lung with its favorable compliance becomes excluded from the ventilatory circuit and converts to true shunt. Ventilation now is restricted to the noncompliant lower lung [2,46].

One-lung ventilation and acute lung injury

Ventilatory management for patients undergoing OLV has long focused on the issue of hypoxia avoidance. Hypoxia, however, has become less frequent because of more effective lung isolation, particularly the use of fiberoptic bronchoscopy for confirmation of bronchial blocker or double-lumen tube position, and the use of anesthetic agents with less or no detrimental effects on HPV. Acute lung injury (ALI) has replaced hypoxia as the chief concern associated with OLV, as far as recent publications are concerned. Lung injury after lung resection has long been recognized in the form of

postpneumonectomy pulmonary edema (PPPE) [47]. Although pneumonectomy carries a particularly high risk of lung injury, lesser resection can result in similar pathology [48]. PPPE is part of a spectrum of lung injury, from the milder ALI to the severe acute respiratory distress syndrome (ARDS). Diagnosis relies on the oxygenation index of P_aO_2/F_iO_2 ratio. Critical care consensus definitions specify a P_aO_2/F_iO_2 ratio of less than 300 for ALI and less than 200 for ARDS. ALI after lung resection is fortunately infrequent, occurring in 2.45% of all lung resections combined, with a peak incidence of 7.9% after pneumonectomies. Although infrequent, it is associated with significant morbidity and a mortality rate around 40% [48]. Causative factors of lung injury after lung resection have remained elusive. Initially, risk factors were felt to be right-sided surgery and large perioperative fluid loads. Over the years, impaired lymphatic drainage, surgical technique, ventilatory trauma, transfusion, aspiration, infection, oxidative stress, and ischemia–reperfusion were added to the list of potential contributors [49]. It has long been recognized that ventilation may have detrimental effects in the critically ill patient in the form of ventilator-induced lung injury (VILI). Early animal studies demonstrated that high tidal volumes (45 mL/kg) are particularly injurious to the lung, irrespective of the applied pressure. This has led to the term volutrauma and the realization that end-inspiratory stretch plays a dominant role in lung injury [50]. In patients who have ARDS, application of protective lung ventilation with smaller tidal volumes and high positive end-expiratory pressure (PEEP) improves survival [51]. Follow-up studies showed that the benefit of tidal volume reduction is independent of whether high or low PEEP is applied and even occurs in the setting of low plateau pressures. Additionally, protective ventilation was shown to inhibit progression of lung injury when compared with high tidal volume ventilation [50]. Whether mechanical ventilation causes lung injury in normal lungs and if protective ventilation should be applied routinely in anesthesia are being debated. Tidal volume reduction toward 6 mL/kg for patients who have risk factors for lung injury, and no higher than 10 mL/kg for the remainder, has been proposed for routine two-lung ventilation (TLV) [52,53]. This debate has particular traction for thoracic anesthesia, as tidal volumes of 10 mL/kg are routinely applied to a single lung, often in patients with risk factors for lung injury (Box 1).

The causal role of OLV in the establishment of lung injury is becoming clearer. Radiologic density changes in patients who have ALI after thoracic surgery are worse in the nonoperative, ventilated lung [54]. A retrospective analysis of risk factors for ALI after lung resections showed that an increased duration of OLV in itself is a risk factor for the development of ALI [55]. In animal models, OLV results in histologic changes compatible with lung injury, including vascular congestion and alveolar wall thickening and a decrease in NO in the ventilated lung [56]. Re-expansion of lung after short-term OLV has been shown to cause proinflammatory cytokine release in animals [57]. Similar cytokine elevations are being found in patients

Box 1. Risk factors for acute lung injury after OLV

Patient
Poor postoperative predicted lung function
Preexisting lung injury
- Trauma
- Infection
- Chemotherapy

EtOH abuse
Female gender

Procedure
Lung transplantation
Major resection (pneumonectomy > lobectomy)
Esophagectomy Large perioperative fluid load
Transfusion
Prolonged OLV (> 100 minutes) Peak pressure > 35–40 cm H_2O
Plateau pressure > 25 cm H_2O

undergoing thoracic surgery [58,59]. Much of the blame for the creation of ALI after OLV has fallen on the use of high tidal volumes. OLV has been compared with ARDS, as both involve ventilation of a so-called baby lung with reduced lung capacitance [60]. High tidal volumes therefore may cause excessive end-inspiratory stretch during OLV, similar to ARDS. Some initial evidence for tidal volume reduction exists in the form of reductions in cytokine levels after OLV with low tidal volumes (Fig. 4) [58,59].

Tidal volumes: *less may be more*

OLV traditionally has been performed with tidal volumes that are equal to those being used on TLV [4,61]. This practice was recommended, because large tidal volumes were shown to improve oxygenation and decrease shunt fraction during TLV [62] and OLV, irrespective of PEEP applied [63]. Improved oxygenation was thought to occur because of end-inspiratory alveolar recruitment. Excessive tidal volumes (eg, 15 mL/kg) on the other hand were shown to worsen oxygenation, likely because of elevations in PVR resulting in increased shunt flow [64]. However, OLV with high tidal volumes (referring to 10 to 12 mL/kg) has been pervasive for decades, and as such has an established safety record [65].

Until recently, retrospective case series provided the only insight into lung injury after lung resection. Van de Werff and colleagues and Licker and colleagues identified multiple risk factors among more than 1000 patients undergoing lung resection surgery. Both studies agreed that high

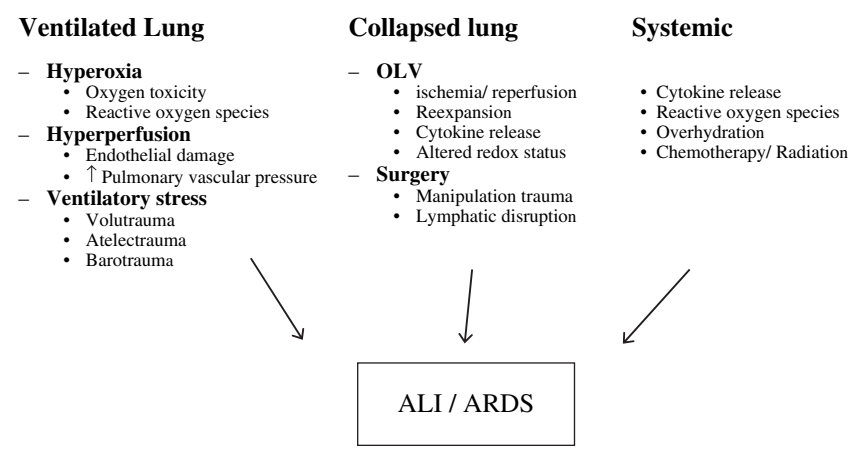

Fig. 4. Proposed mechanisms for Acute Lung Injury and Acute Respiratory Distress Syndrome after lung resection surgery.

ventilating pressures were significantly associated with lung injury. Neither was able to identify tidal volume as an independent risk factor in the analyses [55,66]. These findings contrast with a single-institution review of 170 pneumonectomies. Postoperative respiratory failure occurred in 18% of cases (n = 30). Perioperative risk factors associated with the development of respiratory failure included larger intraoperative tidal volumes (8.3 versus 6.7 mL/kg) and larger fluid administration [67]. Ventilatory pressures were not analyzed, which is significant considering the positive association identified by van de Werff and Licker. Limitations of this study include the fact that tidal volumes referred to the largest volume charted on the anesthetic record, with the assumption that this had been carried over to OLV, and patients who developed respiratory failure received a median of 2.2 L of fluid intraoperatively. The association with a large fluid load has been questioned by some as a possible indicator of inappropriate anesthetic technique [68].

Gama de Abreu and colleagues [69] published one of the earliest and most widely quoted animal studies investigating tidal volume reduction for OLV. Isolated rabbit lungs were subjected to OLV with either 8 mL/kg zero end-expiratory pressure (ZEEP) or 4 mL/kg PEEP 1 cm H_2O. OLV was associated with increases in surrogate markers of lung injury, pulmonary artery pressure (PAP), lung weight gain (LWG), and TXB_2 cytokine levels. All of these markers were reduced in the protective ventilation group. However, the protective ventilation group only received half the minute ventilation of the control group, as no compensatory increase in respiratory rate was used in the low tidal volume group. Rather than a clear tidal volume benefit, outcome changes may have been related to minute ventilation reduction, tidal volume reduction, and/or application of external PEEP. Recently, Kuzkov and colleagues [70] showed that when comparing equal minute ventilation in anesthetized sheep undergoing pneumonectomies, protective ventilation

with 6 mL/kg PEEP 2 cm H_2O lowered extravascular lung water (surrogate for lung injury), compared with 12 mL/kg ZEEP. Again, this study fails to answer the question as to whether tidal volume reduction or application of PEEP is the beneficial intervention.

Because of the infrequent occurrence of lung injury, prospective clinical studies have focused on cytokine levels as a surrogate marker for potentially harmful ventilation. Cytokine elevations are part of the disease process, as levels of interleukin (IL)-6, IL-8, intercellular adhesion molecule 1 (ICAM-1) and vWF are elevated even before intubation in patients who have ALI [71], and baseline plasma levels of IL-6, IL-8 and IL-10 are associated with an increased risk of death in patients who have ARDS [72]. Wrigge and colleagues [73] investigated tracheal cytokine levels in patients who underwent procedures by means of thoracotomy or laparotomy. Individuals were ventilated with 12 to 15 mL/kg ZEEP or 6 mL/kg PEEP 10 cm H_2O during TLV and OLV. Cytokine levels before, during, and after OLV were no different between groups. Tracheal aspirates, however, are less sensitive than broncho–alveolar lavage for pickup of early alveolar damage. Michelet and colleagues [59] randomized 52 patients with normal lung functions undergoing esophagectomy with OLV 9 mL/kg ZEEP or 5 mL/kg PEEP 5 cm H_2O. Cytokine levels (IL-1, IL-6, IL-8) were elevated perioperatively, but to a lesser degree in the protective ventilation group. The degree of lung injury and cytokine elevation may have been exaggerated by the fact that despite almost 6 hours of ventilation and 8 L of fluid, only the low tidal volume group received PEEP during OLV, and no patient received PEEP during the remainder of the operation [59]. Esophageal surgery also may present a higher risk for lung injury, as it is associated with cytokine elevations secondary to intestinal ischemia, potentially acting as a first hit [74]. The most compelling evidence to date that tidal volumes per se are linked to the etiology of ALI after lung surgery comes from a study by Schilling and colleagues [58], which investigated 32 patients undergoing OLV for thoracotomy. Minute ventilation and PEEP were identical between groups, and only tidal volumes were altered. Patients received OLV with 10 mL/kg or 5 mL/kg, both without PEEP. OLV was associated with cytokine elevations (tumor necrosis factor α [TNF-α], sICAM-1), but to a lesser degree with low tidal volume ventilation.

The impact of protective lung ventilation regimes on oxygenation during OLV is not clear. Two studies that investigated protective lung ventilation (lower tidal volume and PEEP) during OLV reported improved oxygenation and shunt fraction as compared with traditional high tidal volume OLV [59,70]. With inadequate or no PEEP, however, low tidal volume ventilation is associated with worse oxygenation and shunt fraction [58]. Recruitment studies performed during protective OLV with a tidal volume of 6 mL/kg and PEEP 8 cm H_2O showed significant recruitability of the ventilated lung, suggesting hypoventilation and atelectasis despite the significant PEEP. Despite the presence of atelectatic lung before the

recruitment maneuver, however, oxygenation was adequate in all patients [75].

OLV by itself is associated with the creation of auto-PEEP and dynamic hyperinflation [76]. Protective OLV with low tidal volumes and high respiratory rate increases dead space, P_aCO_2, and auto-PEEP significantly compared with high tidal volumes at the identical minute volume [77]. This may be a particular issue in cases of severe obstructive lung disease that are prone to, or have pre-existing, dynamic hyperinflation.

Positive end-expiratory pressure

The application of PEEP minimizes alveolar collapse and atelectasis formation by providing resistance to expiration during mechanical ventilation. Adequate PEEP reduces or prevents atelectasis formation and therefore should be routine for all ventilated patients during TLV [52]. Additionally, existing lung injury is attenuated by PEEP, both in the setting of high and low tidal volumes [50]. Intrinsic or auto-PEEP, on the other hand, occurs if expiratory time is insufficient to allow for emptying of lung units toward their resting volume. Lung areas with high compliance and poor recoil, characteristic of patients with emphysema, are particularly vulnerable. Auto-PEEP is inhomogeneous throughout the lung and therefore cannot be relied upon for effective avoidance of de-recruitment [76]. Because of the heterogeneous nature of auto-PEEP, the total PEEP after application of external PEEP is unpredictable [78].

Endotracheal intubation prevents glottic closure, resulting in the absence of auto-PEEP in patients without obstructive lung disease on TLV. Initiation of OLV with 10 mL/kg ZEEP, however, has been shown to create auto-PEEP and air trapping in most patients. Auto-PEEP was insignificant in patients without obstructive lung disease, but patients who had severe chronic obstructive pulmonary disease (COPD) developed auto-PEEP levels up to 16 cm H_2O, which were associated with air trapping of up to 284 mL [76]. Patients who have pre-existing auto-PEEP have an unpredictable response to the application of extrinsic PEEP. In a study of ICU patients on TLV, application of PEEP changed total PEEP up, down, or not at all [79]. In a small study of patients during OLV, the additive effect of PEEP to total PEEP was related inversely to the pre-existing auto-PEEP level. In other words, total PEEP increased less in those patients who had significantly elevated auto-PEEP levels; however, the extent of the response was not predictable [78]. Excessive total PEEP and dynamic hyperinflation are clearly undesirable, as they may cause cardiovascular depression and may necessitate fluid loading and/or inotropic support [53].

Traditionally, OLV has been performed with ZEEP, with selective application of PEEP to the nonoperative lung as part of a hypoxemia pathway. The effect of PEEP on oxygenation during OLV is variable. It is beneficial in patients whose intrinsic PEEP is well below the lower inflection point of the

compliance curve, more commonly the patient who has normal lung function. In that scenario, application of external PEEP will increase the total PEEP toward the lower inflection point (LIP) of the pressure–volume curve, resulting in more open lung and improved oxygenation (Fig. 5A). If, however, total PEEP is increased well above the LIP, worse oxygenation results, likely because of increased shunt secondary to alveolar overdistention and increases in PVR (Fig. 5B) [80]. Neither intrinsic PEEP nor the compliance curve are acquired routinely or easily during thoracic surgery, so identification of the PEEP responder based on pulmonary function tests has been sought. Valenza and colleagues [81] showed that patients who had relatively normal lung function (forced expiratory volume in 1 second [FEV_1] greater than 72%) exhibited improved oxygenation on application of PEEP 10 cm H_2O. Whether applied PEEP is able to decrease ALI after OLV is unclear, as it has not been studied in isolation. However, PEEP application as part of a protective ventilation regime has been shown to decrease surrogate markers of lung injury [59,69,70].

Use of protective OLV with low tidal volumes but no PEEP is not rational, as de-recruitment is harmful and auto-PEEP unreliable in terms of homogeneous lung recruitment. Lack of PEEP in the setting of low tidal volume OLV has been shown to worsen oxygenation [58]. Low levels of PEEP are safe—likely beneficial in terms of lung injury avoidance—and should be used in all patients. PEEP levels, however, need to be adjusted to the individual and their respiratory mechanics. Patients who have normal lung function or restrictive lung disease should benefit from, and will tolerate, 5 to 10 cm H_2O PEEP. Patients who have severe obstructive lung disease, as evidenced by preoperative hyperinflation (right ventricular/total lung capacity

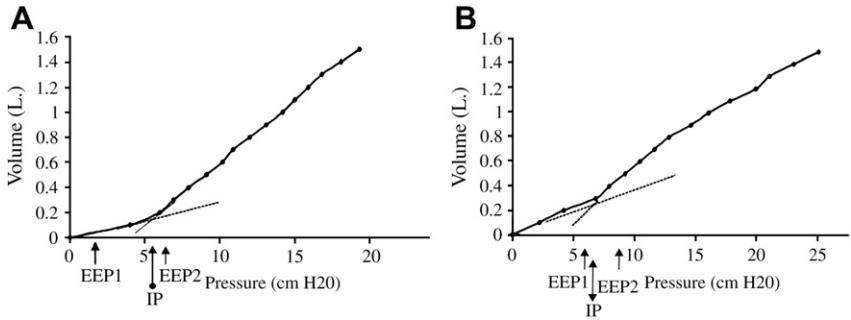

Fig. 5. Effect of applied positive end-expiratory pressure (PEEP) on total PEEP and oxygenation during one-lung ventilation (OLV). Static compliance curves of patients undergoing OLV. End-expiratory pressure before (EEP1) and after application of 5 cm H_2O PEEP (EEP2) and lower inflection points (IP) are indicated. Patients who had normal pulmonary function and low EEP1 (*A*), in whom EEP2 moved closer to IP were more likely to show oxygenation benefits after PEEP application, than patients who had poor lung function and intrinsic PEEP (*B*). See text for details. (*From* Slinger PD, Kruger M, McRae K, et al. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiol 2001;95(5):1098; with permission.)

[RV/TLC] greater than 140%), may develop worsening dynamic hyperinflation with PEEP application, and air-trapping has to be considered as a potential cause of any intraoperative hypotensive episode. However, low levels of PEEP (3–5 cm H_2O) are unlikely to be detrimental and are commonly used in patients with end-stage COPD undergoing lung transplantation. Rational PEEP titration requires measurement of total PEEP [78], which in the operative setting is accomplished most easily with in-line spirometry (Fig. 6) [82].

Inspired oxygen (F_iO_2)

Routine management of OLV long has included the use of 100% oxygen, because of the high rate of desaturation events and the fact that hyperoxia was thought to act as a vasodilator in the ventilated lung. The incidence of hypoxemia has been decreasing, however, and oxygen induced vasodilation may not be clinically significant. Oxygen toxicity, on the other hand, is a well-recognized complication with prolonged exposure to high F_iO_2, characterized by histopathologic changes similar to ALI. Oxygen toxicity occurs during OLV and involves ischemia–reperfusion injury and oxidative stress [49]. Collapse of the operative lung and surgical manipulation result in relative organ ischemia, which leads to the production of radical oxygen species on reventilation-induced reperfusion. Increasing durations of OLV and the presence of tumor result in increased markers of oxidative stress, which after 120 minutes are associated with significant increases in rates of respiratory failure and death [83]. Lung re-expansion likely should occur at a lower F_iO_2, as hypoxemic reperfusion has been shown to attenuate the reperfusion syndrome [84]. This may be particularly important after lung transplantation. Even short-term exposure to high F_iO_2 during the

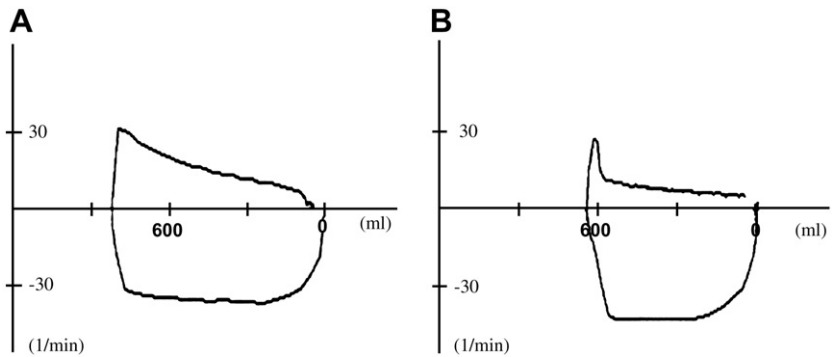

Fig. 6. Auto positive end-expiratory pressure (auto-PEEP) detection by in-line spirometry. Flow volume curves with expiration above and inspiration below the line. Expiratory flow normally returns to zero before inspiration (*A*), interrupted air flow at end-expiration indicates the presence of auto-PEEP (*B*). (*Adapted from* Dueck R, Cooper S, Kapelanski D, et al. A pilot study of expiratory flow limitation and lung volume reduction surgery. Chest 1999;116:1766; with permission.)

induction of anesthesia has been shown to cause significant absorption atelectasis [85], although unpublished work by the author's group was unable to identify clinically relevant absorption atelectasis during OLV with 10 mL/kg ZEEP 100% oxygen (J Lohser and colleagues, unpublished data, 2007). Studies have shown that an F_iO_2 as low as 0.4 may provide adequate oxygenation for OLV in the lateral decubitus position [22]. Because of the potential for lung injury, particularly in the at-risk patient after adjuvant therapy or undergoing lung transplantation, F_iO_2 should be titrated to effect. At the initiation of OLV, an F_iO_2 of 0.8 may be appropriate, but after 15 to 20 minutes when the nadir of oxygenation has occurred, the F_iO_2 should be decreased to the minimum that is required to maintain a saturation above 90%. During lung resection surgery, further decreases in F_iO_2 are possible once the vasculature to the resected lobe or lung has been disrupted, effectively reducing or eliminating the shunt fraction.

Minute ventilation and permissive hypercapnea

Permissive hypercapnea has been a hallmark of the management of ALI/ARDS in the critical care setting. Reduced minute ventilation allows for a decrease in tidal volumes and ventilatory pressures, thereby minimizing mechanical stress and secondary volu- or barotrauma. Recent studies indicate that beyond the reduction in minute ventilation and mechanical trauma, there may be a potential beneficial role of the actual elevated CO_2 levels [86], as hypercapnea appears to attenuate the cytokine response [87].

Permissive hypercapnea has been investigated in the OLV setting. In the previously mentioned study, Gama de Abreu and colleagues exposed isolated rabbit lungs to OLV with 8 mL/kg ZEEP or 4 mL/kg PEEP 1 cm H_2O, without respiratory rate compensation. The protective ventilation group, which received half the minute ventilation, exhibited a reduction in surrogate markers for lung injury (PAP, LWG, cytokine levels) [69]. Similar ventilatory parameters were studied during OLV in thoracotomy patients. Sticher and colleagues [88] ventilated patients with 7 mL/kg PEEP 2 cm H_2O or 3.5 mL/kg PEEP 2 cm H_2O, again without respiratory rate compensation, effectively halving minute ventilation similar to Gama de Abreu and colleagues. $PaCO_2$ values rose from 42 to 64 mm Hg, which was associated with a 42% increase in PVR, but no change in oxygenation. Hypercapnea was tolerated well; however at-risk patients who had elevated pulmonary pressures or major cardiac rhythm disturbances were excluded. A case series of 24 patients who had advanced emphysema undergoing volume reduction surgery documented permissive hypercapnea as part of a barotrauma avoidance strategy. The mean P_aCO_2 value was 56 mm Hg with a peak of 86 mm Hg, resulting in pH values between 7.11 and 7.41 (mean 7.29). The authors state that hypercapnea was tolerated well; however, inotropic support was required in over 50% of patients [89]. Even higher P_aCO_2 levels have been described in a series of 10 patients with

severe emphysema who were managed with elective hypoventilation and hypercapnea for barotrauma avoidance. P_aCO_2 values rose to a peak of 70-135 mm Hg, resulting in pH values as low as 7.03 (despite bicarbonate administration). Hypercapnea was not as well tolerated at these levels. All patients required inotropic support during anesthesia. Four patients developed ventricular dysrhythmias, and three patients required tracheal gas insufflation for treatment of hypoxemia [90]. Significant hypercapnea has the potential to be detrimental, as it can cause increased intracranial pressure, pulmonary hypertension, decreased myocardial contractility, decreased renal blood flow, and release of endogenous catecholamines. At high levels, CO_2 can be lethal because of excessive sympathetic stimulation, cardiac rhythm disturbances, and/or cardiac collapse [53,90]. Moderate hypercapnea potentiates the HPV response and is therefore unlikely to adversely affect oxygenation [11]; however, the same may not hold true for extreme CO_2 elevations [90]. Permissive hypercapnea should become a routine component of OLV management and is already routinely used in lung transplantation. Assuming a reasonable cardiovascular reserve, and in particular RV function, P_aCO_2 levels up to 70 mm Hg are likely to be well tolerated in the short-term and clearly beneficial in terms of lung injury avoidance and attenuation. Hemodynamic support with inotropic agents may be required at higher CO_2 levels or in more compromised patients.

Inspiratory to expiratory ratio and respiratory rate

Selection of an appropriate inspiratory to expiratory (I:E) ratio and respiratory rate is important in cases of severe obstructive disease or significant restrictive disease. In severe obstructive disease, an I:E ratio of 1:4 with a low respiratory rate of six to eight breaths per minute allows for maximal expiratory time, thereby minimizing the risk of auto-PEEP and dynamic hyperinflation. On the other hand, in restrictive lung disease, equalizing the I:E ratio to 1:1 (or using inverse ratio ventilation) and dividing the minute volume by a higher rate of 10 to 15 breaths per minute help to maximize inspiratory time per volume breath, thereby reducing peak and plateau ventilatory pressures. As anatomic dead space remains unchanged, dividing the minute volume by a higher respiratory rate results in more dead space and less alveolar ventilation, leading to reduced CO_2 elimination. Additionally, OLV with small tidal volume and rapid respiratory rate results in statistically higher auto-PEEP [77]. Although auto-PEEP elevations in this study were unlikely to be clinically significant, they serve as a reminder that protective ventilation has the potential to increase dynamic hyperinflation.

Peak and plateau pressure

The peak inspiratory pressure is a reflection of the dynamic compliance of the respiratory system and depends on issues such as tidal volume, inspiratory time, endotracheal size, and bronchospasm. Plateau pressure, on the

other hand, relates to the static compliance of the respiratory system (ie, chest wall and lung compliance). Double-lumen endobronchial tubes (DLTs) have small internal diameters, resulting in a high air flow resistance [91]. Application of the full TLV minute volume to a single lumen of the DLT results in a 55% increase in peak inspiratory pressure and 42% increase in plateau pressure [92]. Although plateau pressure reflects alveolar pressure, peak pressure is unlikely to be fully applied to the alveolus. A retrospective study of 197 patients undergoing pneumonectomies did, however, show that peak ventilation pressures above 40 cm H_2O were associated with the development of PPPE [66]. Similarly, patients exposed to a plateau pressure of 29 cm H_2O were at significantly higher risk of developing ALI after lung resection surgery than those who had a plateau pressure of 14 cm H_2O [55]. Based on the critical care literature, there does not appear to be a plateau pressure level that is truly safe. Plateau pressures less than 25 cm H_2O are achievable in most patients with a well-positioned endobronchial tube [92]. With implementation of permissive hypoventilation, peak pressure levels well less than 35 to 40 cm H_2O and plateau pressures less than 25 cm H_2O therefore should be achievable in most patients.

Ventilatory mode

Volume control ventilation (VCV) has been the dominant ventilatory mode both in the ICU and operating room. VCV uses a constant inspired flow (square wave), creating a progressive increase of airway pressure toward the peak inspiratory pressure, which is reached as the full tidal volume has been delivered. Inspiratory pressure during VCV depends on the set tidal volume and PEEP, gas flow rates and resistance, and respiratory system compliance. The set tidal volume will be delivered unless the inspiratory pressure exceeds the pressure alarm limit, in which case flow ceases. With the realization that ventilatory pressures may be one of the inciting factors of lung injury, other ventilatory modes have been explored. Pressure-controlled ventilation (PCV) uses a decelerating flow pattern, with maximal flow at the beginning of inspiration until the set pressure is reached, after which flow rapidly decreases, balancing the decreasing compliance of the expanding lung. This resembles the spontaneous mammalian breath, which also follows a decelerating pattern, as negative intrathoracic pressure induced by contracting diaphragm and intercostal muscles causes a high initial airflow [52]. Tidal volumes during PCV are highly variable and may fall precipitously with changes in lung compliance, such as surgical retraction. As most of the tidal volume is delivered in the early part of the inspiration, mean airway and alveolar pressure tend to be higher. The decelerating flow pattern results in more homogeneous distribution of the tidal volume, improving static and dynamic lung compliance because of recruitment of poorly ventilated lung regions, and improving oxygenation and dead space ventilation [93].

Tugrul and colleagues [94] studied 48 patients undergoing thoracotomy and lung resection. Patients received VCV or PCV during OLV, both delivering 10 mL/kg ZEEP 100% O_2, in a crossover fashion. PCV was associated with statistically significant decreases in peak and plateau airway pressures and improved oxygenation and shunt fraction. Oxygenation improved more in patients who had poor preoperative lung function, which may relate to the more homogeneous distribution of ventilation achieved with the pressure control breath. The same group investigated the benefit of adding PEEP 4 cm H_2O to OLV with PCV and showed that it provided an additional significant improvement in oxygenation and shunt fraction in their patients [95]. Other groups, however, have failed to reproduce the oxygenation benefit in PCV studies during OLV [96,97]. Although the evidence is contradictory on the benefit of PCV for oxygenation during OLV, in light of concerns about lung injury, the decrease in ventilatory pressures in itself makes PCV the preferable ventilatory mode. The fact that the pressure control breath appears to recruit lung units may become more relevant as more low tidal volume ventilation is employed.

