Protective Ventilatory Approaches to One-Lung Ventilation: More than Reduction of Tidal Volume

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Abstract The thoracic surgical patient is at special risk for increased postoperative pulmonary complications, such as atelectasis, impaired lung function and pneumonia, as well as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) with high mortality after lung resections. One-lung ventilation (OLV) induces proinflammatory responses especially in the ventilated lung, based on mechanical stress, persistent hyperperfusion, increased gas content and ventilation to perfusion mismatching. ALI may occur, even in previously healthy lungs. Ventilation management can cause and exacerbate but also attenuate ALI after OLV. Protective ventilatory approaches can improve the outcome by minimizing lung damage. However, ventilation with lower tidal volumes during OLV does not completely abolish alveolar inflammation. The present review addresses the effects of OLV and their role in ventilator-induced lung injury. Lung protective strategies to one-lung ventilation that additionally include reduction of cyclic alveolar recruitment, PEEP ventilation, limitation of inspired oxygen and pharmacological preconditioning by volatile anesthetics are discussed.

Keywords Thoracic anesthesia · One-lung ventilation · Ventilator-induced lung injury · Atelectrauma · Lung-protective ventilation strategies · Alveolar recruitment maneuver · Anesthetics · Cytokines

Introduction

The patient scheduled for thoracic surgery is at risk of increased perioperative respiratory morbidity and mortality [1–3]. Lung resection is associated with a mortality of about 2.5 %, which is mainly determined by pulmonary complications [4–7], but the underlying mechanisms have not been fully understood yet.

Pulmonary injury has been recognized as a complication of lung resection since Zeldin et al. [8] reported ten cases of acute lung injury following thoracic surgery and introduced the term “post-pneumonectomy pulmonary edema” (PPE) in 1984. A former study of 806 patients with pneumonectomy revealed an incidence of 2.5 % for PPE with 100 % mortality in affected patients [9]. However, PPE is not limited to pneumonectomy but may also occur after lobectomy and minor procedures with lower incidence and better outcome.

In the comprehensive form, the clinical course of PPE is indistinguishable from acute respiratory distress syndrome (ARDS) as defined by the American-European Consensus Conference on ARDS [10]. However, many patients do not meet the diagnostic criteria for ARDS but fulfill those of less severe acute lung injury (ALI). Hence, the reported incidence for PPE differs with rates of 4–7 % for pneumonectomy and 1–7 % for lobectomy with a mortality of 40–70 % [11]. In fact, ALI/ARDS is the major cause of death in the respective patient group after thoracic surgery [12].

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The following factors were identified as independent predictors of primary ALI after lung resection: The use of high intraoperative ventilation pressures, excessive volume replacement, pneumonectomy and preoperative alcohol abuse [6]. In addition, ALI characteristics include an incidence after pneumonectomy of 2–4 %, greater occurrence after right compared with left pneumonectomy, onset 1–3 days post-surgery, high mortality and resistance to standard therapies.

Pathogenesis of Lung Injury: Surgical Trauma

Surgical lung trauma is a potent trigger of postoperative alveolar damage. The mechanism of lung injury produced by surgical intervention itself is different from that induced by mechanical ventilation. The operated, nondependent lung suffers from temporary collapse, instrumentation and manipulation. The surgery-induced injury depends on the duration and invasiveness of the procedure [13–15], the lung resection type [16] and location of the thoracic surgical procedure [17]. Hypoperfusion induced by hypoxic pulmonary vasoconstriction [18], dysfunction of the surfactant system [19] and oxidative stress resulting from re-expansion [20], ischemia and reperfusion [21] may increase alveolar injury during and after thoracic surgery as observed in rabbit lungs after complete collapse and re-ventilation [22]. Impaired lymphatic drainage and fluid overload were also identified as corroborating the deleterious effect of mechanical ventilation.

In addition, translocation of proinflammatory mediators from the lung [23] induced by either surgery or injurious ventilation is considered a source of systemic inflammation that in turn possibly affects the contralateral lung.

Alveolar Inflammation After Thoracic Surgery

Acute proinflammatory responses are evident in all types of thoracic surgery [11]. They are well described in relation to ALI/ARDS [24]. The damage after lung resection probably represents the pulmonary manifestations of an inflammatory injury. The disturbance of endothelial integrity leads to changes in permeability, the loss of high amounts of protein into the alveolar space and characteristic histological changes. These histological and morphological changes are equivalent, if not identical to those of ARDS.

