



Acute lung injury in thoracic surgery

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Purpose of review

This review will analyze the risk factors of acute lung injury (ALI) in patients undergoing thoracic surgery. Evidence for the occurrence of lung injury following mechanical ventilation and one-lung ventilation (OLV) and the strategies to avoid it will also be discussed.

Recent findings

Post-thoracotomy ALI has become one of the leading causes of operative death. The pathogenesis of ALI implicates a multiple-hit sequence of various triggering factors (e.g. preoperative conditions, surgery-induced inflammation, ventilator-induced injury, fluid overload, and transfusion). Conventional ventilation during OLV is performed with high tidal volumes equal to those being used in two-lung ventilation, high FiO_2 , and without positive end-expiratory pressure. This practice was originally recommended to improve oxygenation and decrease shunt fraction during OLV. However, a number of recent studies using experimental models or human patients have shown low tidal volumes to be associated with a decrease in inflammatory mediators and a reduction in pulmonary postoperative complications. However, the application of such protective strategies could be harmful if not still properly used.

Summary

The goal of ventilation is to minimize lung trauma by avoiding overdistension and repetitive alveolar collapse, while providing adequate oxygenation. Protective ventilation is not simply synonymous of low tidal volume ventilation, but it also involves positive end-expiratory pressure, lower FiO_2 , recruitment maneuvers, and lower ventilatory pressures.

Keywords

acute lung injury, one-lung ventilation, protective ventilation, recruitment maneuvers, thoracic anesthesia

INTRODUCTION

Lung resections are classified as intermediate-to-major surgical procedures with in-hospital mortality rates expected to be less than 2% for lobectomy and less than 6% for pneumonectomy [1,2]. During the last decade, despite increasing patient ages and comorbid conditions, the length of hospital stay has become shorter with a reduction of procedure-related complications. Nowadays, the main causes of mortality have shifted away from cardiac and surgical complications toward pulmonary problems [pneumonia, empyema and sepsis, and acute lung injury (ALI)] [3]. This review will analyze the risk factors of ALI during lung surgery with special attention being placed on lung injury following mechanical and one-lung ventilation (OLV), and the strategies that should be used to avoid it.

ACUTE LUNG INJURY AND THORACIC SURGERY

Lung injury following lung resection has long been recognized in the form of postpneumonectomy

pulmonary edema, low-pressure edema, and permeability pulmonary edema [3,4]. Although pneumonectomy carries a particularly high risk of lung injury, lesser resection can result in similar pathologies [5]. The guidelines of the Consensus Conference on acute respiratory distress syndrome (ARDS) have been widely adopted to describe post-thoracotomy ALI [6].

A wide spectrum of lung injuries are now being encountered [7]. Some authors describe two clinical patterns of post-thoracotomy ALI, corresponding to different pathogenic triggers: primary

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KEY POINTS

- Mechanical ventilation during OLV causes lung injury by different mechanisms.
- High tidal volume and $\text{FiO}_2 = 1$ during OLV should be avoided.
- Protective ventilation with low tidal volume, low FiO_2 positive end-expiratory pressure (PEEP), and recruitment maneuvers should be considered.
- No guideline has still been defined: OLV ventilation should be tailored on patient and surgical procedure.

ALI developed within 3 days triggered by surgery and a delayed form triggered by postoperative complications, such as bronchoaspiration, pneumonia, or bronchopleural fistulas, generally observed between days 3 and 10 after surgery [3,4,8,9]. ALI following lung resection is fortunately infrequent, occurring in just 2.5% of all lung resections combined, with a peak incidence of 7.9% after pneumonectomies [5]. Unlike other complications, the incidence has not shown any decrease over the last two decades, although the mortality rate has decreased from almost 100% to less than 40% owing to improved medical management [4,8,10–14].

