CME

Lung Injury After One-Lung Ventilation: A Review of the Pathophysiologic Mechanisms Affecting the Ventilated and the Collapsed Lung

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Lung injury is the leading cause of death after thoracic surgery. Initially recognized after pneumonectomy, it has since been described after any period of 1-lung ventilation (OLV), even in the absence of lung resection. Overhydration and high tidal volumes were thought to be responsible at various points; however, it is now recognized that the pathophysiology is more complex and multifactorial. All causative mechanisms known to trigger ventilator-induced lung injury have been described in the OLV setting. The ventilated lung is exposed to high strain secondary to large, nonphysiologic tidal volumes and loss of the normal functional residual capacity. In addition, the ventilated lung experiences oxidative stress, as well as capillary shear stress because of hyperperfusion. Surgical manipulation and/or resection of the collapsed lung may induce lung injury. Re-expansion of the collapsed lung at the conclusion of OLV invariably induces duration-dependent, ischemia-reperfusion injury. Inflammatory cytokines are released in response to localized injury and may promote local and contralateral lung injury. Protective ventilation and volatile anesthesia lessen the degree of injury; however, increases in biochemical and histologic markers of lung injury appear unavoidable. The endothelial glycocalyx may represent a common pathway for lung injury creation during OLV, because it is damaged by most of the recognized lung injurious mechanisms. Experimental therapies to stabilize the endothelial glycocalyx may afford the ability to reduce lung injury in the future. In the interim, protective ventilation with tidal volumes of 4 to 5 mL/kg predicted body weight, positive end-expiratory pressure of 5 to 10 cm H_2O, and routine lung recruitment should be used during OLV in an attempt to minimize harmful lung stress and strain. Additional strategies to reduce lung injury include routine volatile anesthesia and efforts to minimize OLV duration and hyperoxia. (Anesth Analg 2015;121:302–18)

The pathophysiologic mechanisms that underlie the creation of acute lung injury (ALI) after 1-lung ventilation (OLV) are different for the ventilated and collapsed lung. In this review, we will describe the mechanisms known to be involved in the creation of lung injury in the operating theater and critical care units and then relate them to the setting of OLV, examining each lung in isolation. Strategies to reduce lung injury and the relevant supportive evidence are discussed at the conclusion of the review.

OLV has enabled increasingly complex intrathoracic surgery and is a de facto necessity with the increased use of minimally invasive techniques. However, OLV is associated with postoperative pulmonary complications in 20% of lung resections.[1] Historically feared for its high rate of hypoxemia, OLV is now recognized to be a risk factor for ALI.[2] Postthoracotomy ALI occurs in 4% to 15% of patients, with an escalating incidence from minor (wedge) resections, to major lung resections (lobectomy, pneumonectomy).[1] ALI and acute respiratory distress syndrome (ARDS) are the leading cause of death after thoracic surgery[3–5] and significantly reduce 1-year survival (56% vs 92%).[4] The most recent ARDS consensus criteria have replaced the formal diagnosis of ALI with the term "mild ARDS" to emphasize the fact that it represents the same disease spectrum.[6] In addition, the oxygenation criteria now demand the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥5 cm H_2O, whether invasively or noninvasively.[6] These changes will bring about a lesser incidence of the disease, albeit with a greater acuity, illustrated by a recent study of ARDS after lung resections using the aforementioned criteria, which demonstrated an incidence of 2% with a mortality of 54%.[7] For the purpose of this review, we will continue to use the term ALI but focus on histopathologic and biochemical end points of the diagnosis.

Ventilator-induced lung injury is a major contributor in the creation of ARDS, and its basic pathophysiologic mechanisms need to be appreciated to understand their relative contribution during OLV-induced lung injury (Fig. 1). Regional lung overdistension, the end-inspiratory lung volume, and tidal recruitment are the main recognized factors in the 2-lung ventilation setting.[8] Physical forces are exerted onto the alveolus both at high and at low lung volumes, which often coexist in different regions of the lung, and may result in alveolar damage and subsequent inflammatory response (Fig. 1).[8] The alveolar-capillary membrane and, in particular, the endothelial glycocalyx, a complex layer of membrane-bound proteins on the luminal surface of the vascular endothelium, appears to play a central role

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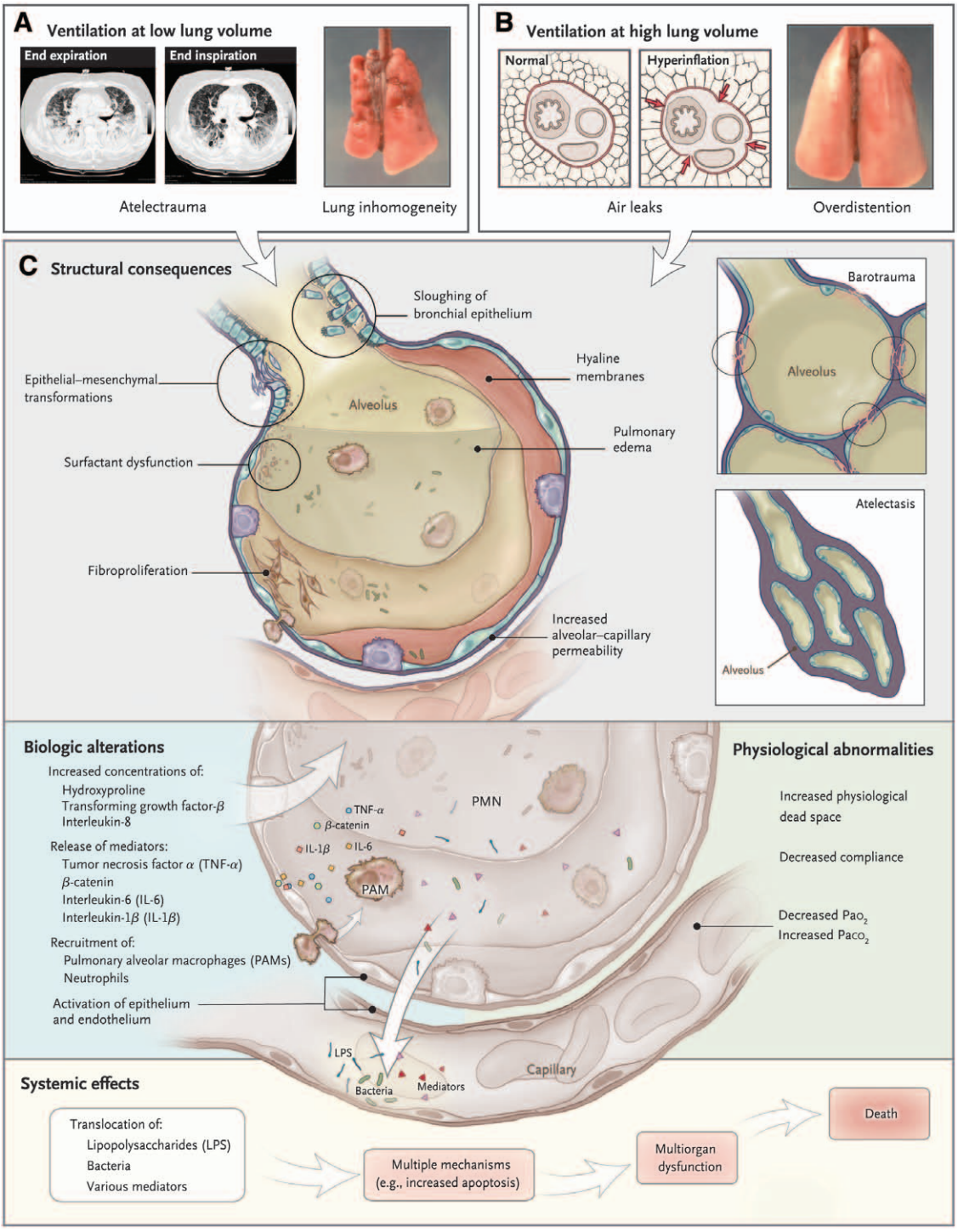