Accordingly, histological analysis of diffuse alveolar damage in a porcine model of thoracic surgery [25] established considerable alveolar and interstitial edema, neutrophil infiltration, alveolar overdistension, microhemorrhage and microatelectasis in the temporarily collapsed, surgically manipulated lung, but much more in the

ventilated lung [26]. The detection of a diffusely distributed alveolar damage in both lungs indicates that mechanical ventilation may be as harmful as a period of complete lung collapse and manipulation during thoracic surgery.

Ventilator-Induced Lung Injury (VILI)

Mechanical two-lung ventilation itself produces homogeneously distributed alveolar damage [26] and generates an inflammatory response in the alveoli, even in healthy lungs [27]. The resulting ventilation-induced lung injury (VILI) [28] is characterized by dysfunction of the surfactant system [29], alveolar and interstitial edema [30], leukocyte recruitment [31], cytokine production [32] and neutrophil-dependent tissue destruction [33].

Different mechanisms during mechanical ventilation may lead to cellular activation and mediator release. These are in particular mechanical forces applied to the lung tissue, which may result in alveolar cell stretch and overdistension, shearing forces secondary to repeated tidal collapse and re-opening of alveolar units [34] and increased vascular shearing stresses [35–38]. As a result, experimental and clinical studies on two-lung ventilation [39, 40] have already revealed progressive alteration of the pulmonary immune function during anesthesia and surgery.

One-Lung Ventilation (OLV)

The ventilator-induced pulmonary trauma is further amplified by exclusion of the surgically treated lung from ventilation and the delivery of the entire tidal volume to the remaining lung (one-lung ventilation, OLV). The ventilation of only a single lung may be associated with life-threatening gas exchange impairment [41, 42]. In fact, OLV may be associated with a decrease of arterial oxygen saturation below 90 % in ~10 % of patients [43, 44]. Hypoxemia during thoracic surgery is not mainly caused by a reduced alveolar surface but much more by venous admixture resulting from residual perfusion of the non-ventilated lung and from atelectasis and poorly aerated regions in the ventilated lung. Atelectasis formation has been demonstrated to be connected with decreased arterial oxygen tension of more than 50 % and increased intrapulmonary shunt of >11 % during OLV [45]. Therefore, a traditional approach to mechanical ventilation during OLV [46, 47] included the application of relatively high tidal volumes in the range of 10–12 ml/kg with zero PEEP in the dependent ventilated lung to maintain hypoxic pulmonary vasoconstriction and thus to overcome hypoxemia during OLV.

Relatively too high tidal volumes (V_T) and subsequently increased airway pressures are considered to be injurious during OLV [6, 48] in terms of increased mechanical stress, characterized by increased cyclic recruitment/de-recruitment during OLV [49, 50••]. As a result, OLV may aggravate the alveolar damage followed by a permeability-type pulmonary edema with diffuse alveolar injury [51], leukocyte sequestration [31] and alveolar cytokine release [52]. OLV thus contributes to postoperative pulmonary morbidity through induction of a truly asymmetric lung injury following thoracic surgery [53]. Lung computed tomography (CT) scans indicated an enhanced lung density in comparison with preoperative images in thoracic surgical patients who developed ALI/ARDS after lung resection [53]. Importantly, consolidated lung tissue was detected almost exclusively in the non-operated, ventilated lung. As a consequence, OLV is considered to be a major pathogenic factor in the development of clinically relevant pulmonary complications after thoracic surgery [2].

However, as understanding of the underlying mechanisms of ventilation-induced lung injury increases, anesthetic care for patients undergoing OLV has been questioned as well. Protective ventilation approaches during OLV including smaller tidal volumes [54, 55] with lower inspiratory pressures (volume- and pressure-limited ventilation) seem to be also favorable in patients undergoing thoracotomy [56]. Furthermore, experimental data from an isolated rabbit lung model suggest that protective one-lung ventilation with tidal volumes and PEEP set to avoid lung collapse and overdistension is able to minimize ventilation-induced lung injury [57].

In contrast, a time-dependent increase of proinflammatory parameters was established in thoracic surgical patients undergoing OLV with high and low V_T . The concentrations of inflammatory mediators in tracheal aspirates were not different between the two ventilator settings, and neither time course nor concentrations of pulmonary or systemic mediators differed between the patient groups [52].