Over the years, multiple risk factors have been added as potential contributors related to patient preoperative conditions (severe pulmonary dysfunction, neoadjuvant chemotherapy, and chronic alcohol consumption) and are now to be considered in perioperative medical and surgical management; other risk factors include right pneumonectomy, extended lung resection, impaired lymphatic drainage, ventilatory trauma, fluid overload transfusion, aspiration, infection, oxidative stress, and ischemia–reperfusion because of OLV [8,14–16]. Rather than a single risk factor being involved, it is probable that a multiple-hit sequence of deleterious events interact that result in alveolar epithelial and capillary endothelial injuries, with associated alterations in the extracellular matrix [17].

THE EFFECT OF MECHANICAL VENTILATION

A combination of direct surgical trauma and mechanical ventilation (lung overinflation, hypoxia/hyperoxia with oxidative stress, and possibly reperfusion injury) may lead to the release of proinflammatory mediators and the activation of circulating neutrophils that alter endovascular permeability [8,9,14,18,19]. The effect of mechanical ventilation using the same tidal volume during both two-lung

ventilation (TLV) and OLV was investigated in pigs. This study revealed that only animals submitted to a period of OLV and re-expansion after lung surgery showed substantial ventilation/perfusion (V/Q) mismatch in both the dependent and nondependent lung, despite the normalization of hemodynamic and ventilatory patterns [20]. The low V/Q regions increased in the ventilated lung in particular, as did the signs of alveolar damage, suggesting that OLV has more damaging consequences than a period of complete lung collapse and surgical manipulation [20]. TLV induced diffuse alveolar damage compared to spontaneous breathing, but the period of OLV and surgical manipulation aggravated the alveolar injury and increased leukocyte recruitment in both lungs. With regard to the ‘multiple hit hypothesis’, the authors suggested that TLV-induced lung injury should be considered as a first hit. The second hit may result from OLV or surgical manipulation, and the third hit from alveolar recruitment and accompanying re-expansion/reperfusion lung injury [21].

CONVENTIONAL VERSUS PROTECTIVE VENTILATION: HIGH TIDAL VOLUME VERSUS LOW TIDAL VOLUME

Traditionally, ventilation during OLV has been performed with tidal volumes equal to those used in TLV, high FiO_2 , and zero end-expiratory pressure (ZEEP) [9]. This practice was recommended to control hypoxemia, because large tidal volumes (10–12 ml/kg) were shown to improve oxygenation and decrease shunt fraction [22]. Recently, retrospective case series have shown that high ventilating pressures and high tidal volume are significantly associated with lung injury [8,12,13]. Studies using both animal models and humans have evaluated the impact of protective lung strategies versus conventional ones during OLV. They report an increase in inflammatory proteins when high are used [23–25]. One study showed that the ventilated lung (that was never collapsed during the study period) sustained inflammatory injury that was similar or even worse than that in the lung that was collapsed for 3 h [26]. Patients undergoing esophagectomy and receiving low tidal volume have been found to present an attenuated systemic proinflammatory response and a lower extravascular lung water index compared with those receiving high tidal volume [27]. Only one prospective study has been performed that analyzed the postoperative period in 100 patients undergoing lung resection. In this case series, patients in the lower tidal volume (6 ml/kg) group were associated with better postoperative gas exchange and lower postoperative complications, with reduced atelectasis and ALI episodes than in

the high tidal volume group (10 ml/kg) [28[•]]. No differences between groups were found for hypoxemia events, whereas in the high tidal volume group more patients recorded a peak inspiratory pressure exceeding 30 cm H₂O. These studies provide strong support for the use of a protective lung ventilation (PLV) strategy in patients undergoing OLV for thoracic operative procedures. Although the causes of perioperative ALI are clearly multifactorial, hyperinflation and repetitive inflation/deflation cycles of lung units are now thought to contribute to injury, and excessive tidal volume is associated with insults in susceptible patients [29^{••}]. This leads to the primary recommendation for PLV during OLV: the tidal volume should be reduced to a maximum of 6 ml/kg of predicted body weight (and ideally less) [9,30]. It is interesting to note that the normal mammalian tidal volume is 6.3 ml/kg; it may thus be that PLV represents physiologic lung ventilation [31].