Another ventilatory mode that has been employed in thoracic surgery is high-frequency jet ventilation (HFJV) [98]. HFJV, when applied to the operative lung during prolonged OLV in aortic surgery, is more effective than continuous positive airway pressure (CPAP) in improving P_aO_2 [99]. This may be particularly relevant in the poor operative candidate after prior contralateral lung resection [100]. One recent study evaluated the value of two-lung HFJV by means of a standard endotracheal tube for thoracic surgery. Sixty patients were randomized to HFJV (1 atm pressure, rate 200/min, 100% O_2) or standard OLV (10 mL/kg, 100% O_2, ZEEP). HFJV was associated with lower ventilating pressures, improved oxygenation and shunt fraction, and importantly no detriment in surgical exposure [101]. Difficulties in monitoring ventilating pressures, tidal volumes and end-tidal CO_2 concentrations, in addition to the inherent risks of barotrauma associated with this technique, continue to hamper its widespread adoption [98].

Recruitment and re-expansion

Atelectasis long has been known to occur in dependent lung areas of most patients under anesthesia. Primary reasons for alveolar collapse during anesthesia are extrinsic compression and gas resorption. Recent studies have shown that atelectatic alveoli are not simply airless, but also fluid- or foam-filled. Beyond simple lung collapse, atelectasis now is considered both a cause and a manifestation of ALI [85]. Interestingly, re-expansion of collapsed alveoli causes injury not only to the alveoli that are being recruited but also to remote nonatelectatic alveoli [85]. This may be in part because of the early realization by Mead that expansion of a gas-free alveolus with a transpulmonary pressure of 30 cm H_2O creates a shear force of

140 cm H_2O to adjacent alveoli [50]. PEEP has been shown to prevent lung injury associated with high and low tidal volumes, by stabilizing alveoli, and preventing their collapse [85]. In animal models of ARDS, it has been shown that atelectasis is associated with vascular leak and RV failure and eventual death in 31% of rats, and it is easily avoided with PEEP [102].

Atelectasis formation in the nonoperative lung is highly undesirable during OLV, as it worsens the already high shunt fraction, increasing the potential for hypoxemia. Among the risk factors that predispose to lung de-recruitment during OLV are high F_iO_2, traditional lack of PEEP, and extrinsic compression by abdominal contents, heart, and mediastinum. The best evidence for the presence of atelectasis during OLV comes from a lung recruitment study, which investigated an aggressive recruitment regimen with increasing pressure breaths over a 4-minute period up to a peak pressure of 40 cm H_2O and a PEEP level of 20 cm H_2O. Recruitment increased P_aO_2 on OLV from a mean of 217 mm Hg to a mean of 470 mm Hg (Fig. 7) [75]. Recruitability also was shown by a group comparing identical minute ventilation delivered by either VCV 9 mL/kg ZEEP or by biologically variable ventilation (BVV: tidal volumes of 5 to 18 mL/kg ZEEP) in anesthetized pigs. BVV consists of variable tidal volume ventilation, essentially incorporating large sigh breaths into regular ventilation. Lungs in the BVV remained more compliant; oxygen tensions were higher and

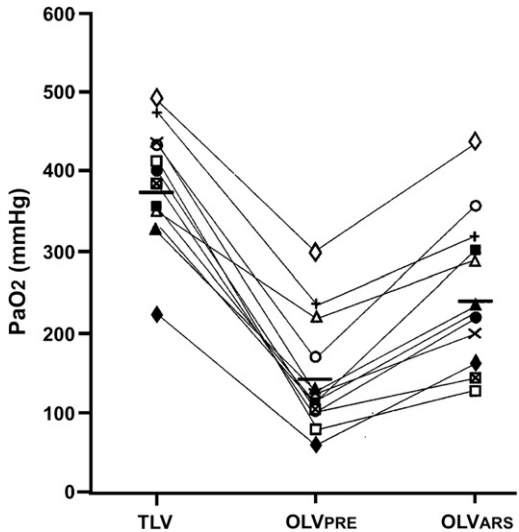

Fig. 7. Lung recruitment improves oxygenation during one-lung ventilation (OLV). P_aO_2 (mm Hg) in patients during two-lung ventilation (TLV) and during OLV, before (OLV_{PRE}) and after (OLV_{ARS}) the alveolar-recruitment strategy. Each symbol represents one patient in every point of the study. Horizontal bars represent mean values at each point. (*From* Tusman G, Bohm SH, Sipmann FS, et al. Lung recruitment improves the efficiency of ventilation and gas exchange during one-lung ventilation. Anesthesia Anesth Analg 2004;98(6):1608; with permission.)

shunt fraction lower, arguing for less atelectasis than standard VCV [103]. Interestingly, unpublished work by the author's group suggests that absorption atelectasis does not appear to occur at clinically relevant levels during OLV with tidal volumes of 10 mL/kg on 80% or 100% oxygen (J Lohser and colleagues, unpublished data, 2007). Caution is required with the implementation of protective lung ventilation, as low tidal volumes and plateau pressures may promote atelectasis formation and increase F_iO_2 and PEEP requirements [53]. Frequent derecruitment and therefore need for repeated recruitment maneuvers, as may be the case with low tidal volume ventilation with insufficient PEEP, are potentially deleterious. In animal models of lung injury, repeated de-recruitment and recruitment maneuvers are associated with histologic evidence of lung injury [104,105]. Even a single recruitment maneuver of 40 cm H_2O for 40 seconds has been shown to elevate biomarkers of lung injury in the rat model without pre-existing lung injury [106]. This creates a curious dilemma, as the increased use of protective lung ventilation, with low tidal volumes, may promote atelectasis formation and therefore increase the need for recruitment maneuvers [53].

Atelectasis formation in the operative lung is routine and occurs gradually over a 10- to 20-minute period as residual oxygen is being absorbed, which parallels the gradual decline in P_aO_2 on OLV. Atelectasis is complete, unless continuous positive airway pressure (CPAP) is applied to the operative lung. CPAP, or its variant HFJV, if applied to the at least partially recruited operative lung, effectively improves V/Q matching and hypoxemia [99]. Gradual re-expansion of the operative lung at the conclusion of OLV is achieved with a continuous pressure hold of 30 cm H_2O, which is lower than standard recruitment regimens, to prevent disruption of the staple line. Re-expansion of lung may be harmful. Re-expansion injury after prolonged lung collapse consists of alveolar–capillary membrane edema and increases in lymphocyte and neutrophil infiltration [107]. Re-expansion of isolated rabbit lungs after 55 minutes of lung collapse showed significant elevations in myeloperoxidase levels, IL-1β, and TNF-α mRNA when compared with an open lung control [57]. Intermittent lung re-expansion may mitigate these effects, as intermittent recruitment of the operative lung during OLV has been shown to decrease proinflammatory mediators during esophagectomy [108]. Lung recruitment with a continuous high pressure hold may result in significant hypotension if applied to both lungs. Recruitment is well tolerated, however, even in the setting of hypovolemia, if it is only selectively applied to one lung at a time, with the other lung open to atmosphere [109]. Re-expansion pulmonary edema is fortunately rare if a gradual, gentle recruitment technique is applied, and is more likely after sudden recruitment of long-standing lung collapse [110]. Yet, even a single recruitment maneuver has the potential to cause lung injury in animal models [106]. Low oxygen tensions likely should be used for re-expansion, as recruitment of the operative lung is associated with substantial oxidative stress, particularly after prolonged OLV [83,84].

One-lung ventilation duration

Mechanical stress due to OLV can be minimized by optimization of ventilatory parameters. Even minimal stress using protective parameters, however, becomes significant if exposure is prolonged. Retrospective case series have shown that OLV lasting more than 100 minutes is associated with an increased risk for postoperative lung injury [55]. Part of the damage may be caused by oxidative stress. A recent animal study exposed rats to increasing durations of OLV from 1 to 3 hours. At the conclusion of the experiment, animals were sacrificed, tested for indicators of oxidative stress, and lung tissue was examined histologically. Increasing the duration of OLV from 1 hour to 3 hours resulted in significant elevations of malondialdehyde (MDA) activity and increasing tissue damage on histologic analysis [111]. A prospective analysis of patients undergoing lobectomy for nonsmall cell cancer with either TLV or OLV lasting more than 60, 90, or 120 minutes compared MDA plasma levels at lung re-expansion. Again, MDA levels increased significantly with increasing OLV duration, indicating cumulative oxidative stress [83]. Anesthesiologists have limited control over the duration of OLV, as it is determined mostly by the surgical procedure. Initiation of OLV, however, should occur as close to pleural opening as possible, and TLV should resume as early as possible. With the increasing use of OLV outside the thoracic theater, it is essential to ensure that the non-thoracic surgeon appreciate the need to minimize the length of OLV.

Summary: ventilatory strategy

The jury is still out on the most appropriate ventilation technique for OLV. Based on the current level of evidence, it appears likely that protective ventilation will decrease the incidence or severity of ALI after lung resection. Protective ventilation is not synonymous with simply low tidal volume ventilation but also includes all of routine PEEP, lower FiO_2, and particularly lower ventilatory pressures through the use of PCV and permissive hypercapnea. De-recruitment of lung tissue, impaired CO_2 elimination, and dynamic hyperinflation potentially may complicate this approach. Lung de-recruitment may be more prevalent with low tidal volumes because of the loss of end-inspiratory stretch in the setting of high F_iO_2. External PEEP should help to minimize de-recruitment. PEEP titration, however, is difficult in the intraoperative setting for two reasons. First, determination of inflection points and auto-PEEP requires in-line spirometry, as routine expiratory holds are not feasible intraoperatively. Second, other than the ICU, where as long as cardiac output is maintained PEEP can be increased to maintain open lung, excessive PEEP causes pulmonary blood flow diversion to the operative lung and therefore worsens oxygenation. As such, low tidal volume ventilation has the potential to worsen oxygenation, either because of lung de-recruitment with inadequate PEEP or because of pulmonary blood flow

diversion with excessive PEEP. Ventilation with low tidal volumes (high respiratory rates increase dead space ventilation) and CO_2 elimination is therefore consistently worse with this technique. This should not present a problem in most patients, unless CO_2 elimination already is compromised by severe obstructive lung disease (eg, cystic fibrosis). If inadequate ventilation results in severe respiratory acidosis, marked pulmonary hypertension, or RV dysfunction, protective low tidal volume–high rate ventilation should be aborted in favor of high tidal volume–low rate ventilation to minimize dead space. Dynamic hyperinflation is common during OLV and is increased with the application of PEEP and the use of higher respiratory rates. Providing adequate expiratory time and use of permissive hypoventilation should minimize the risk of significant hyperinflation in all but the most severe obstructive lung disease.

Application of protective lung ventilation is more relevant in patients who have risk factors for lung injury and during procedures that trigger a higher inflammatory response, such as esophageal surgery or lung transplantation (see Box 1). Recall that cytokines are likely to be associated with lung injury, but no causal relationship has been established [53]. This point was illustrated by an animal study comparing low versus high tidal volume ventilation with or without PEEP in ALI. Although animals with high tidal volume ventilation and ZEEP clearly had significant cytokine elevations, all animals exposed to low tidal volumes and ZEEP died during the experiment [112]. In addition to the fact that the relative risk for postoperative lung injury is highly patient- and procedure-dependent, respiratory mechanics vary widely between restrictive and obstructive lung disease. It is therefore difficult and likely undesirable to develop one ventilation method for all-comers (Box 2) [80].

Management of hypoxia

Hypoxia used to be the major concern during OLV anesthesia. Early reports indicated that 40% to 50% of patients suffered hypoxemia during OLV [113]. Efforts to create a list of predictive indicators that may alert the clinician to the likelihood of hypoxia resulted in conflicting results. Hurford and colleagues [113] examined the intraoperative oxygenation of patients who had undergone preoperative V/Q scanning. They found that the amount of preoperative perfusion (and ventilation) to the operative lung inversely correlated with P_aO_2 after 10 minutes of OLV. As HPV is only able to halve blood flow through the operative lung during OLV, the authors concluded that the extent of preoperative blood flow helped to predict the amount of intraoperative shunt. Slinger and colleagues [114] showed that P_aO_2 during OLV relates to oxygenation during TLV, side of operation, and preoperative pulmonary function (FEV1). Over the years, the incidence of hypoxemia has been declining. In 1993, the incidence of hypoxia less than 90% occurring during OLV was quoted at 9% [115]. By 2003, the published

Box 2. Summary of ventilatory strategies (*one size does not fit all*)

Tidal volume
- Protective: 4–6 mL/kg
- Hypoxia or severe hypercapnea: consider 6–10 mL/kg

Positive end-expiratory pressure (PEEP):
- Protective/restrictive/normal: 5–10 cm H_2O
- Obstructive: 3–8 cm H_2O (minimize intrinsic PEEP)

Respiratory Rate
- Protective: 10–15/min
- Severe hypercapnea: 6–8/min

FiO_2
- Transplant: 21%+
- Routine: 50% to 80%
- Hypoxia: 100%

Inspiratory to Expiratory ratio
- Restrictive: 1:1 or inverse ratio
- Normal: 1:2
- Obstructive: 1:3–4

Pressures
- Plateau <25 cm H_2O
- Peak <<35–40 cm H_2O

Minute volume: P_aCO_2 50–70 mm Hg, potentially higher P_aCO_2 with severe obstruction/lung transplantation

Ventilator mode: PCV for all (? HFJV)

incidence of hypoxemia was down to 1% of OLV cases in some centers [116]. Improvements in anesthetic technique including improved lung isolation, confirmation of lung isolation with fiberoptic bronchoscopy, and use of anesthetic agents with less effects on HPV are being credited for the reduction of oxygenation difficulties. Although rare, significant hypoxia still may occur, at times without warning [117].

A few points need to be appreciated in order for a rational approach to hypoxia during OLV. CPAP will always improve shunt flow, and TLV will eliminate shunt flow. Aside from procedures like pneumonectomy and lung transplantation, where these techniques are unavailable, patients should not have to suffer prolonged hypoxemia. Assuming that the lung isolation device is positioned properly, these two maneuvers are the most effective treatments for hypoxemia. They are not chosen as first-line interventions, however, because they will impair surgical access to the lung, particularly during thoracoscopic procedures. Additionally, they require some degree of lung recruitment, which is not always feasible (lung lavage,

Box 3. Approach to hypoxemia during OLV

Mild hypoxemia (90% to 95%)
Confirm position of lung isolation device
Recruit ventilated lung
Ensure adequate cardiac output
Increase F_iO_2 toward 1.0
CPAP or HFJV to operative lung (after recruitment)
Optimize PEEP to nonoperative lung (up or down; toward lower inflection point)
Consider reduction in vapor anesthetic and/or total intravenous anesthesia
Ensure adequate oxygen carrying capacity (hemoglobin)

Severe (<<90%) or refractory hypoxemia
Resume two-lung ventilation with 100% O_2
If not possible, consider
- Pulmonary artery clamp on operative side during pneumonectomy, transplant
- Inhaled nitric oxide and/or infusions of almitrine/phenylephrine
- Extracorporeal support during lung transplantation (Nova lung [Novalung GmbH, Hechingen, Germany], cardiopulmonary bypass, extracorporeal membrane oxygenation)

bronchopleural fistula). Lung de-recruitment in the ventilated lung is common, easily reversed with recruitment maneuvers, and preventable with appropriate PEEP levels. Low mixed venous oxygen saturation secondary to low cardiac output is another frequent and easily treatable cause of desaturation. Pharmacologic modulation with vasoconstrictors (almitrine, phenylephrine) to strengthen HPV in the operative lung and vasodilators (inhaled NO) to improve pulmonary vascular capacitance in the ventilated lung may be helpful in extreme cases. A simplified approach for management of hypoxemia is provided in Box 3.

Summary

These are exciting times for the thoracic anesthesiologist, as OLV, the main staple of the specialty, is undergoing a transformation. Although definitive support for protective OLV remains lacking, the circumstantial evidence is strong enough to reconsider traditional parameters. More than that, it presents an opportunity to rationalize and individualize therapy for each patient. Further studies are needed to identify the true effect of

protective ventilation on the incidence of hypoxemia and extent of dynamic hyperinflation. Only a large multicenter randomized clinical trial may be able to definitively answer whether protective ventilation decreases respiratory morbidity and mortality after lung resection surgery.

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Anesthesiology Clin
26 (2008) 273–280

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Oxygen Toxicity During One-Lung Ventilation: Is It Time to Re-Evaluate Our Practice?

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Lung cancer remains one of the leading causes of cancer-related mortality today [1,2]. Surgical resection remains the mainstay of non–small cell lung cancer therapy. In addition, an increasing number of patients receive preoperative adjuvant chemotherapy. This chemotherapy has improved cancer-related outcomes but may predispose these patients to unique organ toxicities not seen in the surgical population that does not receive chemotherapy. Although advances in surgical, oncologic, and anesthetic care have reduced overall mortality, pulmonary complications, including acute lung injury (ALI), remain a major cause of morbidity and mortality following lung resection [2]. As a result, continued efforts are needed to maintain the trend toward improvement in overall outcome in these patients.

The incidence of ALI is related directly to how it is defined. The literature variably reports this entity as ''postpneumonectomy pulmonary edema,'' ''noncardiogenic pulmonary edema,'' and ''postreperfusion lung'' [3–7] All these entities can be better grouped together to comprise a variable degree of ALI, the most severe form of which is adult respiratory distress syndrome (ARDS). When stricter criteria based on timing (always appearing soon after surgery), chest radiograph findings (diffuse, bilateral infiltrates), and cardiac status (pulmonary capillary wedge pressure < 18 mm Hg) are used to define these problems [8], it is the degree of oxygenation impairment that determines the difference between ALI ($Pa_{O_2}/F_{IO_2} < 300$ mm Hg) and ARDS ($Pa_{O_2}/F_{IO_2} < 200$ mm Hg). Using these international criteria for ALI/ARDS, various studies have demonstrated the overall incidence of

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.008 *anesthesiology.theclinics.com*

ALI to be 2% to 4% of pneumonectomies, 1% of lobectomies, and approximately 0.1% to 0.2% of thoracoscopic procedures [2,8–11].

There are a number of risk factors for ALI during thoracic surgery [8]. Among them are operative trauma, the inflammatory response [12], and oxidative stress [13,14]. Recently, excessive perioperative fluid overload has been increasingly associated with postpulmonary resection ALI, seen more commonly after pneumonectomy than after lobectomy [15–17]. Perturbations of pulmonary lymphatic flow with mediastinal interruption may be a significant contributor, as is localized pulmonary endothelial damage. Induction chemotherapy and adjunct radiation incur further changes to lymphatic flow, and further endothelial damage by ischemia-reperfusion injury mediated by reactive oxygen species (ROS) can occur also. Indeed, oxidative stress may be the mechanism by which excessive oxygen exposure damages lungs (Box 1).

Systemic oxygenation during one-lung ventilation traditionally has been optimized by increasing the F_{IO_2} to 1.0. Although intuitively this approach seems logical in terms of preventing excessive desaturation during periods of reduced oxygenation capacity (by providing a buffer should ventilation and oxygenation become difficult, particularly when one lung is deflated and considerable intrapulmonary shunting is occurring), its therapeutic safety never has been evaluated thoroughly. The potential harmful aspect of a high inspired oxygen concentration is that it may expose lungs to the risk of oxygen toxicity. Although relatively brief exposure to 100% oxygen is unlikely to cause injury in normal lungs, there is evidence suggesting that the thoracic surgical patient may be more susceptible to oxygen toxicity than conventionally thought [8]. This possibility raises the question of whether current practices during one-lung ventilation should be re-evaluated.

The sensitivity of the lung to high levels of oxygen is well described, but this sensitivity depends on both the F_{IO_2} and on the duration of oxygen therapy [18–21]. Traditionally, it has been thought that the lung is not susceptible to injury if exposed to 100% oxygen for less than approximately 12 hours. Few objective data exist to support this tenet during lung resection

Box 1. Proposed mechanisms of acute lung injury/adult respiratory distress syndrome

Elevated pulmonary vascular pressures
Lung capillary endothelial damage
Acute inflammation secondary to operative lung collapse and re-expansion
Ischemia-reperfusion injury of operative lung
Oxygen toxicity and reactive oxygen species generation
Microembolization
Volutrauma

surgery, however. The previously assumed safety of this situation, although demonstrated in volunteers and patients otherwise undergoing two-lung ventilation, may not be completely applicable to the patient at risk of ALI during thoracic surgery.

Evidence for oxygen toxicity has accumulated both experimentally and clinically. In an experimental study in dogs, Royer and colleagues [18] demonstrated that with as little as 12 hours of exposure to 100% oxygen, pulmonary capillary permeability increases significantly, with consequence increases in lymphatic flow. In humans, evidence for oxidative injury has been documented in patients undergoing single-lung ventilation for lung resection [22]. In a study of 28 patients undergoing pneumonectomy, lobectomy (single or bilobectomy), or wedge resection/lung biopsy, Williams and colleagues [13] measured markers of oxidative protein damage. The change from the preoperative baseline in plasma protein thiol concentrations and carbonyl concentrations was used as an indicator of oxidative damage. With the formation of ROS, there generally is a loss of plasma thiols with the formation of protein carbonyls [23,24]. These patients demonstrated corresponding plasma thiol (that is, decreasing levels) and carbonyl changes (increasing levels) with various degrees of thoracic resection demonstrating significant oxidative damage, particularly seen with an increasing extent of lung resection and greatest after bilobectomy (Fig. 1) [13]. Using different methodology to measure ROS production in lung resection patients, Lases and colleagues [14], in a pilot study ($n = 28$), examined exhaled levels of H_2O_2 and urinary malondialdehyde (MDA) as markers for oxidative stress. H_2O_2 is itself an ROS reflecting oxidative burden in the lungs. Urine MDA is considered a systemic marker of lipid peroxidation. The investigators demonstrated that these markers were increased in their patients and correlated strongly with each other, suggesting that the lung itself was the source of the oxidative stress and that the urine reflected this oxidative stress by an increase in MDA. The most significant increases were found after lobectomy (Fig. 2) [14].

Other preoperative factors also have been implicated in ALI. Increasingly, one of these preoperative factors is exposure of the patient to presurgical chemotherapy [25]. Induction chemotherapy has been demonstrated to improve both resectability and long-term survival in patients who have lung cancer with ipsilateral mediastinal lymph-node involvement [26]. It has long been known, however, that certain chemotherapeutic agents (particularly bleomycin) may be associated with lung injury [27–29]. Bleomycin is used infrequently in the treatment of lung cancer and is used more commonly in the treatment of urologic malignancies; cis-platinum and paclitaxel are the most frequently used agents in patients who have lung cancer [30]. Although bleomycin is more likely to be injurious to the lung, these other agents also have pulmonary toxicity [31,32]. Because an increasing number of patients are presenting for thoracic surgery after having undergone preoperative chemotherapy, the influence of and interaction between chemotherapy and oxygen therapy on lung toxicity warrants evaluation.

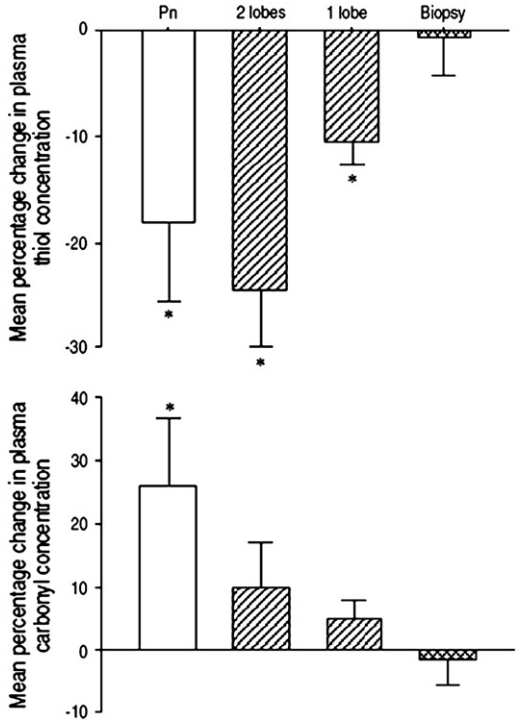

Fig. 1. Perioperative changes (mean ± SEM), from preoperative to postoperative, in plasma protein thiols and carbonyl concentrations for patients undergoing pneumonectomy, lobectomy (one or two lobes), and biopsy/wedge resection. (*From* Williams EA, Quinlan GJ, Golstraw P, et al. Postoperative lung injury and oxidative damage in patients undergoing pulmonary resection. Eur Respir J 1998;11:1031; with permission.)

As a measure of preoperative injury from chemotherapy, Takeda and colleagues [33] recently examined the impact of induction chemotherapy on lung diffusing capacity (DLCO) in patients undergoing thoracic surgery. The basis for their study was reports of increased morbidity and mortality in patients undergoing lung surgery after induction chemotherapy [1,8,34–39]. DLCO previously had been demonstrated to be a sensitive indicator of subclinical chemotherapy-induced lung injury [40]. In the study by Takeda and colleagues [33], 66 patients undergoing induction chemotherapy were compared with 200 control patients undergoing resection without any preoperative chemotherapy. They reported significant reductions in DLCO in the induction chemotherapy group (70.7 ± 13.1% in the chemotherapy group versus 89.7 ± 19.6% in the control group; $P = .0001$). In addition, patients who had experienced pulmonary complications were more likely than patients who had not experienced pulmonary complications to have had a reduction in preoperative DLCO (74.4% versus 62.6%; $P = 0004$).

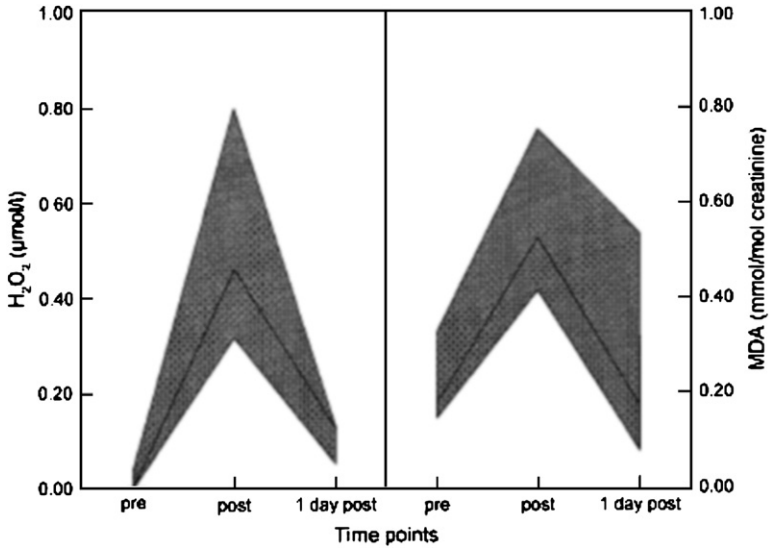

Fig. 2. Median (and 95% confidence interval) of the exhaled H_2O_2 and urinary malondialdehyde (MDA) (represented as a ratio to urinary creatinine) in patients undergoing pulmonary resection with lobectomy demonstrating significant oxidative stress in the immediate postoperative period. (*From* Lases EC, Duurkens VA, Gerritsen WB, et al. Oxidative stress after lung resection therapy: a pilot study. Chest 2000;117:1000; with permission.)

The importance of the DLCO also was addressed by Leo and colleagues [40] in a retrospective observational study (n = 30). They demonstrated that only the DLCO had any relationship to postoperative respiratory complications, with the more traditional indicators of forced expiratory volume in 1 second and forced vital capacity showing little relationship.

Chemotherapeutic agents that have potential lung toxicity frequently are administered to many patients presenting for nonthoracic surgery. These patients rarely manifest any overt ALI, although when investigated they also suffer similar decreases in diffusing capacity. Many patients with other malignancies also undergo surgery with few or no pulmonary complications. Patients undergoing thoracic surgical are unique in that, in addition to pulmonary toxicity from chemotherapy, they also suffer the additional functional loss caused by the resection itself. All these insults compound to increase the chances of pulmonary injury.

If oxidative stress, from either the increased F_{IO_2} or the interaction of chemotherapy itself, is partly responsible for ALI after thoracic surgery, then the intuitive response to this ROS-mediated oxidative injury is to reduce the exposure of the lung to an excessively high F_{IO_2}. Interestingly, this reduction in oxygen exposure may have another practical benefit. Atelectasis is known to occur in the lung exposed to 100% oxygen because of the absorption of the oxygen by the lung units over time (so-called ''absorption

atelectasis''). This atelectasis may be reduced by lowering the F_{IO_2}. In relation to oxidative injury and ALI, a reduction in F_{IO_2} also may have a less immediate benefit. One consequence of this concern for oxygen toxicity is the increasingly common practice of reducing the F_{IO_2} during one-lung ventilation. This response to the concern about oxidative injury coupled with the practice of reducing F_{IO_2} during one-lung ventilation has little objective justification. Although a reduction in inspired oxygen concentrations is central to the concept of reducing ROS production in a lung already susceptible to further injury, one must weigh the potential benefits of this reduction against other risks. Other oxygen-related issues must be considered in the decision to reduce the F_{IO_2} or to maintain it at 100%. For example, there is evidence in other surgical settings (eg, colorectal surgery) that enhanced oxygenation (via an increase in F_{IO_2}) can reduce perioperative infection [41]. Although this possibility has not been studied specifically in the thoracic surgery population, pneumonia remains a common perioperative complication, and any measure that reduces this complication would be warranted. The impact of oxygen therapy on infection after lung resection is not known, but one might deduce that it would be reduced if a higher F_{IO_2} were administered.