Mechanisms of Lung Injury

Several OLV-related factors for postoperative respiratory failure have been recognized including ventilation to perfusion mismatch, increased transpulmonary pressures (i.e., pulmonary capillary pressures), cyclic collapse and recruitment of lung tissue [57] and tidal volumes as used during normal ventilation with subsequently increased airway pressures [58, 59].

Airway pressures above 30 cmH₂O and tidal volumes of 8–12 ml/kg during OLV [60] may promote alveolar overdistension. However, a protective ventilation approach to

prevent lung injury during OLV by reducing tidal volumes and application of PEEP did not completely inhibit thromboxane B₂ formation in isolated rabbit lungs [57] or enhance the alveolar proinflammatory response in rats [61]. Likewise, OLV with tidal volumes of 5 ml/kg only partially decreased expression of proinflammatory interleukin-8, tumor necrosis factor α and neutrophil infiltration in patients undergoing thoracic surgery and OLV [62]. As a consequence, high tidal volume ventilation may not be the only variable that affects alveolar integrity during and after OLV.

Collapsed lung tissue or atelectasis is the major source of deterioration of arterial oxygenation during OLV [41]. In addition, mechanical lung injury by cyclic collapse and re-opening of alveoli cannot solely attribute to the use of high tidal volumes. Low tidal volume ventilation may harm small peripheral airways by cyclic opening and closing, which results in changes in lung mechanics [63]. Supplementary mechanisms contributing to the deleterious effects of OLV contain changes in pulmonary blood flow characteristics and persistent atelectasis formation with increased shunt perfusion.

The increase of pulmonary capillary pressure during OLV [62] may also harm the pulmonary blood-gas barrier and cause fluid extravasations into the interstitial space and the alveoli, resulting in a pulmonary edema.

In summary, perioperative ALI is of multifactor origin. Mechanical stress by hyperinflation, hyperperfusion and cyclic recruitment/de-recruitment in combination with proinflammatory or biochemical factors is thought to contribute to ALI. One can postulate a ‘multiple-hit’ theory including surgery-related factors, one-lung ventilation, underlying diseases and co-morbidity, prior therapy and other unidentified events for thoracic surgery patients that may increase susceptibility to ALI [64].

Pulmonary Perfusion and Lung Density Distribution During OLV

The pulmonary vasculature is the dominant factor in determining perfusion distribution, although gravity influences ventilation to perfusion (V/Q) matching [65, 66]. Single-photon emission computed tomography (SPECT) data before OLV revealed an almost even distribution of perfusion over both lungs in pigs [25]. Ventilation was primarily distributed to the nondependent lung, similar to preferential ventilation of upper lung regions and perfusion of dependent regions in anesthetized humans in supine position [67]. Perfusion distribution was only slightly affected by gravitation [68]; additionally, even PEEP or the lateral decubitus position had no influence on pulmonary blood flow [69, 70]. After OLV, vasoconstriction in the

Fig. 1 Effects of one-lung ventilation on distribution of ventilation and perfusion in the lungs. Data from single-photon emission computed tomography. Perfusion is presented by $^{99\text{mTc}}$ activity and ventilation by $^{81\text{mKr}}$ activity. Whereas ventilation is

equally distributed before and after OLV, postoperative perfusion is preferentially distributed to the previously ventilated lung and results in significant hyperperfusion. Please note the shift of perfusion maxima to the dependent lung

upper lung induced by microatelectasis and hypoxic exposure [18] resulted in a continuous decrease of blood flow.

In addition, mechanical stress alters alveolar type II cell mediator release toward a proinflammatory pattern [71]. Since most immune mediators act as vasodilators, cytokine-induced vasodilatation may result in a shift of perfusion to the dependent lung during OLV. This is underlined by the proinflammatory response preferably in the ventilated lung [62, 72] in humans and by increased neutrophil infiltration in the dependent lung in pigs [73••].

As obtained from computed tomography lung scans in pigs, OLV reduces consolidated lung compartments and increases the gas content and dependent lung volume [49, 50]. Atelectatic lung regions are changed into poorly aerated and poorly aerated into normally aerated lung tissue resulting in a shift of the spectrum towards lower density and in significant tidal recruitment within the different density compartments during OLV [74]. In addition, overstretching implies a mechanical force applied to the lung tissue that may occur at the boundaries of atelectatic, poorly and normally aerated tissue [75].