VENTILATOR-INDUCED LUNG INJURY, AIRWAY PRESSURE, AND VENTILATION MODE

Patients requiring lung surgery and OLV are heterogeneous in terms of both their underlying pathology and the surgical procedures they require [9]. In this setting, ventilation can produce a wide array of both local and systemic adverse effects, known as ventilator-induced lung injury (VILI). These pathophysiological changes occur from the direct effect of high pressure on the lung (barotrauma), damage caused by lung overdistension (volutrauma), the shear stress of repetitive opening and closing of alveoli (atelectotrauma), and the generation of cytokines and their consequential inflammatory cascades that result in biotrauma [31,32].

Applying the full TLV minute volume to a single lumen of the double-lumen tube results in a 55% increase in peak inspiratory pressure and 42% increase in plateau pressure [33]. Peak inspiratory pressure depends on tidal volume, inspiratory time, endotracheal size, and bronchospasm. It is not necessarily the distending pressure transmitted to the alveoli and the consequent elevated peak pressures that are detrimental to the lung per se. Plateau pressure, on the other hand, provides a better reflection of the distending pressure exerted on the alveoli. Transpulmonary pressure is the true cause of alveolar trauma, although it can be more difficult to measure and monitor at the bedside. Peak pressures that exceed 40 cm H₂O have been associated with the development of ALI [13]. Similarly, patients exposed to a plateau pressure of 29 cm H₂O have been found to have a significantly higher risk of

developing ALI following lung resection surgery than those receiving a plateau pressure of 14 cm H₂O [8]. In fact, no airway pressure threshold has been identified that is truly safe, but a peak pressure less than 35 cm H₂O and plateau pressures less than 25 cm H₂O are recognized as not being harmful. The implementation of protective permissive hypventilation has made it easier to adhere to these limits.

Volume control ventilation (VCV) is the predominant ventilatory mode used in the operating room. Pressure-controlled ventilation (PCV) uses a decelerating flow pattern that results in a more homogeneous distribution of the tidal volume and improves lung compliance because of the recruitment of poorly ventilated lung regions and a reduced plateau pressure [9]. The evidence pertaining to the benefits of PCV during OLV in relation to oxygenation and protection against lung injury is contradictory [34–38,39^{••}]. Moreover, tidal volumes during PCV are highly variable and may fall sharply with changes in lung compliance, as in the case of surgical lung retraction. PCV is the preferable ventilatory mode when using lower ventilatory pressures, especially when high intraoperative airway pressures are present despite correct tube positioning.

PERMISSIVE HYPERCAPNIA, ATELECTASIS, HYPERDYNAMIC INFLATION, AND POSITIVE END-EXPIRATORY PRESSURE

The goal of lung protective ventilation is to minimize lung trauma by avoiding overdistension and associated elevated pressure [32]. Protective OLV with low tidal volumes and high respiratory rate increases dead space and PaCO₂ [9,40]. Hypercapnia is well tolerated, but should be avoided in patients with elevated pulmonary pressures, major cardiac rhythm disturbances, or increased intracranial pressure [41,42]. Assuming a reasonable cardiovascular reserve with normal right ventricular function, PaCO₂ levels up to 70 mmHg are likely to be well tolerated in the short term and are clearly beneficial in terms of lung injury. Hemodynamic support with inotropic agents may be required at higher CO₂ levels or in more compromised patients.

Low tidal volume ventilation necessitates increases in respiratory rate in order to maintain minute ventilation, but this leads to an increase in alveolar cyclic recruitment and derecruitment and, in turn, the risk of VILI. The application of positive end-expiratory pressure (PEEP) keeps the alveoli open and minimizes the atelectotrauma [43]. Injury can be reduced by limiting the amplitude of cell deformation [44], suggesting that ventilator strategies that limit changes in tidal volume and