Figure 1. Lung injury is caused by ventilation at low and high lung volumes. At low lung volumes, repetitive opening and closing of lung units will be injurious, particularly when lung inflation is not homogeneous (A). At high lung volumes, overdistension can lead to gross barotrauma (air leaks), as well as increased alveolar-capillary permeability and gross pulmonary edema (B). Lung injury as the result of high and low lung volumes has structural, physiologic, biologic, and systemic effects (C). Inflammatory mediator release into the lung can cause further lung injury, recruit neutrophils to the lung, or set the stage for the development of pulmonary fibrosis. In addition, the increased alveolar-capillary permeability associated with ventilator-induced lung injury can lead to translocation of mediators, lipopolysaccharides, and bacteria into the systemic circulation, potentially leading to multiple organ dysfunction and death. Reproduced with permission from Slutsky and Ranieri.[8] PMN = polymorphonuclear leukocytes.

in lung injury.[9] The glycocalyx regulates oncotic pressure, modulates plasma–endothelial cell interactions, and prevents leukocyte and platelet adhesion to the endothelium in the unactivated state.[10] Breakdown of the glycocalyx is present in all types of lung injury[11] and is an integral component of inflammation, capillary leak, and edema formation.[9]

Protective low tidal volume (Vt) ventilation mitigates lung injury and reduces mortality in ARDS[12,13] and has

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been shown to decrease pulmonary and extrapulmonary complications after nonthoracic surgery in patients with healthy lungs.[14] Whether this benefit derives from ensuring "open lung" ventilation (the process of avoiding atelectasis and maintaining lung expansion near normal functional residual capacity [FRC] with alveolar recruitment and PEEP),[15] or the use of low Vt remains a topic of debate.[16] Protective OLV techniques appear similarly effective in reducing the incidence of postthoracotomy ALI,[17] but studies with end point reductions in mortality are lacking, and most investigations are focused on surrogate markers, such as inflammatory cytokines.

PHYSIOLOGIC CONSIDERATIONS

Lung Volumes

The breach of the pleural interface, which occurs during thoracotomy and thoracoscopy, significantly alters intrathoracic lung volumes. Of particular importance is the disruption of the normal relationship between FRC and closing capacity, which underlies gas exchange abnormalities during anesthesia in general and intrathoracic surgery in particular. Closing capacity is an intrinsic property of the lung, whereas FRC hinges on the interplay of the inward elastic recoil of the lung parenchyma and the outward recoil of the chest wall. FRC decreases by 40% with the induction of general anesthesia[18] but ceases to exist once the surgical pneumothorax is established. The collapsing lung is released from the outward "spring" of the chest wall and collapses toward residual volume. Although the ventilated lung retains intact pleural attachments, it loses mediastinal and diaphragmatic support. Because of the compressive forces of abdominal and mediastinal contents, the ventilated lung therefore depends on positive airway pressure to stay above residual volume. The end-expiratory lung volume of the ventilated lung therefore becomes dependent on the respiratory rate, Vt, inspiratory/expiratory ratio, and PEEP chosen by the anesthesiologist.[19,20] The loss of a stable end-expiratory lung volume is easily appreciated in computed tomography images of a pig OLV model where, even in the presence of PEEP, 80% of the ventilated lung is poorly aerated or atelectatic at end expiration (Fig. 2, A and C).[21] Given that closing capacity commonly exceeds FRC in awake, older patients, particularly those in the supine position,[22] it can therefore be assumed that a substantial portion of the ventilation during OLV occurs below closing capacity, unless active measures to restore the end-expiratory lung volume are taken.

Lung Mechanics

The focus in lung protection increasingly is being placed on concepts such as lung stress and strain which, in our opinion, are particularly relevant to the lung injury associated with OLV. The fibrous network of the lung consists of elastin fibers responsible for the elastic recoil and collagen fibers, which provide a "stop-length" at total lung capacity.[23] Lung cells are anchored to the fibrous skeleton and do not bear the full force of distention but may activate the inflammatory cascade if subjected to abnormal stretch.[23] The fiber tension corresponds to lung "stress," which, during mechanical ventilation, is represented by transpulmonary pressure and may be calculated as airway pressure minus pleural pressure. The elongation of the fibers from their resting position is called lung "strain" and can be thought of as ΔVt/FRC. Stress and strain are mathematically linked by the elastance of the respiratory system (lung and chest wall), which represents the reciprocal of respiratory system compliance.[23]

$$\text{Stress} = \text{Elastance} \times \text{strain} = \text{Elastance} \times \Delta Vt / \text{FRC}$$

Lung stress and strain are global values and therefore not reflective of the regional risk of lung injury. Heterogeneity between lung units, in particular the interface between atelectatic and normally expanded alveoli, has been described as a stress modifier,[24] which is of particular importance during OLV, given that atelectasis is prevalent in the ventilated lung (Fig. 2). The ventilated lung is overdistended during OLV, particularly at high Vt, as illustrated by mediastinal shift in Figure 2, B and D, and Figure 3A, which may expose the lung to excess strain. High lung strain is known to produce an inflammatory response in patients with ARDS[25] and correlates with lung injury after short-term, 2-lung ventilation in healthy patients.[18] Stress and strain can be determined in critical care, with the measurement of esophageal pressures (as a surrogate for pleural pressure) and FRC. Unfortunately, this is not routinely possible in the operating room, and standard ventilation parameters (Vt, airway pressures) are not reflective of lung stress or strain in mechanically ventilated patients.[26] Even low Vt ventilation is capable of producing high strain in the setting of low end-expiratory lung volumes.[26] OLV therefore creates a milieu of high lung strain, given the markedly reduced end-expiratory lung volumes secondary to the loss of a stable FRC, coupled with the traditional use of relatively large and nonphysiologic Vts.

Hypoxic Pulmonary Vasoconstriction

It is unknown whether hypoxic pulmonary vasoconstriction (HPV) is a contributing factor in lung injury creation; however, the markers of ischemia–reperfusion injury are present in the collapsed lung after reventilation. The importance of HPV in the diversion of blood flow to the ventilated lung during OLV relative to other factors (nonventilated lung collapse, gravity, surgical manipulation, etc.) has been difficult to quantify because of the interconnected nature of all relevant factors. Models in animals have led to contradictory claims, likely because of interspecies differences in potencies of the HPV response and differences in study protocols from clinical 1-lung anesthesia, involving lobar hypoxia, closed chest preparations, or awake subjects as models.[29] Even among human subjects, there is a large interindividual variability of the HPV response.[29] The effect of HPV during OLV may have been underestimated by the use of blood flow during 2-lung ventilation as a baseline. Blood flow to the collapsing lung transiently increases at the start of OLV because of the sudden airway pressure differential between the ventilated and the nonventilated lung.[30] This increased blood flow will then be diverted back to the ventilated lung because of HPV and lung collapse. Within 5 minutes of the onset of OLV, blood flow to the nonventilated lung will start to decrease.[31] Extrapolating from the

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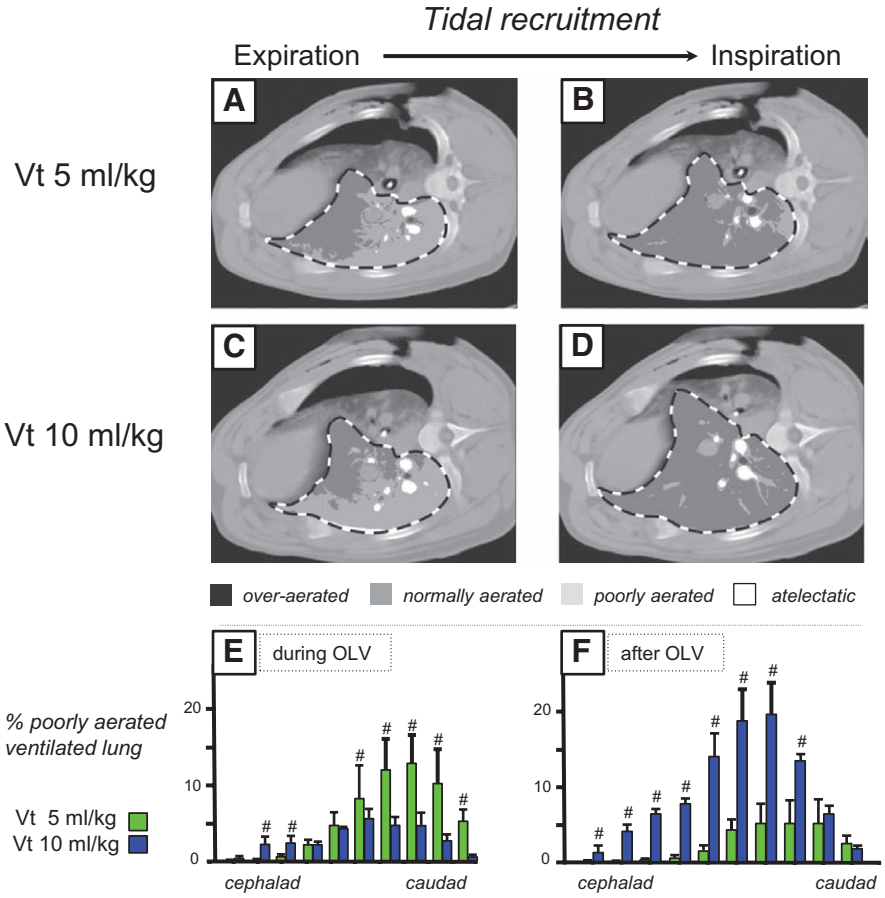