After collapse, density distribution of the nondependent lungs returned to that before OLV despite complete lung collapse and repetitive vital capacity maneuvers. In contrast, previously ventilated lungs retained an increased lung volume with higher gas content. The fraction of normally aerated lung regions increased according to redistribution of ventilation toward dependent areas. Possible causes include decreased alveolar recoil forces or air trapping (Fig. 1).

OLV-induced lung tissue damage can thus be attributed to hyperperfusion and hyperinflation of the ventilated lung. The increased pulmonary capillary pressures during OLV may cause stress failure of the pulmonary blood-gas barrier with extravasations of fluid into the interstitial space (interstitial edema) and the alveoli (alveolar edema) as well as rupture of small blood vessels (microhemorrhage). This effect is amplified by hyperinflation of the ventilated lung during OLV. Increased airway pressures by relatively high tidal volumes produced overdistension of alveoli and stretching of lung capillaries. In fact, barotrauma of the lung has been associated with ultrastructural changes in the alveolo-capillary membrane, loss of plasma and red blood cells into interstitial and alveolar space [76] (Fig. 2).

Fig. 2 Histopathological consequences of OLV. Representative lung histology (hematoxylin–eosin staining, $\times 10$ and $\times 40$) of the dependent ventilated porcine lung after one-lung ventilation. Please note the characteristic changes: dystelectasis, atelectasis, alveolar overdistension, interstitial edema, microhemorrhage and neutrophil infiltration

Cyclic Alveolar Recruitment

Lung consolidation preferentially in dependent regions is observed rapidly after induction of anesthesia and muscle paralysis in animals and humans [77–79]. Several factors may influence the lung density distribution along the vertical axis. These include regional differences of pleural and transpulmonary pressures with cephalocaudal and vertical gradients, the shape and weight of lung tissue as well as gravity-dependent changes in pulmonary blood volume and compression of the lungs from adjacent anatomical structures [intraabdominal organs [80], exertion and weight of the heart [81].

Influenced by the shape and weight of the lung tissue, the tidal volume is preferentially distributed to nondependent regions [82]. Lateral body position additionally decreases the functional residual capacity in dependent regions and shifts the ventilation maxima to nondependent areas [83].

The volume of atelectasis and poorly aerated lung tissue is already increased before OLV. This can be attributed to bronchoscopic manipulation of the airways open to the atmosphere while inserting and inflating double-lumen tubes and bronchus blockers. However, this procedure is obligatory to obtain sufficient airway separation.

Cyclic recruitment of alveolar units results in shear stress with extensively elevated transmural pressures to the

lung parenchyma [84]. Shearing and stretching may have profound consequences on lung function and mediator release, and they have been detected as key factors in initiating an inflammatory response [85–87].

Lung Protection During Thoracic Anesthesia

The management of patients undergoing thoracic surgery may offer opportunities for anesthetic intervention. Besides the well-recognized advantages of a restrictive fluid management [88•] and sufficient pain therapy in thoracic surgery [89], protective ventilation approaches including pressure-controlled ventilation [90] with low tidal volumes [91, 92, 93•], restriction of inspired oxygen concentrations [94], limitation of inspiratory pressure [6], use of repetitive alveolar recruitment maneuvers [95, 96••] and PEEP [97] as well as inhalation of volatile anesthetics and alternative ventilation approaches are progressively employed. Biologically variable ventilation [98] or even spontaneous breathing [99] may offer new aspects to reduce mechanical stress to lung tissue during OLV [100••].

There is a growing body of evidence that only low tidal volume ventilation of the dependent lung decreases the risk of postpneumonectomy respiratory failure [91, 92]. Consequently, the reduction of tidal volume is an effective

method to improve outcome, but is not sufficient to completely abolish a proinflammatory response to OLV [52, 62].

Injurious OLV has been demonstrated to increase the recruitment of granulocytes and the expression of proinflammatory mediators in the alveoli of the ventilated lung [62]. The immune response is attenuated by volatile anesthetics (desflurane, sevoflurane) as indicated by decreased alveolar expression of proinflammatory cytokines [72, 101••]. TIVA with propofol results in higher alveolar cytokine concentrations and in increased alveolar granulocyte recruitment. Recent data demonstrate that volatiles also decreased expression of systemic proinflammatory cytokines [73••, 101••] as well as mediators from the non-ventilated lung [102]. The immunodepressant effect in the lung seems to be representative for this class of halogenated drugs. Pharmacological preconditioning by inhalation of volatile anesthetics may thus prevent the organism from mounting a systemic proinflammatory response and can improve the clinical outcome [102]; however, clinical outcome studies are needed [103•].

