Perioperative Lung Injury

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Key Points

- Traditional patterns of mechanical ventilation with large (e.g., 10–12 mL/kg) tidal volumes and without PEEP cause a subclinical injury in healthy lungs in proportion to the duration of ventilation.
- Perioperative acute lung injury becomes clinically important when injurious ventilation patterns are used in patients who have other concomitant lung injuries such as large pulmonary resection, cardiopulmonary bypass, or transfusion-related lung injury.
- One-lung ventilation causes a lung injury in both the ventilated and non-ventilated lungs.
- This lung injury is usually subclinical and increases with the duration of one-lung ventilation.
- Lung-protective patterns of mechanical ventilation, using more physiologic tidal volumes and appropriate PEEP, appear to reduce the severity of this lung injury.
- At present, there is no convincing evidence that the use of lung-protective strategies has improved patient outcomes in thoracic surgery.
- The majority of the recent decrease in the incidence of lung injury after pulmonary resections is primarily due to a decrease in the frequency of pneumonectomy.

Introduction

Perioperative lung injury is defined as pneumonitis or acute respiratory distress syndrome (ARDS) occurring in the immediate postoperative period during the initial hospitalization. ARDS definitions include a PaO_2/FiO_2 ratio (mild <300, moderate <200, and severe <100) and radiographic infiltrates characteristic of pulmonary edema in accordance with the European Society of Intensive Care Medicine definition [1]. Lung injury following thoracic surgery has been described by a number of terms over the past 30 years including post-pneumonectomy pulmonary edema, permeability pulmonary edema, and postoperative lung injury. While other causes of postoperative morbidity and mortality in thoracic surgery such as atelectasis, pneumonia, and bronchopleural fistula have declined dramatically in the past 30 years [2], lung injury remains a major problem and now has become the leading cause of death after pulmonary surgery [3].

Acute Lung Injury in Patients with Healthy Lungs

Traditionally, anesthesiologists have been taught to ventilate patients in the operative and postoperative periods with relatively large tidal volumes. Volumes as large as 15 mL/kg ideal body weight have been suggested to avoid intraoperative atelectasis [4]. This far exceeds the normal spontaneous tidal volumes (6 mL/kg) common to most mammals [5]. The use of nonphysiologic large tidal volumes for one-lung anesthesia evolved in the 1960–70s because it was discovered that very large tidal volumes improved PaO_2 during thoracic surgery [6]. However, the incidence of serious oxygen desaturation during one-lung ventilation has decreased from approximately 20–25% of cases in the 1970s to <5% currently [7]. This decrease is primarily due to the development of anesthetic agents that cause less inhibition of hypoxic pulmonary vasoconstriction (see Chaps. 6 and 26) and improved

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lung isolation techniques (see Chaps. 16 and 17). Thus, it is no longer necessary to use large tidal volumes during one-lung anesthesia.

Recently, it has become obvious that these nonphysiologic large tidal volumes can cause a degree of subclinical injury in healthy lungs. Gajic et al. [8] reported that 25% of patients without lung injury ventilated in an ICU setting for 2 days or longer developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The main risk factors associated with the development of lung injury were the use of large tidal volumes, restrictive lung disease, and transfusion of blood products. In a prospective study, the same group have found that tidal volumes >700 mL and peak airway pressures >30 cm H_2O were independently associated with the development of ARDS [9]. In an intraoperative study of patients having esophageal surgery, Michelet et al. [10] compared the use of tidal volumes of 9 mL/kg without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation vs. 9 mL/kg during two-lung ventilation and 5 mL/kg during one-lung ventilation with PEEP 5 cm H_2O throughout. They found significantly lower serum makers of inflammation (cytokines IL-1ß, IL-6ß, and IL-8ß) in the lower tidal volume plus PEEP group (see Fig. 10.1). This study did not find any major difference in postoperative outcome between the two groups; however, it was not powered to do this. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after one-lung ventilation (see Fig. 10.2) but not after 18 h. In a study of major abdominal surgery patients ventilated for >5 h, Choi et al. [11] compared the use of 12 mL/kg tidal volumes without PEEP vs. 6 mL/kg plus PEEP 10 cm H_2O. Bronchiolar lavages were performed before and after 5 h of mechanical ventilation. Lavage fluid from the high tidal volume group showed a pattern of leakage of plasma into the alveoli with increased levels of thrombin-antithrombin complexes (see Fig. 10.3), soluble tissue factor, and factor VIIa. This is the hallmark of alveolar lung injury. A clear pattern seems to be appearing from the clinical research that, even in patients with no lung disease, the use of nonphysiologic patterns of ventilation with large tidal volumes and without PEEP causes a degree of systemic inflammation and lung injury. The severity of this injury seems to be directly related to the duration of mechanical ventilation.

Atelectasis is a frequent postoperative complication of surgical procedures. Atelectasis occurs intraoperatively as part of essentially any general anesthetic [12]. Anesthesiologists are aware of this, and techniques to avoid it with air-oxygen mixtures, PEEP, and recruitment maneuvers are used frequently

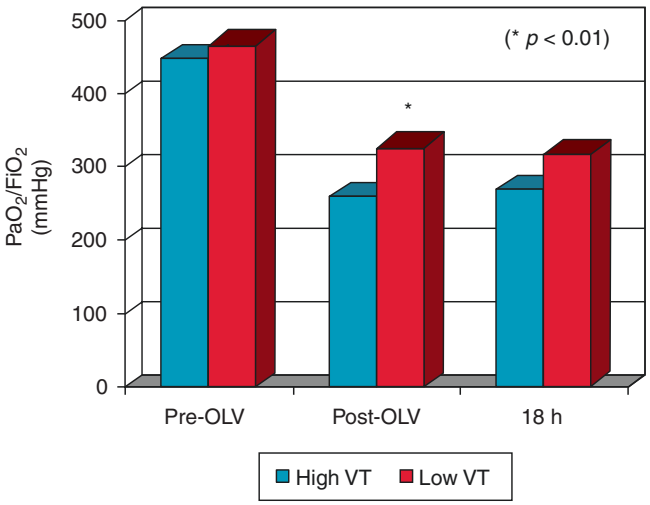

Fig. 10.2 Ratio of arterial oxygen tension to inspired oxygen concentration (PaO_2/FiO_2) in patients ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. (Based on data from Ref. [10])

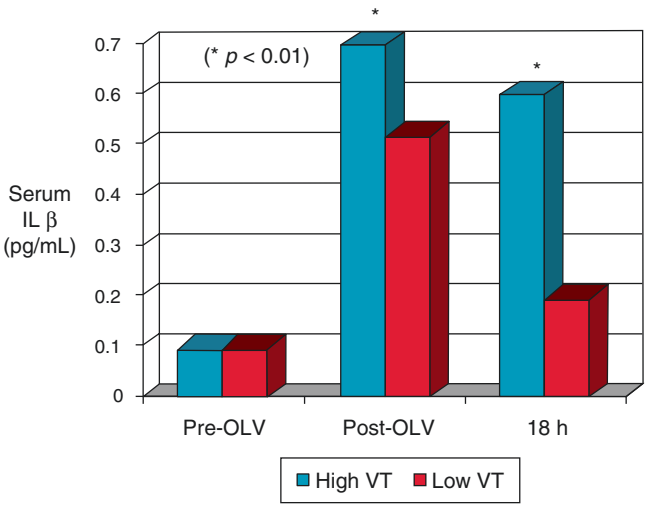

Fig. 10.1 Serum levels of inflammatory cytokine IL-1ß before and after periods of one-lung ventilation (OLV) in patients having esophagectomies. Patients' lungs were ventilated with either a large tidal volume (9 mL/kg) or a small tidal volume (5 mL/kg) plus PEEP (5 cm H_2O) during OLV. (Based on data from Ref. [10])