Figure 2. Tidal recruitment and lung overdistension during 1-lung ventilation (OLV) in a pig model. Lung aeration was determined at end-expiration and end-inspiration based on radiologic densities (Hounsfield units [HU]) on computed tomography (CT) scans in a pig OLV model: overaerated (from −1000 to −900 HU), normally aerated (from −900 to −500 HU), poorly aerated (from −500 to −100 HU), and atelectatic (from −100 to 100 HU) lung areas. A–D, CT images during OLV with tidal volumes (Vt) of 5 or 10 mL/kg (fraction of inspired oxygen 0.4 and positive end-expiratory pressure 5 cm H_2O). Lung regions are coded by gray scale for the degree of lung aeration. End-expiratory images demonstrate marked alveolar collapse with either Vt (A and C). End-inspiratory images demonstrate increased tidal recruitment with Vt 10 mL/kg, with near-complete elimination of poorly aerated lung areas (D). End-inspiratory panels further demonstrate ventilated lung overdistension with mediastinal shift, which is markedly increased at Vt 10 mL/kg (D). A–D, Reproduced with permission from Kozian et al.[21] E and F, Schematic representation of lung aeration at end-inspiration in craniocaudal direction (CT slices 1–100) during OLV and during 2-lung ventilation thereafter. Data are summarized in blocks of 10 slices of the dependent lung and presented as means. Lungs exposed to high Vt OLV exhibited more tidal recruitment during OLV, resulting in increased amounts of poorly aerated lung tissue on resumption of 2-lung ventilation (#$P < 0.05$; Vt 5 vs 10 mL/kg). Based on data from Kozian et al.[21]

most valid animal models, it is likely that the perfusion of the nonventilated lung is decreased by approximately 50%, with HPV being responsible for half of this decrease.[9]

HPV was thought previously to be a simple on/off reflex of pulmonary arteriolar vasoconstriction, largely under the control of the alveolar oxygen tension. It is now appreciated that HPV is a much more complex physiologic process.[29] The HPV reflex seems to be subject to preconditioning, because the onset of HPV will occur more quickly and more profoundly on repeated exposure to alveolar hypoxemia.[29] Of interest to the anesthesiologist is the fact that onset and offset of HPV occur in a 2- or 3-stage fashion (Fig. 3C), possibly not reaching their maximal effect for 6 to 8 hours.[28] Once HPV is fully established, it will not relax completely for several hours (Fig. 3, B and C). This delayed offset is particularly relevant for procedures that require bilateral sequential OLV and may explain the clinical observation of more profound desaturation during OLV of the second lung.

HPV is inhibited by volatile anesthetics in a dose-dependent fashion. However, the modern volatile anesthetics (isoflurane, sevoflurane, and desflurane) are only weak inhibitors of HPV compared with the older volatile anesthetics (halothane, enflurane).[2] The newer volatile anesthetics also do not cause clinically relevant decreases in OLV oxygenation at dosages <1 minimal alveolar concentration compared with IV anesthetics.[31] Alkalosis caused by hyperventilation is a potent inhibitor of HPV and interferes with blood flow redistribution during OLV.[2] Conversely, acidosis caused by hypoventilation will contribute to vasoconstriction in both lungs even during OLV, but there is no evidence that it improves the blood flow redistribution between the lungs. The increase in pulmonary vascular resistance associated with severe hypercapnia may adversely affect right ventricular function, and cardiac output, which may exacerbate both mixed venous and arterial oxygen desaturation during OLV.[2]

MECHANISMS OF LUNG INJURY IN THE VENTILATED LUNG

Injury at High Lung Volumes (Volutrauma)

Excessive end-inspiratory lung volumes may be reached because of large Vt (Fig. 2D) or air trapping in the setting of inadequate expiratory-time or excess PEEP. The detrimental effects of excessive Vt during OLV are well documented. OLV with 12 mL/kg resulted in increased extravascular lung water after pneumonectomy in sheep.[32] OLV with 10 mL/kg produced lung overdistension and lung weight gain relative to protective ventilation in rabbits[33] and diffuse alveolar damage and leukocyte sequestration after only 90 minutes in pigs (Fig. 4).[27] The alveolar damage after OLV with 10 mL/kg was 3-fold greater than after 2-lung ventilation with the same settings.[34] Large Vt OLV does produce end-inspiratory lung overdistension (Fig. 2), a recognized risk factor of lung injury.[27,35] On the basis of an ex vivo rat lung model, it is the degree of overinflation that determines the degree of lung injury not the time spent at the particular volume.[36]

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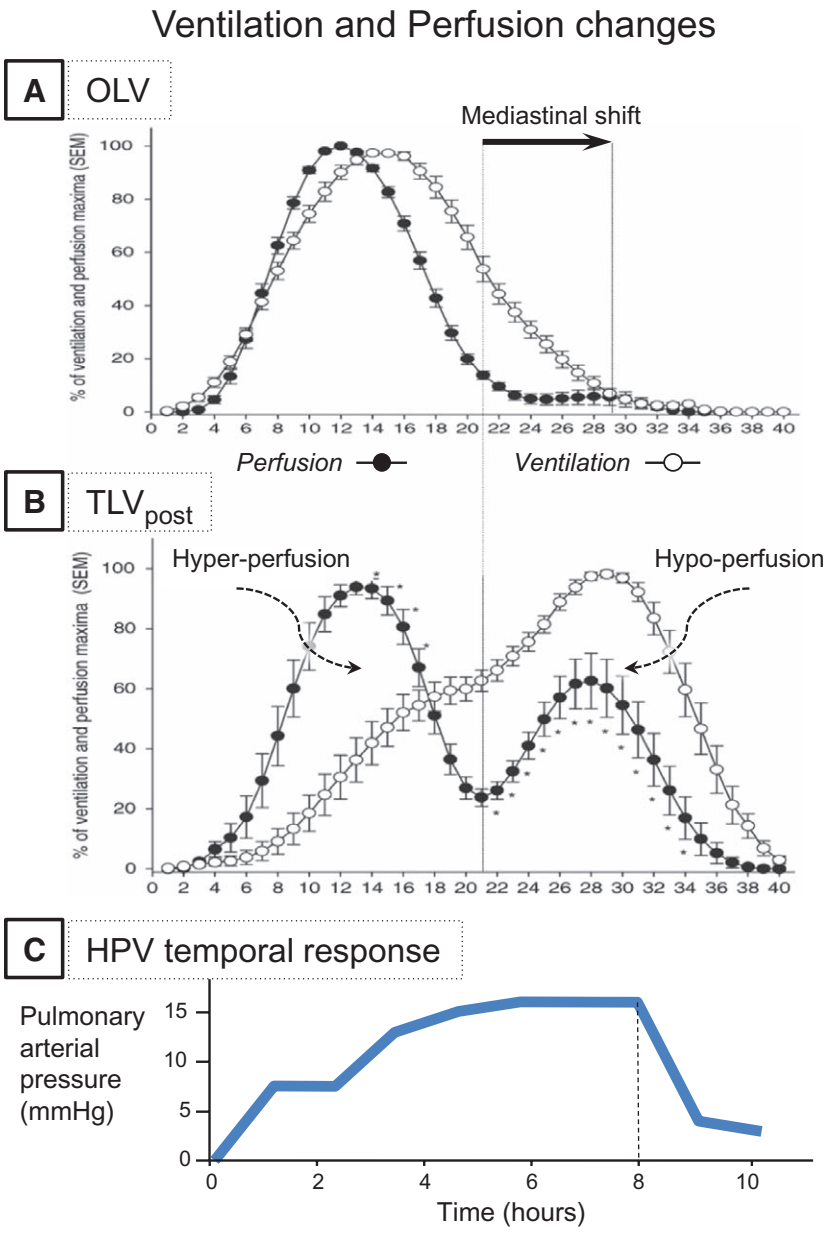