In addition, there is evidence that undetectable cerebral hypoxia can occur in elderly patients undergoing major nonthoracic surgery despite otherwise normal pulse oximetry measurements. Casati and colleagues [42] studied 122 elderly patients undergoing major intra-abdominal surgery using near-infrared spectroscopy to monitor noninvasively for the occurrence of cerebral desaturation. They found a significant degree of desaturation intraoperatively and also found that this desaturation was associated with a poor performance on postoperative neuropsychologic testing. Maneuvers to reduce this impairment in oxygenation, including increasing the F_{IO_2}, might alleviate this problem.

One must balance the relative risks of all these complications with their respective benefits, but data related to the patient undergoing thoracic surgery are limited, again suggesting that current practices perhaps should be re-evaluated.

In summary, although the evidence indicating that 100% oxygenation during one-lung ventilation is injurious to the lung is incomplete, the absence of evidence does not necessarily indicate the absence of such an effect. Similarly, if there are few data suggesting that a reduced F_{IO_2} is effective or safe, then its use similarly should be re-evaluated. Just as studies have re-evaluated fluid therapy in the patient undergoing thoracic surgery [15], so should oxygen therapy in this population be re-evaluated. Although there clearly is a potential disadvantage to decreasing the F_{IO_2} (ie, a potential increase incidence in desaturation), it is likely that a balanced approach should be considered. For example, once lung isolation has occurred, it may be prudent to reduce the F_{IO_2} to the level that decreases the risk of oxygen toxicity but maintains an adequate systemic oxygenation. This

practice, coupled with objective studies examining potential oxygen toxicity issues and balanced against all the other potential risks, will provide useful information in this clinical area. There are a number of unresolved issues related to oxygen therapy in this population. A thorough re-evaluation of current practice with objective data obtained from controlled clinical investigations could add significantly to the overall understanding of the state of the art.

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Anesthesiology Clin
26 (2008) 281–291

ANESTHESIOLOGY
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Anesthetic Considerations for Airway Stenting in Adult Patients

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Central airway obstruction results from a variety of benign and malignant causes (Box 1). Regardless of cause, airway stenosis is associated with significant morbidity and mortality [1]. During the past 2 decades, new interventional techniques have evolved to help manage these challenging patients. The current therapeutic armamentarium includes surgical reconstruction, dilation, stenting, coring-out, brachytherapy, cryotherapy, electrocautery, photodynamic therapy, and laser vaporization [1–3]. Anesthesiologists are integral participants whenever the safe relief of a central airway obstruction is attempted [4]. This article focuses on the relevant anesthetic considerations of airway stenting in adult patients.

The application of airway stents was pioneered by Montgomery in the mid-1960s for patients who had subglottic stenosis [5]. In 1990, Dumon [6] introduced a silicone stent that was positioned completely within the lumen of the trachea (Fig. 1). Since then numerous types of stents have been deployed to re-establish patency of compromised airways. Modern tracheobronchial stents are constructed from either silicone or metal.

The properties of the ideal stent include (1) easy insertion and removal; (2) stability within the airway providing resistance to migration; (3) ability to withstand compressive forces while being sufficiently elastic to conform to the airway; (4) resistance to granuloma formation and infection; (5) availability of diverse sizing and (6) preservation of mucous clearance [7,8]. Unfortunately, no currently available manufactured stent achieves all of these objectives.

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.005 *anesthesiology.theclinics.com*

Box 1. Causes of central airway obstruction

Benign
Traumatic: postintubation; blunt, penetrating, or inhalational injury
Inflammatory: Wegener's granulomatosis; amyloidosis; systemic lupus erythematosus
Infectious: papillomas; tuberculosis; rhinoscleroma; viral tracheobronchitis; bacterial tracheitis; diphtheria
Vascular: rings; aneurysms; postpneumonectomy syndrome; anatomic anomalies (eg, right innominate artery, double aortic arch)
Neoplastic: neurofibroma, chondroma, chondroblastoma, hemangioma, pleomorphic adenoma
Anastomotic: lung transplantation; sleeve resection
Other: tracheomalacia; relapsing polychondritis; sarcoidosis; foreign body

Malignant
Primary intraluminal malignancy
- Adenoid cystic
- Carcinoid
- Mucoepidermoid
- Bronchogenic

Primary extraluminal malignancy
- Esophageal
- Mediastinal (thymus, thyroid, germ cell)
- Lymphoma
- Sarcoma

Metastatic malignancy
- Bronchogenic
- Renal cell
- Breast
- Thyroid
- Melanoma
- Colon

Stent considerations

Silicone stents are recommended for patients who have benign disease because of their relative ease of removal (Box 2). Major disadvantages of silicone stents include predisposition to migration, potential obstruction with secretions, flammability, and a reduced inner diameter compared with metal stents of similar size. Placement of silicone stents also requires rigid bronchoscopy. Although many authors cite this requirement as

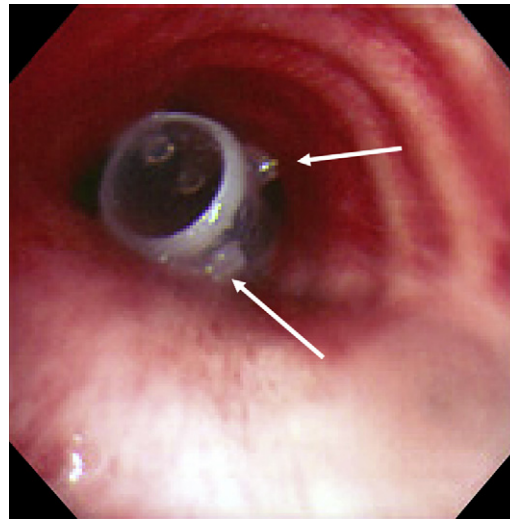

Fig. 1. Silicone stent in situ. Arrows indicate regularly placed studs designed to minimize movement within the airway. (*Courtesy of* Jay B. Brodsky, MD, Palo Alto, CA.)

a disadvantage, the experienced clinician appreciates the value of this instrument, as discussed later [8–13].

Metal stents are available in covered and uncovered forms. Generally, metal stents are indicated only for palliation in patients who have malignant disease [14] because they are difficult to extract and are associated with granuloma formation [15] and risk of perforation [2]. Nevertheless, successful management of benign central airways obstruction using metal stents is reported [16]. Long-term safety data for these devices are unavailable [17]. After reviewing their own experience, Ehller and colleagues [18] suggest that if metal stents are considered in this population, their application should be limited to patients who repeatedly fail conservative endoscopic management, are medically unsuitable for open procedures, refuse management with a silicone stent, and are able to undergo frequent screening and therapeutic endoscopies.

The purported advantages of covered metal stents are resistance to granuloma formation and arguably easier removal [19,20]. Of note, metal stents may transmit laser energy and injure surrounding tissue [21] and, when covered, also pose a fire risk [22]. Advantages of metal stents over silicone ones include ease of placement (by flexible bronchoscopy or fluoroscopy), a larger inner diameter, stability within the airway, and preservation of mucociliary transport (Fig. 2) [7].

Utility

Experienced operators report instantaneous symptomatic improvement in up to 95% of selected patients undergoing airway stenting [2,23]. For

Box 2. Stent properties

Metal
Advantages
- Large inner-to-outer diameter ratio
- Resistance to migration
- Preserved mucociliary clearance
- Placement under local anesthesia

Disadvantages
- Susceptibility to granulation and restenosis
- Transmission of laser energy
- Flammability when covered
- Risk of long-term airway perforation
- Difficult removal (considered permanent)

Silicone
Advantages
- Need for rigid bronchoscopy (see text)
- Ease of repositioning and extraction

Disadvantages
- Need for rigid bronchoscopy (see text)
- Reduced inner-to-outer diameter ratio
- Susceptibility to migration
- Inhibition of mucociliary clearance
- Secretion impaction
- Flammability

patients who have end-stage malignancies, this improvement translates into meaningful palliation and relief of impending suffocation [24]. Noppen and colleagues [25] demonstrated that stenting facilitated immediate postoperative extubation in 93% of ventilatory-dependent patients. Bronchial dehiscence, malacia, and stenosis are anastomotic complications of lung transplantation that are managed effectively by stenting [26]. Recently, a French group employed silicone stents to support a trachea reconstructed from an aortic allograft [27]. Regardless of device selection or indication, the short-term therapeutic impact of airway stenting often is dramatic. Long-term patency of airway stents commonly demands repeated endoscopic interventions [28].

Anesthetic considerations

Multiple anesthetic considerations must be addressed when embarking on tracheobronchial stenting. Airway stenting generally is performed in high-risk patients [10], often in remote locations outside the operating

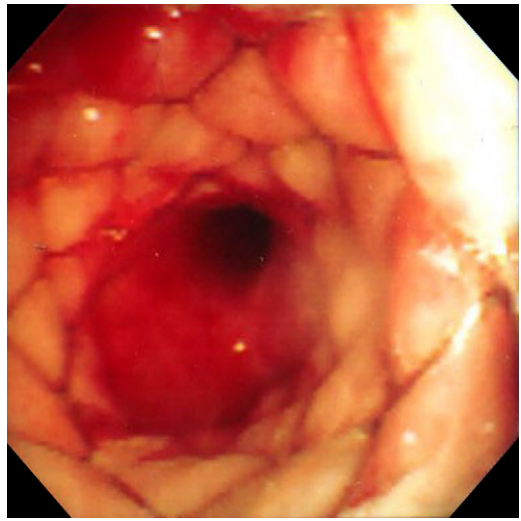

Fig. 2. Metallic stent in situ demonstrating incorporation within the airway mucosa. (*Courtesy of* Jay B. Brodsky, MD, Palo Alto, CA.)

room. In patients who have malignancies, consideration must be given to the potential for local mass effect (eg, superior vena cava obstruction, cardiac compression), distant metastases with end-organ dysfunction, complications from adjuvant chemotherapy or radiotherapy, and paraneoplastic syndromes. Similarly, patients who have nonmalignant airway obstruction may have severe extrapulmonary disease that can influence anesthetic technique (eg, Wegener's granulomatosis, sarcoidosis, amyloidosis, lung transplantation). Historical information and physical examination should address these issues and be supplemented with appropriate investigations.

Central airway lesions may be fixed or variable, intrathoracic or extrathoracic (Fig. 3) [29]. Symptoms of airway obstruction are insidious, and patients often present with advanced stenoses (5–8 mm) before developing dyspnea, stridor, or wheezing [30]. Anesthesiologists should determine whether symptoms are positional and, if so, consider appropriate patient positioning during anesthetic induction or to relieve life-threatening airway obstruction.

The nature and extent of airway obstruction needs to be defined clearly in all but the most emergent cases [31]. Traditionally, pulmonary function tests and upright and supine flow-volume loops have been used to evaluate and stratify the risks of general anesthesia [32–34] in patients who have extrinsic airway compression. Although abnormal pulmonary function tests may indicate higher risk [33], the value of upright and supine flow-volume loops is questionable [34]. Reconstructed multislice CT scans are particularly informative [35–37], because they can detail the nature and location of the airway obstruction and its effects on adjacent structures. Dynamic CT scans offer

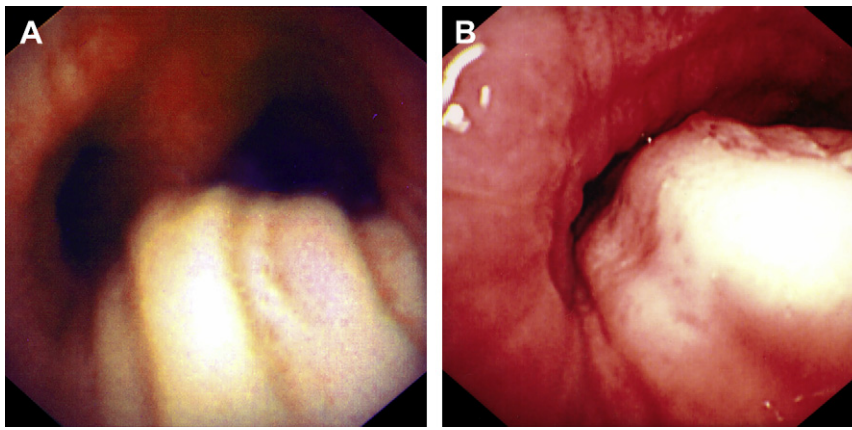

Fig. 3. A variable intrathoracic obstruction caused by tracheomalacia is characterized by (*A*) airway opening during inspiration and (*B*) marked reduction in the cross-sectional area of the trachea during expiration. Stents can be used to maintain airway patency during all phases of breathing. (*Courtesy of* Jay B. Brodsky, MD, Palo Alto, CA.)

functional anatomy that will obviate the perceived requirement for obtaining flow-volume loops in these patients [13,38].

If time allows, significant medical comorbidities require optimization before proceeding, particularly in individuals who have obstructive lung disease or concurrent infections. Before the procedure, the routine use of anxiolytics should be avoided because of the limited physiologic reserve in many of these patients. Antisialogogues can be useful for drying secretions that may interfere with airway topicalization or fiberoptic examination [10,39]. Heliox may improve the work of breathing and gas exchange temporarily in patients who have severe obstruction and turbulent airflow [40]. Standard American Society of Anesthesiologists monitors [41] are required, and, given the shared control of the airway, an arterial line is useful for frequent blood gas analyses.

Of foremost concern is the potential for critical airway compromise and obstruction to ventilation. Although metal stents can be positioned under local anesthesia [42], general anesthesia often is used to facilitate the procedure by establishing a quiet operative field [43]. Traditional teaching has recommended maintenance of spontaneous ventilation and avoidance of neuromuscular blockade to defend against complete airway obstruction [13,30,31,44], particularly with lesions causing a variable obstruction. Others contend that control of the airway is achieved best with an intravenous induction, thereby minimizing the potential for coughing and catastrophic narrowing of an already critical airway [10]. Conacher [10] suggests a primary concern in central airway obstruction is not the limitation of inspiratory airflow but rather dynamic hyperinflation with hypercarbia and hemodynamic collapse. Case series attest to the safety of an intravenous induction and neuromuscular blockade in these patients, even those who have stridor at rest [24].

Immediate access of the airway with a rigid bronchoscope is paramount, however [39,45]. An experienced thoracic or head and neck surgeon should be present, because few respirologists now have expertise in rigid bronchoscopy [4]. When critical airway obstruction is anticipated despite the use of rigid bronchoscopy, selective use of percutaneous cardiopulmonary support is appropriate [46]. This scenario occurs most often with critical tracheal carina lesions. Because of the inherent delays in instituting emergent percutaneous cardiopulmonary support, it should be established before the patient experiences a critical deterioration.

Following anesthetic induction, blind passage of an endotracheal tube down the airway may traumatize friable intrinsic tumors and cause complete airway obstruction [44]. In these situations, secure placement of an endotracheal tube below the glottis should be guided by fiberoptic bronchoscopy [3]. The use of a laryngeal mask airway or suspension laryngoscope [35,47] is another strategy to avoid this complication.

Various ventilatory modalities have been used successfully for airway stenting. These techniques include spontaneous ventilation, intermittent positive pressure ventilation, and low- or high-frequency jet ventilation [39,43]. Anesthesia can be maintained with inhalational or intravenous agents. The primary disadvantages of inhalational agents are inadequacy of scavenging during rigid bronchoscopy and anesthetic delivery that is necessarily coupled to ventilation. Intravenous agents may be administered more reliably in these scenarios when ventilation is predictably compromised. Ultrashort-acting narcotics and judiciously used local anesthetics are useful adjuvants for periods of noxious stimulation. Succinylcholine may be used to prevent movement during airway dilation and stenting. Regardless of anesthetic technique, it is imperative to render the patient awake with intact airway reflexes at the conclusion of the procedure. Repeated manipulation of the upper airway may jeopardize its patency and mandate postoperative support with an endotracheal tube. Selective use of steroids [8] and racemic epinephrine may help reduce glottic edema.

Complications

Relevant complications may present acutely or long after stent placement; they must be anticipated to ensure their prevention and/or timely resuscitation. Major immediate complications include airway perforation with pneumothorax or pneumomediastinum; airway obstruction from stent malposition, secretions, or laryngeal edema; and disseminated pneumonia after the relief of a chronic obstruction (Fig. 4) [35,48].

Following incorporation into the airway mucosa, metal stents are prone to granulation, restenosis, and complete obstruction [21]. Silicone stents may become impacted with secretions and are susceptible to migration [21]. Erosion of metal stents through the airway may result in exsanguinating hemoptysis from a bronchovascular fistula [49] or aspiration pneumonia

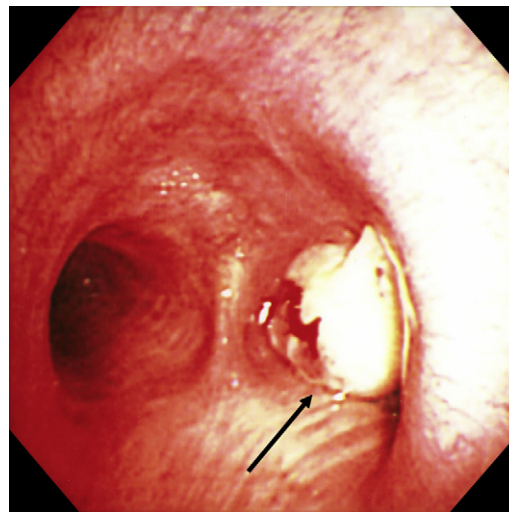

Fig. 4. Sudden relief of an endobronchial obstruction (*arrow*) by stenting can allow contamination of the healthy contralateral lung and result in disseminated pneumonia. (*Courtesy of* Jay B. Brodsky, MD, Palo Alto, CA.)

from an esophagorespiratory fistula. These complications and the considerations of laser safety need to be addressed when patients who have airway stents are scheduled for repeat endoscopic interventions [50,51].

Patients who have stents undergoing unrelated procedures

The increasing use of tracheobronchial stents mandates that all anesthesiologists become familiar with these devices, because these patients may present emergently for unrelated procedures. Mismanagement may have catastrophic complications, including complete airway obstruction with stent migration or airway dissection and formation of a false lumen [52]. In these situations, tracheostomy through a stent may be impossible or require an innovative approach [53]. Careful preoperative planning is paramount. Critical preoperative information includes the indication for stent insertion, the location and type of stent, the complications incurred, and whether symptoms of airflow limitation are present.

When appropriate, tracheal intubation should be avoided in patients who have an airway stent in situ. Preference should be given to a neuraxial or regional anesthetic technique. When general anesthesia is required, the use of a laryngeal mask minimizes the risk of stent displacement [54]. When tracheal intubation is indicated, fiberoptic inspection of the airway is mandated, and the tube should be visually guided within the lumen of the stent or immediately proximal (in the case of a carinal stent) [52]. Direct examination of the airway and stent also are advised following extubation [6].

Communication with the primary surgeon or radiologist involved in placing the patient's stent is valuable and fulfils several objectives. Most importantly, detailed information on the current status of the airway and stent may be obtained. Arrangements for emergent rigid bronchoscopy can be established when stent migration or stenosis is a genuine concern, and, finally, appropriate clinical follow-up can be arranged.

Summary

Metal and silicone tracheobronchial stents provide immediate relief of central airway obstruction from benign and malignant lesions. Patients requiring these devices often are critically ill with diverse medical comorbidities. Complete airway obstruction during induction of anesthesia, stent deployment, or emergence is a principal concern that demands the immediate availability of a skilled rigid bronchoscopist. Unique complications of stent insertion must be anticipated to ensure safe perioperative care, particularly during repeated endoscopic interventions. Whenever patients who have stents in situ present for an unrelated procedure, unnecessary and blind manipulation of the airway should be avoided.

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Anesthesiology Clin
26 (2008) 293–304

ANESTHESIOLOGY
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Perioperative Anesthetic Management for Esophagectomy

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Esophageal cancer is the sixth leading cause of cancer-related deaths worldwide, and its incidence is increasing rapidly in the United States [1]. The changing epidemiology from squamous cell to adenocarcinoma may reflect the increasing incidence of morbid obesity and gastroesophageal reflux (GER) disease, coupled with reduced fiber intake, in the West [2]. Although perioperative mortality and morbidity from esophagectomy have declined during the past 30 years, it still carries a high overall mortality rate of 8.8% [3]. In contrast to most other major surgery, improvements in anesthetic care, surgical technique, and intensive care management have not markedly lowered the incidence of mortality and morbidity. An understanding of the factors that influence outcome may help anesthesiologists adjust and improve perioperative anesthetic management. Although it is accepted that outcomes are closely related to the number of esophageal resections performed by individual surgeons and medical centers [4,5], some analyses have found other factors, such as advanced patient age, performance status, pulmonary complications, and need for transfusion, to be predictive of mortality [6–8].

Minimally invasive surgical (MIS) techniques have emerged for esophagectomy, including various combinations of thoracoscopy, laparoscopy, or laparoscopic-assisted methods, mediastinoscopy, and open thoracotomy and laparotomy [9]. There is a lack of consensus on which technique is superior, and randomized, controlled trials comparing MIS techniques with open esophagectomy, and especially addressing the impact on postoperative respiratory complications and survival, are needed.

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.004 *anesthesiology.theclinics.com*

The most frequently seen surgical complication after esophagectomy is anastomotic leakage, and the most common medical complication is arrhythmia [6,7]. The reduction of pulmonary complications, the most common serious morbidity and a predictor of mortality [6,8,10], deserves more discussion, as do the benefits of epidural analgesia and the controversial topic of optimal fluid management. It is unlikely that a single intraoperative intervention alone will show benefit in outcome. An approach addressing several factors that either are shown to affect outcome or have promising benefits may demonstrate significant impact, however. The multimodal approach and/or standardized perioperative clinical care pathways may help improve the infrastructure for the management of these patients in high-volume centers and improve outcome [11,12].

Cardiovascular morbidity

Perioperative arrhythmias have been reported in 20% to 60% of esophagectomies [6,7,10,13–15]. Although most are benign and may occur commonly during mediastinal manipulation in transhiatal esophagectomy [13], symptomatic arrhythmias may be associated with worse outcome [14,16]. Atrial fibrillation has been linked with pulmonary complications, anastomotic leakage, surgical sepsis [14], and supraventricular tachydysrhythmias with a higher rate of ICU admission and longer hospital stay [16]. In a recent meta-analysis, calcium-channel blockers and beta-blockers were effective in reducing atrial tachyarrhythmias in patients undergoing general thoracic surgery [17]. For esophagectomy, prophylactic digitalization has not been shown to reduce the incidence of cardiac dysrhythmias [15], but a diltiazem infusion has been used successfully to suppress supraventricular tachydysrhythmias [18]. Thoracic epidural analgesia (TEA) attenuated supraventricular tachydysrhythmias after pulmonary resection [19], and the presence or absence of TEA showed a temporal relationship with the incidence of atrial arrhythmias [20]. TEA, however, did not reduce the incidence of arrhythmias in patients undergoing transthoracic esophagectomy [21].

The reported incidence of myocardial infarction after esophagectomy ranges from 1% to 2% [6,7,10]. Although it would seem beneficial for high-risk patients to receive perioperative beta-blocker therapy [22], its role will be more clearly defined when results of the Perioperative Ischemic Evaluation) trial [23] are revealed. Interestingly, statin use has been associated with a decreased incidence of atrial fibrillation after noncardiac thoracic surgery [24] and with decreased mortality after major vascular surgery [25].

Pulmonary morbidity

Pulmonary complications are the most common cause of postoperative death in patients who have esophageal cancer [7,8]. Factors found predictive

of pulmonary morbidity and/or acute lung injury (ALI) include age, performance status, lung function, duration of surgery and one-lung ventilation (OLV), perioperative cardiorespiratory instability (measured by perioperative hypoxemia, hypotension, and fluid and blood requirements) and the occurrence of a postoperative anastomotic leak [7,8,26]. Although the benefits of a short period of cardiopulmonary rehabilitation in preparation for esophagectomy to lower the risk of postoperative pulmonary complications has yet to be investigated, there are some perioperative strategies that may address some of the risk factors mentioned previously.

Ventilation strategies

Esophagectomy is marked by a significant inflammatory response [27], with a proinflammatory cytokine release that has been linked to the development of postoperative pulmonary morbidity [27–29]. The intraoperative use of prostaglandin E_1 was associated with reduced interleukin-6 production and improved postoperative oxygenation in patients undergoing esophagectomy [30]. Although there is no clear cause-and-effect relationship between inflammatory cytokine release and the development of lung injury, the balance between proinflammatory and anti-inflammatory cytokines may be key. In patients who have ALI, "lung-protective" mechanical ventilation with a lower tidal volume resulted in decreased mortality, number of ventilated days, and plasma interleukin-6 levels than seen with conventional ventilation [31].

Both volutrauma and atelectrauma (low-volume injury) should be avoided. Guidelines for treating acute respiratory distress syndrome emphasize maintaining inspiratory plateau pressure below 35 cm H_2O by reducing tidal volume to as low as 5 mL/kg [32]. Lung damage also may be caused by ventilation at low lung volume. Shear forces generated during repetitive opening and closing of atelectatic lung units exacerbates, or even initiates, significant lung injury and inflammation [33]. Positive end-expiratory pressure (PEEP) splints open the distal airways, maintaining recruitment throughout the ventilatory cycle. In thoracotomy patients undergoing OLV, pressure-controlled ventilation (PCV) with PEEP resulted in lower peak and plateau airway pressures compared with volume-controlled ventilation (VCV) with no PEEP, and improved oxygenation compared with PCV and no PEEP [34]. For patients who had good preoperative pulmonary function, however, the use of PCV during OLV did not lead to better oxygenation than seen with VCV [35]. Therefore the settings, rather than the mode of ventilation, are important.

Lung-protective ventilation strategies during OLV should include a 5- to 6-mL/kg tidal volume, optimizing PEEP (setting the PEEP above the lower inflection point) [36], and limiting plateau and peak inspiratory pressures to less than 25 cm H_2O and less than 35 cm H_2O, respectively. The use of smaller tidal volumes and PEEP during OLV after esophagectomy was

associated with a decrease in the proinflammatory response, improved lung function, and earlier extubation [37].

OLV has become standard practice during thoracic surgery and esophagectomy. OLV is used commonly to achieve good surgical exposure for aggressive lymphadenectomy during thoracotomy and during thoracoscopic mobilization in MIS esophagectomy. The proficiency of thoracic anesthesiologists in the positioning of double-lumen endobronchial tubes and bronchial blockers and the routine use of fiberoptic bronchoscopy have helped reduce the incidence of hypoxemia during OLV to less than 1% [38]. The clinical implications of the oxidative stress and ischemia/reperfusion injury generated by OLV are unclear. The high inspired oxygen concentration administered to the contralateral lung during OLV may promote the release of oxygen free radicals and reactive nitrogen species, which can lead to cellular damage and, ultimately, lung injury [39]. The reventilation of atelectatic lung after a period of OLV provoked severe oxidative stress, supporting the concept of reperfusion injury [40]. The degree of oxidative stress was related to the duration of OLV [40], which is one of the features associated with ALI after elective esophagectomy [26].

Earlier studies used two-lung ventilation rather than OLV during transthoracic esophagectomy [41,42]. Greater pulmonary shunting was evident in patients having OLV [41], and patients who received high-frequency positive-pressure ventilation experienced fewer sever hypoxic episodes and lower peak and mean airway pressures than seen in patients having OLV [42]. Whether newer ventilation strategies during esophagectomy can decrease the effect on ALI and improve pulmonary outcome remains to be investigated.

Prevention of tracheal aspiration

Patients undergoing thoracotomy are at risk of acid GER, which may lead to tracheal acid aspiration in an appreciable proportion of patients [43]. This effect may be enhanced in esophageal cancer, because variable degrees of obstruction may be present together with abnormal esophageal sphincter function. Some postoperative pulmonary complications are thought to be the result of GER and tracheal contamination [44,45]. Aside from prophylactic pharmacologic management of GER, rapid-sequence induction, securing the airway with a cuffed endotracheal tube, and using gel lubrication on the tracheal cuff of the single- or double-lumen tube has been shown to reduce pulmonary aspiration in anesthetized patients [46,47].

Intraoperative tube substitution is common during esophagectomy and may subject the patient to additional risks of aspiration. Moreover, GER and pharyngeal reflux commonly occur during emergence from anesthesia and during bucking on the endotracheal tube [48]. It therefore is important to perform proper and repeated suction of the nasogastric tube and oropharynx before and after extubation. Application of continuous low-grade

suction to the nasogastric tube may be the best way to prevent the significant and persistent tracheal acid aspiration present in all patients following esophagectomy [49].

Timing of extubation

The potential complications associated with mechanical ventilation (including barotrauma and nosocomial pneumonia) and the side effects of sedation have led to studies looking at immediate or early extubation of patients after esophagectomy. This procedure was shown to be safe, was not associated with increased respiratory morbidity, and also reduced the length of ICU stay, potentially reducing costs [50–53]. A randomized, controlled trial evaluating early and late extubation after esophagectomy found that the early extubation group after transthoracic esophagectomy had a higher hospital mortality than the prolonged ventilation group (9.8% versus 1.9%), although this difference did not reach statistical significance [54]. Although early extubation does not reduce morbidity independently, as part of a multipronged management plan it assists in decreasing the number of ventilator days and the duration of ICU stay and contributes to improved outcome, as demonstrated in several series [11,12,55].