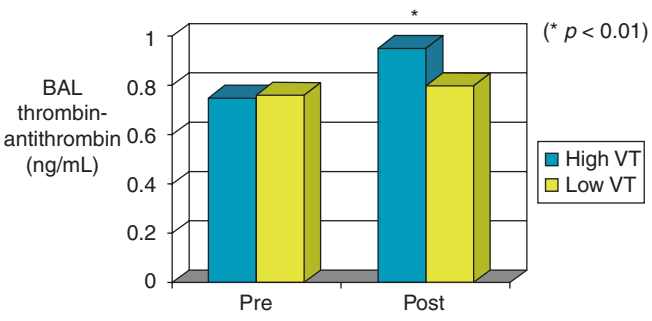

Fig. 10.3 Bronchoalveolar lavage (BAL) levels of thrombin-antithrombin complexes as a marker of lung epithelial injury in patients ventilated for >5 h during abdominal surgery with either a large tidal volume (12 mL/kg) without PEEP vs. a small tidal volume (6 mL/kg) with PEEP (10 cm H_2O). (Based on data from Ref. [11])

[13]. However, anesthesiologists are often not aware that atelectasis is a pathological state and, if it persists in the postoperative period, leads to an increased capillary permeability and an inflammatory response with subsequent lung injury. Atelectasis injures the lung while it is atelectatic due to local release of inflammatory mediators, and it injures the lung if the lung is repeatedly subjected to collapse and recruitment [14]. Atelectasis also contributes to injury in the non-atelectatic lung regions which develop a volutrauma injury due to excessive distribution of inspiration to these remaining, ventilated, lung regions [15]. Both retrospective [16] and prospective [17] studies have consistently shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia, and respiratory failure) after major abdominal and thoracic surgery. The benefits of epidural analgesia seem to be in direct proportion to the severity of the patients underlying lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia. It has also been recently demonstrated that aggressive physiotherapy with CPAP in the postoperative period in patients who develop early desaturation after major abdominal surgery leads to lower rates of major respiratory complications [18].

Pulmonary Resection

There are some situations when the anesthesiologist appreciates that a patient presenting for surgery may have a lung injury (trauma/ARDS, lung transplantation, etc.). However, there are many more cases where the lung injury is subclinical and underappreciated in the perioperative period (cardiopulmonary bypass, large pulmonary resections [19]). Acute lung injury following pulmonary resection has been described since the beginning of one-lung ventilation (OLV) for thoracic surgery. One-lung ventilation is injurious to both the ventilated and non-ventilated lung. This injury seems to be more serious in the ventilated lung (see Fig. 10.4), and this injury increases with the duration of one-lung ventilation [20].The most publicized report is a compilation of ten cases of pulmonary edema following pneumonectomy published in 1984 [21] which focused on the role of intravenous overhydration as a cause of post-pneumonectomy pulmonary edema. Subsequently there have been several reviews of this topic identifying a variety of other potentially causative factors for lung injury such as the administration of fresh frozen plasma, mediastinal lymphatic damage, inflammation, and oxygen toxicity [22]. The most thorough study to date [23] is a retrospective survey of 806 pneumonectomies which found 21 cases (2.5%) of post-pneumonectomy pulmonary edema, one of the lowest incidences reported of this complication. There were no differences in perioperative fluid balance between post-pneumonectomy pulmonary edema cases (positive fluid balance at 24 h, 10 mL/kg) and matched pneumonectomy controls (13 mL/kg). These authors used rigorous fluid restriction compared to other reports [24] (e.g., 24 h positive balance, 21 ± 9 mL/kg) suggesting that limiting intraoperative fluids might decrease but not eliminate post-pneumonectomy pulmonary edema. Subsequent reports demonstrate improved survival from post-pneumonectomy pulmonary edema due to improved postoperative management of established cases [25].

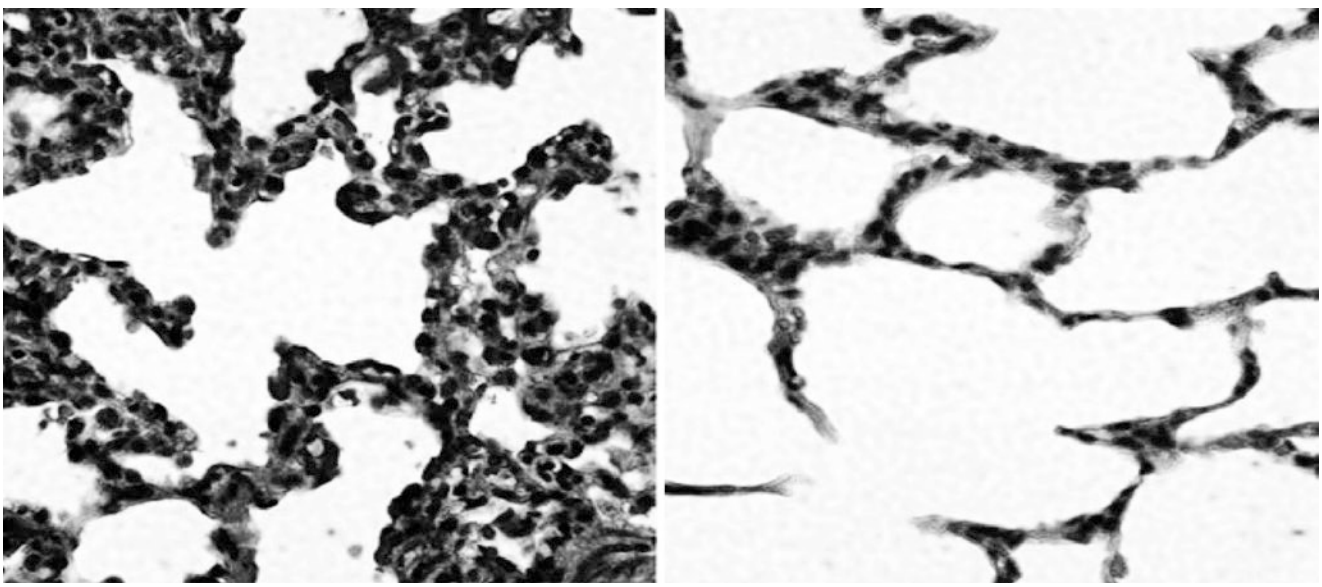

Fig. 10.4 Histologic specimens from the ventilated lung (left) and the non-ventilated lung (right) show evidence of lung injury with neutrophil infiltration in the alveolar septa after 90 min of one-lung ventilation in a pig model. The injury is more severe in the ventilated lung. (Reproduced with permission from Lohser and Slinger [20])

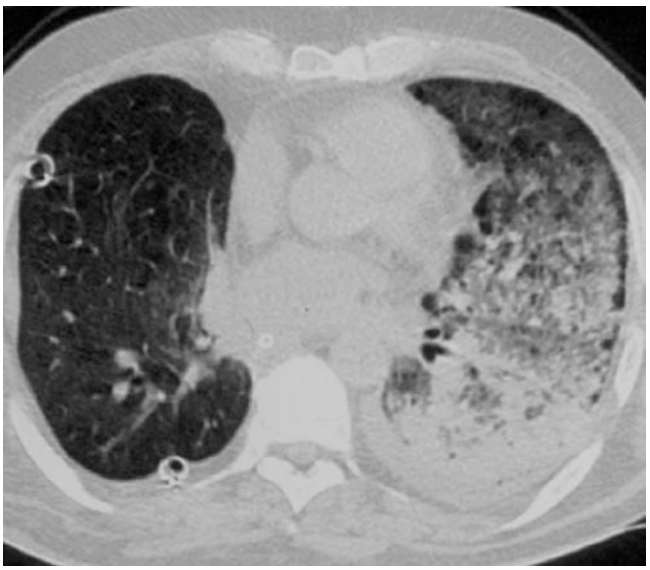

Fig. 10.5 Axial CT scan image of a patient who developed acute lung injury of the left lung (on the right in the image) after a right-sided lobectomy. The majority of lung injury after lobectomy presents in the ventilated (anesthesiologist's) lung, not the non-ventilated (surgeon's) lung

