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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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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

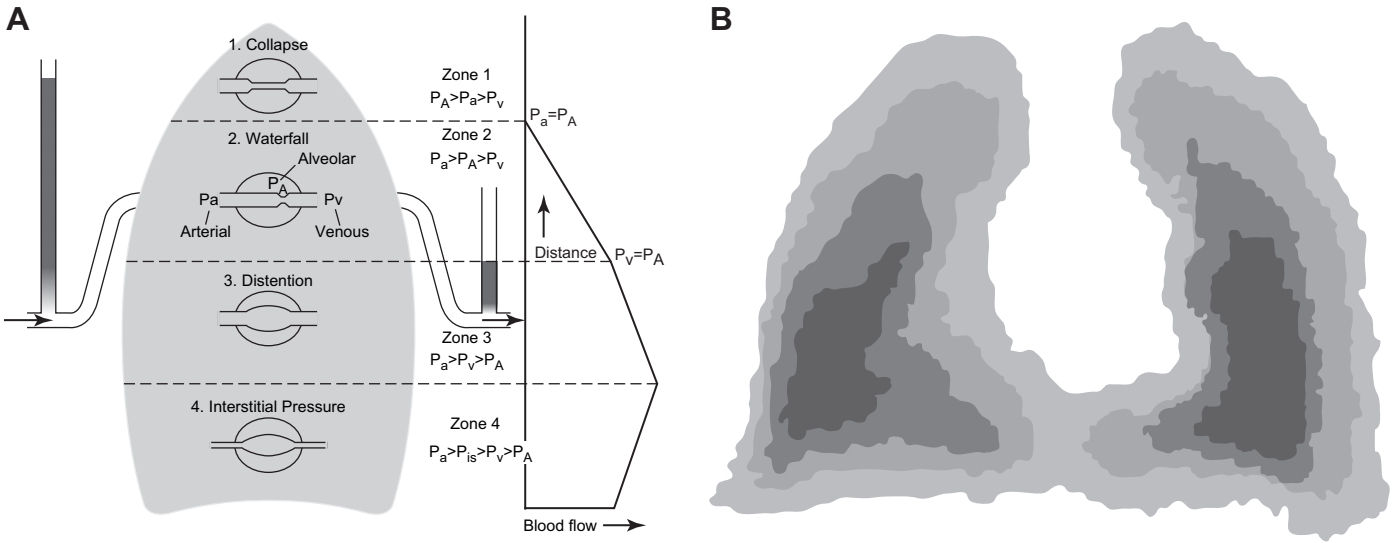

Fig. 1. Pulmonary blood flow distribution relative to the alveolar pressure (P_A), the pulmonary arterial pressure (P_a), the pulmonary venous pressure (P_v), and the interstitial pressure (P_{is}) at various gravitational levels. (*A*) Classic West Zones of blood flow distribution in the upright position. (*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.