Other strategies for reducing pulmonary morbidity

In a meta-analysis, the use of TEA with local anesthetic, compared with systemic opioids, was found to decrease the incidence of atelectasis, pulmonary infections, and pulmonary complications overall in upper abdominal and thoracic surgery [56]. The role of TEA is discussed later. The role of excessive fluid administration in adverse respiratory function is controversial. Although perioperative fluid overload is not the primary cause of pulmonary complications after esophagectomy, excessive infusion of fluids after the development of ALI may exacerbate or prolong the clinical condition.

Thoracic epidural analgesia

TEA has a number of potential benefits after major surgery. Although evidence is lacking with regards to its effects on stress response and immune function in radical esophagectomy [57], there are clear benefits in other important areas including pain relief [58,59], reduction in respiratory complications [56,60–62], facilitating immediate or early postoperative tracheal extubation, reducing the length of intensive care stay, and possibly reducing cost [50–52]. TEA also plays a central role in a multimodal approach or standardized perioperative clinical pathway, which has shown improved outcomes [11,12,55]. The superior dynamic pain relief after esophagectomy with TEA is important for effective cough, vigorous physiotherapy, and mobilization in the early postoperative period. This control of acute

postoperative pain also is vital for the reduction in the incidence of chronic postthoracotomy pain syndrome [63,64].

Earlier studies demonstrated a reduced incidence of respiratory complications and mortality with TEA after esophagectomy [60,61]. More recently, TEA for more than 48 hours reduced morbidity (pneumonia, reintubation), ICU stay, hospital stay, and in-hospital mortality when compared with either no epidural or TEA for less than 48 hours. The absence of epidural analgesia was an independent risk factor for pneumonia, and TEA was the key factor that facilitated immediate or early postoperative tracheal extubation [62]. These findings further substantiate the role of TEA for esophagectomy.

It also has been suggested that TEA is associated with a decreased incidence of anastomotic leakage [65]. Ischemia of the gastric conduit and impairment of oxygen delivery have been postulated to be the main culprits in anastomotic leaks [66]. TEA may improve microcirculation of the distal part of the gastric tube in an experimental model [67] and also facilitates intensive physiotherapy, thereby preventing hypoxemia. TEA improved microvascular perfusion of the gastric conduit in the anastomotic area after esophagectomy [68], although larger clinical studies are required to evaluate the clinical relevance of this finding.

In a recent meta-analysis, paravertebral block provided pain relief comparable to that achieved with epidural analgesia, had a better side-effect profile, and reduced pulmonary complications after thoracic surgery [69]. The successful use of paravertebral analgesia for esophagectomy has been described [70] and may be useful when epidural analgesia is contraindicated, but its role has not been clearly established.

Fluid management

There is a delicate balance between the maintenance of perfusion pressure and delivery of oxygen to vital organs and the gut mucosa and the prevention of pulmonary and peripheral edema [71]. Covert hypovolemia and inadequate tissue perfusion may lead to gut hypoperfusion with increased morbidity and duration of hospital stay [72], whereas excessive perioperative fluid administration may delay recovery of gastrointestinal function, impair wound/anastomotic healing and coagulation, and impair cardiac and respiratory function [71,73–75].

Recent evidence suggests that crystalloid restriction may improve outcome after major elective gastrointestinal surgery [76]. In elective intraabdominal surgery, a more restrictive fluid management reduced the total number of patients who had complications and shortened the time to recovery of gastrointestinal function and to hospital discharge [74,75]. A similar restrictive fluid regimen, however, demonstrated improvements in pulmonary function and oxygen saturation but no difference in overall functional recovery, with a tendency for increased morbidity [77]. Specific

to esophagectomy, Kita and colleagues [78] found that restricting intraoperative fluid administration reduced postoperative pulmonary complications and shortened the in-hospital recovery period. This report, however, was a small, retrospective and nonrandomized case series. Moreover, there was significantly more blood loss in the ''early period'' or ''nonrestricted fluid'' group, and the need for blood transfusion and blood loss has been shown to be an intraoperative risk factor for morbidity [6,7]. Neal and colleagues [55] reported a significant reduction in esophagectomy-related morbidity with standardized multimodal management and intraoperative fluid restriction. This report was an observational, nonrandomized small case series of 56 patients, and the mean intraoperative crystalloid infused was about 4 L, which is not necessarily ''fluid restriction'' but rather is an avoidance of excessive volume infusion. Naturally, the different fluid regimens and end points used in these studies make it difficult to derive guidelines regarding perioperative fluid therapy, including the amount and choice of fluid.

Liberal fluid regimens have contributed to poor outcomes after lung surgery [79], and although the pathophysiology of postpneumonectomy pulmonary edema or ALI after lung resection probably is multifactorial, any excess fluid will exacerbate the problem. No pulmonary resection is performed in esophagectomy, but there is potential for ALI during OLV and a high incidence of pulmonary complications after esophagectomy [26–28,40]. With regards to anastomotic healing, the risk of decreased oxygen tension secondary to interstitial edema (excessive crystalloids) also should be weighed against the problems of dehydration and gut hypoperfusion.

The optimum perioperative fluid administration is a matter of continuing discussion. Instead of either a ''restricted'' or ''liberalized'' approach, the amount of fluid should be titrated individually to dynamic changes in appropriate monitoring. A recent review of goal-directed therapy with individual maximization of flow-related hemodynamic parameters showed that this approach reduced hospital stay, reduced postoperative nausea and vomiting, and facilitated faster gastrointestinal functional recovery [80]. In eight of nine studies, patients undergoing major cardiac, intra-abdominal, or orthopedic surgery received more fluid and relatively more colloid than persons in control groups. The esophageal Doppler monitor was used as a guide to plasma volume expansion. Some of the observed benefits may be attributable to the use of colloids rather than to the total amount of fluids infused. The use of the esophageal Doppler monitor is impractical in esophagectomy, but the dynamic changes in central venous pressure in response to a fluid challenge can be monitored; in hip surgery this approach has been shown to produce equivalent results [81]. The FloTrach/Vigileo system (Edwards Lifesciences, Irving, California), which has been evaluated in cardiac surgery, may be a feasible alternative for use in esophagectomy [82]. Goal-directed therapy has not been investigated in thoracic noncardiac surgery or esophagectomy.

Summary

It is unlikely that a single intraoperative intervention will show a benefit in outcome. A multimodal management plan that includes the use of TEA seems to demonstrate improved results in high-volume centers. Anesthetic management may contribute to the containment of pulmonary morbidity and anastomotic leakage by the use of TEA, protective ventilation strategies during OLV, prevention of tracheal aspiration, and judicious fluid management.

Acknowledgments

The author thanks Dr. Philip M. Hartigan for his invaluable advice and encouragement in the preparation of this article.

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Anesthesiology Clin
26 (2008) 305–314

ANESTHESIOLOGY
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Anesthetic Considerations for Patients with Anterior Mediastinal Masses

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Tumors presenting in and around the mediastinal cavity are uncommon. It has been said that a general practitioner in the United Kingdom will see, on average, one case during a professional lifetime, and in the United Kingdom approximately 250 to 300 procedures are performed annually in adults for the open surgical of resection of mediastinal tumors [1]. Many more procedures are performed for biopsy of mediastinal masses, and variable but much smaller numbers of resections are undertaken by means of video-assisted thoracic surgery (VATS) (Table 1). It also is likely that thymectomy for myasthenia gravis is not fully represented in these figures, because some of these procedures are undertaken in neurosurgical units.

Mediastinal masses are a heterogeneous collection of benign and malignant tumors [2], and they usually are designated as located in the anterior, middle, or posterior mediastinum (Box 1). This anatomic description is somewhat arbitrary, but, in general, anterior mediastinal tumors cause the most severe and often life-threatening complications relating to compression of the airways and vascular structures. These problems are exacerbated by general anesthesia, as outlined later.

There is considerable overlap in the effect of anterior and middle mediastinal tumors, and anterior masses often encroach on and invade the middle mediastinum. The mortality for surgery and anesthesia in patients who have a mediastinal mass is low (see Table 1). At the extreme end of the disease spectrum, however, anterior mediastinal tumors can be very difficult to manage in the perioperative period, and the literature provides many examples of cardiorespiratory disasters and even death [3–6]. Many of these publications relate to pediatric practice.

There are differences between adult and pediatric populations in the histology, location, and symptomatology in mediastinal tumors [7]. In particular,

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.002 *anesthesiology.theclinics.com*

Table 1
Surgery for mediastinal procedures[a]

Procedure	2002–2003		2003–2004		2004–2005	
	Total	Deaths (%)	Total	Deaths (%)	Total	Deaths (%)
Resection mediastinal mass	333	4 (1.2)	269	1 (0.4)	252	1 (0.4)
Mediastinoscopy/ mediastinotomy	2767	9 (0.3)	2525	9 (0.4)	2533	13 (0.5)
Video-assisted thoracic surgery resection of mediastinal mass/tumor	154	0	106	0	43	0

[a] United Kingdom data from 36 centers (2002–2005).

Data from Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS) (2002–2005) Thoracic aurgical register. Available at: www.scts.org. Accessed March 24, 2008.

there is an increased incidence of neurogenic tumors in children [8]. These factors may account for the increased incidence of problems in the pediatric patient, but intuitively one would think the smaller airways and lack of respiratory reserve found in children account for most of the increased difficulty. Slinger and Karsli [9] have recently re-emphasized the risk that general anesthesia poses to children who have an anterior mediastinal mass.

Imaging

CT scanning provides the bulk of information relating to extent of a mediastinal mass, its anatomic location, and the invasion of surrounding structures. A thyroid scan may be helpful if a thyroid mass is suspected and should be undertaken before iodinated contrast is given to enhance a CT scan.

MR imaging is not used routinely, but it may be helpful if a posterior neurogenic tumor is suspected. Positron emission tomography is not used for primary imaging but can be used to follow up germ-cell tumors after initial treatment.

If invasion or obstruction of vascular structures such as the pulmonary arteries or superior vena cava (SVC) is suspected, angiography and/or echocardiography may provide further useful information, but a high-quality CT scan usually is sufficient.

Diagnosis and treatment

The majority of anterior mediastinal masses, including thymomas, require surgical resection, although Hodgkin lymphomas respond well to chemotherapy and/or radiotherapy, with a high cure rate. A biopsy diagnosis is essential to establish a precise diagnosis and guide therapy.

Box 1. Mediastinal tumors

Anterior mediastinum
Benign
- Thymoma
- Thymic cyst
- Thymic hyperplasia
- Thyroid
- Cystic hygroma

Malignant
- Thymic carcinoma
- Thyroid carcinoma
- Seminoma
- Mixed germ cell
- Lymphoma

Middle mediastinum
Benign
- Benign adenopathy
- Cysts
- Esophageal mass
- Hiatus hernia
- Cardiac/vascular structure

Malignant
- Lymphoma
- Metastases
- Esophageal cancer
- Thyroid cancer

Posterior mediastinum
Benign
- Neurofibroma
- Schwannoma
- Chemodectoma
- Foramen of Bochdalek hernia

Malignant
- Neuroblastoma

Data from Yoneda KY, Louie S, Shelton DK. Mediastinal tumors. Curr Opin Pulm Med 2001;7:226–33.

Biopsy

A needle biopsy or a "Tru-cut" type biopsy performed under CT guidance often provides sufficient tissue for diagnosis. This procedure can be performed under local anesthesia in adults but may be difficult in children. In some circumstances insufficient tissue is obtained, or the tumor may be adjacent to vascular structures such as the aorta, making this approach inadvisable. In these situations patients may be referred for a surgical biopsy under general anesthesia, possibly via mediastinoscopy, mediastinotomy, or thoracoscopy. In this circumstance symptomatic patients who have airway obstruction are exposed to the risks of anesthesia discussed later.

Tracheobronchial stenting

Developments in airway stenting have revolutionized the treatment of adult patients who have lymphoma and severe airway obstruction. In the past it often was very difficult, even following anesthesia for a biopsy procedure, to extubate patients who had a large tumor mass causing severe extrinsic tracheobronchial compression. On occasions the author and colleagues have ventilated patients using a double-lumen endobronchial tube in the postoperative period to maintain some degree of airway patency during chemotherapy. Now, stenting of the trachea and bronchi is used to maintain an adequate airway and allow spontaneous respiration [10]. As chemotherapy/radiotherapy progresses, assuming the tumor responds, the stents can be removed. Anesthesia for tracheobronchial stent insertion has been reviewed by both Brodsky and Conacher [11,12] and is not considered further here. It is worth noting, however, that stenting is less practical in small children.

The controversy over blind pretreatment

Patients at high risk of airway obstruction intraoperatively may benefit from pretreatment of the mediastinal mass with steroids, empiric chemotherapy, and/or radiotherapy. This approach is advocated in some treatment algorithms for children [13]. This treatment can cause rapid tumor lysis and alleviate airway obstruction but also may adversely affect the accuracy of tissue diagnosis once a biopsy is taken. Robie's group [13] found tissue diagnosis was not affected if biopsies were taken within 72 hours of starting treatment. Other groups, however, believe that an accurate tissue diagnosis can be compromised by pretreatment. Ferrari and Bedford [14] reported a series of children requiring surgery for an anterior mediastinal mass. None of the 44 children undergoing an anesthetic procedure died or sustained permanent injury as a result of the procedure. Two patients, however, required airway management with a rigid bronchoscope intraoperatively (see later discussion), two patients needed a change in position to alleviate airway

obstruction, and four patients could not be extubated at the end of surgery. The authors conclude that, except in extreme circumstances, it is preferable to acquire a tissue diagnosis before starting treatment, even if doing so necessitates the use of general anesthesia.

Anesthesia for resection of anterior mediastinal tumors

Evaluation of risk factors

Patients who have marked symptoms of airway compromise such as dyspnea at rest, postural dyspnea, orthopnea, or even stridor are at high risk of intraoperative airway problems. Compression of the heart, SVC, and pulmonary arteries also can cause syncope, arrhythmias, head and neck edema, and even a degree of cyanosis, particularly in children [13]. These symptoms usually correlate with the CT findings, which delineate airway obstruction and vascular and pericardial involvement.

Lung function tests, including arterial blood gas analysis, usually are performed as a baseline but in the author and colleagues' experience do not play a large part in evaluating the risk of surgery. It is important to realize that the symptoms described can be much worse in the postoperative period, particularly following a biopsy procedure; hence difficulty in extubating these patients sometimes is experienced. After a biopsy under general anesthesia, the patient is exposed to the deleterious effects of anesthesia, with diminished lung volumes and other effects, without the benefits of tumor excision [5].

A recent study of adults who had a mediastinal mass looked at the cardiorespiratory complications in the perioperative period [15]. This group found that intraoperative complications were associated with a pericardial effusion seen on the CT scan. Postoperative respiratory complications were related significantly to tracheal compression of more than 50% on CT scan and a mixed (obstructive/restrictive) picture of abnormal pulmonary function preoperatively. A similar study of 63 children (1964–2002) found that the presence of at least three respiratory symptoms/signs, tracheal and vascular compression, and infection significantly increased the risk of general anesthesia [6]. Of these features, tracheal compression, which led to two deaths, was the strongest predictive factor for complications . Findings from a similar but more recent study by Lam and colleagues [16] are listed in Box 2.

Anghelescu and colleagues [17] recently have reported a larger series of 117 children who had malignant mediastinal masses. Risk factors associated with anesthesia-related complications were similar to those reported by Lam and colleagues [16], but the severity of complications was low. The authors attribute this reduced severity to a number of factors, including the use of interventional radiology to obtain tissue diagnosis, thorough preoperative evaluation, and minimal anesthetic intervention.

Box 2. Mediastinal tumors in children

Factors associated with acute airway compromise
- Airway narrowing/displacement on imaging
- Anterior location of tumor
- Histologic diagnosis of lymphoma
- Symptoms/signs of superior vena cava obstruction
- Radiologic evidence of vessel compression
- Pericardial effusion
- Pleural effusion

Data from Lam JCM, Chui CH, Jacobsen AS, et al. When is a mediastinal mass critical in a child? An analysis of 29 patients. Pediatr Surg Int 2004;20:180–4.

Systemic effects of the tumor

Patients who have an intrathoracic goiter may have abnormalities of thyroid function that require monitoring and treatment before surgery. Up to 30% of patients who have a thymoma have symptomatic myasthenia gravis, which obviously has significant anesthetic implications [18,19].

Management of airway obstruction

Management of the airway in patients who have a large anterior mediastinal mass causing airway compression remains controversial. Treatment modalities that can (or have been) used to minimize risk are listed in Box 3.

During anesthesia lung volume is reduced, and bronchial smooth muscle relaxes, thereby increasing the compressibility of large airways [20]. Partially obstructed respiration, which can occur during an inhalational induction, generates large negative pressures that tend to flatten further a trachea weakened by extrinsic compression. Muscular relaxation, on the other hand, causes loss of chest wall tone and disrupts the forces of active airway inspiration, thereby further reducing external support of the narrowed airway. Abnormal patterns of spontaneous breathing on emergence also can cause partial obstruction of breathing on inspiration.

Maintenance of spontaneous respiration

Maintenance of spontaneous respiration and avoidance of muscular relaxation during anesthesia has been advocated by several authors and is a major part of some management algorithms. This approach is based on local experience in individual centers and on case-report evidence in the literature. There are inconsistencies in the use of this technique, however.

Box 3. Airway management during anesthesia: anterior mediastinal masses

Posture
- Induce in sitting position
- Change supine position to lateral or prone position (access ?)

Maintain spontaneous respiration
- Awake fiberoptic intubation
- Inhalational induction
- Intravenous induction (ketamine?)

Airway stenting: conventional intravenous induction
- Long endotracheal tube
- Double-lumen endobronchial tube
- Rigid bronchoscope
- Insertion of tracheobronchial stents

Cardiopulmonary bypass
- Commenced under local anesthesia before induction
- Vessels prepared under local anesthesia, then general anesthesia

Goh and colleagues [21], for example, describe the use of awake intubation but follow this intubation with intravenous thiopentone and a muscle relaxant. Pullerits and Holzman [5] advocate the use of spontaneous ventilation intraoperatively but then state, ''After diagnostic procedures such as mediastinoscopy, bronchoscopy and thoracoscopy, severe respiratory failure requiring re-intubation and ventilation may occur when the SVC obstruction has not been relieved.'' John and Narang [22] reported the use of an inhalational induction in a 12-year-old child who had an anterior mediastinal mass that precipitated immediate severe airway obstruction. The case reports of Victory et al [3] include a death where an inhalational induction led to respiratory obstruction in a child, which could not be relieved with either an endotracheal tube or a bronchoscope.

Airway stenting—conventional intravenous induction

The most experienced surgeons consistently have used rigid bronchoscopy to establish an airway in adult patients who have an anterior mediastinal mass, following conventional intravenous anesthesia in the semi-upright position (P. Goldstraw, personal communication, 2007). The variable narrowing of the tracheobronchial tree usually is caused by extrinsic compression and will have been assessed fully from a preoperative CT scan. In experienced hands a rigid bronchoscope therefore can be advanced to stent the airway. After initial assessment of the anatomy/pathology, it may be possible to stent the airway for resection surgery with an endotracheal

tube or a double-lumen endobronchial tube placed under direct vision into the most patent main bronchus. If this technique is not possible, ventilation can be maintained down the rigid bronchoscope via a Venturi injector, in the usual way, and anesthesia can be maintained intravenously. Once surgery has commenced and the tumor has been lifted anteriorly, the degree of airway obstruction tends to lessen, and it may be possible to replace the bronchoscope with an endotracheal tube at some stage.

Gas exchange relies on ventilation and perfusion. When possible, therefore, the state of the pulmonary arteries should be evaluated on the CT scan. The author and colleagues have had least one case in which the pulmonary artery blood supply to the lung with "most patent" main bronchus was severely compromised. Fortunately, endobronchial intubation of the contralateral lung, which had a patent pulmonary artery, proved feasible.

Cardiopulmonary bypass

A number of authors have advocated the use of cardiopulmonary bypass to overcome the problems of intraoperative gas exchange in patients who have severe airway narrowing and pulmonary artery involvement [23–26]. These reports include the use of femorofemoral bypass instituted using local anesthesia before induction [24] and the use of venoarterial extracorporeal membrane oxygenation in a child [25] to facilitate initial diagnosis and subsequent chemotherapy treatment over a number of days.

The author and colleagues have not used cardiopulmonary bypass in relation to airway problems but have had the facility on stand-by on occasions. One of the surgeons at The Royal Brompton Hospital institutes cardiopulmonary bypass when tumor is invading the SVC to facilitate resection and, if necessary, replacement of the SVC with a graft.

Vascular involvement/intraoperative bleeding

As discussed previously, mediastinal tumors may invade or compress many of the intrathoracic vascular structures. SVC obstruction is a common presenting sign of large anterior mediastinal tumors, and bleeding from the SVC is a relatively common problem intraoperatively. If tumor involvement of this structure is suspected, it is prudent to place a large intravenous cannula in the lower half of the body, preferably in the femoral vein, to facilitate transfusion if the vessel is breached surgically. Occasionally, it may be necessary to clamp or resect the SVC. The anesthetic considerations for this surgical maneuver have been reviewed by Galatoudis and colleagues [27].

Effects of chemotherapy

Patients presenting for surgery and anesthesia may have undergone chemotherapy previously. This setting has many implications for anesthesiologists, which have recently been reviewed by Heuttemann and Sakka [28].

Bleomycin, in particular, is used in the treatment of a variety of tumors, including primary and secondary teratomas, that can occur in the mediastinum. The pulmonary toxicity of bleomycin has been well documented, and it is important to have baseline pulmonary function tests in these patients. The provocation of further lung injury in these patients who have high inspired oxygen concentrations is controversial. It is probable that this effect occurs only if the bleomycin has been administered relatively recently. This problem is complex, however, and it is prudent to keep the inspired oxygen concentration as low as possible but compatible with reasonable arterial oxygen saturation.

Nerve section

Anterior mediastinal tumors may advance to surround or invade the phrenic and/or recurrent laryngeal nerves. Surgical division of these nerves may affect the postoperative course and in the case of the phrenic nerve is an indication for postoperative ventilation.

Resection of a complex tumor is often a long procedure, however. The author and colleagues electively ventilate most patients postoperatively because of the long procedure times and the associated comorbidities.

Summary

Anterior mediastinal tumors can cause severe airway and vascular compression, and these effects are exacerbated by general anesthesia, particularly in children. Tumor biopsy using a local anesthetic technique is preferable, if possible. General anesthesia for a biopsy procedure or resection of an anterior mediastinal mass should be undertaken only after a thorough preoperative assessment. Treatment protocols for surgery and anesthesia vary from institution to institution, and management remains operator dependent.

Maintenance of spontaneous respiration during anesthesia is considered optimal by some clinicians, particularly for biopsy procedures. Airway stenting, with a rigid bronchoscope in the first instance, is advocated by others. Cardiopulmonary bypass, instituted at the outset of surgery under local anesthetic, is rarely indicated but may be used as a fall-back technique in extreme circumstances.

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Anesthesiology Clin
26 (2008) 315–324

ANESTHESIOLOGY
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The Emerging Role of Minimally Invasive Surgical Techniques for the Treatment of Lung Malignancy in the Elderly

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Although cancer can occur at any age, it disproportionately strikes the elderly, with persons older than 65 years exhibiting a 9.8-fold higher incidence compared with a younger population [1]. Demographic projections now indicate that by the year 2030, the number of United States citizens older than 65 years will double to a projected 70 million, with those older than 80 years making up 5.4% of the total population [2]. Consistent with the age-related incidence of cancer and the overall aging of the population is an increase in the absolute number of elderly patients presenting with potentially resectable malignancy.

For lung cancer in particular, approximately 175,000 patients per year in the United States are diagnosed with bronchogenic carcinoma, with a median age at diagnosis now in excess of 70 years [3]. For non–small cell lung cancer (NSCLC), which accounts for roughly 80% of pulmonary malignancy, anatomic resection (lobectomy) remains the best curative option for early-stage disease. There is, however, a clear association between advanced age and perioperative morbidity and mortality [4]. Accordingly, there is increasing interest in applying minimally invasive surgical techniques in elderly patients requiring lobectomy because of the belief that it will improve outcome. The purpose of this review is to examine the available data regarding this belief.

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.009 *anesthesiology.theclinics.com*

The risk/benefit relationship of surgical intervention for lung cancer in the elderly

Compared with a younger patient, an elderly person may have different therapeutic goals when the inherent surgical risks of thoracotomy and lung resection are considered in the context of comorbid conditions and the potential disparity between chronologic and physiologic age (ie, the wide range of physical and mental capacity). For patients 80 years and older, data from the Lung Cancer Study Group published in 1983 indicated that complication rates and mortality were substantially higher than for patients younger than 65 years (30-day mortality rate of 8.1% versus 1.6%) [5]. Recent studies, however, have suggested improved survival following lung resection in octogenarians. For example, a 1998 report of 7099 operations over 1 year in Japan noted 30-day mortality rates after thoracotomy and lung resection of 0.4% for patients younger than 60 years, 1.3% for those aged 60 to 69 years, 2.0% for those aged 70 to 79 years, and 2.2% for those 80 years and older (225 of the 7099 cases) [6]. For patients older than 70 years, Birim and colleagues [7] found a hospital mortality rate of 3.2% in a retrospective study of 126 consecutive patients and concluded that operative mortality is low enough to justify pulmonary resection for lung cancer in this population.

Despite data suggesting somewhat favorable survival statistics, many elderly patients remain concerned about the potential for consequences and complications that would prolong hospitalization and possibly persist following discharge, thus limiting their independence. Accordingly, long-term survival may become less important than relief of symptoms and maintaining their preoperative level of function. These concerns are not without merit. For example, in a recent retrospective review covering a 22-year experience in patients 80 years and older who had stage I NSCLC, Brock and colleagues [8] reported that 44% experienced one or more postoperative complications, most of which were cardiopulmonary. Other investigators reported morbidity rates ranging from 20% to 60% [9–13] in patients older than 80 years. Ultimately, elderly patients may not be inclined to accept the risks of major surgery, even if it might be curative, in favor of less invasive alternatives [14]; however, data indicate that for patients older than 75 years who have stage I or II NSCLC and opt for nonsurgical treatment, most deaths will be related to the progression of lung cancer rather than to other causes [15]. It is within this context that less extensive and less invasive procedures become attractive options to elderly patients.

The emerging role of minimally invasive surgical techniques

Although it is clearly beneficial for institutions and clinicians to offer less invasive approaches for the surgical treatment of lung cancer—and patients are appropriately drawn to the prospect of less postoperative pain and faster

recovery—it is important to first consider what ''less invasive'' or ''minimally invasive'' means and whether the techniques are oncologically equivalent to standard thoracotomy. Given the association between the magnitude of pulmonary resection and postoperative complications in elderly patients, some surgeons advocate less extensive lung-sparing techniques such as wedge resection and segmentectomy whenever possible [16]. Although controversy exists as to whether these procedures, which still involve at least a limited thoracotomy, carry a higher risk of local recurrence, Mery and colleagues [17], using data from the Surveillance, Epidemiology, and End Results database, found that, among patients 75 years and older, there was no difference in overall survival between patients undergoing lobectomy and those undergoing limited resection.

The scientific literature and the lay press contain a wide variety of publications relating video-assisted thoracoscopic surgery (VATS) as a truly minimally invasive approach to the treatment of lung cancer. Published data suggest that relative to thoracotomy, VATS patients experience shorter postoperative hospital stays, lower narcotic requirements for postoperative pain, and reduced shoulder dysfunction [18]. Similarly, patients who undergo VATS lobectomy report less postoperative pain, decreased time until return to preoperative activities, and higher satisfaction with the results of surgery than patients undergoing conventional thoracotomy [19]. In addition, there is a lower observed incidence of postoperative confusion [20], which has been associated with increased postoperative morbidity and mortality. A recent review of 1100 VATS lobectomies with lymph node sampling or dissection in patients who had a mean age of 71.2 years demonstrated low rates of mortality ($<1\%$) and morbidity, with 84.7% of patients exhibiting no significant complications [21].

When considering the published scientific data and the promotional literature disseminated to the public, it is important to understand exactly what is meant by ''VATS lobectomy.'' Careful examination of the described methods reveals variation in the technique among experienced practitioners, particularly with regard to the number of access ports used for insertion of a camera and instruments, and the size and manipulation (ie, use of a mechanical rib-spreader) of the utility incision used for instrument insertion and removal of the specimen [22]. Recently, in an effort to standardize the approach to VATS lobectomy, the Cancer and Leukemia Group B reported results of a prospective trial to elucidate its feasibility for early NSCLC [23]. The standard definition for VATS lobectomy included (1) videoscopic guidance, (2) the use of one 4- to 8-cm access and two 0.5-cm port incisions without rib spreading, and (3) pulmonary lobectomy by way of traditional individual hilar dissection and ligation. Using this ''standard'' definition, the investigators were able to demonstrate acceptable perioperative results.