Figure 3. Ventilation and perfusion changes associated with 1-lung ventilation (OLV) consist of lung overdistension and malperfusion. A and B, Ventilation and perfusion patterns in a pig OLV model. Ventilation: The mediastinum is located in slices 19 to 23 during 2-lung ventilation (TLV) (at baseline and post-OLV) but shifted upward to slices 29–33 during OLV secondary to lung overdistension (A). Resumption of TLV normalizes the ventilation distribution to that seen at baseline (not shown). Perfusion: Hypoxic pulmonary vasoconstriction (HPV) results in near-complete diversion of pulmonary perfusion to the ventilated lung, with consequential hyperperfusion of the ventilated lung and hypoperfusion of the collapsed lung (A). Forty-five minutes after recruitment of the collapsed lung and resumption of TLV, the pulmonary perfusion is incompletely reversed and remains significantly altered from baseline (B; *P < 0.05 TLVpost versus TLVpre). Data [mean (SEM)] derived from single-photon emission computed tomography scans in transverse planes from OLV pigs before (TLVpre, not shown), during (OLV, A), and after OLV (TLVpost, B) in the lateral decubitus position. Perfusion (Technetium-labeled macroaggregated albumin) and ventilation (Krypton activity) was calculated as percentage of individual maximal ventilation and perfusion. Modified with permission from Kozian et al.[27] C, The temporal HPV response in humans exposed to isocapnic hypoxia beginning at 0 h with a return to normoxia at 8 h. HPV response was measured as the increase in pulmonary artery systolic pressures. Note the 2-phase, rapid and slow, onset of HPV. Also note that after prolonged HPV, the pulmonary pressures do not return to baseline for several hours. Based on data from Dorrington et al.[28]

Clinical cohorts similarly show an association between high Vt and ALI. In a group of 146 pneumonectomies, any increase in Vt of 1 mL/kg predicted body weight increased the odds ratio of ALI by 3.37 (95% confidence interval, 1.65–6.86).[37] Similarly, respiratory failure after pneumonectomy was associated with greater Vt (8.3 vs 6.7 mL/kg).[38] Multiple randomized, control trials of patients undergoing esophagectomy or lung resection with low Vt OLV (5 mL/kg PEEP 5) or high Vt OLV (8–10 mL/kg PEEP 0) demonstrated a lessened cytokine response with protective ventilation settings.[39–41] More importantly, randomized control trials have demonstrated that high Vt OLV is associated with a worse oxygenation index 18 hours postoperatively[39] and increased pulmonary complications.[39,42]

High ventilating pressures achieved during high Vt OLV are similarly harmful. Postpneumonectomy pulmonary edema was shown to be associated with increased peak airway pressures.[43] Each increase of 1 cm H_2O in peak airway pressures was associated with an odds ratio of 2.32 for ALI in a retrospective analysis of 146 pneumonectomies (95% confidence interval, 1.46–3.67; actual 28.9 vs 27.2 cm H_2O).[37] Elevated plateau pressures were implicated in a retrospective trial, where a ventilator hyperpressure index (product of inspiratory plateau pressure >10 cm H_2O and the duration of OLV) was strongly associated with an increased risk of ALI (odds ratio 3.53, 95% confidence interval, 1.71–8.45).[44] Although high peak pressures need to be avoided during OLV, the actual values are exaggerated by the increased airflow resistance of lung isolation devices.[45] Pressure-control ventilation markedly reduces peak airway pressures measured proximally by the ventilator,[46] but the intrabronchial pressure differences between pressure- and volume-control ventilation are small and likely not clinically significant.[47] Protective ventilation settings decrease airway pressures, as illustrated in a crossover trial in which the authors compared

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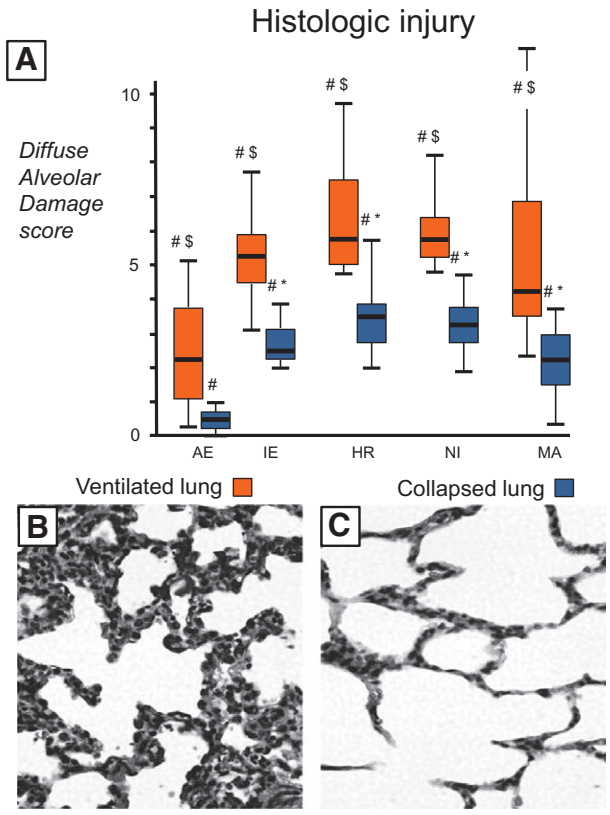

Figure 4. Histologic evidence of alveolar injury after 1-lung ventilation (OLV). Diffuse alveolar damage as evidenced by alveolar edema (AE), interstitial edema (IE), microhemorrhage (HR), neutrophil infiltration (NI), and microatelectasis (MA) in a pig OLV model after resumption of 2-lung ventilation (TLV). A, Ninety minutes of OLV induced significantly greater diffuse alveolar damage scores in the dependent, ventilated ($; $P < 0.05$) and nondependent, collapsed (*; $P < 0.05$) lung compared with TLV control lungs (data not shown). Diffuse alveolar damage scores are significantly greater in the ventilated lung than the previously collapsed lung (#; $P < 0.05$). Data from Kozian et al.[27] B and C, Light microscopic photomicrograph demonstrating increased neutrophil infiltration in the ventilated lung (B) compared with the collapsed lung (C) after 90 min of OLV (hematoxylin and eosin staining, magnification ×40). Modified with permission from Kozian et al.[27]

rate-compensated OLV with 5 mL/kg with traditional OLV with 10 mL/kg in the same patients, where peak and plateau airway pressures decreased significantly from 27 to 21 cm H_2O and 22 to 18 cm H_2O, respectively.[48]

This finding begs the question: Which contributes more to lung injury during OLV, large Vts or high airway pressures? There is no simple or clear answer to this question because it is difficult to separate the effects of large Vts from high airway pressures in the clinical context of OLV. Studies in animals suggest that it is the volume, primarily lung overdistension at end-inspiration, which causes lung injury.[35] In the clinical arena, safe volumes and pressures during OLV are determined primarily by intrinsic patient factors, such as lung compliance, elastic recoil, and predisposition to auto-PEEP.[35,49] A Vt that may be acceptable for a healthy patient during OLV may produce excessively high airway pressures in a patient with pulmonary fibrosis. Conversely, relatively normal Vts and airway pressures may result in markedly increased end-inspiratory lung volumes secondary to air trapping in patients with severe emphysema.[2,50]

Alveolar recruitment maneuvers intentionally create high alveolar pressures to expand low compliance alveolar units, which may result in regional overdistension in high compliance units.[51] Recruitment maneuvers are considered an integral part of lung protective ventilation and advocated during routine OLV.[52] However, re-expansion of collapsed alveoli may be harmful, as stress is amplified at the interface between aerated and collapsed alveoli resulting in opening pressures of up to 140 cm H_2O in collapsed alveoli.[23,53] A recent study argued against substantial harm from recruitment maneuvers. Healthy pigs received repeated recruitment maneuvers (40 cm H_2O for 10 seconds) during either OLV or 2-lung ventilation. Only the OLV group exhibited a proinflammatory cytokine response, leading the authors to conclude that it is OLV not lung recruitment that is harmful.[54] This, however, does not rule out the possibility that recruitment maneuvers may not exacerbate the lung injury during OLV. Preventing alveolar collapse and maintaining open lung ventilation with sufficient PEEP may reduce the need for repeated recruitment maneuvers.[55,56]