concomitant epithelial deformation stabilize the alveolus and may limit epithelial injury [45,46]. In short, reducing the amplitude of cell deformation by superimposing small cyclic deformations on a tonic deformation significantly reduces cell death [47[■]]. The effect of PEEP on oxygenation during OLV is variable [48–51,52[■]]. It is beneficial in patients in whom intrinsic PEEP is well below the lower inflection point of the compliance curve – generally patients with normal lung function. Otherwise, the application of external PEEP increases pulmonary pressure and worsens the degree of oxygenation, likely because of an increase in pulmonary shunt secondary to alveolar overdistension [43,49,50]. Neither intrinsic PEEP nor the compliance curve is easy to acquire during thoracic surgery. Application of PEEP during OLV as part of a protective ventilation regime has been shown to decrease the markers of lung injury [24,25,27]. Low levels of PEEP (5 cm H₂O) applied during thoracic surgery in healthy patients is hemodynamically well tolerated, but it does not improve oxygenation in all cases [53]. The level of PEEP needs to be adjusted according to the individual and their respiratory mechanics. In patients who have severe obstructive lung disease, the application of excessive PEEP may develop dynamic hyperinflation, and the air-trapping created needs to be considered as a potential cause of intraoperative hypotension. The ideal PEEP value should be low enough to prevent hemodynamic impairment and overdistension of the lung, but high enough to induce alveolar recruitment, keeping the lung more aerated at end expiration [54].

ATELECTASIS, ALVEOLAR RECRUITMENT MANEUVERS, RE-EXPANSION, AND FIO₂

Atelectasis has been known to occur in dependent lung areas of most patients under anesthesia. Atelectasis formation in the nonoperative lung is highly undesirable during OLV because it worsens the already high shunt fraction, increasing the potential for hypoxemia [55]. Among the risk factors that predispose lung derecruitment during OLV are high FiO₂, low tidal volume, the traditional lack of PEEP, and extrinsic compression by abdominal contents, the heart, or the mediastinum [4,52[■],56]. The efficacy of alveolar recruitment during thoracic anesthesia was investigated by Tusman *et al.* [57], who demonstrated increases in oxygenation following the application of an aggressive recruitment regimen with increasing pressure breaths over a 4-min period that achieved peak pressures of up to 40 cm H₂O and a PEEP level of 20 cm H₂O. Re-expansion of collapsed alveoli causes injury not only to the alveoli that are being recruited, but also to the

remote nonatelectatic alveoli [58,59]. Even a single recruitment maneuver of 40 cm H₂O for 40 s has been shown to elevate biomarkers of lung injury [60]. Sustained inflation may also be associated with circulatory side-effects, increasing the risk of barotrauma/volutrauma and worsened oxygenation levels [39[■],61,62]. Some pathologies, including the presence of bullae, severe cardiac disease, and airway injury, may represent contraindications to ARM in thoracic surgery [55]. New strategies have been proposed, consisting of longer duration recruitment maneuvers with slower airway pressure increases that yield improvements in lung function with less biological impact [54,63,64[■]]. Atelectasis formation in the operative lung is routine and occurs gradually over a 20-min period following ARM because of residual oxygen being absorbed [57]. Frequent derecruitment and therefore the need for repeated alveolar recruitment maneuvers (as may occur with low tidal volume ventilation with insufficient PEEP) is potentially deleterious. A randomized, computed tomography (CT) study has shown that the combination of a lung recruitment maneuver before OLV, ventilation with a tidal volume of 5 ml/kg, and PEEP of 5 cm H₂O during OLV is associated with a more homogeneous distribution of lung density and less cyclic recruitment/derecruitment in the dependent ventilated lung compared with high tidal volume ventilation [65[■]]. These findings reconfirm that a protective ventilation strategy with preceding ARM, reduced tidal volume, and sufficient PEEP ensures oxygenation during OLV and may decrease the mechanical stress in the lung by reduced cyclic alveolar collapse.

Gradual re-expansion of the operative lung at the conclusion of OLV is achieved with a continuous pressure hold of generally 30 cm H₂O or less (lower than standard recruitment regimens) to prevent disruption of the staple line. Re-expansion of the lung may be harmful because of the occurrence of traumas to the surgically manipulated parenchyma and ischemia/reperfusion injuries. The damage that follows prolonged lung collapse consists of alveolar–capillary membrane edema and increases in lymphocyte and neutrophil infiltration [66,67].