Questions remain as to whether lobectomy by way of thoracotomy and VATS is an equivalent therapeutic intervention for cancer despite favorable perioperative outcome data. A series of 159 VATS lobectomies for stage I

and stage II NSCLC revealed long-term outcomes and local recurrence rates that were at least equivalent to those of open thoracotomy [24], and a prospective, randomized trial of 100 patients who had stage IA NSCLC concluded that long-term survival and local recurrence rates after VATS lobectomy were comparable to those for open thoracotomy [25]. Another study reported a better 5-year survival rate of stage I lung cancer after VATS versus thoracotomy, perhaps due in part to superior postoperative pulmonary function [26]. For the geriatric population, a retrospective study of 32 lobectomy patients 80 years and older (17 VATS, 15 thoracotomy) also demonstrated better 5-year survival following VATS [27].

To date, most large reports show that across all age groups, VATS lobectomy is safe, with morbidity rates in some reports lower than seen historically with thoracotomy [24,25,28–31]. Other data suggest that pulmonary function as measured by vital capacity and forced expiratory volume in 1 second may be better preserved in patients undergoing VATS rather than thoracotomy [26]. Kirby and colleagues [32] reported that, although they found no difference in intraoperative time, blood loss, or length of hospital stay between patients who underwent VATS versus thoracotomy, the thoracotomy group experienced significantly more postoperative complications, most notably prolonged air leaks. The prospect of superior pulmonary function following VATS relative to thoracotomy has particular significance in the elderly population. Aging alone imparts changes in virtually every aspect of respiratory performance (ie, central regulation, chest wall dynamics, parenchymal elasticity, and gas exchange) and as such, pulmonary complications are a major cause of morbidity and mortality after lung resection in the elderly population (Box 1). To determine whether the VATS approach for lobectomy offers specific advantages over thoracotomy in the elderly, retrospective studies have compared the two approaches in aged patient populations. Jaklitsch and colleagues [20] reported that VATS procedures for patients 65 years and older resulted in superior 30-day operative mortality, which was essentially unrelated to age, and a decreased length of hospital stay compared with previous reports for standard thoracotomy. Of the 307 procedures reviewed in this report, however, only 32 involved anatomic resection such as lobectomy or segmentectomy. More recently, Park and colleagues [33] compared data from patients who had undergone elective lobectomy for clinical stage I NSCLC by VATS or thoracotomy and who were in normal sinus rhythm preoperatively. Study groups were matched for size ($n = 122$ in each), age (mean, 67 ± 10 years), sex, comorbidities (chronic obstructive pulmonary disease, hypertension, myocardial infarction, coronary artery disease, diabetes mellitus), and pharmacotherapy (β-blockers and calcium channel blockers). Although the two groups differed in duration of surgery and preoperative pulmonary diffusing capacity, there were no discernable differences with regard to the incidence of individual cardiopulmonary complications (Table 1). When all observed postoperative complications were analyzed, however, they occurred with greater

Box 1. Respiratory changes with aging

Functional manifestations
Increased functional residual capacity
Increased air trapping
Decreased forced expiratory volume exhaled in 1 second
Decreased forced vital capacity
Decreased diffusing capacity
Decreased venous blood oxygenation
Increased closing capacity
Decreased maximal voluntary ventilation
Increased work of breathing
Widened alveolar-arterial gradient for oxygen
Increased dead-space fraction
Increased ventilation-perfusion mismatch
Increased propensity for infection
Decreased resting Pa_{O_2}

Central regulation
Blunted ventilatory response to hypoxia
Blunted ventilatory response to hypercarbia
Increased periodic breathing during sleep

Structural
Decreased number of alveoli
Decreased number of lung capillaries
Decreased elastic recoil, collapse of peripheral airways
Decreased airway size
Decreased alveolar-capillary surface area
Decreased negative intrapleural pressure
Weakening of respiratory muscles

Secretory and immune
Less efficient mucociliary transport
Less sensitive protective airway reflexes
Diminished delayed-type hypersensitivity response to foreign antigens
Increased response to autologous antigens
Decreased polymorphonuclear leukocyte function

Adapted from Castillo MD, Heerdt PM. Pulmonary resection in the elderly. Curr Opin Anaesthesiol 2007;20(1):5; with permission.

Table 1
Comparison of lung resection populations matched for age, sex, comorbidities, and preoperative pharmacotherapy

Data collected	Thoracotomy (n = 122)	VATS (n = 122)	*P*
Age (years)	67 ± 10	67 ± 10	.99
Surgery duration (hours)	3.0 ± 1.0	3.7 ± 1.0	.001
FEV_1 (% predicted)	86 ± 14	90 ± 19	ns
D_{LCO} (% predicted)	80 ± 18	92 ± 28	.001
Preoperative potassium (mEq/L)	4.4 ± 0.4	4.3 ± 0.4	ns
Preoperative calcium (mg/dL)	9.3 ± 0.6	9.3 ± 0.5	ns
Atelectasis (%)	4.1	1.6	ns
Prolonged air leak (%)	5.7	3.8	ns
Pneumothorax (%)	2.5	0.8	ns
Pneumonitis (%)	4.1	1.6	ns
Atrial fibrillation (%)	16	12	ns
Total complications	27.9	17.2	.05
Deaths	2.5	0	ns

Abbreviations: D_{LCO}, diffusing capacity of lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; ns, not significant.

Data from Park BJ, Zhang H, Rusch VW, et al. Video-assisted thoracic surgery does not reduce the incidence of postoperative atrial fibrillation after pulmonary lobectomy. J Thorac Cardiovasc Surg 2007;133:775–9.

frequency in the thoractomy group. To more specifically focus on an advanced-age population, Cattaneo and coauthors [34] analyzed the incidence and grade of postoperative complications in patients 70 years and older undergoing a VATS approach versus a thoracotomy for lobectomy. The two groups were identically matched for age, sex, comorbities, and clinical stage (ie, 90% of each group was stage IA). VATS resulted in a lower overall complication rate, less pulmonary morbidity, and a decreased median length of hospital stay (Table 2). In addition, the severity of complications was less in the VATS group, suggesting that the minimally invasive approach can lead to better tolerance in a high-risk, elderly population.

Whether there are cardiovascular benefits to VATS lobectomy remains unclear. Multiple studies have established the relationship between age and the occurrence of atrial fibrillation following lobectomy [35], with recent data indicating an incidence of 27% in patients older than 60 years when continuous telemetry is used for diagnosis [36]. Two large series have reported lower than expected rates of postoperative atrial fibrillation following VATS lobectomy relative to thoractomy, ranging from 2.9% to 10% [21,37]. These studies, however, did not use routine postoperative telemetry in the highest risk patients (ie, elderly patients) and likely under-reported asymptomatic episodes of atrial fibrillation. In contrast, the matched, case-control study by Park and colleagues [33] comparing 244 patients undergoing lobectomy by VATS or by thoracotomy showed no difference in the rate of postoperative atrial fibrillation, with VATS patients exhibiting a 12% rate of postoperative atrial fibrillation compared with 16% for

Table 2
Comparison of lung resection populations older than 70 years and older matched for age, sex, comorbidities, and clinical stage of cancer

Data collected	Thoracotomy (n = 82)	VATS (n = 82)	*P*
Cardiac disease (%)	45	39	ns
Diabetes mellitus (%)	14	32	.02
% Predicted FEV_1 (median and range)	88 (37–277)	88 (29–136)	ns
% Predicted D_{LCO} (median and range)	83 (36–129)	85 (43–196)	ns
Induction chemotherapy	2	4	ns
Length of stay in days (range)	6 (2–27)	5 (2–20)	<.001
No complications (%)	55	72	.04
Pulmonary	33	15	.01
Atrial fibrillation (%)	23	17	ns
Genitourinary (%)	6	2	ns
Gastrointestinal (%)	5	0	ns
Infectious (%)	5	1	ns
Neurologic (%)	1	4	ns
Death (%)	4	0	ns

Abbreviations: D_{LCO}, diffusing capacity of lung for carbon monixide; FEV_1, forced expiratory volume in 1 second; ns, not significant.

Data from Cattaneo SM, Park BJ, Wilton AS, et al. Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. Ann Thorac Surg 2008;85(1):231–5.

thoracotomy patients ($P = .36$). Predictably, in both groups, patients suffering atrial fibrillation were significantly older (median age, 72 years) than those who did not develop the arrhythmia (median age, 66 years).

Changes in cardiac function after lung resection have generally been attributed to an increase in right ventricular (RV) afterload secondary to pulmonary arterial ligation, which ultimately leads to total right heart dilation. Although this simple paradigm is attractive because it potentially accounts for the reduced exercise capacity and enhanced atrial arrhythmogenesis observed after major lung resection by way of thoracotomy, multiple clinical and experimental observations complicate universal application. In particular are data indicating that performance of the right and left ventricles may be depressed following pneumonectomy [38,39] and a study demonstrating that reduced RV ejection fraction following lobectomy is independent of afterload [40]. Given that the cardiovascular sequelae of thoracotomy and lobectomy tend to occur more than 48 hours postoperatively, these studies raise the possibility that a progressive response to overall surgical trauma, not just removal of a segment of the pulmonary circulation, can affect cardiac performance. Accordingly, it has been suggested that in patients who have diminished contractile reserve due to advanced age, cardiac performance in general and RV function in particular may be better preserved by using a minimally invasive surgical technique to perform lobectomy. Nominal support for this contention can be found in a small clinical study of elderly subjects indicating that resting stroke index and RV ejection fraction are significantly higher following lobectomy by way of VATS than by

thoracotomy [41]. Potential mechanisms for this response, however, were not explored.

Summary

As the population ages, increasing numbers of elderly patients will present with lung cancer. Due to recent advances in neoadjuvant therapies and accumulating data demonstrating a favorable risk/benefit relationship even in octogenarians, more of these geriatric patients will be surgical candidates. Although preoperative functional status and comorbidities seem to have more of an influence on outcome than age alone, the normal process of cardiopulmonary aging can serve to limit the physiologic reserve necessary to compensate for perioperative stress even in otherwise healthy elderly patients. Emerging experience now also suggests that minimally invasive surgical techniques for the treatment of lung cancer may parallel conventional thoracotomy in terms of oncologic efficacy while decreasing perioperative morbidity in the elderly.

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Anesthesiology Clin
26 (2008) 325–335

ANESTHESIOLOGY
CLINICS

Prevention and Management of Perioperative Arrhythmias in the Thoracic Surgical Population

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Severe perioperative bradyarrhythmias requiring treatment have been reported in 0.1% to 0.4% of 17,021 patients, of whom 6.4% were American Society of Anesthesiologists physical status III or IV [1]. In general, perioperative bradyarrhythmias respond well to short-term pharmacologic therapy, noninvasive transesophageal atrial pacing in anesthetized individuals or to noninvasive transcutaneous pacing in awake or anesthetized patients [2]. With the easy access to noninvasive pacing modalities, the preoperative insertion of temporary cardiac pacing wires rarely is required unless a patient is symptomatic and/or meets criteria for permanent pacemaker placement, even in the presence of preoperative asymptomatic bifascicular block or left bundle branch block [3]. Sustained ($>$ 30 seconds) ventricular arrhythmias that cause symptoms and require immediate treatment are rare in the perioperative setting [1,2]. Little data are available on whether repeated or frequent ventricular ectopy after noncardiac surgery is associated with poor long-term cardiovascular outcome. To date only one study evaluated the relationship of the development of ventricular tachycardia (VT) in patients without ischemia during hospitalization following noncardiac surgery and showed that VT was not associated with adverse long-term outcome [4]. The author and colleagues determined the incidence and short-term outcome of nonsustained ventricular arrhythmias in 412 patients who had lobectomy ($n = 243$) or pneumonectomy ($n = 169$) and were continuously monitored with Holter recorders for 72 to 96 hours postoperatively [5]. Sixty-one of

Financial Support: Departmental.

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.001

the 412 patients (15%) developed one or more episodes of nonsustained VT (three or more consecutive wide complexes) [5]. There were no episodes of sustained VT, and no patient required treatment for hemodynamic compromise associated with any VT episode. Patients who had nonsustained VT had a greater incidence of a preoperative left bundle branch block but did not differ unit from those who did not have VT in other clinical characteristics, operative data, or core temperature on arrival to the postanesthesia care. On multivariate logistic regression analysis, only the occurrence of postoperative atrial fibrillation/flutter (AF) was associated independently with nonsustained VT (relative risk, 2.6; 95% confidence interval, 1.4–4.8) [5]. The incidence of sustained VT or fibrillation following cardiac surgery has been reported to be 0.5% to 1.6% in large observational studies of patients who were monitored postoperatively [6–8]. Patients who developed postcardiac surgery VT/ventricular flutter had a greater 30-day mortality [8,9]. Attempts to suppress nonsustained ventricular arrhythmias after cardiac surgery prophylactically with lidocaine failed to show that such a strategy improves outcome [10]. Surprisingly, when used for the prophylaxis of AF after cardiac surgery amiodarone, a class III antiarrhythmic drug approved for the treatment of malignant ventricular arrhythmias, did not prevent sustained VT from occurring in a study comparing patients receiving and not receiving amiodarone [7]. The mortality rate from VT/ventricular flutter in patients who had chronic class II or III congestive heart failure and an ejection fraction of less than 35% who were assigned randomly to amiodarone was similar to that in patients assigned to placebo [11]. In patients who are hypomagnesemic, magnesium prophylaxis reduces the incidence of ventricular arrhythmias and perhaps AF after heart surgery [12].

Guidelines are not available for the work-up of patients developing perioperative ventricular arrhythmias. In the general population or following an acute myocardial infarction, electrophysiologic testing in patients who have no symptoms or only mild symptoms related to frequent ventricular ectopy or nonsustained VT now is considered inappropriate because of the lack of evidence that therapeutic strategies for such events have improved outcome [13]. Exceptions to these guidelines may be applied to highly symptomatic patients who have a low ejection fraction and a positive signal-averaged ECG. Because current data in surgical patients do not show a clear link between nonsustained ventricular arrhythmias and poor outcome, it is reasonable to adapt these published practice guidelines to perioperative patients [13].

It is estimated that perioperative rapid atrial arrhythmias affect more than 1 million elderly Americans annually and often are associated with significant morbidity, longer hospital stay, and related costs [14]. A greater number of patients undergoing noncardiac surgery may suffer these arrhythmias (but with a lower overall incidence), because many more patients undergo noncardiac surgery than cardiac surgery [14]. The incidence of AF is less than 4% after exploratory thoracotomy or wedge or segmental resection of the lung. In contrast, in age-matched patients who undergo an anatomic resection

such as lobectomy, bilobectomy, or pneumonectomy, the incidence of AF is very similar, ranging between 12.5% and 33% [14–24]. Despite the belief that minimally invasive surgery is associated with fewer adverse effects, the authors found no difference in the occurrence of AF after lobectomy done by open thoracotomy versus that done by the video-assisted approach in 244 age- and gender-matched patients [17]. One retrospective analysis found that in patients undergoing single or bilateral pulmonary transplantation the incidence of AF was 39% within 14 days of surgery [23]. The incidence of AF/supraventricular tachycardia (SVT) after esophagogastrectomy is reported to be 17% and ranges between 13% and 25%. Some authors have made an association between increased mortality and AF following esophagogastrectomy, but others have not [24–26].

When comparing the rates of arrhythmia occurrence reported in the literature, one must consider the definitions of AF used, monitoring techniques, and age matching of groups. At the onset of these arrhythmias patients often present with one or more of the following: dyspnea, palpitations, dizziness, syncope, respiratory distress, and/or hypotension. Although usually well tolerated in younger patients, perioperative atrial arrhythmias can be associated with hemodynamic instability in elderly patients. For nonsurgical patients presenting with new-onset AF, newly revised consensus guidelines recommend performing a transthoracic echocardiogram to rule out significant structural heart disease as part of a minimum evaluation [27]. A prospective study of 4181 patients (age $\geq$ 50 years) in sinus rhythm who had major noncardiac (including intrathoracic) surgery and routine postoperative monitoring showed that supraventricular arrhythmia including AF that was persistent or required treatment occurred in 2% of patients during surgery and in 4% after surgery [16]. The clinical symptoms, time of onset, and natural course of atrial arrhythmias are identical, whether a patient has had cardiac, thoracic, or other surgery [14]. Atrial arrhythmia onset peaks 2 to 3 days after surgery with nearly 85% of these episodes reverting to sinus rhythm with rate- or rhythm-control strategies during hospitalization [28,29]. The timing of the onset of atrial arrhythmias is intriguingly similar to that of postoperative myocardial ischemia and probably is related to autonomic nervous system imbalance. Few patients have persistent AF on discharge from the hospital; of these, 98% are free of AF 2 months after surgery [14]. Despite this good prognosis, patients who have postoperative AF have a greater risk of stroke, especially when AF is persistent [7,14,28].

Risk factors and mechanisms

To date, the only consistent preoperative risk factor for an increased incidence of atrial arrhythmias following surgery has been an age of 60 years or older [14–20,24]. In addition to older age, male gender, history of AF, prolonged preoperative P wave duration from the 12-lead ECG, and low

postoperative cardiac index also have been implicated as independent, albeit softer, predictors of AF after cardiothoracic surgery [20,30]. Using logistic regression analysis and weighted scores for AF occurrence, the author and colleagues found that male gender (1 point), preoperative heart rate higher than 72 beats per minute (1 point), an age between 55 and 74 years (3 points), and age greater than 75 years (4 points) were predictive of AF risk in both the derivation and validation models [20]. For patients who had scores of 4, 5, and 6 points, the risk of developing AF was approximately 14%, 21%, and 32%, respectively [20]. The author and colleagues recently showed that a twofold elevation in white blood cell count on the first postoperative day corresponded to a 3.3-fold increase in the odds of developing AF after thoracic surgery [31]. Adrenergic predominance after surgery probably is responsible for the lymphocytosis and leukocytosis that is mediated by β2-adrenergic receptors of the spleen and venular system. A more recent paper showed that elevated perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer [32].

It is well known that aging causes degenerative and inflammatory changes in atrial myocardium that lead to alterations in the electrical properties of the sinoatrial and atrioventricular nodes and atria, including prolonged sinoatrial and atrioventricular nodal conduction times and shorter atrial effective refractoriness, all of which contribute to fragmentation of the propagating impulse [33,34]. The concept of a pre-existing anatomic or electrophysiologic substrate for arrhythmias caused by aging, which may be present in varying severity among individuals who are susceptible to AF, may explain why some patients, but not others who undergo exactly the same operation, develop postoperative atrial arrhythmias [14].

In comparison with the overall 4% incidence of postoperative atrial arrhythmias among elderly patients who undergo major noncardiac surgery, the greater incidence of postoperative arrhythmias observed in elderly patients who had thoracic (20%) or cardiac (30% average for coronary artery bypass grafting and up to 65% for valvular surgery) operations probably corresponds to the amount of blunt or sharp surgical trauma to the atria and to sympathovagal fibers innervating the sinus node. Autonomic neural injury then may sensitize the atrial myocardium to catecholamines (denervation supersensitivity) to promote arrhythmias. AF and SVT often are initiated by a premature atrial contraction and later degenerate into one or more circuits that continuously re-enter themselves or one another (random reentry) [2,33,34]. Once initiated, atrial arrhythmias cause alterations in atrial electrical and structural properties (remodeling), including both rapid functional changes and slower alterations in ion channel gene expression, which promote the maintenance of the arrhythmia and facilitate its reinitiation should it terminate [34]. In comparison with matched controls, patients who developed AF after major noncardiac thoracic surgery demonstrated significant changes in heart rate variability that are consistent with vagal

resurgence competing in a background of increasing sympathetic activity as the primary autonomic mechanism responsible for triggering postoperative AF [35]. These novel results represented the largest study using heart rate variability to understand autonomic influences preceding postoperative AF and suggest that interventions that modulate both the sympathetic and parasympathetic nervous systems may be beneficial in suppressing postoperative AF [35].

The author and colleagues could not demonstrate an association between right or left heart dysfunction on serial transthoracic echocardiograms done before and after major thoracic surgery [18,36]. The role of inflammation and a genetic predisposition to postoperative atrial arrhythmias has been proposed recently by assessment of the interleukin-6 promoter gene variant [37]. Elevations in C-reactive protein levels were described in patients who had atrial arrhythmias unrelated to surgery but not in comparably large studies involving patients undergoing cardiac or thoracic surgery [38–40]. In contrast with the general population [38], there is controversy as to whether C-reactive protein elevations in the postsurgical patient indicate general systemic inflammation or more specific myocardial inflammation of atrial muscle injury that may be associated with AF promotion. Use of high-dose prednisone in an animal model also attenuated the electrophysiologic remodeling seen with rapid pacing and AF promotion [41]. These laboratory data were confirmed by a recent clinical trial in patients having cardiac surgery and suggest that anti-inflammatory agents may have a role in AF prevention strategies [42]. Other pathophysiologic mechanisms proposed for the occurrence of postoperative AF are alterations in atrial oxidative stress and elevations in the gap-junctional protein connexin40 expression [43,44]. Whether ectopic atrial activity from the pulmonary veins contributes to the genesis of AF after major pulmonary resection remains unknown.

Prevention

In comprehensive reviews the results of numerous studies examining the efficacy of a variety of drugs to prevent postoperative atrial arrhythmias were summarized [12,14]. It is unclear whether prophylactic treatment against postoperative atrial arrhythmias improves clinical outcomes (ie, stroke) or shortens hospital stay. The author and colleagues have found diltiazem to be moderately effective and safe in reducing postoperative AF and SVT [28,36]. β-Blockers have not been found useful after thoracic surgery [12] and in one study were associated with a significant incidence of hypotension and bradycardia [45]. Prophylactic amiodarone to reduce the incidence of postoperative AF has been found safe and particularly effective when given orally for 1 week before cardiac surgery [46]. Only one randomized study, however, examined the efficacy of amiodarone in preventing AF after thoracic surgery and showed no difference when compared with verapamil

at an interim analysis. After this interim analysis, the study was discontinued for fear of the drug's contributing to postpneumonectomy respiratory failure [47]. Since then the short-term use of amiodarone in the treatment or prevention of AF after thoracic surgery was not found to be associated with a greater risk of respiratory failure [48–50]. The results of these studies, however, showed that amiodarone's efficacy was not superior to and perhaps was somewhat inferior to conversion rates reported with diltiazem in a similar population [28]. Furthermore, a recent randomized study comparing amiodarone with diltiazem in preventing AF after coronary surgery found no difference in efficacy between the drug groups when compared with historical controls [51]. Guidelines of the American Heart Association/American College of Cardiology task force do not recommend the use of amiodarone as a first-line drug for acute management of AF unless there is evidence of pre-excitation conduction abnormality [27]. Amiodarone is a Vaughan Williams class III drug but also has α- and β-adrenergic blocking properties, as well as class I and IV actions and potential for proarrhythmia. Partial sympathectomy with epidural analgesia did not reduce AF after cardiac surgery or esophagectomy and only marginally attenuated the incidence of AF after thoracic surgery in a small study in which the control and treated arms were poorly matched for age [52–54]. Unless hypomagnesemia is present, the benefit of prophylactic administration of magnesium during general thoracic surgery to reduce the incidence of postoperative supraventricular arrhythmias is not clear. Data are available from only one study in which some control patients who had hypomagnesemia received magnesium after randomization [12,55]. Recent observational studies have made an association between statin use before surgery and a reduction in the rate of AF after cardiac and thoracic surgery [40,56]. A recent randomized, double-blind study of 7 days of preoperative atorvastatin (40 mg) ($n = 100$) versus placebo ($n = 100$) showed that atorvastatin reduced the rate of AF after cardiac surgery from 57% to 35% and also shortened hospital stay [57]. Other findings in this study were that concomitant β-blocker therapy was additive to this effect and that patients who had AF had the highest postoperative peak levels of C-reactive protein [57].

Treatment

SVT but not AF responds well to treatment with adenosine, but both arrhythmias respond to intravenous rate-control drugs such as β-blockers or calcium-channel antagonists [2]. In patients who have Wolff-Parkinson-White syndrome with AF, amiodarone is recommended as first-line therapy [2]. Recent data suggest that once AF has occurred postoperatively, rhythm control by pharmacologic means or direct current electrical cardioversion offers little advantage to a rate-control strategy [12,14,27,58,59]. Once sinus rhythm is restored, rate- or rhythm-control drugs may be discontinued 4 to 8 weeks after surgery, because more than 98% of patients are free of AF by

this time [14]. In general, digoxin may be used as a first-line drug only in patients who have congestive heart failure, because it is not effective in high-adrenergic states such as after surgery [27]. β-Blockers are preferred in patients who have ischemic heart disease but may be relatively contraindicated in patients who have proven bronchospastic potential, congestive heart failure, or severe sinus bradycardia or high-degree atrioventricular block [14]. Of the class III antiarrhythmic drugs, ibutilide has been used with moderate success to convert acute AF in 57% of patients after cardiac surgery; polymorphic VT was reported in 1.8% of patients, however, and was attributed primarily to electrolyte imbalance [12,27,59]. In the case of chronic AF unrelated to surgery, evidence from well-controlled, randomized trials shows that management with the rhythm-control strategy offers no survival advantages over the rate-control strategy [60]. Other options available in patients who have recent-onset AF without structural heart disease (defined as the presence of one of the following: left ventricular hypertrophy, mitral valve disease, coronary artery disease, or heart failure) include a single oral dose of the class Ic drugs. Flecainide (300 mg) or propafenone (600 mg) have been shown to be safe, with conversion rates at 8 hours of up to 91% and 76%, respectively [27].

Prevention of thromboembolism

The overall risk of a perioperative stroke in all patients undergoing anesthesia has been estimated at 0.08% in a retrospective study of 24,641 patients who had general and vascular surgery [61]. In a study of patients undergoing noncardiac thoracic surgery the authors and colleagues found a 1.7% incidence of stroke related to postoperative AF [28]. The reported incidence of stroke or transient neurologic injury (1.6%–3.3%) after cardiac operations is consistently greater for patients who develop persistent postoperative AF than in those who do not develop AF (0.2%–1.4%) [14]. Because the potential for thromboembolism with new-onset AF develops early (within 24–48 hours), prompt attempts should be made to restore sinus rhythm within this period. If the arrhythmia persists beyond 24 to 48 hours, anticoagulant therapy should be considered after weighing the risk of postoperative bleeding. Whether these individuals require long-term or even short-term anticoagulation is not clear, and the decision must be individualized for each patient based on the intrinsic risk for thromboembolism [14,27]. Several large trials have established that oral anticoagulation with warfarin is associated with a 60% to 70% reduction from the 9.2% overall risk of ischemic stroke in patients who have persistent or chronic nonvalvular AF not receiving warfarin [27]. Factors creating a high risk for stroke in patients who have AF unrelated to surgery include mitral stenosis, previous transient ischemic attack, stroke, or embolism, and a prosthetic heart valve. Moderate risk factors include age of 75 years or greater, hypertension (including treated hypertension), heart failure or a left ventricular ejection

fraction of less than 35%, and diabetes mellitus [27]. Short- or long-term therapy in nonsurgical patients may range from aspirin alone (81–325 mg/d) in patients who have no risk factors, to aspirin and/or anticoagulation depending on the presence of moderate- or high-risk factors [27]. Whether intravenous heparin is needed in patients who develop postthoracotomy AF requires further study, and individual practice may vary by institution. Later, warfarin may be given to maintain an international normalized ratio in the range of 2.0 to 3.0. In patients who have multiple risk factors for thromboembolism who are not candidates for or do not wish to receive systemic anticoagulation, transesophageal echocardiography is an acceptable and frequently used approach to conversion of AF when such services are available [14,27]. Patients who received standard anticoagulation therapy on discharge from the hospital can return for cardioversion between 3 to 12 weeks after initiation of anticoagulant therapy [27].

Summary

In this era of cost containment, the use of proposed prediction rules defining the subgroup of patients who are at highest risk for perioperative atrial arrhythmias will help target the most aggressive pharmacologic therapies to these patients [20,30]. Use of a minimally invasive, non–rib-spreading video-assisted thorascopic surgery approach does not decrease the incidence of postoperative AF when compared with standard thoracotomy, nor does off-pump cardiac surgery [17,62]. Patients deemed at high risk preoperatively should be considered for proven prophylactic therapy regardless of the planned operative approach. This important step will lead to more useful studies to determine whether reduction of atrial arrhythmias among high-risk patients improves outcomes and shortens length of hospital stay. Finally, current data suggest that once postoperative AF has occurred, a rate-control strategy during the first 24 hours is reasonable, because more than 85% of those episodes resolve during this period. Beyond this period, a more aggressive approach using class Ic or III antiarrhythmic drugs may reduce drug-related toxicity and the number of patients requiring anticoagulation [14,27]. Early anticoagulation in high-risk patients is likely to reduce the risk of devastating cerebrovascular events.

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Anesthesiology Clin
26 (2008) 337–353

ANESTHESIOLOGY
CLINICS

Pulmonary Vasodilators—Treating the Right Ventricle

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Pulmonary vasodilators are typically employed to improve right ventricular (RV) function in the setting of pulmonary hypertension (PH) or in an effort to enhance regional pulmonary blood flow and improve intrapulmonary shunt. In PH, pulmonary vasodilators are used acutely and chronically. Because patients who have chronic PH may require operative intervention, a working knowledge of these vasodilators by anesthesiologists is relevant.