Table 10.1 Factors associated with acute lung injury following pulmonary resection

Large pulmonary resections (right pneumonectomy, extrapleural pneumonectomy)
Large tidal volumes during OLV (>9 mL/kg ideal body weight)
Excessive intravenous fluids (>20 mL/kg positive fluid balance first 24 h)
Decreased lung function (low predicted postoperative DLCO or FEV1)
Duration of OLV
Preoperative chemotherapy
Restrictive lung disease
Administration of fresh frozen plasma and other blood products
Age
Preoperative alcohol abuse

DLCO diffusing capacity of the lung for carbon monoxide; *FEV1* forced expiratory volume in 1 s

Table 10.2 Causes of post-resection lung injury

Probable	Possible
Endothelial injury	Inflammatory response
Epithelial injury (large tidal volumes)	Right ventricular dysfunction (raised CVP)
Increased pulmonary capillary pressure	Oxygen toxicity
Fluid overload	
Lung lymphatic injury	

Post-pneumonectomy lung injury [26] has been found to have a bimodal distribution of onset. Late cases (10/37, 27%) presented 3–10 days postoperatively and were secondary to obvious causes such as bronchopneumonia, aspiration, etc. "Primary" lung injury (27/37, 73% of cases) presented on postoperative days 0–3. Four factors were independently significant predictors of primary lung injury: high intraoperative ventilation pressures, excessive intravenous volume replacement, pneumonectomy, and preoperative alcohol abuse. The known facts about lung injury following lung surgery include an incidence of 2–4% following pneumonectomy, greater frequency in right vs. left pneumonectomies, symptomatic onset 1–3 days after surgery, high associated mortality (25–50%), and resistance to standard therapies. While lung injury occurs following lesser pulmonary resections such as lobectomy, it has a much lower mortality rate. Of interest, in 8/9 cases who developed unilateral lung injury following lobectomy, the injury was in the nonoperated (i.e., the ventilated) lung (see Fig. 10.5) [27].

While there is some association between postoperative lung injuries with fluid overload, the finding of low/normal pulmonary artery wedge pressures and high-protein edema fluid in affected patients suggests a role of endothelial damage (low-pressure pulmonary edema). Postoperative increases in lung capillary permeability of the nonoperated lung occur after pneumonectomy but not lobectomy [28]. This capillary-leak injury may be due to an inflammatory cascade affecting even the nonoperative lung that is triggered by lung resection and is proportional to the amount of lung tissue resected (Table 10.1) [29, 30]. Free oxygen radical generation in lung cancer patients is related to the duration of OLV [31]. Nonetheless, there is no single mechanism that can fully explain acute lung injury after lung resection, and its etiology is likely multifactorial (Table 10.2). A unifying hypothesis is that post-pneumonectomy pulmonary edema is one end of a spectrum of lung injury that occurs during all lung resections. The more extensive the resection, the more likely there is to be a postoperative injury (see Fig. 10.6). The increased dissection and trauma associated with extrapleural pneumonectomy place these patients at high risk to develop postoperative ALI [32].

Understanding that lung endothelial injury occurs after lung resection supports management strategies similar to other conditions associated with ARDS. As a general principle, it seems that the lung is least injured when a pattern of ventilation as close as possible to normal spontaneous ventilation can be followed: FiO_2 as low as acceptable, variable tidal volumes [33], beginning inspiration at FRC, and avoiding atelectasis with frequent recruitment maneuvers [34]. Studies in ARDS demonstrate that lung injury is exacerbated by the use of large tidal volumes and that lung-protective ventilation strategies with low tidal volumes and PEEP are less injurious. The most important factor in the etiology of ventilator-induced lung injury seems to be the end-inspiratory lung volume [35]. Many patients, particularly those with emphysema, develop auto-PEEP during one-lung ventilation [36], thus beginning inspiration at a lung volume above functional