Injury at Low Lung Volumes (Atelectrauma/Tidal Recruitment)

Dependent lung tissue is prone to atelectasis during general anesthesia, secondary to extrinsic lung compression and oxygen absorption in areas with low ventilation/perfusion ratios.[57,58] Even short-term exposure to high fraction of inspired oxygen (F_{IO_2}) during the induction of anesthesia causes significant absorption atelectasis.[56] Atelectasis is prevalent in the ventilated lung during OLV, as demonstrated by the marked oxygenation benefit achievable with lung recruitment.[59] Atelectasis predisposes the patient to lung injury as a result of worsened lung compliance and oxygenation, which demand greater ventilating pressures and increased F_{IO_2}.[56] In addition, tidal recruitment, the process of repeated alveolar opening during inspiration and recollapse during expiration, is known to result in alveolar barotrauma and accentuate existing lung injury.[56,60] Ex vivo studies in rats have demonstrated that cyclic alveolar recruitment/collapse creates more lung injury than simple atelectasis.[36] Tidal recruitment exists during OLV in pigs, despite lung recruitment, low F_{IO_2}, and PEEP (Fig. 2), illustrating the propensity of the ventilated lung to collapse toward residual volume as discussed.[21] Although OLV with Vt 5 mL/kg maintained tidal recruitment at levels comparable with 2-lung ventilation before and after recruitment, high Vt OLV (10 mL/kg) increased tidal recruitment by 50% and was associated with substantially worse lung function after OLV (Fig. 2, E and F).[21]

Hyperperfusion/Capillary Shear Stress

Capillary stress failure is described as the disruption of the capillary endothelium, alveolar epithelium, or sometimes all layers.[61] Capillary stress failure is a recognized mechanism involved in ventilator-induced lung injury and may occur because of increased vascular shear stress or lung overinflation.[61] In a rabbit lung model, high pulmonary blood flow was more harmful than high capillary perfusion pressure. Lungs exposed to high pulmonary flow displayed more pulmonary edema and hemorrhage and experienced larger decreases in compliance plus larger increases in vascular

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resistance.[62] The combination of high pulmonary perfusion pressures and high alveolar pressures is more damaging to the endothelium and epithelium than either in isolation.[63] In lungs exposed to harmful ventilation, a 50% increase in pulmonary blood flow, akin to flow increases seen during OLV, results in worse lung compliance, lung weight gain, and alveolar hemorrhage compared with low flow conditions.[64] Pulmonary blood flow redistribution during OLV occurs due to HPV,[29] gravity (in the lateral position), and surgical manipulation of the collapsed lung.[65] OLV in pigs was shown to produce near-complete diversion of pulmonary blood flow to the ventilated lung during OLV (Fig. 3A) and also persistent hyperperfusion (of the ventilated lung) 45 minutes after the resumption of 2-lung ventilation (Fig. 3B).[27] Histopathologic evidence of increased interstitial edema and microhemorrhage in the ventilated lung after OLV support the fact that hyperperfusion is damaging to the capillaries (Fig. 4).[27] One of the mechanism may be transcription-dependent changes in the glycocalyx (mechanotransduction), which have been shown to occur in response to high capillary vascular pressures and result in increased vascular permeability.[9,66]

Biotrauma

OLV-induced injury to the alveolar-capillary membrane results in all facets of lung injury, including cytokine release, recruitment of inflammatory cells, and flooding of the alveolus. Prolonged overexpression of inflammatory mediators and prolonged activation of neutrophils are important in promoting parenchymal cell death[67] and deterioration of the glycocalyx.[41] Exhaled breath condensate pH levels, a validated biomarker of lung inflammation in respiratory disease, drop rapidly during OLV.[68] The increase in inflammatory markers is significantly more pronounced in the ventilated lung after OLV than after comparable periods of 2-lung ventilation.[69,70] Cytokine increases are greater after high Vt OLV (10 mL/kg) than protective OLV (5 mL/kg).[41] Inflammatory cells are recruited into the alveolus during OLV in pigs[34] and humans,[41,70] particularly if ventilated with nonprotective high Vt OLV.[39–41]

Oxidative Injury

Oxidative injury because of reactive oxygen species is a well-described component of ARDS.[67] Prolonged exposure to high F_{IO_2} in healthy volunteers elicits capillary leak of albumin into the alveolus[67] and is associated with oxidative stress and histopathologic changes similar to ALI.[71] Lung re-expansion after OLV elicits severe oxidative stress, particularly in patients with lung cancer.[72] Increasing OLV duration results in worsening oxidative stress upon lung re-expansion (Fig. 5A)[72] and is associated with respiratory failure.[73] The presence of reactive oxygen species after pneumonectomy indicates that oxidative stress also is present in the ventilated lung, presumably because of the high F_{IO_2} (Fig. 5B).[74] In an animal model of OLV, oxidative stress markers of lung injury were exacerbated by hyperoxia (F_{IO_2} 1.0, Pa_{O_2} 400) relative to normoxemia (F_{IO_2} 0.5, Pa_{O_2} 100).[75] Exposure to high perioperative F_{IO_2} has been found to be associated with significantly reduced long-term survival after nonthoracic cancer surgery, with lung injury because of reactive oxygen species being the presumed culprit.[76,77] Given that most thoracic procedures are cancer operations and high F_{IO_2} is required, it is plausible, but unproven, that this finding may translate to the OLV setting.

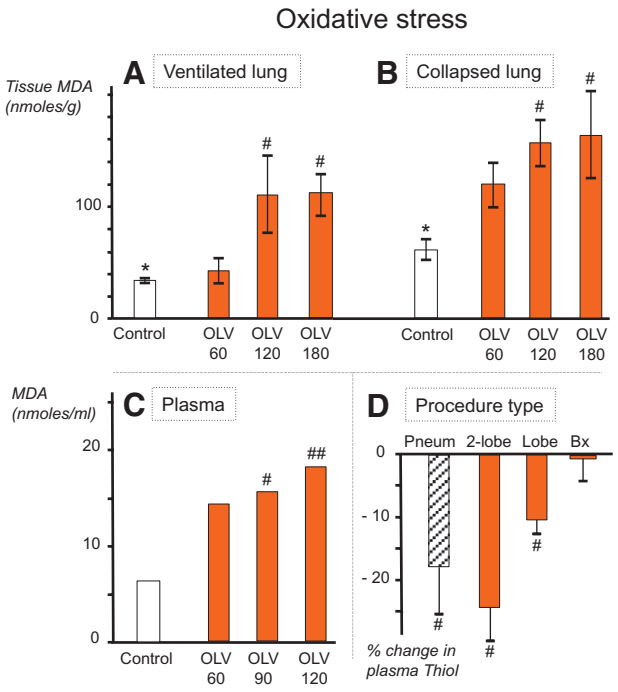

Figure 5. Oxidative stress rises with increasing 1-lung ventilation (OLV) duration and is more pronounced in the collapsed lung. A and B, Bronchoalveolar MDA levels are greater at all time points during OLV than in 2-lung ventilation controls (*$P < 0.01$). The increase is time-dependent, with levels at 120 and 180 min significantly greater than after 60 min (#; $P < 0.005$). Greater levels are achieved in the collapsed lung (B) than in the ventilated lung (A). Data from Tekinbas et al.[78] C, Plasma MDA levels increase dramatically after reventilation 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 (#/##; $P < 0.001$). Data from Misthos et al.[73] D, Changes in plasma thiol concentration associated with OLV comparing levels from postinduction 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. Data from Williams et al.[74] Bx = lung biopsy; Lobe = lobectomy; 2-lobe = bilobectomy; MDA = malondialdehyde; Pneum = pneumonectomy.