PH is defined as an elevation of mean pulmonary artery pressure (PAP) to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise [1]. The World Health Organization Venice conference (2003) classification system attempts to base its classification of disease on underlying pathology and pathophysiology rather than on whether the disease is primary or secondary (Box 1) [2]. In addition, primary PH is now referred to as idiopathic pulmonary arterial hypertension. The classification further distinguishes pulmonary arterial hypertension from the broader definition of PH by excluding those diseases that are associated with primary cardiac or pulmonary diseases. Diseases that are grouped along with idiopathic pulmonary arterial hypertension in this new schema include connective tissue disease, HIV, portal hypertension, and drug-related causes [3]; however, this classification is likely to change because a pulmonary arteriopathy may be present in a broader series of causes for PH.

It has long been held that PH is characterized by a regional imbalance between vasodilation and vasoconstriction. Reductions in the nitric oxide (NO) pathway and prostacyclin and increases in thromboxanes and endothelin have been described [4,5]. These homeostatic imbalances are probably

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.010

Box 1. Classification of pulmonary hypertension

Idiopathic
Associated with
- Connective tissue disease
- Left-to-right intracardiac shunt
- Portal hypertension
- HIV
- Drug/toxin
- Other (thyroid disease, hereditary hemorrhagic telangectasia, myeloproliferative diseases, hemoglobinopathies)

Venous or capillary
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

PH of the newborn
PH with left heart disease
PH associated with lung disease or hypoxemia
- Chronic obstructive lung disease
- Pulmonary fibrosis
- Hypoventilation syndromes/obstructive sleep apnea
- High altitude

Venous thromboembolism–related
- Proximal or distal
- Nonthrombotic embolism (tumor, parasite, talc)

Miscellaneous (sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, hyposplenism, compression of mediastinal vessels)

Data from Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5S–12S.

the consequence of pulmonary endothelial cell dysfunction or injury [6,7]. More recently, there has been a shift in focus and an appreciation that the major alterations in PH extend beyond simple vasoconstriction. Alterations in growth inhibitors, mitogenic factors, and antithrombotic and prothrombotic determinants have been described. The benefits of the use of pulmonary vasodilators in the chronic setting likely extends beyond their vasodilator properties and relates more to their effects on smooth muscle proliferation, apoptosis, and modification of the intracellular matrix.

In the acute care setting, it is these agents' pulmonary vasodilatory effects that are being exploited. In the setting of PH, it is worth emphasizing that it is the consequences of an elevation of pulmonary vascular resistance (PVR), namely the ensuing RV dysfunction, that should be considered the primary goal of therapy with pulmonary vasodilators. The right ventricle,

unlike the left ventricle, is very susceptible to increases in afterload. Owing to the contractile properties of the naïve right ventricle, attempts at improving its contractility are not very effective. Therefore, principles of management of acute RV dysfunction center on reducing RV afterload while preserving coronary perfusion by avoiding reductions in systemic blood pressure.

This article provides a brief review of pulmonary vasodilators and a review of the literature as it relates to the use of therapies to treat various clinical conditions that may be relevant to the reader. The authors have attempted to keep the focus on the acute care setting.

Pulmonary vasodilators

Intravenous vasodilators

Intravenous vasodilators such as sodium nitroprusside and nitroglycerin mediate their effects on PVR through the release of NO. Both agents are nonselective and, as a consequence, can concomitantly decrease systemic blood pressure. In the setting of poor RV function, this reduction in systemic blood pressure may impair RV coronary perfusion and cause ischemia [8]. With PH, the failing right ventricle is made more susceptible to ischemia through an attendant increase in the right ventricle's intracavitary and transmural pressure.

Prostanoids, located in the vascular endothelium [9], induce relaxation of vascular smooth muscle, inhibit growth of smooth muscle cells [10], and are powerful inhibitors of platelet aggregation [9,11]. Currently, epoprostenol (prostaglandin [PG]I_2) and prostin (PGE_1) are available for intravenous administration in the acute setting. When infused chronically, epoprostenol has been shown to improve survival in patients who have advanced pulmonary arterial hypertension. In the acute setting, however, the therapeutic benefits of parenteral prostanoids are often limited by their systemic effects. Similar to sodium nitroprusside and nitroglycerin, prostanoids can lead to systemic hypotension. Additional care needs to be considered with several prostanoids because they are unstable in unbuffered solutions and inactivated by light and heat.

In addition to their systemic effects, all parenteral vasodilators are hampered by their relatively nonselective actions in the pulmonary vascular bed. As a result, their administration may lead to perfusion of underventilated alveoli, worsen intrapulmonary shunt, and in turn, worsen oxygenation. The ideal pulmonary vasodilator would have a rapid onset of action and a short half-life. It would produce regional pulmonary vasodilation, thereby avoiding issues related to systemic hypotension and potential adverse effects on ventilation-perfusion matching that limit the utility of systemic agents in critically ill patients. In this regard, inhaled vasodilators are attractive because they preferentially dilate ventilated alveoli and have less systemic effects.

Inhaled vasodilators

Inhaled NO (iNO) is delivered primarily to ventilated lung units, thereby causing increased perfusion to areas that are able to participate in gas exchange, which in turn may lead to a decrease in intrapulmonary shunt [8]. Shortly after NO was identified as the ubiquitous endogenous pulmonary vasodilator, it was rapidly embraced as a therapeutic agent in acute lung injury. iNO has been shown to produce pulmonary vasodilation without any significant effect on systemic circulation. Despite these advantages, there are inherent problems with iNO, such as costs, concerns surrounding methemoglobinemia, modulation of the immune system (pro- and anti-inflammatory), and cytotoxicity from free radical production. There is also the possibility of rebound PH with abrupt cessation of iNO. At present, iNO is approved only for use in infants who have respiratory distress syndrome. This approval stems from large prospective placebo-controlled studies demonstrating that NO reduced the need for extracorporeal membrane oxygenation and reduced the requirement for oxygen therapy following ICU discharge [12,13].

Inhaled prostaglandins, by contrast, involve an aerosol delivery mechanism that is attached by a nebulizer to the ventilator circuit. Despite having biologic rationale in practical terms, treatment is limited by inefficiencies in aerosolization. One study reported that as little as 3% of the drug that is administered reaches the lung [5]. Owing to the short half-life of epoprostenol, the drug must be continuously nebulized. As a result, changes of dose delivery with alterations in ventilator volumes, fraction of inspired oxygen (FiO_2), airway pressures, and solvent evaporation are other disadvantages [8]. Treprostinil, a synthetic prostanoid, has a much longer half-life and, in theory, holds promise as an inhaled vasodilator because it may require only intermitted administration [14]. To date, beyond acute hemodynamic studies, there are no clinical trials comparing these agents.

Inhaled nitroglycerin has been shown to decrease PH without producing systemic vasodilation [15]. Milrinone, a cyclic AMP–selective phosphodiesterase enzyme (PDE) inhibitor has also been administered by nebulization. Haraldsson and colleagues [16] evaluated a cohort of post–cardiac surgery patients and reported on the hemodynamic effects of the combination inhaled milrinone and inhaled prostacyclins. The inhalation of milrinone selectively dilated the pulmonary vasculature without systemic effects. When combined with inhaled prostacyclin, there seemed to be a potentiation and prolongation of the pulmonary vasodilatory effect.

Oral vasodilators

PDE_5 inhibitors mediate their pulmonary vasodilatory effect by preventing the degradation of cyclic GMP, allowing the prolonged effect of cyclic GMP as a secondary signal messenger, thus potentiating the effects of NO. PDE_5 inhibitors such as zaprinast and sildenafil produce pulmonary

vasodilation and enhance the effect of iNO on pulmonary hemodynamics [17–19]. Lepore and colleagues [20] studied the hemodynamic effect of the addition of oral sildenafil to iNO in patients who had chronic congestive heart failure and demonstrated that PDE_5 inhibition improved cardiac output and augmented the hemodynamic effects of iNO.

Endothelin is a potent vasoconstrictor and smooth muscle mitogen that exerts its effects on the vasculature by acting on two receptors. Bosentan and ambrisentan (nonselective endothelin receptor A and endothelin receptor B antagonists) and sitaxsentan (a highly selective endothelin receptor A antagonist) have been studied for treatment of chronic PH. To date, only case reports have showed potential benefit of oral bosentan working in combination with other agents to aid in the acute treatment of PH. Owing to these agents' slower onset of action and long half-life, they will likely not have a prominent role in the management of acute pulmonary hypertensive crisis or acute RV failure. Concerns about potential liver toxicity (that manifest as an elevation in transaminases) may preclude their use in the critical care environment.

Disease-specific applications of pulmonary vasodilators

Cardiac surgery

When present, PH remains a significant cause of morbidity and mortality in patients undergoing cardiac surgery for valvular replacement/repair or correction of congenital cardiac defects. It is unfortunate that there are few prospective controlled studies of pulmonary vasodilators in this population to guide the clinician.

In an observational study of atrioventricular canal defect repair, 25 children received NO and 39 received conventional treatment. Comparison between the two groups showed a significant difference in mortality (NO group, 24% [95% confidence interval: 7%–41%]; versus control, 56% [95% confidence interval: 37%–75%]; $P = .02$) [21]. A separate prospective randomized unblinded study of 62 cardiac surgery patients evaluated differences in PVR with varying doses of iNO ranging from 10 ppm to 40 ppm [22]. There were no statistically different effects on PVR among the groups with varying concentrations of iNO. The ability of iNO to prevent hypertensive crisis in children undergoing cardiac repair has been controversial; however, review of the available literature suggests that iNO may be efficacious in managing hypertensive crises when they do occur [23,24].

Fullerton and coworkers [25] showed that the response to iNO may be variable in different contexts. They demonstrated a decrease in PVR and PAP following coronary bypass, but no change in PVR and PAP following mitral valve surgery. It is important to recognize that the relative benefit derived form iNO depends on the baseline PAP. Two studies have reported

a correlation between vasodilator response with iNO and baseline PVR [26,27]. Rich and colleagues [27] found that the degree of NO-induced (20 ppm) pulmonary vasodilation was proportional to the severity of PVR at baseline. This effect did not appear to be altered by cardiopulmonary bypass (CPB), the presence of a ventricular assisted device, or infusion of nitrates.

Several studies have compared iNO with other vasodilators. Schmid and colleagues [28] compared iNO with intravenous PGE_1 and nitroglycerin in a randomized crossover study of 14 cardiac patients who had severe PH and preserved RV function. There was no difference between iNO and PGE_1 on cardiac index and RV performance; however, PGE_1 caused systemic vasodilation. Solina and colleagues [29] compared iNO to intravenous milrinone in a prospective randomized trial with 45 cardiac surgery patients. They found that, on separation from CPB, NO produced an improvement in RV ejection fraction and less need for vasopressors on arrival to the ICU. A prospective double-blind randomized trial of 58 patients undergoing mitral valve repair showed no difference between inhaled prostacyclin and iNO on PAP or on PVR. Both agents produced an increase in cardiac index and RV function [30].

Lamarche and colleagues [31] studied the possibility of using inhaled milrinone to reduce PH and to facilitate weaning from CPB. Seventy-three patients were enrolled, and their postoperative course was evaluated. Thirty received inhaled milrinone before CPB and 40 received inhaled milrinone after CPB. Patients receiving inhaled milrinone before CPB had lower pulmonary pressures and less frequent re-initiation of CPB (3%–23%) compared with those in whom inhaled milrinone was initiated late.

The potential additive role of combination therapy in cardiac surgery has also been studied. Stocker and colleagues [32] combined iNO with intravenous sildenafil in a prospective trial in 15 infants after cardiac surgery. They demonstrated that the combination produced a greater decrease in PVR compared with iNO alone. This improvement, however, was at the expense of a reduction in systemic blood pressure and worsening arterial oxygenation and alveolar-arterial gradient. Santini and colleagues [33] showed that after the addition of dipyridamole (a cyclic GMP–specific PDE inhibitor) to iNO, there was a decrease in pulmonary pressures and PVR from baseline and an increase in cardiac index. Further studies are required to look at other vasodilators and possible combinations of therapy. Although inhaled and intravenous prostaglandins have been studied in cardiac transplant patients, they have not been extensively evaluated in other cardiac surgeries.

Although there seems to be some evidence to support the notion that iNO administered perioperatively can control PH and facilitate CPB weaning, definitive studies are lacking. Furthermore, the optimum dose and duration of therapy has not been established. Prospective comparison to other agents in a controlled fashion is required. This need has been made more relevant given the expense of iNO and ongoing theoretic concerns

about the generation of potential proinflammatory mediators. Although improvements in pulmonary hemodynamics following cardiac surgery are reported with pulmonary vasodilators, it is unclear whether these agents lead to an improvement in outcomes that are of meaning to patients (eg, duration of ICU stay, hospitalization, ventilator days, or mortality). Consequently, it is difficult to advocate for the routine use of any specific pulmonary vasodilator.

Cardiac transplant

The adverse effects of high PVR on the naïve right ventricle may lead to significant morbidity and mortality following heart transplantation [34,35]. Post and colleagues [36] attempted to risk stratify 21 congenital adult cardiac patients to midterm outcomes based on response to iNO. The primary end point was cardiopulmonary death, and mean follow-up was 5 years. Four of the 11 patients who did not respond acutely to iNO died. None of the 10 responders to iNO died. The results suggest that patients who have an elevation in PVR may be further risk stratified and, more important, they raise the possibility that an elevation of PVR in these patients may be a modifiable risk factor. The current view is that the preoperative differentiation of fixed and reversible PH is essential to predict the response to vasodilator therapy and risk stratification of cardiac transplant candidates. A fall in mean PAP of more than 25% or a fall of more than 33% in PVR indicates reversibility in vascular resistance and may identify patients who would benefit from preoperative vasodilator therapy and subsequent heart transplantation [8] Recent studies suggest that regardless of severity, when PH can be reversed, these patients may have acceptable post-transplant survival [37].

Other vasodilators have been evaluated in the heart transplant patient. Haraldsson and colleagues [38] evaluated 10 pretransplant candidates and reported on the response of PVR to iNO at 40 ppm compared to inhaled prostacyclin. The results suggested that the effects of inhaled prostacyclin on pulmonary pressures and on PVR were comparable to iNO. There was no effect on systemic blood pressure with either drug. Kieler-Jensen and colleagues [39,40] performed studies of hemodynamic measurements post cardiac transplantation in the ICU with iNO, intravenous prostacyclin, PGE_1, sodium nitroprusside, and nitroglycerin. The greatest effect on cardiac output, stroke volume, RV end-diastolic volume, and central filling pressures was with prostacyclin. Intravenous prostacyclin, however, also produced a systemic effect by lowering systemic vascular resistance. Only iNO produced a selective pulmonary effect.

Although several studies have evaluated the acute hemodynamic responses to various pulmonary vasodilators, there are no randomized trials that have evaluated the effect of specific vasodilators on patient relevant outcomes.

Acute respiratory distress syndrome and acute lung injury

It is known that acute respiratory distress syndrome (ARDS) is frequently associated with PH due to increased vascular resistance [41]. There are a variety of factors in ARDS that contribute to PH, including lung parenchymal destruction, microthrombi, airway collapse, and pulmonary vasoconstriction related to hypoxemia, hypercarbia, and mechanical ventilation with high positive end-expiratory pressure settings [42–44]. In the face of demonstrable acute improvements in oxygenation, no controlled trials have demonstrated a benefit in patient outcome when NO is used in all comers who have ARDS. Adhikari and colleagues [45] performed a meta-analysis and, after reviewing the literature, concluded that NO had limited improvement in oxygenation, conferred no mortality benefit, and may cause harm. In this meta-analysis, NO was associated with an increased risk of renal insufficiency. In term infants who had acute lung injury (a disease characterized by more severe PH), the use of NO has may have more merit [12,13]. More recent studies suggest that NO may lead to an improvement in late sequelae (bronchopulmonary dysplasia) in some premature infants who have mild to moderate respiratory distress syndrome without significant increase in short-term side effects such as pulmonary hemorrhage, intracranial hemorrhage, pneumothorax, or acute deterioration [46,47]. This beneficial effect, however, has not been seen across all baby weights or studies [46–49]. Caution about the use of NO in this population needs to be exerted based on the findings of a recent Cochrane review in which it was suggested that iNO may not be a reasonable treatment in the ill preterm infant and may increase interventricular hemorrhage [50].

One of the difficulties with the use of iNO relates to rebound worsening of PAP or oxygenation on weaning. To this end, PDE_5 inhibitors have been shown facilitate weaning. In a case report by Giacomini and colleagues [51], vardenafil, a PDE_5 inhibitor was used to successfully wean an ARDS patient off iNO without significant systemic hypotension. In the pediatric population, Namachivayam and colleagues [52] investigated the role of sildenafil in preventing rebound PH after discontinuation of iNO. Thirty ventilated patients receiving 10 ppm or more of iNO were randomized to sildenafil or placebo 1 hour before discontinuing iNO. Rebound PH occurred in 10 of 15 placebo patients, whereas 0 of 15 patients in the sildenafil group had rebound PH.

Other therapeutic options may still be available for the treatment of hypoxemia in ARDS. Levosimendan exerts a positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C. It also has a vasodilatory effect by opening ATP-sensitive potassium channels in vascular smooth muscle to cause smooth muscle relaxation. Morelli and colleagues [53] studied the effects of levosimendan versus placebo on RV afterload in patients who had ARDS. Compared with placebo, levosimendan decreased mean PAP, increased cardiac index, and produced a reduction

in PVR. Dahlem and colleagues [54] showed that aerosolized prostacyclin compared with placebo in children who had acute lung injury improved oxygenation by 26%, with no significant adverse side effects, although long-term outcomes were not assessed during this trial. Van Heerden and colleagues [55] performed an unblinded interventional prospective trial that compared different doses of prostacyclin and their effect on oxygenation. The study showed that there was a significant dose-related improvement in the Pa_{O_2}/F_{IO_2} ratio and in the alveolar-arterial difference in partial pressure of oxygen, without any significant side effects. Further studies are needed to determine whether inhaled prostanoids are advantageous in long-term outcomes; as of yet, this has not been evaluated. It is likely, however, that inhaled prostanoids will be susceptible to the same shortcomings as iNO use in ARDS.

Although acute physiologic studies are encouraging, the use of pulmonary vasodilators has not been shown to confer a survival benefit in ARDS. The use of strategies aimed solely at improving oxygenation and RV function in ARDS is hampered by the fact that most patients who have ARDS do not succumb to refractory hypoxemia or RV failure, rather they die as the result of multisystem organ failure. Insofar as vasodilators are able to reduce the required intensity of mechanical ventilation, they have theoretic benefit. Although the routine use of vasodilators for ARDS cannot be advocated, they may still have a role in certain patients who have refractory hypoxemia or RV failure.

Lung transplant

With the advent of targeted therapies for PH, many patients have been successful in deferring time to transplantation; however, the clinical condition of these patients (who deteriorate in the face of receiving targeted therapies such as epoprostenol) at transplantation may be precarious. As a rule, these medications are continued until the grafts are perfused or the patient is placed on bypass. Some centers resume epoprostenol postoperatively if PH persists or cardiac dysfunction occurs [56]. In general, however, cardiac function improves significantly post lung transplantation, allowing the discontinuation of pulmonary vasodilators without sequelae [57].

Despite advances in organ procurement, primary graft dysfunction (PGD) remains a common problem after lung transplantation. PGD is a consequence of endothelial and epithelial dysfunction following reperfusion and is characterized by hypoxemia, bilateral airspace disease, and PH. In addition to its vasodilatory properties, NO may have important anti-inflammatory effects. NO has been shown to reduce the frequency and severity of ischemia reperfusion and PGD in animal models [58]. Although early uncontrolled studies of NO to prevent PGD appeared promising, a prospective randomized placebo-controlled trial in 84 patients from the authors' center showed no difference in the incidence or severity of

PGD, ventilator-free days, or postoperative survival when NO was administered at the time of reperfusion [59]. Whether earlier administration of NO (before reperfusion) affects outcome is still a matter of debate. More commonly, iNO has been advocated for the treatment of established PGD [60,61]. Used in this context, it has the same acute effects as in those seen in ARDS: an improvement in oxygenation and concordant reduction in pulmonary pressures.

Based on similar acute hemodynamic effects and potential anti-inflammatory effects, other agents have been evaluated to treat PGD. Some animal studies have shown a beneficial effect of intravenous prostacyclins in preventing lung transplant injury [62,63]. Wittwer and colleagues [64] looked at pretreatment of the donor lung with iloprost to optimize postischemic function of non–heart beating donor lungs in asystolic pigs. Compared to a control animal that did not receive iloprost, it was found that inspiratory pressure, dynamic compliance, and wet-to-dry ratio were significantly superior. Another study investigated the effects of iNO and PGI_2 on single porcine transplanted lungs. Parameters such as PVR, mean PAP, and blood flow distribution were investigated. Animals were divided into three groups: iNO, PGI_2, and a control group. The results concluded that iNO initially decreased PVR more than PGI_2 within the first hour and that both reduced PVR compared with control [65]. Fiser and colleagues [66] published a case report of the use of inhaled prostacyclin in the management of lung reperfusion injury post single lung transplant. The case report indicated that inhaled protacylcin is as effective as iNO and could potentially be used instead of iNO thereby reducing concerns related to costs and lack of potential toxic metabolites. At present, however, definitive studies are lacking; therefore, additional studies are needed to determine the best management options for PH and PGD in the lung transplant population.

Obstetrics

In a normal pregnancy, maternal cardiac output increases by 30% to 50%, blood volume by 40% to 50%, and oxygen consumption by up to 20% [67,68]. Reduced vascular tone, increased arterial compliance, and arterial load alterations help to accommodate the increased circulating volume and to maintain the efficiency of ventricular-arterial coupling and perfusion pressure [68]. With a progressively increasing uteroplacental blood flow, fetal growth, and ''peripheral'' oxygen consumption with limited oxygen delivery in the third trimester [69], the demands on the cardiac system may exceed the patient's adaptive capabilities. Historically, these physiologic demands have translated into high maternal mortality rates ranging from 30% to 56% in patients who have PH [70].

Weiss and colleagues [71] performed a systematic review of outcomes in vascular disease in pregnancy and completed an analysis of neonatal outcomes. When only patients in the late stages of pregnancy were included,

they found a surprisingly good infant survival rate of 90%. With the inclusion of patients who had Eisenmenger's syndrome, the infant survival rate was 82%. The largest obstetric series, conducted by Gleicher and colleagues [72], was less optimistic. In 70 pregnancies in women who had Eisenmenger's syndrome physiology, these researchers reported a disturbing 52% maternal mortality rate. There were no differences in maternal mortality between primiparous or multiparous women. Neonatal outcome was also discouragingly low: only 25.6% of pregnancies reached term, and at least 54.9% of all deliveries occurred prematurely [73]. The difference in neonatal mortality rates between Weiss and colleagues [71] and Gleicher and colleagues [72] may be due to the fact the former group included only women in the later stages of pregnancy. In general, the presence of hemodynamically significant PH is considered an absolute contraindication to pregnancy. Most experts recommend termination of the pregnancy in these patients.

The management of PH in the peripartum period has not been well studied, with most of the literature confined to case reports [74]. Several case reports have used iNO in the operating room and ICU for emergency cesarean section to decrease pulmonary pressures in parturient patients [74–76]. Other reports focusing on the postpartum period in the ICU have commented on the use of intravenous prostacyclin and nebulized iloprost [73,76]. Although animal studies have raised concerns about potential teratogenicity of these agents, there are no data to suggest that they confer fetal harm when used at term [70]. Endothelin antagonists such as bosentan, however, have shown to be teratogenic and are avoided during pregnancy [77]. To date, there is no good evidence to suggest that one vasodilator is better than another in the treatment of PH during the peripartum period.

In Eisenmenger's syndrome, there are no established guidelines on peripartum treatment. There are two case reports that attempted to use NO to control the hypoxemia during the third trimester and labor. In both cases, the patient died in labor or post partum [78,79].

Pulmonary embolism

The mortality of acute massive pulmonary embolus causing hemodynamic instability is approximately 31% [80]. Aims of therapy include reducing PVR and, if possible, relieving the mechanical obstruction through thrombolysis or pulmonary endarterectomy. Current guidelines support the use of thrombolysis of pulmonary embolus when associated with hemodynamic instability unless contraindicated. If thrombolysis has failed, then surgical embolectomy can be performed with an experienced surgical team [81]. Although data supporting pharmacologic treatment of increased PVR and right heart failure with pulmonary vasodilators are very limited, there have been case reports of iNO improving gas exchange [82].

Studies evaluating the use of pulmonary vasodilators post pulmonary thromboendarterectomy weakly advocate for the use iNO or iloprost in

improving of oxygenation and hemodynamics. Imanaka and colleagues [83] performed a prospective crossover study following seven patients immediately after pulmonary endarterectomy for chronic thromboembolism. iNO was given at 30-minute intervals for 30 minutes following surgery until extubation. Although iNO improved oxygenation and decreased vascular resistance, the changes were small and of uncertain clinical relevance [83]. Inhaled iloprost was also studied post pulmonary endarterectomy to control residual PH. Twenty-two patients were randomized to a single dose of 25-μg aerosolized iloprost or to normal saline. Iloprost enhanced cardiac index and reduced mean PAP and PVR [84].

Portopulmonary hypertension

Portopulmonary hypertension (PPHTN), an uncommon (<1%) complication of cirrhosis and portal hypertension, is defined as a mean PAP greater than 25 mm Hg with a normal pulmonary capillary wedge pressure (<15 mm Hg) and an increase in calculated PVR of greater than 240 dyne·s·cm^{-5} [85]. Moderate PPHTN (mean PAP >35 mm Hg) results in a significantly higher perioperative risk, and severe PPHTN (mean PAP >50 mm Hg) is frequently considered an absolute contraindication for liver transplantation [86].

For patients who have suspected PPHTN, a right heart catheterization is required, as is hemodynamic assessment to determine whether the patient can safely undergo transplantation [85]. In the perioperative period, preservation of RV function through control of pulmonary pressures is a critical component of the overall management goals [86]. Formerly considered an absolute contraindication to liver transplantation, new therapeutic options have become available that may alter these patients' eligibility for liver transplantation [87]. In a multicenter survey, Krowka and colleagues [88] provided some rationale for the use of epoprostenol to improve pulmonary pressures in patients who have PPHTN. The use of iNO has not been shown to be of any benefit during the perioperative management of these patients [89]. In the postoperative period, epoprostenol is generally continued for at least 6 months until it can be gently weaned as tolerated by the patient [87]. There is scant literature in this regard, however, and patients must be judged on their own merits. It is difficult to determine whether the pulmonary pressures will continue to be elevated after successful liver transplantation.

There is even less experience with other vasodilators in this population. The use of sildenafil has been reported in the preoperative and postoperative period [90,91], and there is one case report on the use of bosentan [92]. Based on the authors' experience and that of others, the authors believe that there is some merit in attempting to reduce pulmonary pressures in patients who have PPHTN to improve their surgical risk.

Summary

Hemodynamically significant PH remains a significant challenge. The goal of treatment should focus on improving RV function by reducing afterload and by augmenting RV coronary perfusion. Inhaled agents appear to have the most attractive physiologic and pharmacologic profile, although PDE_5 inhibition may provide additional benefit in some instances.

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Anesthesiology Clin
26 (2008) 355–367

ANESTHESIOLOGY
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Postthoracotomy Pain Management Problems

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A thoracotomy requires a very painful incision, involving multiple muscle layers and rib resection, that is subject to continuous motion as the patient breathes. Treatment of acute postthoracotomy pain is particularly important to keep the patient comfortable and to minimize pulmonary complications. It enables patients to ambulate and to breathe normally (without splinting) and deeply (to allow cough). The effects of chronic postthoracotomy pain are generally less detrimental to respiration but can be incapacitating, making daily activities impossible.

Many methods of pain management, each with attendant problems, have been tried with varied success: intercostal nerve block [1,2], intrapleural analgesia [3,4], cryoanalgesia [5,6], lumbar epidural [7,8], thoracic epidural [9,10], paravertebral block [11–13], intravenous narcotics [8,14,15], intrathecal [16–18] or epidural [2,15,19,20] narcotics, nonsteroidal anti-inflammatory drugs (NSAIDS) [1,21,22], and transcutaneous nerve stimulation [23–25].

Acute postthoracotomy pain

Severe acute pain after thoracotomy caused by retraction, resection, or fracture of ribs, dislocation of costovertebral joints, injury of intercostal nerves, and further irritation of the pleura by chest tubes is a normal response to all these insults [26]. Acute pain after video-assisted thoracoscopic surgery is considered less severe.

Suboptimal management of pain after thoracotomy (or after video-assisted thoracoscopic surgery in patients who have severely limited respiratory reserve) has major respiratory consequences. Inspiration is limited by pain, which leads to reflex contraction of expiratory muscles and consecutively

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.007 *anesthesiology.theclinics.com*

to diaphragmatic dysfunction (decreased functional residual capacity and atelectasis, shunting, and hypoxemia).