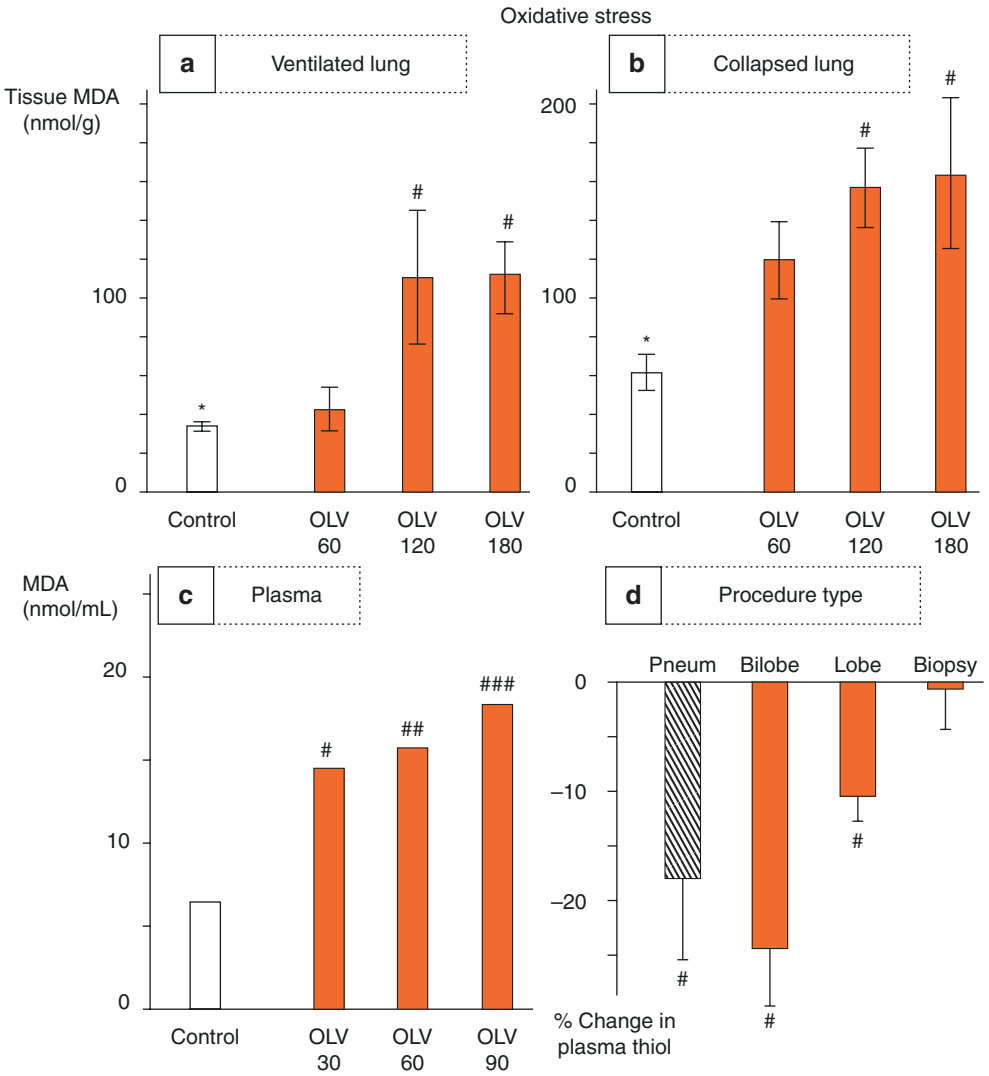

Fig. 10.6 Oxidative stress rises with increasing OLV duration and is more pronounced in the collapsed lung. Panel (**a/b**): bronchoalveolar MDA levels are higher during OLV than TLV controls at all time points (*; $p < 0.01$). The increase is time-dependent, with levels at 120 and 180 min significantly higher than after 60 min (#; $p < 0.005$). Higher levels are achieved in the collapsed lung (**b**) than the ventilated lung (**a**). Panel (**c**): plasma MDA levels increase dramatically after re-ventilation of the collapsed lung. Each increase in OLV duration of 30 min was associated with a significant increase in MDA levels over shorter OLV durations (#/##/###; $p < 0.001$). Panel (**d**): changes in plasma thiol concentration associated with OLV comparing levels from post-induction and postemergence. Major lung resections cause significant decreases in antioxidant activity from baseline values (#; $p < 0.05$), as opposed to lung biopsy or wedge resections. Bx, lung biopsy; lobe, lobectomy; 2-lobe, bilobectomy; MDA, malondialdehyde; OLV, one-lung ventilation; pneum, pneumonectomy. (Reproduced with permission from Lohser and Slinger [20])

residual capacity. It is conceivable that routine use of a large tidal volume (10–12 mL/kg) during OLV in such patients produces end-inspiratory lung volumes close to levels that contribute to lung injury.

Changes in respiratory function during OLV in the lateral position with an open nondependent hemithorax are complex. Initial studies of the application of PEEP during OLV suggested that it led to a deterioration of arterial oxygenation [37]. It is now appreciated that the effects of applied PEEP during OLV depend on the lung mechanics of the individual patient. Most patients with COPD develop auto-PEEP during OLV, and thus adding external PEEP leads to hyperinflation and increased shunt [38] (see Fig. 10.7). However, patients with normal lung parenchyma or those with restrictive lung diseases tend to fall below their FRC at end-expiration during OLV (see Fig. 10.8) and benefit from applied external PEEP [39]. Intraoperative atelectasis may contribute to injury in the dependent lung. It is now appreciated that atelectasis is a pre-inflammatory state predisposing to injury both in the atelectatic portion of the lung and in ventilated regions in the same lung which become hyperinflated [40].

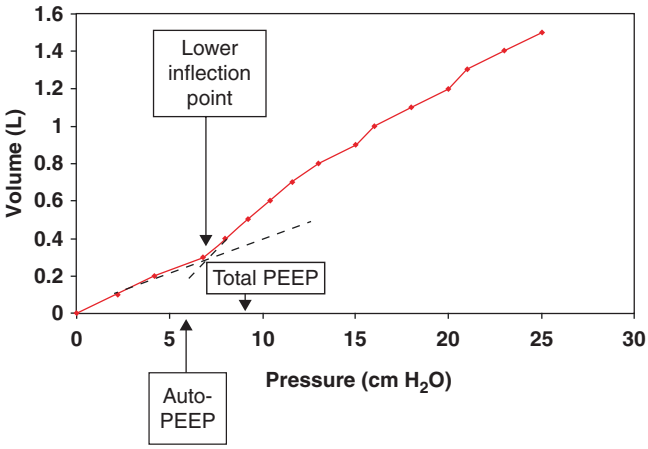

Fig. 10.7 The inspiratory compliance curve (lung volume vs. airway pressure) during one-lung ventilation as the lung is slowly inflated by 100 mL increments in a patient with COPD. The lower inflection point of the curve (thought to represent functional residual capacity (FRC)) is at 7 cm H_2O. During OLV this patient developed an intrinsic PEEP (measured by end-expiratory airway occlusion plateau pressure "auto-PEEP") of 6 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 9 cm. The addition of PEEP in this patient raised the end-expiratory lung volume above FRC, thus raising pulmonary vascular resistance in the ventilated lung and caused a deterioration in oxygenation. (Based on data from Ref. [36])

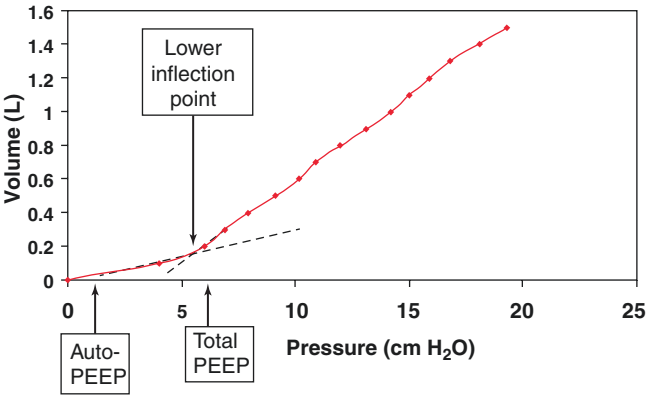

Fig. 10.8 The inspiratory compliance curve during OLV in a patient with normal pulmonary function. The lower inflection point of the curve is at 6 cm H_2O. During OLV this patient developed an intrinsic PEEP of 2 cm H_2O. The addition of 5 cm PEEP through the ventilator resulted in a total PEEP in the circuit of 7 cm. The addition of PEEP in this patient raised the end-expiratory lung volume to FRC, thus decreasing pulmonary vascular resistance in the ventilated lung and caused an improvement in oxygenation. (Based on data from Ref. [36])

There is evidence that when an element of lung injury is added to large tidal volume ventilation during OLV, this contributes to lung injury. In a rabbit model of OLV during isolated perfusion, large tidal volume (8 mL/kg) ventilation produced a picture of lung injury absent in animals randomized to a lung-protective ventilation pattern (4 mL/kg plus PEEP). Another consideration is the management of patients who have received preoperative chemotherapy with agents

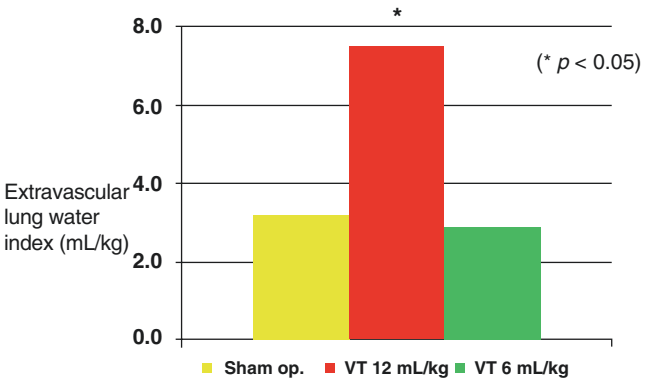

Fig. 10.9 Postmortem extravascular lung water index measured by gravimetry after 4 h of mechanical ventilation in sheep. Sham op. = control thoracotomy group, no lung resection, tidal volume two-lung ventilation 12 mL/kg. VT 12 mL/kg = pneumonectomy group ventilated with tidal volume 12 mL/kg no added PEEP. VT 6 mL/kg = pneumonectomy group ventilated with tidal volume 6 mL/kg + PEEP 5 cm H_2O. (Based on data from Ref. [44])

such as cis-platinum and gemcitabine that may affect respiratory function and may increase the risk of postoperative respiratory complications including lung injury in some patients [41]. Large pulmonary resections (pneumonectomy or bilobectomy) should be considered to be associated with some degree of lung injury. Acute lung injury, diagnosed radiographically, was reported in 42% of pneumonectomy patients who had been ventilated with peak airway pressures >40 cm H_2O [42]. A small retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intraoperative tidal volumes (8.3 vs. 6.7 mL/kg in pneumonectomy patients who did not develop respiratory failure) [43]. In a sheep model, Kuzkov et al. demonstrated that the use of large tidal volume ventilation without PEEP for 4 h following a pneumonectomy resulted in an increase of extravascular lung model more than double compared to a control (sham operation) group or a pneumonectomy group ventilated with 6 mL/kg tidal volume plus PEEP 5 cm H_2O (see Fig. 10.9) [44].