Alveolar Recruitment Maneuver and PEEP

Alveolar recruitment maneuvers (ARM) are sufficient to improve arterial oxygenation by the transformation of consolidated lung regions into normally aerated compartments and by the improvement of ventilation and perfusion matching in both lungs during conventional TLV [104] or within the ventilated lung during OLV [95, 96••, 105]. Consolidated dependent and basal regions of the ventilated lung as a result of induction of anesthesia and bronchoscopic airway manipulations could be significantly reduced by application of constant airway pressure of 40 cmH₂O to the whole lung for 10 s and PEEP of >5 cmH₂O. The restoration of physiological gas/tissue relationships decreases consolidated lung compartments and thereby improves initial conditions for subsequent OLV [49, 50].

However, ARM combined with PEEP may be valuable not only to treat hypoxemia during OLV, but more importantly, as part of a protective ventilation strategy, it may also decrease cyclic alveolar collapse and facilitate reopening of alveolar units. It could be demonstrated that based on the redistribution of gas and tissue after ARM and sufficient PEEP, reduction of tidal volume ($V_T = 5$ ml/kg) during OLV was sufficient to minimize tidal recruitment by preservation of density distributions in the dependent lung and may thus exert protective effects on lung tissue [50]. Moreover, OLV with lower V_T is not associated with increased atelectasis formation [106].

Mild to moderate PEEP levels are sufficient to keep recruited alveoli open in healthy subjects without

deterioration of hemodynamics or hypoxic pulmonary vasoconstriction [107, 108]. An external PEEP of 5 cmH₂O did not increase the total PEEP in patients during OLV [109]. In pigs, PEEP levels of 5–10 cmH₂O are associated with improved oxygenation and continuous lung volume recruitment. Appropriate PEEP however is found only after a recruitment maneuver. A maximum amount of effectively expanded alveoli is yielded by the highest compliance with the lowest dead space fraction [110].

The reduction of FiO_2 to 0.4 will protect the lungs from re-collapse for a prolonged period [111]. Furthermore, evidence exists that the lowest possible F_iO_2 should be delivered to the thoracic patient to prevent oxidative damage and postoperative ALI [112]. High oxygen concentrations are associated with a considerable rise in systemic markers of oxidative stress that correlates with postoperative outcome [113].

Conclusions

One-lung ventilation for thoracic surgery results in significant alveolar damage [26] even in previously healthy lungs [27]. However, this injury may be resolved in normal lungs within hours after mechanical ventilation [31].

One-lung ventilation results in persistent hyperperfusion in the dependent lungs and ventilation/perfusion mismatch. The increased pulmonary blood flow may aggravate stresses to the alveolo-capillary unit and may thus contribute to pulmonary complications after thoracic surgery [25]. During OLV, mechanical stress is additionally increased by enhanced cyclic tidal recruitment of alveoli, indicated by lower compliance and increased airway pressures. This atelectrauma is associated with persistently decreased dependent lung density and increased lung volume after OLV [49]. It is considered to be the main mechanism in the pathogenesis of ventilated lung injury [61]. Alveolar recruitment maneuvers and PEEP reduce consolidated lung compartments during mechanical ventilation. After ARM, OLV with reduced tidal volume does not aggravate cyclic closure and re-opening of alveoli in the ventilated lung. This may have protective effects from mechanical stress on lung tissue and may thus reduce lung injury after OLV. In patients who developed ALI/ARDS after pulmonary resection, the coincidence of OLV-induced lung injury, postoperatively persistent ventilation/perfusion mismatch and hyperperfusion in the ventilated lung after OLV may have contributed to pathogenesis.

Modern thoracic surgery includes an increasing number of video-assisted thoracoscopic procedures with limited lung manipulation that may lead to lesser-pronounced lung damage [15]. In addition, lung protective ventilation

strategies are needed to reduce potentially harmful OLV-induced pulmonary injury. It remains to be studied whether protective ventilation modes, the repetitive application of ARM with different PEEP levels, pharmacological preconditioning with inhalational anesthetics or even techniques using spontaneous breathing may result in less severe lung injury and improve outcome.

Compliance with Ethics Guidelines

Conflict of Interest Alf Kozian and Thomas Schilling declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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