In addition, most patients are extubated early to decrease the risk of pulmonary barotrauma (particularly "blowout" of the bronchial suture line) and to prevent respiratory sequelae such as pulmonary infection. Deep breathing requires stretching the incision. Because this stretching may be extremely painful, patients without adequate analgesia try to prevent stretching of the skin incision by contracting their expiratory muscles (ie, splinting), thus limiting the stretch on the incision during inspiration. This failure to inspire deeply before a forceful exhalation results in an ineffective cough, which in turn promotes retention of secretions, leading to airway closure and atelectasis, reinforcing the importance of adequate analgesia following thoracotomy to avoid the need for reintubation because of inadequate pulmonary toilet.

Diaphragmatic contraction is also impaired; however, thoracic epidural anesthesia has been shown to increase diaphragmatic shortening after thoracotomy in the awake lamb [27,28].

Chronic postthoracotomy pain

Postthoracotomy pain syndrome (chronic postthoracotomy pain or postthoracotomy neuralgia, PTPS) is defined by the International Association for the Study of Pain as "pain that recurs or persists along a thoracotomy incision at least two months following the surgical procedure." In general, it is burning and stabbing pain with dysesthesia and thus shares many features of neuropathic pain [29]. PTPS is acknowledged increasingly by anesthesiologists and surgeons alike [30].

Prevalence of postthoracotomy pain

Chronic postthoracotomy pain was noted commonly by surgeons during the Second World War in men who had had a thoracotomy for chest trauma; it was called "chronic intercostal pain." Unfortunately, not much has changed since then, because the majority of patients do not seek help for their pain but mention it only when specifically asked.

Furthermore, despite a commonly held belief that postthoracotomy pain is transient, there is no evidence that the pain experience decreases significantly over time. For example, incidence of long-term postthoracotomy pain has been reported to be 80% at 3 months, 75% at 6 months, and 61% at 1 year after surgery; the incidence of severe pain is 3% to 5%, and pain that interferes with normal life is reported by about 50% of patients [31]. In one study, 66% of the patients who had PTPS received treatment for pain [32]. In another study, more than 70% of the patients who had PTPS received three or more of the treatment modalities and regimens that have been reported to be of value. More than 50% needed

to be referred to three different types of specialists. Nevertheless, no patient claimed to have become free of symptoms as a result of treatment, and a significant proportion implied that therapy was either more disabling than PTPS or made it worse [33]. For many patients, even the gentlest stimulation provokes intense pain, making participation in routine daily activities impossible. The rate of long-term persistent pain (3–18 months) has been found to be the same after thoracotomy and thoracoscopic procedures [34,35]. Other authors, however, concluded that chronic pain and disability might be less common after video-assisted thoracic surgery for pulmonary resection than after thoracotomy [36,37].

Although there is a wide variation in the reported incidence (probably attributable to differences in the definition of pain), postthoracotomy pain clearly can be seen as the most common complication of thoracotomy [38].

Mechanism of postthoracotomy pain

There are several mechanisms for chronic pain after thoracotomy, and no consensus exists regarding causality.

Intercostal nerve damage

Surgery routinely crushes the intercostal nerve, particularly because the nerve is quite exposed on the caudal side of the rib. It also is common for the nerve to be totally severed or included in a suture when the chest is closed. Among the many possibilities for nerve injury are mechanical damage during rib resection and compression with a retractor. Furthermore, incidental rib fractures may damage the intercostal nerve immediately or may entrap an intercostal nerve during healing, leading to symptoms of neuropathic pain. The sensation of pain in response to a normally nonpainful stimulus (allodynia) or an exaggerated response to a slightly painful stimulus (hyperalgesia), especially when accompanied by numbness, is considered diagnostic for nerve injury. These symptoms occur frequently along the distribution area/innervation area of the intercostal nerves and are the most frequent feature of postthoracotomy pain [39].

Neurophysiologic assessment of the intercostal nerve during thoracotomy has demonstrated total conduction block, suggesting nerve injury during rib retraction [40,41]. In another study the authors performed recordings on 24 patients 1 month after thoracotomy and found that patients who had a higher degree of intercostal nerve impairment had greater postthoracotomy pain [42].

Tumor recurrence

Many studies have shown that increasing pain also may be an early sign of tumor recurrence [43,44].

Type of incision

Many surgical techniques have been correlated with the amount of postoperative pain. Even muscle-sparing incisions seem to have no major advantage over posterolateral incisions [45]. Overall, variation in surgical techniques has not been shown to reduce subsequent pain [46].

Other mechanisms

Studies suggest that personality traits are strong modulatory factors in the overall experience of postthoracotomy pain. Preoperative anxiety seems to play a major role [47].

The costochondral and costovertebral junctions may be disarticulated because of extensive rib retraction, and ipsilateral shoulder disability also is common as a result of the division of serratus anterior muscles and latissimus dorsi. Injuries to the muscles responsible for moving the shoulder as well as insufficiently treated pain lead to inadequate rehabilitation and may produce frozen shoulder.

Current treatment options and their associated problems

Epidural analgesia

Technique

Median or paramedian approach. Most practitioners prefer either the median or paramedian approach. There seems to be little difference in terms of patient safety. The paramedian approach makes it much easier to locate the epidural space when overlapping spinous processes might prevent the operator from reaching the epidural space in the median plane.

Asleep versus awake technique. The difference between an awake technique and an asleep technique should have a major impact on potential spinal cord cannulation. Surprisingly, a survey of the practice of thoracic epidural analgesia in the United Kingdom in the not-too-distant past revealed that thoracic epidural cannulation is most often (60%) performed following induction of general anesthesia [48]. The author and colleagues strongly discourage insertion of thoracic epidural catheters in anesthetized/paralyzed patients in all but the rarest circumstances (for example, a thoracoscopic surgery that is converted to a thoracotomy in a patient who has a severely compromised respiratory reserve, when extubation is most likely to fail) and then only by very experienced operators. Similarly, others also state that "techniques above the termination of the cord … should be avoided (in anesthetized patients)" (Horlocker TT, personal communication, 2001). In addition, when epidural anatomy was examined by cryomicrotome section in humans, it was found that the ligamentum flavum is more frequently discontinuous at the thoracic level than at the lumbar level [49], further

pointing out the high risk of inserting a catheter into the intrathecal space and even into the spinal cord in anesthetized patients [50].

Outcome

Many researchers have addressed outcomes after thoracic epidural anesthesia. No major new approaches have been proposed since the publication of an extensive review of techniques for pain control after thoracic surgery more than 10 years ago [51]. Some strongly suggest improved outcomes with use of epidural catheters, whereas others have found no improvement. In general, it is difficult to compare these studies. Some authors looked at the effects of different analgesia techniques on long-term postthoracotomy pain [52], whereas others investigated the effect of epidural analgesia in the reduction of postoperative myocardial infarction via a meta-analysis [53]. Similarly, cumulative meta-analysis of randomized, controlled trials that evaluated the comparative effects of postoperative analgesic therapies on pulmonary outcome concluded that "epidural pain control can significantly decrease the incidence of pulmonary morbidity" [54]. Some randomized studies, however, looked at epidural versus intravenous (or intramuscular) on-demand analgesia and, not surprisingly, found a superior outcome with the epidural group. Overall, it seems to be important not only whether the patient received epidural analgesia, but also how the epidural was managed. For example, untreated hypotension with epidural analgesia is clearly detrimental for cardiovascular outcomes.

The shoulder pain reported by patients who have undergone thoracotomy is mostly referred pain and is not covered by the epidural analgesia. Most surgeons would agree that shoulder pain is a major postoperative pain problem that deserves special attention.

Shoulder pain

More than 75% of thoracotomy patients report constant severe ache in the ipsilateral shoulder after surgery [55]. This pain is relatively resistant to intravenous opioids and is only partially relieved by NSAIDs. Postulated mechanisms include transection of a major bronchus, ligamentous strain from malposition or surgical mobilization of the scapula, pleural irritation caused by the thoracostomy tube, or referred pain from irritation of the pericardium or mediastinal and diaphragmatic pleural surfaces.

Several methods of alleviating shoulder pain have been investigated with varying results. Intrapleural bupivacaine did not provide effective pain relief [56]. Superficial cervical plexus or interscalene brachial plexus blocks effectively reduced localized shoulder pain in some patients [57,58], whereas suprascapular nerve block was not helpful [59]. Phrenic nerve block achieved by intraoperative infiltration of the periphrenic fat pad with lidocaine reduced the incidence of shoulder pain from 85% to 33% and lowered overall pain scores [60]. Ropivacaine 0.2% reduced the incidence and

delayed the onset of shoulder pain for the first 24 hours postoperatively with no adverse effect on respiratory function [61].

It seems that the main origin of shoulder pain may be referred pain via the phrenic nerve (blocked by periphrenic infiltration and interscalene brachial plexus block) with contributions from positioning and surgery (coracoid impingement syndrome and coracoclavicular ligament strain), which is partially relieved by the use of NSAIDS [58,62] and acetaminophen [63]. Some patients who received phrenic nerve infiltration still reported pain, perhaps because of anatomic variations in the emergence of the sensory fibers from the phrenic nerve reaching the fibrous pericardium and parietal layers of the pleura.

The most effective management strategy would be multimodal, consisting of acetaminophen (pre-emptive and regularly), NSAIDS if not contraindicated, and infiltration of the phrenic nerve with a long-acting local anesthetic.

Intercostal nerve block

Intercostal nerve blockade is used routinely at some centers. The simplest method is a single injection of local anesthetics in multiple intercostal nerves before closure of a thoracotomy incision (five interspaces usually are blocked: two above, two below, and one at the site of the incision). Single-shot intercostal nerve blocks with local anesthetic generally do not provide effective long-term analgesia, however, and frequently must be repeated. A longer-lasting method involves continuous infusion of local anesthetics for several days through an indwelling catheter placed in a subpleural/extrapleural pocket, allowing the local anesthetic to diffuse to the nerves. Most surgeons use this approach for thoracoscopic surgeries, although others argue that an intercostal catheter is equivalent to epidural analgesia combined with patient-controlled analgesia [64,65].

Another approach is intraoperative cryoneurolysis of the intercostal nerves before closure of the thoracotomy incision. Similar to single-shot intercostal blocks, direct application of the probe onto the intercostal nerve at the site of the incision and to the nerves two levels above and below leads to axon degeneration. Because endoneurium and perineural connective tissue are preserved, restoration of nerve structure occurs 1 to 3 months after freezing.

Although cryoneurolysis has been shown to be effective in decreasing postoperative pain and the amount of oral and parenteral analgesics required postprocedure, long-term outcomes have been less positive because of the high incidence of development of neuropathic pain, dysesthesia, and intercostal muscle paralysis [5,66–68].

As can be seen in Fig. 1, an intercostal nerve block by a needle inserted perpendicular to the skin in the posterior axillary line does not cover pain in the more posterior parts of the back. In addition, if a chest tube is not in place, the risk of pneumothorax from the block needs to be considered.

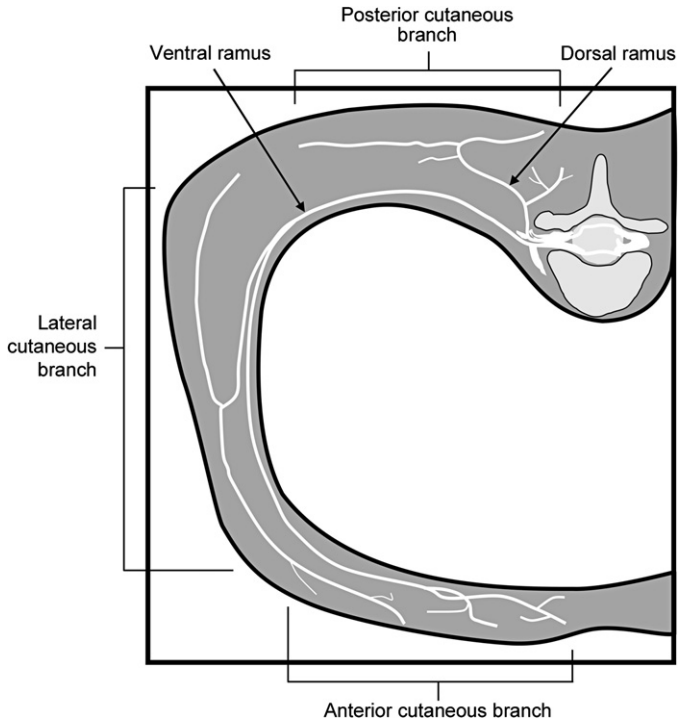

Fig. 1. A typical intercostal nerve and its branches.

Paravertebral nerve block

Some authors consider paravertebral block nearly equivalent to epidural analgesia, without the detrimental effects of bilateral sympathetic blockade [69,70]. It is somewhat surprising that this technique is not more widespread, possibly because it has become reintroduced into clinical practice only recently. Therefore fewer practitioners are familiar with it, it is more difficult to thread the catheter in a paravertebral nerve block than in an epidural, and a loss of resistance is not as appreciable as with an epidural approach.

Another problem with paravertebral blocks with either the percutaneous approach or the open technique is the relatively high failure rate of approximately 10%. This failure rate might be caused by the interference by the endothoracic fascia. Once the tip of the needle or of the catheter is ventral to this fascia, the diffusion of the local anesthetic back to the nerve(s) is severely hindered [71].

With the advent of video-assisted pulmonary resection, more patients undergoing thoracic procedures became candidates for ambulatory surgical. Central neuraxial techniques, even those incorporating very low concentrations of neuraxial local anesthetics and opiates, do not seem to be useful in the ambulatory setting. Although paravertebral nerve blocks are

a well-established and safe technique, most published results are from patients admitted to the hospital, and application of these principles in the ambulatory setting may not be feasible.

Pre-emptive analgesia and thoracotomy

Some of the mechanisms for the development of allodynia and hyperalgesia are well known. The concept of sensitization has led to an increased effort to control acute pain by a more or less total afferent blockade, with the goal of reducing the development of postthoracotomy pain.

Pre-emptive analgesia is intended to prevent the establishment of central sensitization caused by incisional and inflammatory injuries. Evidence from basic research has indicated that analgesic drugs are more effective if administered before, rather than after, a noxious stimulus [72,73]. The benefit of pre-emptive analgesia has been supported by some clinical studies using local anesthetics [74,75], opioids, and NSAIDS [76,77]. The clinical usefulness of pre-emptive analgesia has remained controversial, however [78–80], probably in part because of the wide variation in study conditions such as surgery, drugs, doses, routes of administration, and treatment duration as well as pain assessment methods used in different studies [81–83].

Previous studies comparing the effects of preoperative and postoperative epidural block in abdominal surgery have failed to demonstrate any benefit of pre-emptive analgesia [78,79]. This lack of benefit was attributed in part to the less discrete, visceral nature of pain after abdominal surgery. Thoracotomy produces high-intensity noxious stimuli sufficient to cause central sensitization [84,85], and the area of postthoracotomy pain is more discrete, largely restricted to the site of surgery. Hence, any benefit of pre-emptive epidural analgesia should, theoretically, be more apparent in thoracic surgery than in abdominal surgery.

Although results from clinical studies so far have not shown a major impact of pre-emptive epidural analgesia on postoperative pain after thoracic surgery [86,87], the concept holds promise, especially in preventing the development of chronic postthoracotomy pain [52,88].

It also has been suggested that although pre-emptive analgesia is beneficial in some surgical procedures, it is ineffective in others [14]. One explanation offered is that the surgical area is innervated by multiple segmental and cranial nerves [89].

It also has been shown that the degree of acute pain after thoracic surgery predicts long-term postthoracotomy pain, and hence aggressive management of early postoperative pain may reduce the likelihood of long-term postthoracotomy pain [84]. A good analgesic regimen reduces pulmonary complications in the immediate perioperative period [90] and helps in early mobilization [91,92]. The most common technique for pain relief is a thoracic epidural with the catheter in the mid-thoracic region providing a continuous infusion of local anesthetic and narcotics [93].

Some recent studies have shown beneficial effects (both immediate and late) when pre-emptive analgesia (nerve blockade either by epidural or intercostal nerve block) was begun before the surgical incision [52,85,88,94]. Other researchers, however, have found marginal or no benefits even when a multimodal approach was used [86,87,95,96].

In summary, it seems that the most logical explanation for the failure of pre-emptive analgesia has two components: first, afferent impulse blockade should be complete, which is impossible given the variety of incoming stimuli, and should also last for at least several days postoperatively [97,98]. Secondly, a complete "humoral blockade" would be necessary, because it has been shown that circulating proinflammatory cytokines lead to central cyclooxygenase-2 induction (eg, interleukin-1β–mediated induction of cyclooxygenase-2 in the central nervous system contributes to inflammatory pain hypersensitivity) [99].

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Anesthesiology Clin
26 (2008) 369–380

ANESTHESIOLOGY
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Postthoracotomy Paravertebral Analgesia: Will It Replace Epidural Analgesia?

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The pain associated with thoracic surgery is notable for both its severity and its duration. Thoracic epidural analgesia has long been considered the reference standard for management of postthoracotomy pain. Paravertebral block, which was first performed in 1905 to produce abdominal analgesia [1], is an alternative technique. The classic approach uses loss of resistance to air or saline as the superior costotransverse ligament is traversed [2]. Injection of local anesthetic into the paravertebral space (Fig. 1), by blocking the intercostal nerve, its dorsal ramus, the rami communicantes, and the sympathetic chain, produces a dense sensory and sympathetic block (see Fig. 1) [2].

Although there is universal agreement that for patients undergoing thoracotomy a combined regional and general anesthesia technique confers greater benefits than general anesthesia alone, there recently has been much debate about whether thoracic epidural or paravertebral anesthesia is the best regional technique. When reflecting on the question "Postthoracotomy paravertebral analgesia: will it replace epidural analgesia?," consideration must be given to the limitations of available evidence. There are no double-blind clinical trials comparing paravertebral and epidural techniques. Indeed, there are no large randomized trials comparing the two techniques, and a recent meta-analysis of 10 studies included a total of only 520 patients [3].

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.003

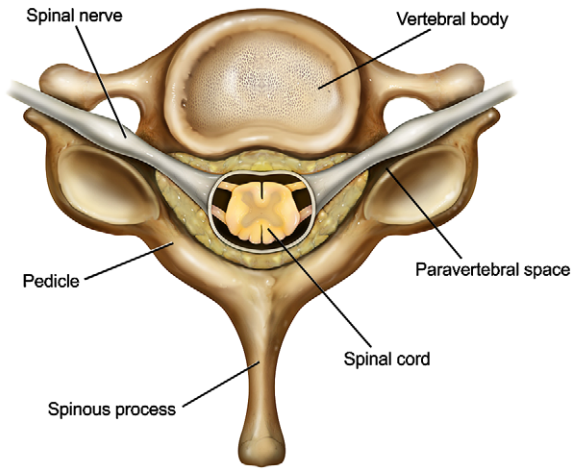

Fig. 1. Cervical vertebra. The drawing illustrates the paravertebral space with a spinal nerve coursing through it.

Within the restrictions of the available evidence, comparison of the two techniques from the point of view of analgesic efficacy, complications, side effects, contraindications, and development of chronic pain will help elucidate the issue.

Analgesic efficacy

The nociceptive pathways responsible for postthoracotomy pain remain poorly understood, but the intercostal, phrenic, and vagus nerves have been implicated [4]. Afferent input from the structures of the chest wall and most of the pleura is via the intercostal nerves[input from the diaphragmatic pleura is via the phrenic nerve; and input from the lung and mediastinum (including the mediastinal pleura) is via the vagus nerve [5]. Intercostal nerve stimulation results from a combination of surgical incision, rib retraction, trocar insertion, and suture placement [6]. Phrenic nerve stimulation is believed to be the source of the shoulder tip pain that frequently occurs after thoracic surgery and that is not blocked despite effective thoracic epidural analgesia. This mechanism was demonstrated in a randomized, controlled trial of 48 patients, which showed an incidence of shoulder pain after lung resection of 33% when 10 mL of 1% lidocaine was infiltrated into the periphrenic fat pad at the level of the diaphragm and an incidence of 85% after infiltration of 10 mL of 0.9% saline ($P < .008$) [7].

When comparing postthoracotomy paravertebral analgesia and epidural analgesia, a primary consideration is analgesic efficacy. Adequate pain control in the immediate postoperative period is important for patient satisfaction and also reducing postoperative pulmonary complications. Poorly

controlled pain can result in inadequate coughing and secretion clearance with atelectasis and progression to pneumonia and is considered an independent risk factor for postthoracotomy morbidity and mortality [8]. Unrelieved acute pain also may contribute to the development of postthoracotomy pain syndrome [9]. Multiple studies have examined paravertebral blockade with patient-controlled analgesia, demonstrating improved analgesia for variable periods of time postoperatively [10]. It perhaps is more important, however, to examine paravertebral and epidural analgesia after thoracic surgery. A recently published systematic review and meta-analysis of randomized trials directly compares the analgesic efficacy of paravertebral versus epidural blockade for thoracotomy [3]. All the included studies used a paravertebral catheter technique. Ten studies published between 1989 and 2005 and including 520 adult patients who underwent thoracotomy were included in the meta-analysis. The included studies were noted to be of moderate quality, mainly because none were blinded. The variables compared between studies included pain scores at 4 to 8 hours, 24 hours, and 48 hours; mean dose of opioids at 24 and 48 hours; and number of patients requiring supplemental analgesia. There was no significant difference in pain scores between the paravertebral block and epidural groups at any of the three time-points (Fig. 2). There also was no difference in morphine consumption at 24 hours or 24 to 48 hours and no difference in the use of supplemental analgesia. Interestingly, there was a significantly lower incidence of pulmonary complications, defined as clinical evidence of pneumonia and atelectasis, in the paravertebral group (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.14–0.92), (Fig. 3). Respiratory function, which was recorded as the percentage change from baseline of either peak expiratory flow rate or forced expiratory volume in 1 second, also was improved significantly at 24 hours in the paravertebral group [3]. This

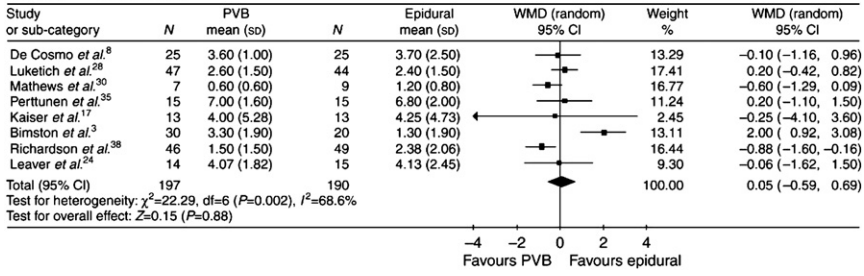

Fig. 2. A meta-analysis of trials comparing paravertebral block (PVB) with epidural analgesia on pain visual analogue scale (VAS) scores 24 hours postoperatively. WMD, weighted mean difference. (*Modified from* Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. Br J Anaesth 2006;96:422; with permission.)

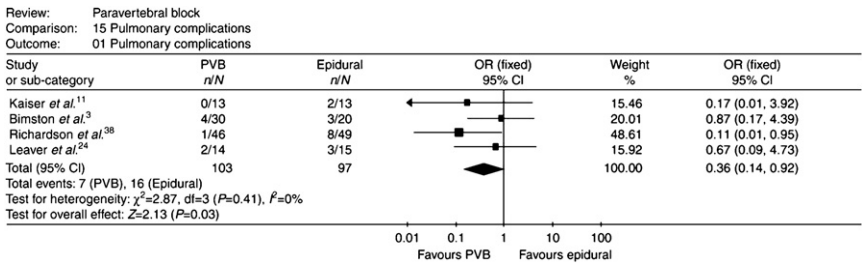

Fig. 3. A meta-analysis of trials comparing postoperative pulmonary complications with paravertebral block (PVB) or epidural analgesia. CI, confidence interval; OR, odds ratio. WMD, weighted mean difference. (*From* Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. Br J Anaesth 2006;96:418–26; with permission.)

improvement probably results from the unilateral nature of a paravertebral block, with preservation of respiratory effort on the contralateral side.

The available evidence indicates that paravertebral block and epidural analgesia provide comparable pain relief after thoracic surgery, but paravertebral block is associated with a lower incidence of pulmonary complications.

Complications

Although it has been reported that a blood vessel is punctured in 2.8% to 11.5% of epidural insertions, usually without any sequelae [11], instrumentation of the epidural space potentially can result in epidural hematoma and paraplegia. The exact incidence of permanent neurologic damage after thoracic epidural catheterization is unknown, but a meta-analysis in 1995 that included both thoracic and lumbar epidural catheterization estimated the incidence of major spinal hematoma at 0.0007% [12]. A review that included studies published between 1995 and 2005 with primary intent of investigating neurologic complications of regional anesthesia estimated the rate of paraplegia after epidural placement at 0.0009% and the rate of cauda equine syndrome at 0.0023% [13]. The incidence of blood vessel puncture is reported to be significantly greater during lumbar epidural placement than during thoracic epidural placement, so the risk for thoracic epidural placement alone may be lower than the combined incidence [14]. This risk is increased if the patient has a coagulation disorder or has received any anticoagulant medications [15,16]. Epidural abscess can cause spinal cord compression and requires emergency decompression to avoid permanent neurologic damage [17].

Accidental dural puncture, with an incidence of 1% to 5% [18], is a common complication of thoracic epidural catheterization. A higher incidence has been reported in the lumbar (1.16%) and lower thoracic regions

(0.85%) than in the upper thoracic region (0.20%–0.29%) [14]. The regional variation probably can be explained by the more frequent use of the paramedian approach in the upper thoracic region. Although postdural puncture headaches occur in up to 70% of patients after accidental dural puncture, persistent neurologic sequelae are extremely rare [18]. Other infrequent neurologic complications of epidural placement include radiculopathies and peripheral neuropathies, with an incidence of 0.0219% [13]. Almost all are transient and do not require treatment [19].

Paravertebral blocks also have been associated with neurologic complications. The literature reports only four cases that resulted in significant morbidity. Three cases of myelopathy after paravertebral injection of efocaine were reported in 1931, and a single case of Brown Sequard syndrome after paravertebral injection of alcohol was reported in 1954 [1]. Extradural injection, intrathecal injection with total spinal anesthesia, and postural headache with presumed meningeal penetration have been reported on rare occasions [2]. Segmental thoracic pain that lasted for 3 months after surgery, presumably secondary to intercostal nerve trauma, also has been reported in a patient after cholecystectomy [20]. Paravertebral blocks also are associated with inadvertent pleural puncture, with an incidence of 1.1%; the frequency of pneumothorax development is 0.5% [21].

As described, complications can arise from both epidural and paravertebral block techniques. Most are minor and self-limiting. The exception is spinal cord injury, a rare but catastrophic complication, which can result from instrumentation of the epidural space. Paravertebral block does not carry this risk and therefore may be a better option for anesthesiologists and patients alike.

Side effects

Many of the unwanted side effects of regional analgesia techniques are secondary to the associated sympathetic, sensory, and motor blockade or the addition of opioids to the local anesthetic solution. Both hypotension and urinary retention are commonly reported sequelae of thoracic epidural and paravertebral analgesia techniques. The perils of hypotension in the thoracic patient can lie as much in the treatment as in the occurrence: excessive fluid administration, especially during pneumonectomy, can lead to elevated pulmonary artery pressures and pulmonary edema [22]. It would be reasonable to expect a higher incidence of these complications with an epidural technique, because of the bilateral nature of the associated sympathetic and sensory block, in contrast to a unilateral paravertebral block. Richardson and colleagues [23], in a prospective, randomized comparison of epidural versus paravertebral bupivicaine in 95 patients, found a significantly higher incidence of both urinary retention, defined as the requirement for catheterization, and hypotension, defined as a decrease in preoperative systolic or diastolic blood pressure of 20% or more, in the epidural group.

In fact, no patient in the paravertebral group experienced hypotension [23]. The meta-analysis by Davies and colleagues [3] reinforced these findings. They showed a significant reduction in hypotension (OR, 0.12; 95% CI, 0.04–0.34) and urinary retention (OR, 0.23; 95% CI, 0.10–0.51) in the paravertebral group.

Another frequently reported and troublesome side effect is nausea and vomiting. Although this side effect may be attributed in part to hypotension, several other factors may play a role. The solution administered and whether it contains local anesthetic alone or is combined with an opioid, with the attendant increased risk of nausea and vomiting, is an important consideration. Paravertebral infusion solutions are more likely to contain local anesthetic without opioids; epidural infusions generally contain a combination. For the same reason, block efficacy is important, because it reduces the requirement for opioid rescue analgesia. It is difficult to dissect out the relative contributions of these factors in the meta-analysis by Davies and colleagues [3], because the included studies showed varied incidences of hypotension, administered several different solutions, and used a variety of rescue analgesia regimens. The combination, however, did show a significantly lower incidence of nausea and vomiting in the paravertebral group (OR, 0.47; 95% CI, 0.24–0.93).