MECHANISMS OF LUNG INJURY IN THE COLLAPSED LUNG

Atelectasis/Recruitment

Dense lung collapse after prolonged lung isolation may in itself not be harmful to the lung. Although multiday lung collapse results in increased reactive oxygen species and edema of the alveolar-capillary membrane in the collapsed rat lung,[79] 3 hours of lung collapse did not result in cytokine release in either a nonperfused rat lung model or an in vivo rat OLV model.[36,80] Lung expansion from the atelectatic state, however, exposes the alveolar units to significant mechanical stress and strain[23] and creates high shear forces to adjacent alveoli.[53,81] Lung recruitment after complete lung collapse does induce inflammatory cytokine production in the collapsed lung. Even in the absence of HPV, lung recruitment after 55 minutes of lung collapse resulted in increased

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expression of proinflammatory cytokines tumor necrosis factor-α and interleukin-1β.[82] Lung re-expansion and reventilation after 1 or 3 hours of OLV in an in vivo rat lung model resulted in cytokine release, protein extravasation, and neutrophil recruitment into the alveolus.[80] Neutrophil infiltration and alveolar structural damage increases with the duration of lung collapse.[78]

The type of lung recruitment may affect the extent of injury. Cycling recruitment maneuvers with stepwise increases in peak pressure and PEEP are less harmful in the 2-lung ventilation setting, particularly if pressures are built up slowly.[83] Vital capacity maneuvers or sustained pressure holds, the most widely practiced recruitment maneuver in the operating room, appear to be more harmful to the alveolar-capillary membrane.[84] Sustained pressure holds additionally may cause hemodynamic instability because of acute increases in right ventricular afterload.[85] The aforementioned issues have led to recommendations in critical care to abandon vital capacity maneuvers in favor of cycling maneuvers.[85]

Hypoperfusion/Ischemia–Reperfusion Injury

The addition of ischemia to the lung collapse model results in marked worsening of the lung injury based on increased levels of tumor necrosis factor-α, decreases in nitric oxide metabolites, increased microvascular permeability, and lung edema.[86] Organ ischemia induces capillary leak because of near-complete loss of the glycocalyx in guinea pig hearts.[87] Ischemia–reperfusion injury and exposure to inflammatory mediators induce further deterioration of the glycocalyx (Fig. 6B).[88] Although lung injury in the setting of complete lung ischemia is not surprising, even hypoperfusion because of HPV induces hypoxemic changes. Before reventilation after prolonged pneumothorax in rats, the collapsed lung tissue has increased levels of reactive oxygen species[79] and hypoxia-induced gene expression.[89] The same is true after clinically relevant durations of lung collapse in rat models[78] and patients, as reventilation after a period of clinical OLV substantially increased exhaled hydrogen peroxide concentrations in breath condensate, myeloperoxidase levels in bronchoalveolar lavage samples, and systemic markers of oxidative stress.[72,90,91] These findings are more pronounced in patients with cancer, who have a higher oxidative burden and may have less antioxidant capacity.[72] The duration of OLV determines the amount of oxidative stress for 12 hours after OLV (Fig. 5).[72,73] One hour of OLV creates a 3-fold increase in oxidative stress from baseline. Oxidative stress is lower after pneumonectomy and in patients managed with 2-lung ventilation, which confirms that lung re-expansion is the primary culprit.[72] Oxidative stress predominates in the re-expanded collapsed lung[78] and is greater after lobectomy than wedge resection, likely because of the difference in OLV duration (Fig. 5C).[74] Unilateral pulmonary edema of the previously collapsed

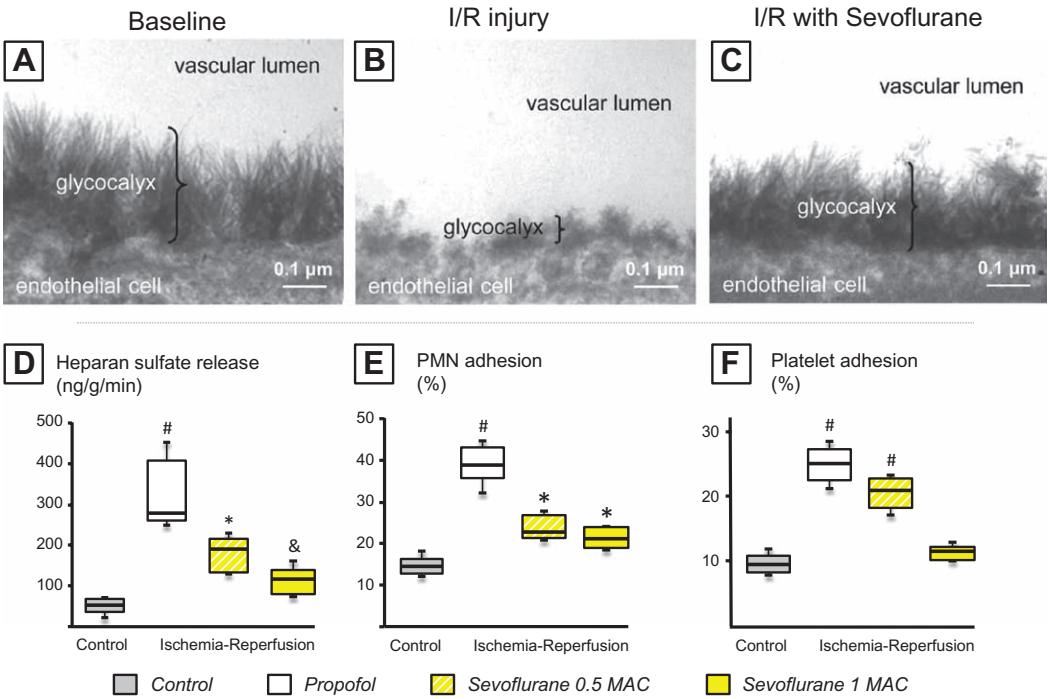

Figure 6. Sevoflurane reduces endothelial glycocalyx (EG) shedding in response to ischemia–reperfusion (I/R). Isolated guinea pig hearts were exposed to 20 min of warm ischemia and 10 min of reperfusion. A–C, Electron micrographs. A, Intact EG in nonischemic perfusion group. B, Marked EG shedding after I/R. C, The EG is relatively preserved after I/R after pretreatment with sevoflurane. Reproduced with permission from Chappell et al.[88] D, Heparan sulfate concentrations in vascular effluent determined by antibody-specific enzyme-linked immunosorbent assay. I/R injury causes marked heparan sulfate release from the EG (#, $P < 0.01$ versus control). Sevoflurane pretreatment significantly reduced heparan sulfate shedding (*, $P < 0.05$ versus I/R), particularly at a minimal alveolar concentration (MAC) of 1 (&, $P < 0.05$ versus I/R and 0.5 MAC Sevo). Polymorphonuclear leukocyte (PMN; E) and Platelet (F) adhesion in response to I/R. E, I/R induces marked polymorphonuclear leukocyte (PMN) adhesion (#, $P < 0.05$ versus control), which is blunted by sevoflurane pretreatment (*, $P < 0.05$ versus I/R for 0.5 and 1 MAC). F, I/R induces marked platelet adhesion (#, $P < 0.05$ versus control). Sevoflurane pretreatment at 1 MAC but not 0.5 MAC reduces platelet adhesion to baseline levels. Data from Chappell et al.[88]

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lung has been described in 25% of patients undergoing minimally invasive cardiac procedures and was associated with increased morbidity (ventilator support, hemodynamic support, critical care length of stay, hospital length of stay) and increased mortality.[92] Patient risk factors included pulmonary hypertension, right ventricular dysfunction, and increased cardiopulmonary bypass times, which may argue for an increased role of ischemia–reperfusion in this surgical setting.[92] Reduced oxygen fractions during reventilation may potentially attenuate the reperfusion injury caused by recruitment from the collapsed state, as hyperoxia worsens reperfusion injury after gut ischemia in pigs[93] and liver ischemia in mice.[94]

Relative hypoperfusion continues after the collapsed lung has been recruited (Fig. 3B) and may be the result of microatelectasis, residual HPV, or lung trauma secondary to surgical resection.[27] Nitric oxide levels, which counteract HPV, decrease at a steady rate throughout OLV in an intact, perfused pig model and reach a nadir at reventilation.[79,95] Histologic analysis demonstrates vascular congestion and alveolar wall thickening persisting for 1 hour after reventilation.[95]

Biotrauma

Inflammatory cytokine levels are increased in bronchoalveolar lavage samples of the collapsed lung after lung resection surgery, particularly with increasing OLV duration.[96] The bronchoalveolar lavage cytokine response is stronger in the previously collapsed lung than the contralateral ventilated lung, even in the absence of surgical manipulation, as demonstrated after esophagectomy.[97,98] Dense atelectasis and lung re-expansion appear responsible, given that the cytokine response starts on reinflation, is most pronounced postoperatively, and can be blunted with CPAP (Fig. 7, B and D).[98]