Since it is not always possible to predict which patient scheduled for a lobectomy may require a pneumonectomy for complete tumor resection, the routine use of several lung-protective strategies during OLV seems logical. Overinflation of the nonoperated lung should be avoided using lung-protective ventilation (5–6 mL/kg) adding PEEP to those patients without auto-PEEP and limiting plateau and peak inspiratory pressures to <25 cm H_2O and <35 cm H_2O, respectively. Minimizing pulmonary capillary pressures by avoiding overhydration for patients undergoing pneumonectomy is reasonable while acknowledging that not all increases in pulmonary artery pressures perioperatively are due to intravascular volume replacement. Other factors such as hypercarbia, hypoxemia, and pain can all increase pulmonary pressures and must be treated. Finally, it must be appreciated that not all

hyperinflation of the residual lung occurs in the operating room. Overexpansion of the remaining lung after a pneumonectomy may occur postoperatively either with or without a chest drain in place. The use of a balanced chest drainage system to keep the mediastinum in a neutral position and avoid hyperinflation of the residual lung following a pneumonectomy has been suggested to contribute to a marked decline in this complication in some centers [45].

Cardiopulmonary bypass causes a subclinical lung injury that can be aggravated by injurious ventilation patterns. Zupancich et al. [46] compared the use of non-protective high tidal volumes (10–12 mL/kg) plus low PEEP (2–3 cm H_2O) vs. lung-protective low tidal volumes (8 mL/kg) plus high PEEP (10 cm H_2O) in patients ventilated for 6 h following cardiopulmonary bypass for coronary artery bypass surgery. Serum and bronchiolar lavage levels of the inflammatory cytokines IL-6 and IL-8 were significantly increased at 6 h only in the non-protective ventilation group.

The Role of the Glycocalyx in Lung Injury

The glycocalyx is a dynamic, fragile, and complex layer of membrane-bound macromolecules that forms an intravascular carpet on the luminal surface of the vascular endothelium [47]. The composition and thickness of the glycocalyx change constantly, as it is continually sheared by plasma flow and replaced. Its components have a net negative charge and therefore repel negatively charged molecules and blood cells. A primary function of the endothelial glycocalyx is to regulate and influence vascular permeability [48]. Together with circulating substances, it forms a barrier that prevents circulating cells and macromolecules from entering the interstitium. In contrast to the original Starling model, which explained the regulation of fluid balance occurring across the entire endothelial cell, a revised model has been proposed whereby the hydrostatic and osmotic forces act only across the glycocalyx surface layer on the luminal aspect of the endothelium. These forces reach equilibrium very quickly, resulting in a much lower fluid flux than predicted by the traditional Starling equation.

The glycocalyx has other functions. It regulates blood cell-endothelial interaction by its negative charge and via specific adhesion molecules for leukocytes and platelets. These are normally hidden deep within the glycocalyx structure but become exposed following damage to the glycocalyx. It also protects the vascular endothelium from shear stress and oxidative damage via nitric oxide-induced vasodilation and scavenging of oxygen free radicals.

The glycocalyx may be injured by inflammatory cytokines, surgical trauma, and ischemia-reperfusion (see Fig. 10.10). Hypervolemia damages the glycocalyx, both by dilution of plasma proteins and via release of atrial natriuretic peptide, which strips the glycocalyx. Loss of the intact glycocalyx causes increased vascular permeability and fluid extravasation. Loss of plasma proteins further compounds this. Leukocyte adhesion molecules are exposed, promoting cellular adhesion,

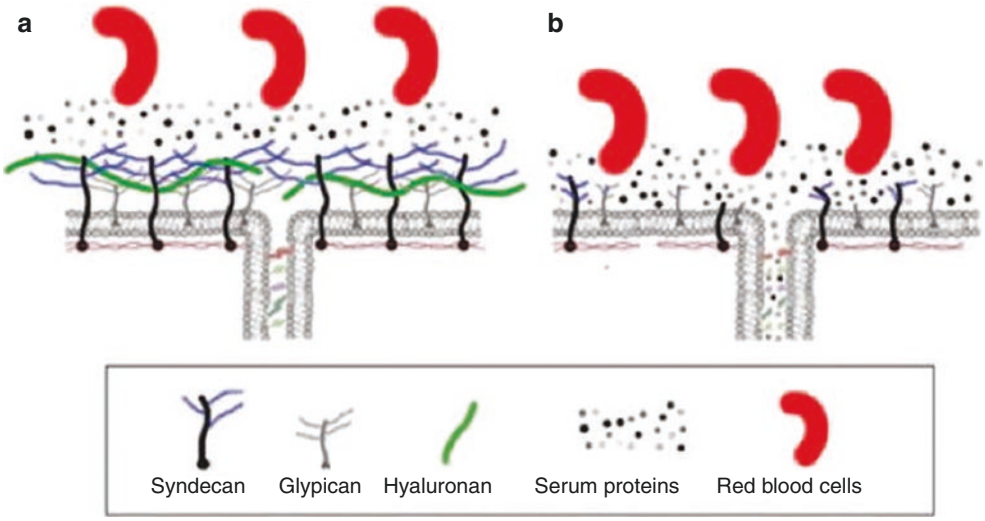

Fig. 10.10 The glycocalyx is a complex layer of proteoglycans, glycosaminoglycans, and glycolipids on the endothelial surface. (**a**) An intact glycocalyx limits water and protein flux into the cell-cell junction by forming a molecular filter over the junctional orifice. The glycocalyx also creates scaffolding on which serum proteins accumulate and form the immobile plasma layer directly adjacent to the vessel wall. Collectively the glycocalyx and the protein layer create the red blood cell exclusion zone used to determine the functional thickness of the glycocalyx. (**b**) During inflammation, proteases degrade the glycocalyx, and endothelial cells shed constituents through cell-associated sheddases. Loss of the glycocalyx scaffolding eliminates the immobile plasma layer. Breakdown of the glycocalyx is associated with increased vascular permeability due to loss of the junctional barrier and opening of the intracellular junction, as evidenced by increased water and protein flux through the junction. Note the protein-free space under the glycocalyx (left panel) that may significantly affect Starling forces across the cell-cell junction. (Reproduced form Ref. [48] with permission)

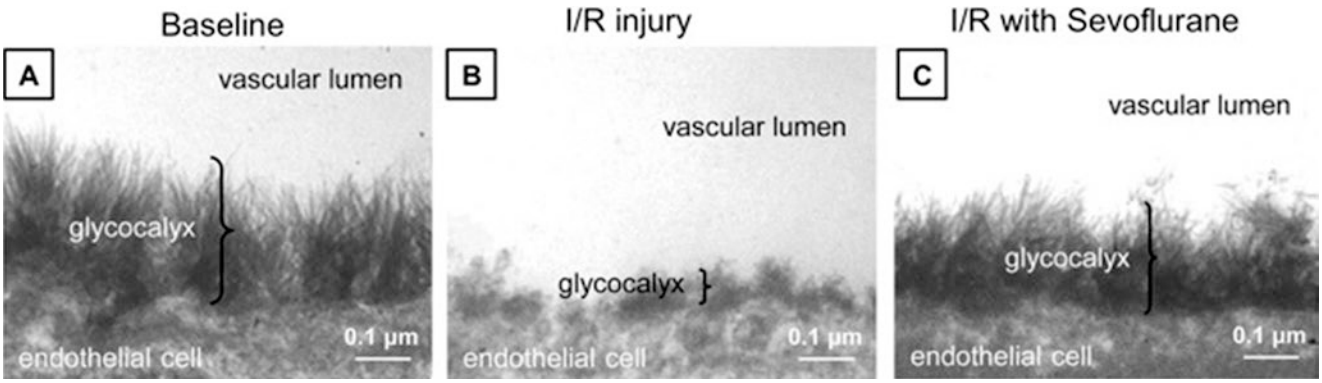

Fig. 10.11 (**a**) Electron micrograph of an intact endothelial glycocalyx from a guinea pig heart. (**b**) The glycocalyx from an animal exposed to ischemia-reperfusion (I/R) injury. (**c**) The glycocalyx from an animal exposed to I/R after pretreatment with sevoflurane. (Reproduced from Ref. [20] with permission)

migration, and further inflammation. This vicious cycle of increased permeability, extravasation, and inflammation leads to pulmonary edema, as is observed in ALI.