The most serious side effect of epidural opioids is respiratory depression, with an incidence following conventional dosing regimens of approximately 1%, similar to the incidence following conventional dosing of intravenous or intramuscular opioids [24]. Respiratory depression may occur from minutes to hours after epidural opioid injection. Early respiratory depression ($<$ 2 hours of injection) is associated most commonly with epidural fentanyl [25] or sufentanil [26], whereas epidural morphine [27] and hydromorphone are more likely to be responsible for late respiratory depression ($>$ 2 hours after injection). Although certain factors such as advanced age and coexisting disease are associated with increased risk of respiratory depression with epidural opioids [24], its occurrence is largely unpredictable, and patients generally need closer monitoring in the postoperative setting than patients who have paravertebral catheters and who are receiving local anesthetic alone [28].

The most common side effect of epidural opioids is pruritus, which can be generalized but more commonly is localized to the face, neck, or upper chest [29]. The incidence is related to the type of opioid used, with epidural morphine being implicated more frequently than fentanyl or hydromorphone [30], and the concentration. A study of epidural pain relief in labor [31] showed a significantly increased incidence of pruritus with bupivicaine plus 4 ug/mL of fentanyl than with plain bupivicaine ($P = .0015$). A study comparing different doses of epidural fentanyl, however, concluded that epidural opioids are associated with concentration-dependent pruritus, with the incidence of pruritus increasing from 17% at 10 ug/mL to 36% at 20 ug/mL [32].

Perhaps the ultimate side effect is block failure. The reported failure rate of paravertebral block varies from 6.8% to 10% [1]. In the meta-analysis by Davies and colleagues [3], the epidural failure rate was significantly higher (OR, 0.28; CI, 0.12–0.64).

An epidural analgesic technique seems to have a higher failure rate and, with a bilateral sympathosensory block and the addition of an opioid to the infusate, is associated with significantly higher adverse effects than a paravertebral technique.

Contraindications

Some of the absolute contraindications to epidural insertion do not exclude the use of a paravertebral technique. In the setting of a coagulopathy, when an epidural technique carries the risk of epidural hematoma and subsequent cord compression, the margin of safety is much higher with a paravertebral block and the more distensible paravertebral space. Thus, a coagulopathy is a relative rather than an absolute contraindication to a paravertebral technique, and regional analgesia with all its attendant advantages still can be provided to the patient.

Pre-existing neurologic disease such as raised intracranial pressure also may contraindicate the use of an epidural technique. A paravertebral technique still can be used safely in this setting. A case report has described the use of a thoracic paravertebral block to manage pain associated with multiple rib fractures in the presence of a lumbar spine injury requiring continuous neurologic assessment [33].

Difficult thoracic spinal anatomy is a relative contraindication to an epidural technique because it makes the technique more difficult and more likely to be associated with complications. In this situation, a paravertebral technique also may be difficult and more likely to result in pleural puncture, but in challenging anatomy it has the added advantage that it can be placed under direct vision by the surgeon before the end of the surgical procedure [34]. If, after a patient is anesthetized, a decision is made to extend the original procedure because of pathology findings, complications, or poor surgical exposure, a paravertebral catheter still can be placed safely without fear of neurologic sequelae. In contrast, most anesthesiologists are uncomfortable with epidural placement in anesthetized patients, although some case series suggest that the practice is not unsafe [35]. Local or systemic sepsis and allergy to local anesthetic drugs contraindicate both epidural and paravertebral block.

Chronic pain

Postthoracotomy pain syndrome is defined as pain that recurs or persists along a thoracotomy incision for at least 2 months following the surgical procedure [36]. The frequency of occurrence makes it a significant issue after thoracotomy: a recent study reported an incidence of 52%, with 32%

described as mild, 16% as moderate, and 3% as severe [37]. Other groups have reported an incidence as high as 80% [38]. The exact mechanism for the pathogenesis of postthoracotomy pain syndrome remains unclear, but it is likely that both myofascial and neuropathic pathways are involved. Whereas tissue damage (such as muscle damage from trocar placement) typically leads to peripheral inflammation, progression to a chronic neuropathic pain syndrome probably is secondary to damage to neural structures [39], and rib retraction with resultant intercostal nerve damage has been implicated. This situation has been characterized in a rat study that compared a thoracotomy incision with rib retraction for 5, 30, and 60 minutes with a control group with thoracotomy incision down to the pleura but without rib retraction [40]. At 2 weeks after surgery, allodynia had developed in 50% of the rats that had undergone 60-minute retraction, in 11% and 10% of the rats that had gone 5- and 30-minute retraction, respectively, and in none of the control group. Histologically, the allodynic rats showed extensive axon loss in the intercostal nerves of the retracted ribs [40]. Modifications in surgical technique with a reduction in intercostal nerve damage, including muscle-sparing thoractomy and intracostal placement of sutures, have been shown variably to result in a reduction in postthoracotomy pain. Benedetti and colleagues [6] compared the degree of intercostal nerve impairment at 1 month after surgery in 24 patients who underwent a standard posterolateral thoracotomy versus a muscle-sparing thoracotomy. Intercostal nerve impairment, measured by amplitude of superficial abdominal reflexes, amplitude of somatosensory-evoked potentials in the incisional area, and sensory thresholds for pain, was significantly greater in the posterolateral thoracotomy group. These findings also correlated with the clinical incidence of pain at 1 month after surgery [6]. Ochroch and colleagues [41], however, failed to replicate these results when they measured postthoracotomy pain during hospitalization and up to 48 weeks postoperatively in 82 patients who underwent muscle-sparing thoracotomy and 38 patients who underwent posterolateral thoracotomy. Incision type predicted neither postoperative pain nor pain after discharge. Cerfolio and colleagues [42], in a study of 280 patients undergoing elective thoracotomy, compared postoperative pain scores in a group of patients who had the chest closed with intracostal sutures and in a group who had the chest closed with the traditional pericostal sutures. Pericostal sutures are placed on top of the fifth and seventh rib, and this placement was hypothesized to contribute to intercostal nerve damage. For intracostal sutures, the lower suture is placed through a hole drilled in the sixth rib. Pain scores were significantly lower in the intracostal group ($P = .004$, $P = .0001$, $P < .0001$, and $P < .0001$ at 2 weeks, 1 month, 2 months, and 3 months postoperatively, respectively). A concurrently administered McGill pain questionnaire revealed that pain in the pericostal group was much more likely to be described as "burning" or "shooting" [42]. Interestingly, video-assisted thoracic surgery is not associated with a reduction in the incidence of chronic pain after surgery, with

Table 1
Comparison of pain at 6 months and lasting more than 2 months between presurgical thoracic epidural analgesia, postsurgical thoracic epidural analgesia, and patient-controlled analgesia

Results	All patients (n = 69)	Pre-TEA group (n = 22)	Post-TEA group (n = 24)	IV-PCA group (n = 23)
Pain at 6 months	43 (62%)	10 (45%)	15 (63%)	18 (78%)
Pain lasting at least 2 months	47 (68%)	11 (50%)	16 (67%)	20 (87%)
Numeric rating scale	1 ± 1.0 (0–4)	0.6 ± 0.8 (0–3)	0.9 ± 0.9 (0–3)	1.4 ± 1.2 (0–4)
Pain affecting daily life	0	0	0	0

Abbreviations: IV, intravenous; PCA, patient-controlled analgesia; TEA, thoracic epidural analgesia.

From Senturk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002;94:11–5; with permission.

rates of chronic pain variably reported from 22% [43] to 63% [44]. This pain can be explained by the disruption of the intercostal nerve and the muscle damage associated with trocar insertion.

When choosing an analgesic strategy for patients undergoing thoracotomy, prevention of chronic pain is as important a consideration as immediate postoperative analgesic efficacy. A randomized, controlled trial compared the effect of three different analgesia techniques (preoperative thoracic epidural analgesia, postoperative thoracic epidural analgesia, and patient-controlled morphine analgesia) on postthoracotomy pain in 69 patients [45]. The incidence of pain was significantly lower at 2 months ($P = .0106$) and 6 months ($P = .0233$) in the group receiving preoperative epidural analgesia than in the group receiving patient-controlled analgesia; there was no difference between the groups receiving postoperative epidural anesthesia or patient-controlled analgesia (Table 1). This study concludes that epidural analgesia significantly reduces the incidence of chronic postthoracotomy pain, but only when instituted pre-emptively [45], and reinforces the concept that acute pain after thoracic surgery predicts chronic postthoracotomy pain [9,46].

In studies of acute pain, paravertebral blocks have been shown to be as effective as thoracic epidural analgesia for postoperative pain control [1], but the authors could find no trials that looked at the effect of paravertebral blocks on chronic postthoracotomy pain. They also found no randomized, controlled trial comparing the efficacy of thoracic epidural analgesia and paravertebral block with regard to chronic pain. The available evidence indicates that thoracic epidural analgesia used pre- and postoperatively is the optimal regimen to minimize the incidence of chronic postthoracotomy pain.

Summary

Paravertebral blocks are easy to perform and have a high success rate. There seems to be no difference in analgesic efficacy between paravertebral techniques and epidural techniques, but paravertebral techniques are

associated with better postoperative respiratory function and a significant reduction in side effects. Unlike epidural catheterization, paravertebral blocks are not associated with serious neurologic complications, and a paravertebral technique may be particularly useful when epidural insertion is contraindicated.

Chronic postthoracotomy pain, which occurs in up to 80% of patients, is a significant issue in thoracic surgery. Acute postoperative pain is a good predictor of the development of chronic pain. One small study has suggested that preoperative initiation of epidural analgesia can reduce the incidence of chronic pain significantly. The effect of paravertebral blockade on chronic postthoracotomy pain has not been studied.

Returning to the question whether postthoracotomy paravertebral analgesia will replace epidural analgesia, the answer is, ''Probably.'' The only hope for the traditionalists and the thoracic epidural is on the issue of chronic postthoracotomy pain. Unless epidural analgesia is proven to reduce the incidence of chronic pain significantly more than paravertebral analgesia, the evidence argues for the paravertebral technique.

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Anesthesiology Clin
26 (2008) 381–391

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Advances in Extracorporeal Ventilation

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Mechanical ventilation remains the signature tool of critical care and has greatly contributed to the tremendous progress in the treatment of critically ill patients. In most cases, mechanical ventilation provides sufficient gas exchange to keep patients alive; however, within the past decade, a growing body of evidence is suggesting that positive pressure ventilation in acute respiratory failure is a double-edged sword that is associated with life-threatening complications such as nosocomial pneumonia and low cardiac performance. One of the most severe complications is ventilator-associated lung injury (VALI), which includes barotrauma, volutrauma, and biotrauma induced by mechanical ventilation [1]. Moreover, VALI involves oxygen-mediated toxic effects [2] and is associated with an inflammatory response secondary to the stretching and recruitment processes of alveoli during mechanical ventilation [3].

Secondary remote organ failure seems to be a consequence of VALI, and there is increasing evidence available for this hypothesis in the literature [4]. A vicious circle is initiated when the failing lung is forced to perform with unphysiologic positive pressure instead of being allowed to rest and heal.

Essentially, solutions are required to provide adequate gas exchange and stable acid-base status while optimizing and maximizing pulmonary as well as remote organ protection. During the past 50 years, investigators have developed and proposed concepts to enable critically ill patients to perform gas exchange outside their natural lungs; however, most of these concepts have failed because of a lack of technology. Most of these approaches were not only cost and labor intensive but were also complex and invasive, ultimately leading to a high rate of serious complications [5].

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1932-2275/08/$ - see front matter
doi:10.1016/j.anclin.2008.01.006 *anesthesiology.theclinics.com*

Recently, the first commercially available extracorporeal membrane ventilator was approved for clinical lung support, the Interventional Lung Assist (iLA) manufactured by Novalung GmbH, Hechingen, Germany. This promising device has been used in Europe in more then 2000 patients with various indications. The University of Toronto, Canada, in 2006 was the first North American institution to use the iLA. This article focuses on the technical details of the iLA and gives an overview of the potential indications for this device and the current clinical evidence in extracorporeal ventilation.

Brief history of interventional lung assistance

In 1951 Potts and colleagues [6] used and described an experimental approach to maintain pulmonary function by an extracorporeally connected homologous lung in a large animal model. Rashkind and colleagues [7] in 1965 was the first to use a self-constructed bubble oxygenator for extracorporeal lung support in a child. He created a shunt between the femoral artery and vein to eliminate CO_2. Although this approach failed due to early device clotting, the concept of interventional lung assistance was born. Thereafter a high volume of experimental work was performed in the field of extracorporeal gas exchange, CO_2 removal, and artificial lung development until the iLA was introduced in 1999 and first clinically applied in a pumpless mode for CO_2 removal in a patient.

Technical aspects of the Interventional Lung Assist

The Novalung iLA device is a membrane ventilator that allows oxygen and carbon dioxide gas exchange to occur by simple diffusion (Fig. 1). It potentially helps to avoid or reduce VALI and remote secondary organ failure related to injurious mechanical ventilation.

Blood flows over the exterior surface of the device's fibers, and the ventilating gas (commonly, O_2 sweep) flows inside these fibers (Fig. 2). In this way, the iLA mimics the native lung. Blood, however, existing the device has higher oxygen and lower carbon dioxide levels compared with blood that exists a normal lung. Based on our clinical experience, oxygen partial pressures measured in the outflow line of the iLA range between 350–500 mmHg and carbon dioxide pressures between 25–35 mm Hg at 6 L of O2 sweep flow. It needs to be taken in mind though, that only approximately 20% of the cardiac output runs through the iLA driven by the left ventricle and that the device blood mixes with the remaining 80% of the cardiac output in the central venous vasculature. In an arteriovenous pumpless shunt, the carbon dioxide elimination is the primary function owing to arterial inflow blood; a veno-venous or veno-arterial pump-supported attachment additionally allows full oxygenation support. The iLA consists of a plastic gas exchange module with diffusion membranes made from polymethylpentene (PMP). These PMP fibers are woven into a complex configuration of hollow

Fig. 1. The iLA membrane ventilator.

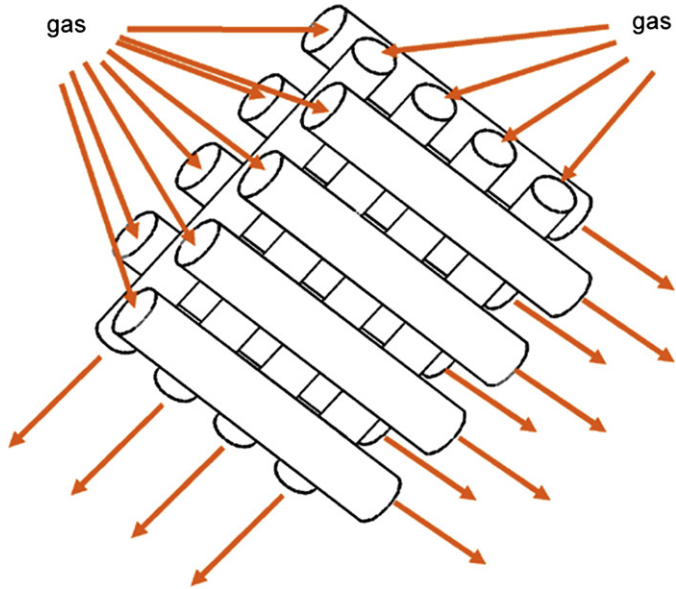

Fig. 2. Air flow through the iLA. Configuration of the hollow fiber system. The blood surrounds the tubular system.

fibers. The PMP material is woven into bundles in a low resistance configuration mat arranged inwell-defined stacks, which provides maximum blood-gas mixing. Gas transfer takes place without direct contact with blood. In addition, the blood-contacting PMP membrane surface is treated with a heparin coating to provide a biocompatible and non-thrombogenic surface.

The iLA is a low-pressure gradient device designed to operate without the help of a mechanical pump. Based on this principle, adequate mean arterial blood pressure is mandatory. The device is attached to the systemic circulation (preferred access sites are the femoral vessels by percutaneous cannulation using Seldinger's technique) and receives only part of the cardiac output (1–2 L/min) for extracorporeal gas exchange. This exchange allows complete CO_2 removal, which can be controlled by varying sweep gas flow. Oxygenation depends on shunt, arterial oxygenation saturation, and other variables. The native lung in this situation also contributes. The limited increase in oxygenation may be life saving in some patients with oxygenation deficiency; however, patients with a primary oxygenation disorder may not necessarily benefit from the pumpless iLA mode.

As Fig. 3 demonstrates, the blood enters the device through the inlet connector. The blood flows into the blood distributing chamber. Any micro-sized air bubbles that may have entered the device are removed through the de-airing ports. The blood flows into the main chamber where gas exchange takes place. The oxygenated and CO_2-depleted blood is returned to the patient via the blood outflow [2].

Two de-airing membranes are integrated at the top apex on both sides of the device. These de-airing membranes allow gas bubbles but not liquids (eg, blood or serum) to cross. The de-airing membranes facilitate priming and de-airing of the device and are also used to eliminate any air trapped in the device during support. An oxygen supply is connected to the upper

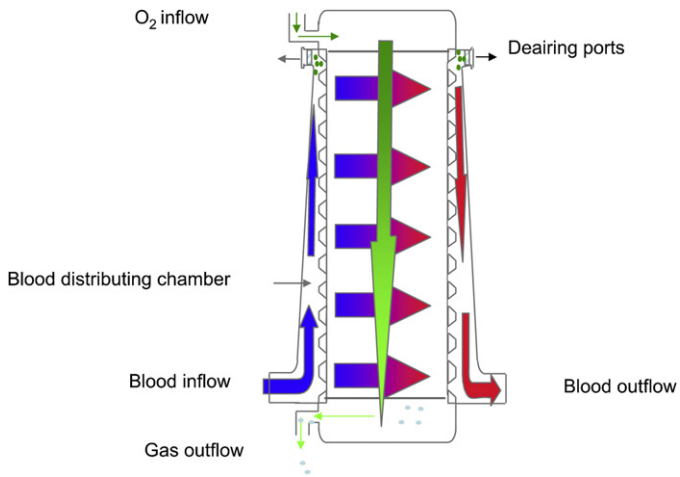

Fig. 3. Inlets, outlets, and ports of the iLA.

gas inflow connector and provides the medium for respiration to take place. The lower gas outflow connector is open to the atmosphere and is the site where gas is exhausted from the device. Table 1 summarizes important technical details of the iLA.

Lung failure and negative effects of mechanical ventilation

There are two modes of acute respiratory failure. One is predominantly hypoxic respiratory failure mostly due to alveolar collapse, leading to a ventilation/perfusion mismatch. The main treatment strategy is pressure-controlled ventilation with high positive end-expiratory pressure (PEEP). The second mode is predominantly hypercapnic respiratory failure often due to respiratory muscle insufficiency, leading to alveolar hypoventilation. Primary hypercapnic failure is frequently found in the weaning period after long-term mechanical ventilation and can be associated with severe respiratory acidosis. The appropriate treatment is volume application by noninvasive or invasive mechanical ventilation.

Two forms of lung damage due to mechanical ventilation can be differentiated: (1) biophysical trauma including barotrauma, volutrauma, and atelectrauma, and (2) biochemical trauma.

Barotrauma

The concept that high airway pressures in positive-pressure ventilation can cause gross injury has been investigated since the initial study by Macklin [8] in 1939. It was realized that high inspiratory pressure is the main reason for complications such as pneumothorax and pneumomediastinum. Nevertheless, based on the findings of Petersen and Baier [9] and Weg and colleagues [10], it was concluded that absolute airway pressure, per se, does not directly lead to injury.

Volutrauma

Dreyfuss and Saumon [11] postulated that high volume ventilation leads to regional overinflation, resulting in increased microvascular permeability,

Table 1
Technical details of the iLA Novalung

Parameter	Value
Maximum blood flow rate (L/min)	4.5
Maximum recommended gas flow (L/min)	15
Maximum blood side mean pressure (mm Hg)	200
Maximum gas pressure (mm Hg)	30
Surface area of diffusion membrane (m^2)	1.3
Static priming volume (mL)	175
Blood inlet/outlet connector size (in)	3/8
Gas port size (in)	1/4
Vent port size (in)	1/4

pulmonary edema, alveolar flooding, and, ultimately, a reduction in lung distensible volume. Parker and colleagues [12] provided additional molecular insight into this concept. Dreyfuss and colleagues [13] showed in experimental studies that albumin sequestration as a marker for pulmonary edema formation correlates with the applied inspiratory tidal volume. Animals in the high inspiratory pressure/low tidal volume group accordingly did not develop pulmonary edema.

Biochemical trauma

In contrast to the previous findings, Ranieri and coworkers [14] demonstrated that high ventilatory volume application is responsible not only for pulmonary edema formation but also for cytokine sequestration and upregulation of proinflammatory cytokines in the mechanically ventilated lung. High volume/non–PEEP-ventilated animals showed an increase in all proinflammatory parameters considered to be the main mediators in the development of acute respiratory distress syndrome (ARDS). A switch to low volume ventilation reduced the concentration of proinflammatory cytokines [15]. In addition, Imai and associates [4] showed a significant increase in cell apoptosis in the lung, intestine, and kidney in animals ventilated with high tidal volumes. These intriguing findings might help to explain why high volume ventilation often leads to multiorgan failure [16].

Atelectrauma

Dreyfuss and co-workers [13] observed in animals that atelectasis was much more pronounced in a low-volume ventilation group. This process, called atelectrauma, leads to a repetitive open-close cycle of distal lung units in the ventilated lung, with shear forces acting on the epithelial layer, and is also responsible for an increase in proinflammatory cytokines and for VALI seen in long-term ventilated patients.

Van Kaam and coworkers [17] used a porcine ARDS model of transbronchial administration of streptococcus B to study the effects of high and low volume ventilation. A major focus of this study was the translocation of infection. High volume ventilation led to a significant proinflammatory stimulus and an increase in infectious disease complications.

Indications and modes of extracorporeal ventilation

There are two major philosophical approaches to extracorporeal ventilation. It can be applied to give the injured or diseased lung a chance to heal and to regain normal physiologic function (bridge to recovery); however, in the field of lung transplantation, the end-stage diseased lung might not have the potential to recover. In this scenario, extracorporeal ventilation might be used as a bridge to lung transplantation. When compared with cardiac

assistance (ie, with the use of left ventricular assist devices), the concept of destination therapy as a theoretic alternative to organ replacement has not been established in lung assistance because no long-term lung replacement beside lung transplantation exists.

In lung failure, the iLA can be used differently depending on the physiologic and respiratory needs of the individual patient. Basically, the iLA can be used with or without an external blood pump. In the pumpless mode, the left ventricular output (CO) is the driving force of the extracorporeal membrane ventilator and no pump is required; therefore, the device is connected in an arteriovenous fashion. In this pumpless mode, approximately 20% of the CO is pumped through the low-resistance iLA device. This release is sufficient to eliminate CO_2 by diffusion; however, oxygenation is dependant on device flow. Although efficient oxygenation can be measured in the outflow cannula of a pumplessly driven iLA, the relatively low amount of iLA blood that mixes into venous (inferior vena cava) blood does not allow for sufficient total oxygenation, as the authors were able to demonstrate at their institution [18]. Fig. 4 depicts the pumpless iLA connected via the femoral artery and vein for CO_2 removal in a patient with severe hypercapnic lung failure and respiratory acidosis despite a maximum of mechanical ventilatory support while waiting for a lung transplant.

The pumpless mode of extracorporeal ventilation has also been used for other indications. Iglesias and colleagues [19] reported on seven cases of severe ARDS after pulmonary resection. All of the patients were supported with the pumpless iLA. One died of multiorgan failure, whereas the other six patients were successfully weaned from mechanical ventilation.

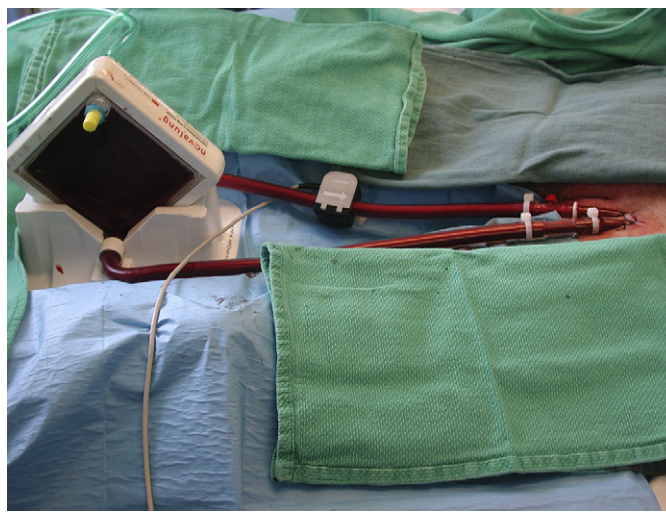

Fig. 4. The iLA in the pumpless arteriovenous mode (femoral artery to femoral vein connection) for CO_2 elimination in a patient with predominantly hypercapnic lung failure (bridge to lung transplantation).

Bein and colleagues [20] at the University of Regensburg reported on the largest single center cohort of 90 patients with ARDS supported with the pumpless iLA. The reported survival rate (weaning of iLA) was 41%, which was higher than expected from the Sequential Organ Failure Assessment Score. The related complication rate was 24.4%, mainly limb ischemia. Most likely, the ischemic complications were associated with the large cannula size for arterial cannulation initially used for iLA (17 F). Recently, smaller cannulae (13 to 15 F) have become available, which have led to a 0% rate of ischemic complications at the authors' institution. This promising study by Bein and colleagues has initiated significant clinical and experimental activity in the field of extracorporeal lung support. The iLA has been used in patients with chest trauma by Brederlau and coworkers [21], in patients with blast injury in the war zone as a rescue tool for military medicine [22], and in patients with exacerbated lung infection and other indications [5].

The authors' expertise is with the use of extracorporeal ventilation as a bridge to lung transplantation. We have previously reported our initial experience using the pumpless iLA in 12 patients with severe hypercapnic failure associated with respiratory acidosis despite maximum mechanical ventilatory support while awaiting a lung transplant [18]. With a mean support time of 15 days we were able to successfully bridge 10 of the 12 patients to lung transplantation. Two patients died of multiorgan failure before transplantation and two other patients after lung transplantation. The other eight patients survived the first year after transplantation. In this study, proper membrane function was observed for the entire support period. This function enabled us to reduce the ventilator setting toward a more protective mode of ventilation.

The authors have also used the pumpless iLA in two patients as a bridge to heart-lung transplantation. Both patients had developed idiopathic pulmonary arterial hypertension with suprasystemic pulmonary arterial pressures. Both were listed for combined heart-lung transplantation. While waiting for surgery, signs of right ventricular failure developed, and the indication for conventional extracorporeal circulation membrane oxygenation (ECMO) support was established; however, we instead performed central cannulation through sternotomy of the main pulmonary trunk and of the left atrium via the left or right upper pulmonary vein. Thereby we created an interatrial shunt with the pumpless iLA with the physiologic function of a septostomy but with additional gas exchange abilities. The driving force for the iLA was the right ventricle and the fact that the iLA had a lower resistance than the pulmonary vasculature in these patients; therefore, the support of a blood pump was not necessary. With a support time of 14 and 8 days, respectively, both patients were successfully bridged to transplant.

As mentioned previously, the pumpless iLA has limited oxygenation abilities; therefore, in patients with predominantly hypoxemic lung failure, we routinely use the iLA with an additional centrifugal pump (veno-venous iLA). There are several potential advantages of this setup over conventional

ECMO. The membrane surface of the iLA is only 1.5 m^2, which is about half of the size of conventional oxygenators. This small size could lead to less inflammation and blood trauma and may be advantageous for long-term support. In addition, we use this apparatus with an extremely short tubing system to further minimize the artificial blood/tubing contact surface area. We have previously reported our initial experience with the veno-venous iLA as a bridge to lung transplantation in patients with predominantly hypoxemic lung failure and now use this setting as a routine procedure in such patients. For both modes, the pumpless iLA as well as the veno-venous iLA, the patient needs to be hemodynamically stable because no hemodynamic support can be provided [23].

In patients with ventricular failure after heart surgery or in patients awaiting a transplant with significant hemodynamic instability, the authors use the iLA supported by a centrifugal blood pump in a veno-arterial connection. Our initial experience using this mode included 24 patients. The mean age was 48 $\pm$ 15 years (n = 14 men). The mean support time was 5 days, and 58% of patients were successfully weaned from veno-arterial iLA-ECMO. The 30-day survival rate was 43% and the 100-day survival rate 40%. We routinely use continuous heparin infusion to maintain activated clotting times of 160 to 180 seconds. Only six of the patients (25%) developed bleeding complications, which, when compared with the results in the literature on conventional ECMO, is low in patients during the initial postoperative period [24]. The indication for veno-arterial iLA-ECMO was acute cardiogenic shock in 18 patients; one patient developed acute heart failure after heart-lung transplantation and five patients died from other causes. The two leading causes of death were myocardial failure and multiorgan failure. Only one patient died of a cerebrovascular injury.

Summary

Extracorporeal lung support or ventilation is a relatively new field which arose out of the concept of protective ventilation [25]. The general concept is to rest the injured or diseased lung to give it time to heal; however, the authors have shown that it provides an exceptional tool for bridging patients to lung transplantation with no potential for lung recovery. It is traditionally used for extracorporeal CO_2 elimination in a pumpless mode. Modifications include the addition of a pump to gain higher device flows and consequently better overall oxygenation. Future studies will have to be performed to test the iLA as a lung support device in the nonsedated awake patient with no additional mechanical ventilatory support.

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