Surgical Trauma/Manipulation

Surgical trauma varies depending on whether the lung is retracted or resected. Manipulation causes diffuse alveolar damage consisting of interstitial edema, microhemorrhage, microatelectasis, and neutrophil infiltration (Fig. 4, A and C).[27,34] The degree of injury is dependent on the amount of manipulation and can be as significant as the ventilator-induced lung injury to the ventilated side.[34]

Systemic Factors Affecting Both Lungs

The activation of neutrophils and the release of proinflammatory cytokines and reactive oxygen species are not localized phenomena but result in systemic effects and potential crosstalk with the contralateral lung. In a rat model of OLV, protein extravasation in the ventilated lung coincided with cytokine release upon lung expansion of the collapsed lung.[80] The crosstalk is equally illustrated by the fact that CPAP application to the collapsed lung reduced alveolar levels of inflammatory cytokines in the contralateral ventilated lung during esophagectomy (Fig. 7, A–D).[98]

Aside from cytokine crosstalk, there are multiple factors that may influence lung injury, including ischemia–reperfusion injury, surgical trauma, parenteral fluids, and lymphatic disruption. Reactive oxygen species are routinely generated in the collapsed lung upon reventilation and reperfusion (Fig. 5B). Systemic release of these reactive oxygen species causes systemic lipid peroxidation, as evidenced by urinary excretion of malondialdehyde.[90] Reactive oxygen species release because of

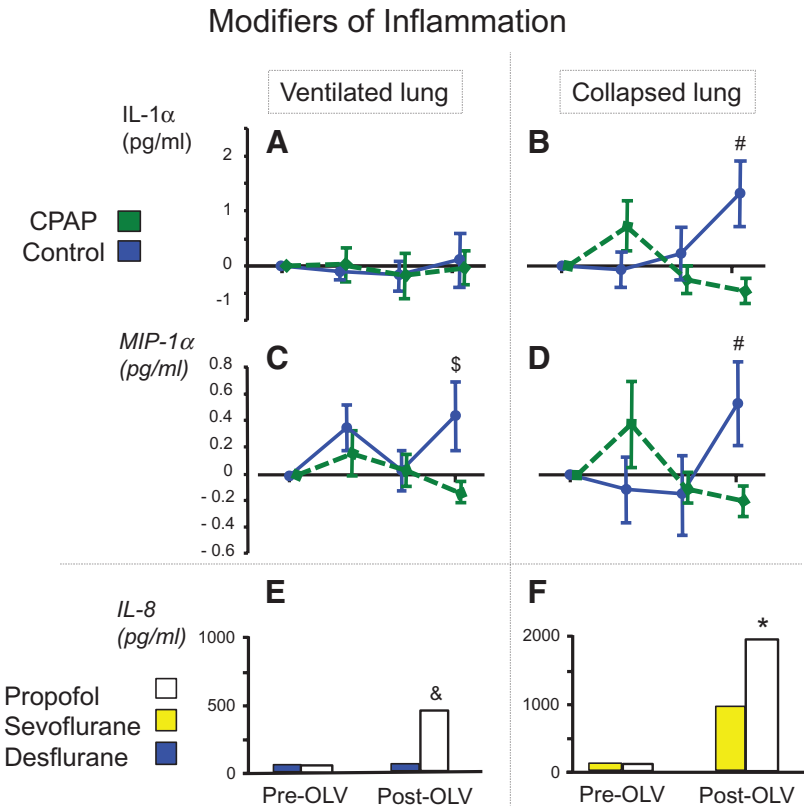

Figure 7. The inflammatory cytokine response to 1-lung ventilation (OLV) can be modulated with continuous positive airway pressure (CPAP) and volatile anesthesia. Bronchoalveolar lavage cytokine levels in the ventilated and collapsed lung at the conclusion of OLV in patients undergoing transthoracic esophagectomy (A–D) or lung resection (E and F). A–D, The application of CPAP to the collapsed lung significantly decreases postoperative cytokine levels in the collapsed lung (IL1α and MIP-1α, #$P < 0.03$), as well as the ventilated lung (MIP-1α, \$$P < 0.035$). Time points: preoperative, 2 h after collapse, 2 h after re-insufflation, postoperative. Data from Verhage et al.[98] E and F, Maintenance anesthesia with volatile agents is associated with significantly reduced IL8 levels in the ventilated lung (&$P = 0.005$) and the collapsed lung (*$P < 0.05$) relative to maintenance anesthesia with propofol infusion. Data from Schilling et al.[99] and De Conno et al.[96] IL = interleukin; MIP-1α = macrophage inflammatory protein 1α.

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lung or gut ischemia–reperfusion is associated with ALI in animal models, which may be a direct effect[100] or mediated via cytokine release.[101,102] The frequent perioperative gastric and jejunal ischemia during esophagectomy may therefore explain the increased risk of lung injury after these procedures.[103] Surgical trauma modulates the inflammatory response, as demonstrated by the fact that the thoracoscopic approach produces less acute phase reactants, inflammatory cytokines, and reactive oxygen species compared with the thoracotomy approach.[104,105] Overhydration has long been considered a risk factor for lung injury after OLV,[106] although the association was later called into question.[107,108] ALI is associated with larger perioperative fluid loads.[44,109] Shedding of the endothelial glycocalyx in response to atrial natriuretic peptide release brought on by hypervolemia[110] and mechanotransduction of the glycocalyx in response to capillary shear stress[9,66] may be some of the underlying mechanisms to explain the harmful effects of overhydration.

Lung resection results in disruption of lymphatic flow, which may impair fluid clearance.[107,111] Because lymphatic drainage of the left chest occurs via lymphatic vessels in the left and right thorax, lung resection in either thoracic cavity will affect left lung drainage.[111] Lymphatic flow may confer resistance to lung injury, as thoracic duct ligation worsened histologic lung injury in a rat model of gut ischemia-reperfusion,[112] and lymphatic disruption has been associated with an increased risk of ALI/ARDS.[113] Finally, preoperative chemotherapy and radiotherapy have been shown to be associated with post-lung resection ALI,[114] and transfusion-related lung injury may compound OLV-mediated injury.[115,116]

Prevention of OLV-Associated Lung Injury

Anesthetic technique may influence the severity of lung injury after OLV. Protective OLV and volatile anesthesia appear effective in reducing adverse outcomes in both retrospective[3] and prospective trials (Table 1). Prospective, randomized OLV trials in which the author explores lung injury–avoidance techniques are limited but reaffirm strategies based on animal models and critical care data (Table 1).

Volatile anesthetics have immune-modulating effects.[123] Studies suggest that volatile anesthetics act as pre- and postconditioning agents and induce lung protection, by inhibiting the expression of proinflammatory mediators.[124] In animal models, preconditioning with isoflurane reduced polymorphonuclear leukocyte recruitment and microvascular protein leakage,[125] whereas postconditioning with sevoflurane attenuated lung damage and preserved lung function.[126] Sevoflurane and desflurane attenuated the inflammatory reaction in patients undergoing thoracic surgery with OLV relative to propofol (Fig. 7, E and F)[70,96,99] and resulted in fewer adverse events. Volatile anesthetics may affect lung injury by protecting the glycocalyx of the pulmonary capillaries.[9] In animal models, sevoflurane reduced the ischemia-reperfusion injury to the endothelial glycocalyx (Fig. 6, B and C).[88,127] Although volatile agents appear to be superior to IV anesthesia with propofol, based on biochemical and histologic profiles, the choice of anesthetic maintenance agent has not yet been proven to substantially affect clinical outcomes.[128]

OLV: Best Practice Recommendations

Protective OLV results in reduced ALI, critical care admissions, and hospital length of stay.[3] Anesthesiologists have been slow to adopt protective ventilation strategies for patients with severe lung injury and often deviate from established protective settings in critical care patients upon transfer to the operating theater.[129] The acceptance of protective ventilation strategies for OLV is undefined, but we hope that this review will help ensure its implementation.