Several empiric strategies, based on animal experiments, have been proposed to protect the glycocalyx, including avoiding hypervolemia, albumin infusion, corticosteroids, antithrombin III, and direct inhibitors of inflammatory cytokines. Volatile anesthetic agents have been associated with less injury to the alveolar-capillary tight junction [49], less local release of inflammatory mediators, and less glycocalyx destruction (see Fig. 10.11) [20].

Transfusion-Related Acute Lung Injury (TRALI)

Over the past 30 years, acute lung injury secondary to transfusion of blood products has become recognized as a distinct clinical entity. It crosses the boundaries between patients with and without lung injury because it can cause injury to healthy lungs or it can exacerbate incipient lung injury [50]. The etiology of TRALI is primarily due to anti-white blood cell antibodies in the transfused serum. These antibodies can be either human leukocyte antigens (HLAs) or human neutrophil antigens (HNAs). HNA antibodies can bind to and trigger neutrophils and leukocytes in the recipient. HLAs are more widespread, and these antibodies can react with white blood cells and/or the pulmonary endothelium of the recipient. Neutrophils normally are flexible and are deformed as they pass through the lung, since the diameter of 50% of the pulmonary capillaries is smaller than the neutrophils. Priming of the neutrophils by sepsis, inflammation, or immune triggering (as in the case of TRALI) stiffens the neutrophils which then become sequestered in the pulmonary capillary bed. This process can be aggravated by any physical injury to the endothelium which causes the release of intercellular adhesion molecules which then cause trans-endothelial migration of the sequestered neutrophils into the interstitium of the lung parenchyma, beginning the process of injury. The process seems to be a two-hit phenomenon usually requiring both a degree of lung injury and priming of the circulating neutrophils. Although TRALI can occur unrelated to surgery, a disproportionate number of cases occur in the perioperative period [51]. Since its first identification 30 years ago, the incidence of TRALI has decreased primarily due to donor management strategies for plasma-containing products that have been adopted by blood bankers. These strategies include some or all of donor deferral based on antibody screening, donor deferral based on a history of pregnancy or transfusion, and deferral of all female donors [52]. However the major burden of prevention falls on the anesthesiologist to avoid unnecessary transfusion of blood products and to decrease the potential for perioperative mechanical lung injury.

Prevention and Therapy for Acute Lung Injury

Much of the research on lung injury due to ARDS has focused on high volume overdistention of distal lung units (volutrauma). However, there is another facet to lung injury in ARDS that involves repeated tidal opening and collapse of alveolar units at low lung volumes [53]. This repeated opening is referred to by several names such as atelectrauma and repeated alveolar collapse and expansion (RACE). Although the histological lung injury may be similar between atelectrauma and volutrauma, the inflammatory response appears to be less with atelectrauma [54]. However, the inflammatory response to atelectrauma appears to be more severe than that due to atelectasis [55]. As can be seen from Fig. 6.2, it appears that between 1/2 and 2/3 of the ventilated lung is repeatedly opening and closing every breath during one-lung ventilation. Thus, a degree of ventilator-induced lung injury to the ventilated lung seems almost unavoidable with our present techniques of anesthetic management.

Apart from mechanical ventilation strategies, a number of other therapies have been suggested to prevent or treat acute lung injury. Early reports comparing the use of volatile vs. intravenous anesthetics [56] have shown mixed results with respect to the ability of anesthetic agents to affect immune

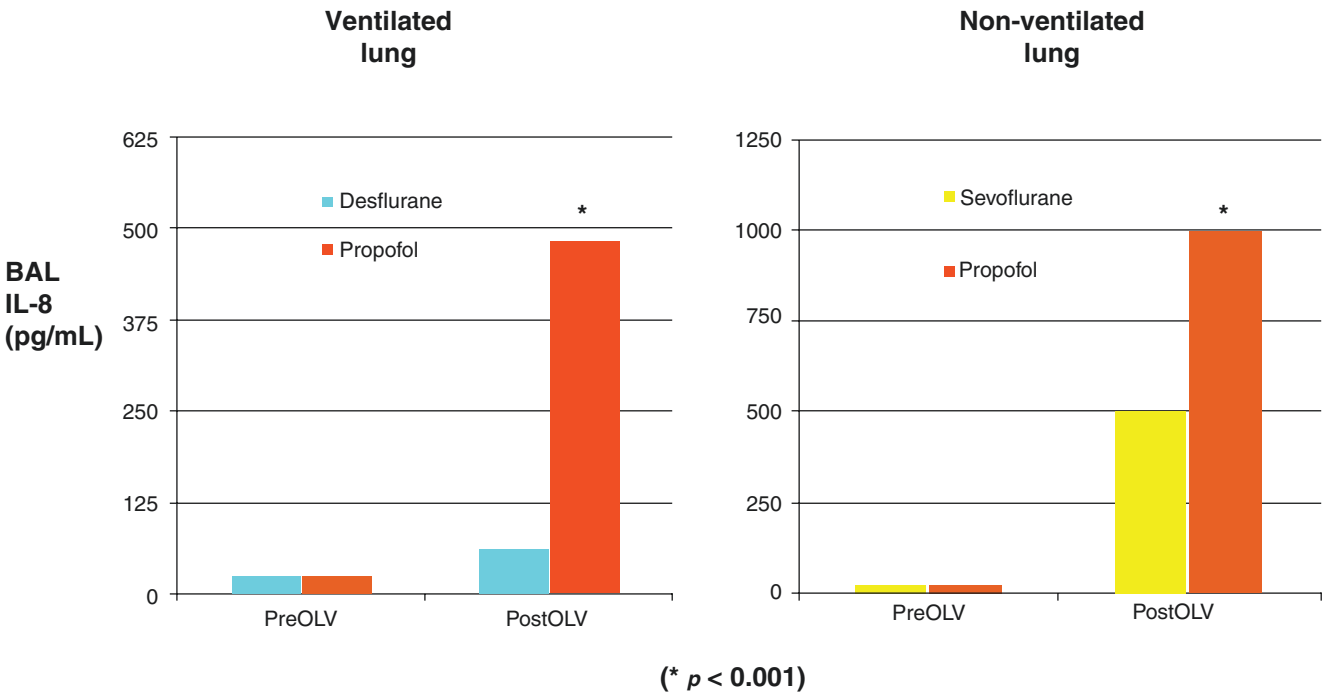

Fig. 10.12 A comparison of intravenous anesthesia (propofol) vs. volatile anesthesia on the inflammatory cytokine IL-8 obtained by bronchoalveolar lavage (BAL) from the ventilated lung (left) and the non-ventilated lung (right) before (preOLV) and after (postOLV) one-lung ventilation for thoracic surgery. The increase in inflammatory markers was significantly attenuated in both lungs by volatile anesthesia. (Based on data from Refs. [62, 63])

responses and lung endothelial injury [57]. Randomized placebo-controlled trials of several different therapies including surfactant, prone positioning, inhaled nitric oxide, and anti-inflammatories have not shown significant clinical benefits in patients with established acute lung injury [58]. ß-Agonists increase the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophosphate (cAMP) in the epithelium [59], and ß-agonists have anti-inflammatory properties. In a randomized placebo-controlled study in 40 patients with acute lung injury, Perkins et al. [60] found that the use of intravenous salbutamol decreased lung water and plateau airway pressure, although there were no significant differences in outcome. A randomized study of inhaled salmeterol has shown that it can reduce the incidence of high-altitude pulmonary edema in subjects at risk [61].