INSPIRED OXYGEN CONCENTRATION (FIO₂)

Routine management of OLV has long 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. Oxygen toxicity occurs during OLV. Collapse of the operative lung and surgical manipulation result in relative organ ischemia, which leads to

the production of radical oxygen species following reventilation-induced reperfusion. Increasing durations of OLV and the presence of tumors result in increased levels of markers of oxidative stress [14,68]. Low oxygen tensions should be used for re-expansion, particularly after prolonged OLV [68]. Because of the potential for lung injury, particularly in at-risk patients after adjuvant therapy or undergoing lung transplantation, FiO_2 should be kept as low as possible and titrated to effect.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is defined as a new ALI that develops during or within 6 h of transfusion of one or more units, not attributable to another ALI risk factor [69]. Although it is increasingly recognized as one of the leading cause of morbidity and mortality associated with transfusion, it is still underestimated because of its difficulty to be recognized and diagnosed [70].

The Canadian Consensus Conference proposed the diagnostic criteria for TRALI, primarily consisting of a clinical presentation of tachypnea, cyanosis, and dyspnea with acute hypoxemia within 6 h following blood transfusion, $\text{PaO}_2/\text{FiO}_2$ less than 300 mmHg, oxygen saturation less than 90% on room air, bilateral infiltrates consistent with pulmonary edema, evidenced by chest radiography, in the absence of cardiac failure or intravascular volume overload and absence of other risk factors for ALI [71].

The precise pathogenesis of TRALI is not fully understood, but immune-mediated (antibody) and nonimmune-mediated processes have been described. The pathogenesis of TRALI has usually been explained by the transfusion of a blood product that contains antihuman leukocyte antigen (anti-HLA) or antihuman neutrophil antigen (anti-HNA) antibodies that recognize cognate antigen in the transfusion recipient [72]. The following reactions lead to neutrophilic inflammation of the lung and disruption of the lung alveolar–capillary permeability barrier, similar to what is seen in other forms of ALI and ARDS [9,73].

Sufferers from TRALI have no antibodies: Silliman and Kelher [74] have proposed a nonimmune-mediated mechanism or ‘two-hit’ mechanism, which involves an initial insult to vascular endothelium leading to the priming of neutrophils to the endothelium. Severe infection, surgery, trauma, massive transfusion, and general anesthesia could contribute to the first insult [72]. Then, a second insult activates adherent neutrophils to release toxic mediators that damage the endothelium causing capillary leak and ALI [75,76].

Similarly to other ALI and ARDS situation, there is no specific treatment for TRALI. In most cases, TRALI is self-limited and carries a better prognosis than other causes of ALI and ARDS. However, prompt diagnosis leads to the implementation of proper supportive advanced care.

In patients who require mechanical ventilation, a low tidal volume strategy, as would be used in other cases of ALI and ARDS, should be used [9,75]. Some partially preventive measures are open to blood bankers such as the use of washed red cells and leukocyte depleted red cells. However, the major burden of prevention that falls on the anesthesiologist is to avoid unnecessary transfusion of blood products to decrease the potential for perioperative mechanical lung injury.

CONCLUSION

In conclusion, the use of high tidal volumes and high FiO_2 during OLV should not be considered a safe practice. Lung ventilation should aim to use protective ventilation to minimize lung trauma by avoiding overdistension and repetitive alveolar collapse, thereby limiting plateau pressure while providing adequate oxygenation [32]. Protective ventilation is not simply synonymous of low tidal volume ventilation, but it also includes routine PEEP, lower FiO_2 , ARM, and, in particular, the use of lower ventilatory pressures through the use of PCV and permissive hypercapnia. Derecruitment of lung tissue, impaired CO_2 elimination, and dynamic hyperinflation may potentially complicate this approach. No guidelines exist on the protective ventilatory setting during lung surgery, which should be tailored to the patient and to the surgical procedure being performed in order to manage ventilation and achieve beneficial effects while limiting detrimental consequences as much as possible.

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None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 100–101).

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