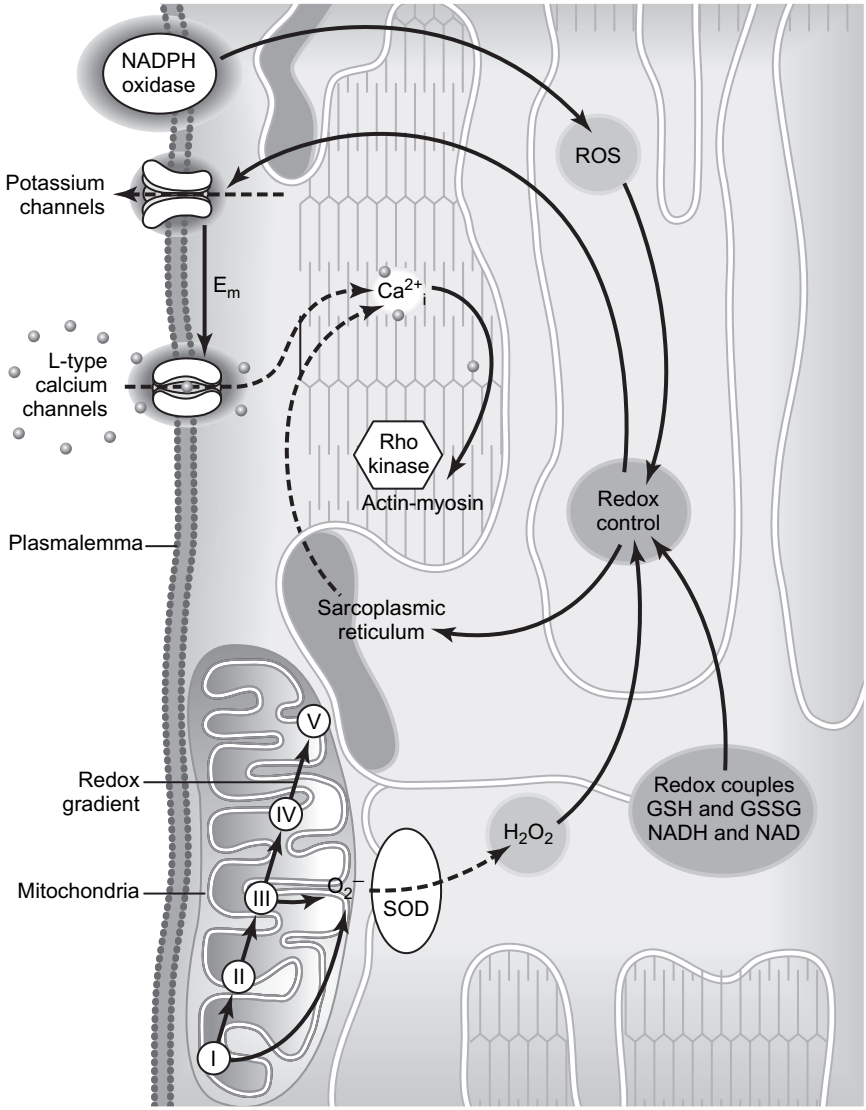

Fig. 2. Proposed redox mechanism for oxygen sensing in specialized tissues. Reactive oxygen species (ROS) from the mitochondria, NADPH oxidase, NADH oxidase, or redox couples may control potassium channel gating and membrane potential (Em) and thus calcium entry. The same redox signaling may control 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]

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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

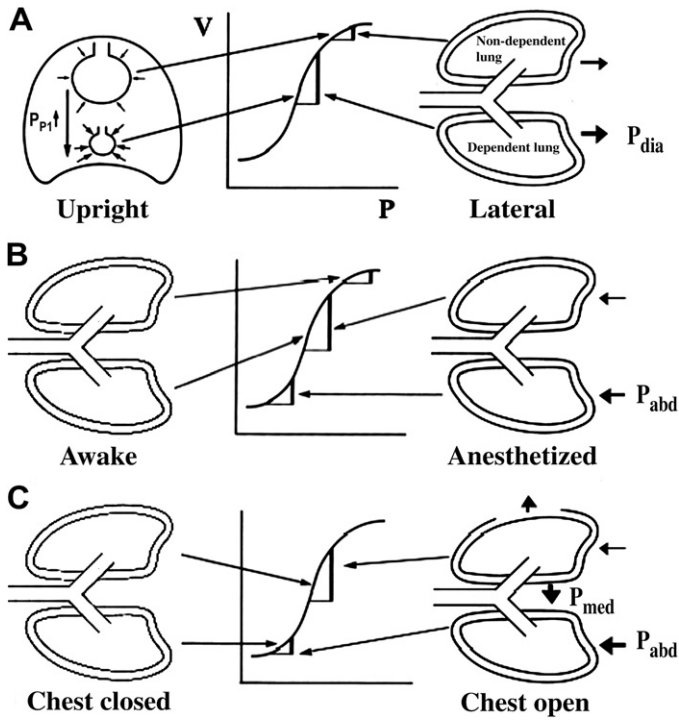

Fig. 3. Positional changes of ventilation as they relate to the pressure–volume curve. Transitions from upright to lateral (*A*), from lateral awake to anesthetized (*B*) and from lateral, anesthetized with chest closed to open (*C*) are illustrated. (*Adapted from* Benumof JL. Anesthesia for thoracic 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