The use of volatile vs. intravenous anesthetics for one-lung ventilation has been shown to decrease the local inflammatory response of both the ventilated [62] and non-ventilated lung [63] (see Fig. 10.12). Also, volatile anesthetics have been shown to decrease ischemia-reperfusion injury in an animal model of lung transplantation (see Fig. 10.13) [64].

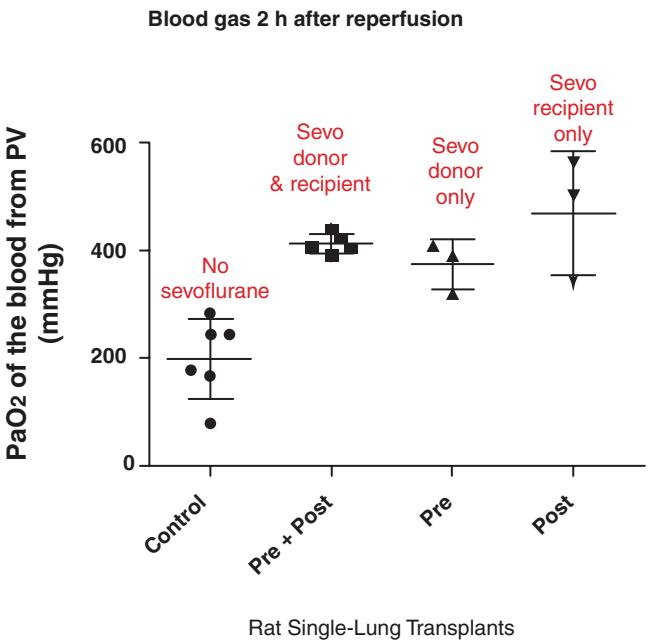

Fig. 10.13 The PaO_2 of the blood from the pulmonary vein (PV) of the donor's lung 2 h after single-lung transplantation. One MAC sevoflurane was associated with significantly improved oxygenation when administered to the donor (pre) and/or the recipient (post). (Based on data form Ref. [64])

Outcomes

There have been no convincing data that demonstrate that the lung-protective strategies outlined above actually improve patient outcomes. In a retrospective study of over 1000 thoracic surgery cases involving OLV, tidal volumes of 5–8 mL/kg ideal body weight were recorded during OLV [65]. There was an inverse relationship between OLV tidal volume and respiratory complication and postoperative morbidity (i.e., low tidal volumes tended to be associated with poorer

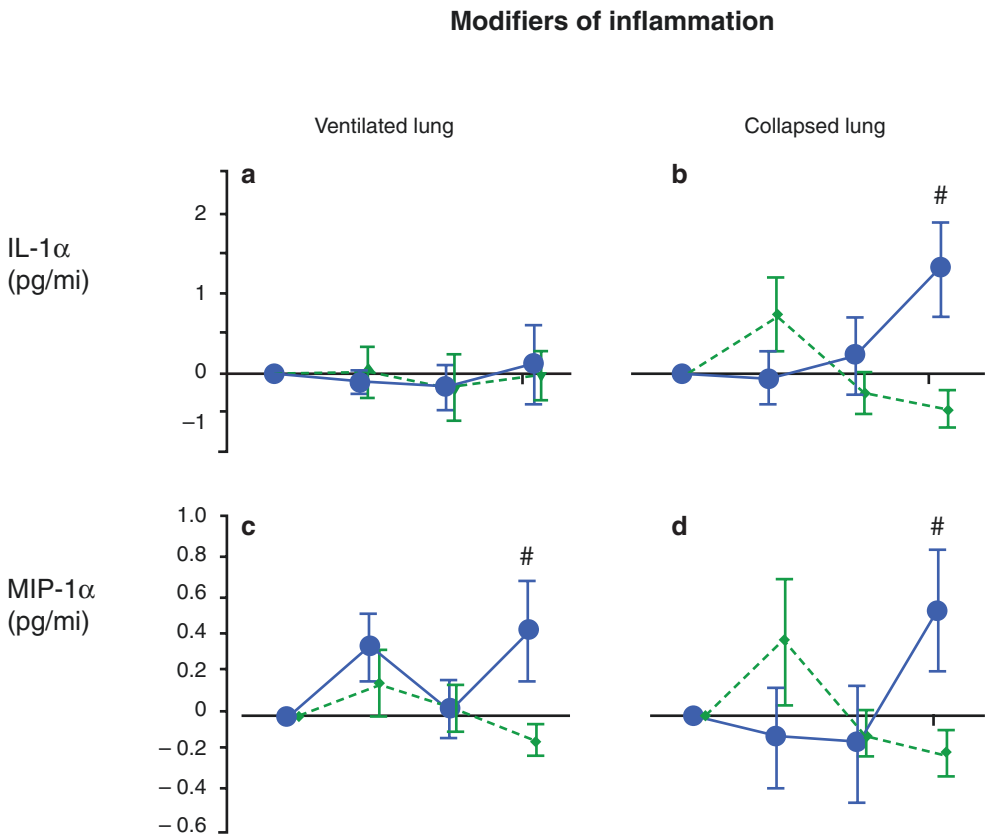

Fig. 10.14 The inflammatory cytokine response to OLV can be modulated with continuous CPAP to the non-ventilated lung. Bronchoalveolar lavage cytokine levels in the ventilated and collapsed (non-ventilated) lung during and after OLV in patients undergoing transthoracic esophagectomy. Panel (**a**): the application of CPAP (green dashed line) to the collapsed lung does not significantly decrease cytokine IL-1α levels in the ventilated lung vs. control (blue solid line) but (panel **b**) does in the collapsed lung itself (#; $p < 0.03$). Panels (**c**) and (**d**): the application of CPAP abolishes the postoperative increase in MIP-1α in both the ventilated and collapsed lungs. Time points: preoperative, 2 h after collapse, 2 h after re-insufflation, postoperative. CPAP, continuous positive airway pressure; IL-1α, interleukin 1 alpha; MIP-1α, macrophage inflammatory protein 1α; OLV, one-lung ventilation. (Based on data from Ref. [67])

outcomes). There was a positive association between ventilator driving pressure (plateau airway pressure, PEEP) and complications. The use of PEEP and recruitment maneuvers could not be analyzed from the data in this study.

A randomized controlled study [66] of >400 patients having lung surgery and OLV compared volatile anesthesia with desflurane vs. intravenous anesthesia with propofol. The incidence of major complications within 6 months of surgery (propofol 40.4%, desflurane 39.6%) was not different between the groups. At present, the reasons why logical strategies for lung protection have not been shown to improve outcome in thoracic surgery remain unclear. This may be because simple strategies to avoid lung injury, such as small tidal volumes, PEEP, and volatile anesthetics, have a small effect compared to the large proportion of the ventilated lung that is exposed to cyclic atelectrauma during OLV.

Avoiding One-Lung Ventilation

Since there seems to be some subclinical lung injury associated with the use of one-lung ventilation, it seems reasonable to limit periods of one-lung ventilation to those clinical situations where it is necessary or to avoid one-lung ventilation whenever possible. Several strategies to modify or avoid one-lung ventilation have been described.

The use of continuous positive airway pressure (CPAP) to the non-ventilated lung whenever possible will improve oxygenation and may decrease the inflammatory response to OLV in both the ventilated and non-ventilated lungs (see Fig. 10.14) [67]. Although the use of CPAP can impede surgery during VATS lung procedures, for many other intrathoracic operations such as open thoracotomies, esophagectomies, vascular surgery, and minimally invasive cardiac

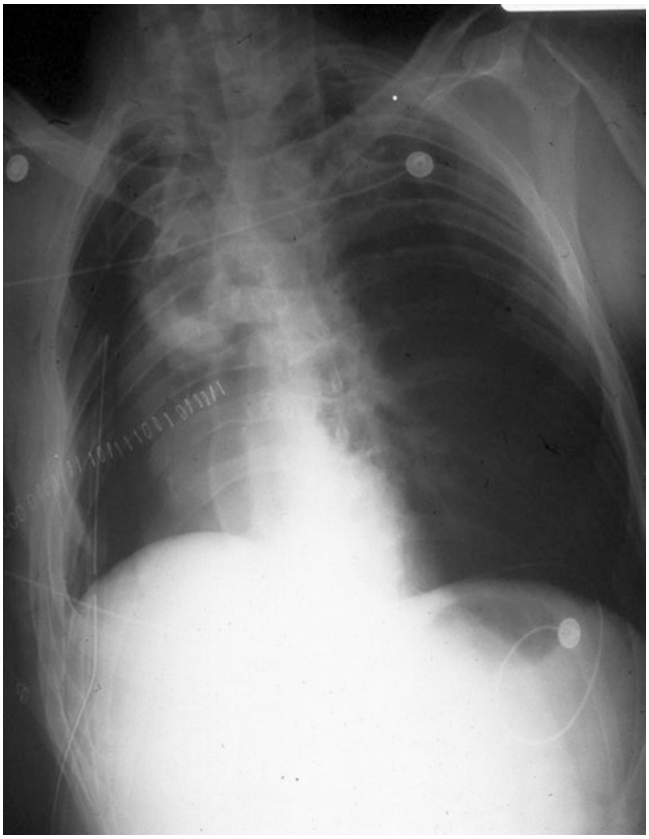

Fig. 10.15 Immediate postoperative chest X-ray of a 68-year-old male following a right pneumonectomy. This is normal post-pneumonectomy film

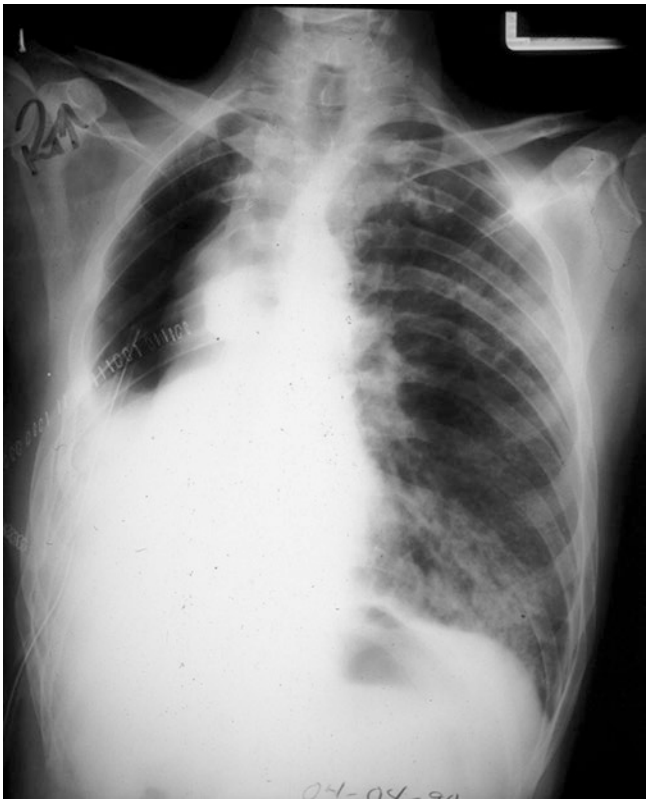

Fig. 10.16 Chest X-ray on postoperative day 3 of the same patient in Fig. 10.15. The patient has gradually become more dyspneic and has significant arterial oxygen desaturation breathing air. Chest X-ray shows signs of increased lung interstitial markings suggestive of pulmonary edema

procedures, the use of CPAP should be considered if a prolonged period of OLV is foreseen.

In some clinical situations, it may be possible to avoid OLV by maintaining spontaneous two-lung ventilation during thoracic procedures [68]. There has been an increase in the reports of case series of non-intubated VATS procedures (see Chap. 25). To date, the numbers are too small to be certain if the outcomes are improved compared to more traditional anesthetic techniques.

Clinical Case Discussion

A 68-year-old 70 kg male presents with bronchogenic carcinoma of the right middle and lower lobes. The patient is a smoker (30 pack-year) with good exercise tolerance. Preoperative FEV1 is 80% predicted and DLCO is 70% predicted. V/Q scan shows 50% ventilation and perfusion to the right lung. The patient has an uncomplicated 3 h right pneumonectomy. During the procedure, he receives 1.5 L of crystalloid and is ventilated with a tidal volume of 700 mL, FiO_2 1.0, during both two- and one-LV. Postoperatively, the patient is stable in the recovery room (see Fig. 10.15) with thoracic epidural analgesia and is discharged to the thoracic surgical floor.

On postoperative day 3, the patient complains of increasing dyspnea. The patient's oximetry saturation is 85% on air and 93% with FiO_2 0.4 mask. His pulse is sinus rhythm at 104 and blood pressure 130/80. A repeat chest X-ray is taken (see Fig. 10.16).

- What is the differential diagnosis?
- How can the diagnosis be confirmed?

The differential diagnosis should include post-thoracotomy ARDS, pulmonary embolus, congestive heart failure and/or myocardial ischemia, aspiration, and pneumonia. ARDS in this setting is a diagnosis of exclusion. A perfusion lung scan should be obtained to rule out emboli and an electrocardiogram to rule out subclinical ischemia, which is

unlikely in the absence of a prior history of coronary heart disease or diabetes. A transthoracic echocardiogram should be performed to rule out myocardial dysfunction. Major aspiration is unlikely without a history of a decreased level of consciousness. Pneumonia is a possibility, but unlikely without signs of sepsis or an elevated white blood cell count, sputum for culture and sensitivity should be obtained. If other common possibilities of postoperative respiratory failure are ruled out, the provisional diagnosis is ARDS.

- What therapy is indicated?

The patient should be transferred to an intensive care unit. All therapy is basically palliative with the aim to support respiratory function and minimize any exacerbation of the lung injury pending spontaneous resolution. Initially respiratory support should begin with noninvasive ventilation and minimizing the FiO_2 to maintain normal physiologic oxygen saturations. Attempts to reduce the pulmonary vascular pressures with inhaled nitric oxide or prostacyclin are logical although not proven and are unlikely to cause harm. The same applies to inhaled β-adrenergic agents. The benefit of corticosteroids is uncertain. If gas exchange deteriorates, then mechanical ventilation using the principles of lung protection will need to be added. In severe ARDS, unresponsive to conventional therapy, the use of extracorporeal lung support should be considered (see also Chap. 55).

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