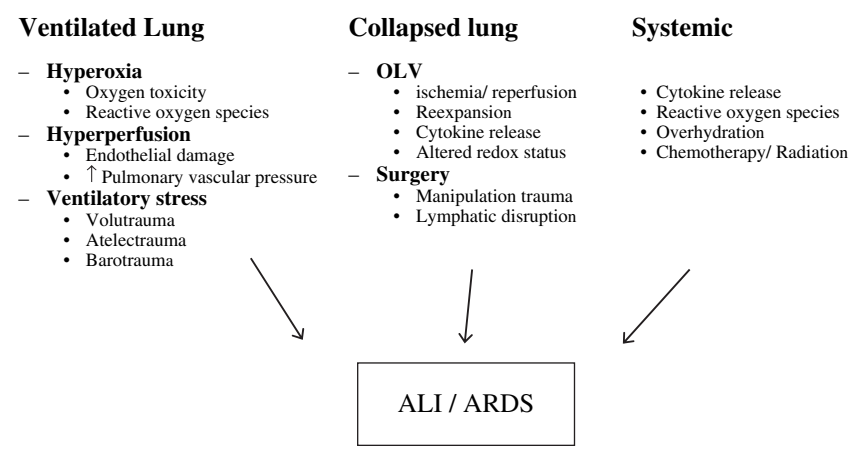

Fig. 4. Proposed mechanisms for Acute Lung Injury and Acute Respiratory Distress Syndrome after lung resection surgery.

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

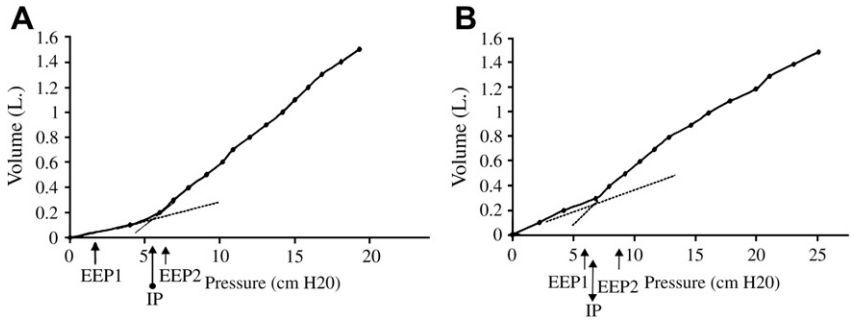

Fig. 5. Effect of applied positive end-expiratory pressure (PEEP) on total PEEP and oxygenation during one-lung ventilation (OLV). Static compliance curves of patients undergoing OLV. End-expiratory pressure before (EEP1) and after application of 5 cm H_2O PEEP (EEP2) and lower inflection points (IP) 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

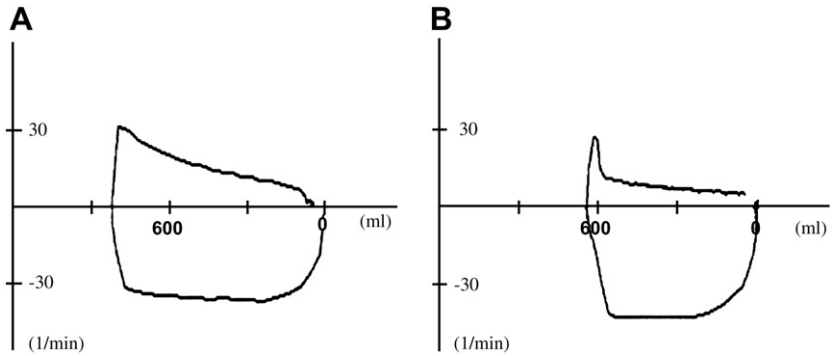

Fig. 6. Auto positive end-expiratory pressure (auto-PEEP) detection by in-line spirometry. Flow volume curves with expiration above and inspiration below the line. Expiratory flow normally returns to zero before inspiration (*A*), interrupted air flow at end-expiration indicates the presence of auto-PEEP (*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

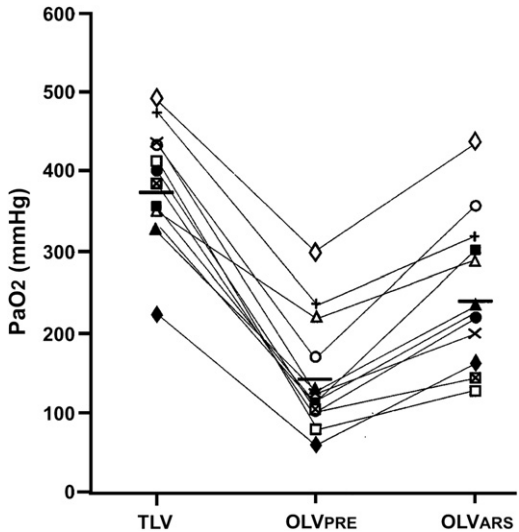

Fig. 7. Lung recruitment improves oxygenation during one-lung ventilation (OLV). P_aO_2 (mm Hg) in patients during two-lung ventilation (TLV) and during OLV, before (OLV_{PRE}) and after (OLV_{ARS}) the alveolar-recruitment strategy. Each symbol represents one patient in every point of the study. Horizontal 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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