OLV is nonphysiologic and results in microscopic and biochemical injury, even if managed with lung protective strategies. OLV therefore should be "administered" only when required and in the smallest "dose" (i.e., duration) necessary. OLV is not essential for all intrathoracic procedures, and high-frequency jet ventilation or 2-lung ventilation with intermittent apnea may be a suitable alternative in select cases, particularly for non-lung surgery. High-frequency jet ventilation is an effective alternative to OLV for minimally invasive coronary bypass procedures,[130] transthoracic esophagectomy,[131] and even some lung resection procedures.[132,133] Although not formally studied, the avoidance of lung collapse, pulmonary flow redistribution, and oxidative stress should, in theory, result in a lower risk of lung injury.

Although the correlation between parenteral fluid and ALI is not clear, overhydration must be avoided, because it worsens lung injury.[108,110] Other interventions have been proposed but are considered experimental at this point. They include remote limb ischemia,[120] statin therapy,[122] lidocaine infusions,[134] and parenteral sivelestat (neutrophil elastase inhibitor).[121] Similarly, stabilization of the glycocalyx has been achieved with hydrocortisone and antithrombin, which may point toward future prophylactic interventions.[87,135]

Before OLV

Optimization of lung compliance lessens inflammatory cytokine release, likely because of reduced mechanical stress.[119] Under anesthesia, this entails lung recruitment, PEEP titration, and consideration for bronchodilation and bronchial toilet. Recruitment maneuvers should be routinely provided to all patients after general anesthesia induction and endotracheal intubation,[136] but caution needs to be exercised in patients with significant emphysema or marked hypovolemia.[52] As previously stated, this may occur via vital capacity maneuvers (30–40 cm H_2O for 10–40 seconds) or with the use of programmed ventilator cycling maneuvers. The theory behind cycling maneuvers is beyond the scope of this article; however, they essentially consist of stepwise increases in PEEP and driving pressure under pressure-control ventilation up to a maximal plateau pressure of 40 cm H_2O and PEEP of 20 cm H_2O over a period of 2 to 5 minutes.[136] Routine lung recruitment before OLV provides a sustained oxygenation benefit for OLV[137] and improves lung compliance and CO_2 elimination,[138] all of which facilitate protective ventilation.[52] Lung isolation should only be established when necessary to minimize its duration.

During OLV: Collapsed Lung

CPAP should be considered to avoid dense atelectasis and minimize the shunt fraction. The incomplete lung collapse associated with CPAP is compatible with many chest wall and peripheral lung procedures. Even during thoracoscopic

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Table 1. Prospective Human Studies on Prevention of Lung Injury After 1-Lung Ventilation

Author (reference)	Design	Procedure	Total patients	Intervention	Surrogate markers of acute lung injury	Clinical outcome
Ventilation						
Schilling et al.[41]	RCT	Thoracotomy, major lung resection	32	PV: Vt 5 mL/kg; CV: Vt 10 mL/kg ($Paco_2$ 35–45 mm Hg, Fio_2 0.8–1, PEEP 0)	PV: attenuated increases in BAL TNFα and sICAM-1 immediately after OLV ($P < 0.05$)	NS
Ferrando et al.[117]	RCT	Thoracic surgery	30	Individualized PEEP versus PEEP 5 for OLV (individualized PEEP determined based on best lung compliance during PEEP decrement trial postcycling ARM)	PEEP titration resulted in greater PEEP (10 vs 5; $P < 0.001$), improved oxygenation at the end of OLV ($P = 0.007$) and improved static compliance throughout OLV ($P < 0.007$)	NS
Qutub et al.[118]	RCT	Thoracoscopy	39	Vt of 4 vs 6 vs 8 mL/kg ($Paco_2$ 35–45 mm Hg, Fio_2 0.5, PEEP 5)	Vt 4 mL/kg: EVLWI lower than TLV baseline or OLV Vt 6/8 mL/kg at all time points ($P < 0.05$); Vt 8 mL/kg: EVLWI greater than TLV baseline post-OLV ($P < 0.05$)	No difference in all-cause morbidity
Végh et al.[48]	Crossover RCT	Thoracotomy, major lung resection	100	PV: Vt 5 mL/kg, PEEP 5, RR 20, Fio_2 1; CV: Vt 10 mL/kg, PEEP 0, RR 10, Fio_2 1; patients were randomly assigned to 1 arm for 30 min and then crossed over after lung recruitment	PV: lower peak (21 vs 27 cm H_2O; $P < 0.001$) and plateau airway pressures (18 vs 22 cm H_2O; $P < 0.001$)	NS
Shen et al.[39]	RCT	Minimally invasive esophagectomy	101	PV: Vt 5 mL/kg PEEP 5 vs CV: Vt 8 mL/kg PEEP 0 (oxygen to achieve Spo_2 >90%, no rate compensation)	PV: Lower ventilated lung BAL IL1β, IL6, IL8 at 18 h postoperatively ($P < 0.05$); PV: Better oxygenation index at 18 h ($P = 0.046$)	PV: Less pulmonary complications (5 vs 13, $P = 0.021$); definition: bronchoscopy/tracheotomy, pneumonia, ALI requiring reintubation, pleural effusion requiring chest drainage, and pulmonary embolism
Yang et al.[42]	RCT	Thoracotomy or thoracoscopy, major lung resection	100	PV: PCV, Vt 5 mL/kg, PEEP 5, Fio_2 0.5; CV: VCV, Vt 10 mL/kg, PEEP 0, Fio_2 1	PV: better oxygenation index POD0 and POD1 ($P < 0.05$)	PV: less pulmonary complications (2 vs 11; $P < 0.05$); definition: Pao_2/Fio_2 ratio, pulmonary infiltrates, atelectasis
Verhage et al.[98]	RCT	Minimally invasive esophagectomy	30	PV: CPAP to collapsed lung; CV: routine lung collapse (CPAP: 5 cm H_2O, Fio_2 1)	CPAP attenuated BAL cytokine elevations both in the collapsed lung (IL1α, IL1β, IL10, TNFα, MIP-1α, IL8; $P < 0.05$) and the ventilated lung (MCP-1 and MIP-1α; $P < 0.05$)	No difference in outcomes; no differences in conversion rates
Anesthetic agents						
Schilling et al.[70]	RCT	Thoractomy, lung resection	30	IH: desflurane; TIVA: propofol	IH: attenuated increases in BAL levels of alveolar granulocytes, TNFα, sICAM-1 in the ventilated lung after OLV ($P < 0.05$)	NS
Schilling et al.[99]	RCT	Thoractomy, lung resection	63	IH: sevoflurane or desflurane; TIVA: propofol	IH: attenuated increases in BAL levels of IL1β ($P = 0.002$), IL8 ($P = 0.025$), TNFα ($P = 0.001$) in the ventilated lung 30 min postoperatively. No difference in systemic cytokine levels	NS
De Conno et al.[96]	RCT	Thoracotomy or thoracoscopy, lung resection	54	IH: sevoflurane or desflurane; TIVA: propofol	IH: attenuated increase in BAL levels of TNFα ($P < 0.001$), IL6 ($P < 0.05$), IL8 ($P < 0.005$), MCP-1 ($P < 0.05$) in the collapsed lung after OLV. TIVA: correlation between length of OLV and increase in systemic CRP on POD1 ($P = 0.03$) not seen with IH.	IH: reduced composite adverse events ($P < 0.05$). Definition: pneumonia, atelectasis, effusion, reintubation, SIRS, sepsis, ARDS, reoperation, death.

(*Continued*)

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Table 1. Continued

Author (reference)	Design	Procedure	Total patients	Intervention	Surrogate markers of acute lung injury	Clinical outcome
Miscellaneous						
Ju et al.[119]	RCT	Thoracotomy, lobectomy	100	Preoperative nebulized budesonide versus placebo	Budesonide pretreatment decreased peak pressure (25 vs 38 cm H_2O; $P < 0.001$) and plateau pressure (22 vs 32 cm H_2O; $P < 0.001$) after OLV. Budesonide pretreatment associated with reduced BAL levels of TNFα, IL1β, IL6, IL8 (all $P < 0.05$) 30 min post-OLV.	NS
Li et al.[120]	RCT	Thoracotomy, lung resection	216	Remote ischemic preconditioning versus none. Procedure: 3 cycles of left upper arm ischemia (BP cuff at 200 mm Hg for 5 min) followed by reperfusion (5 min), completed before OLV	Preconditioning improved oxygenation index during OLV, post-OLV and for 6 h postoperatively ($P < 0.05$). Preconditioning reduced plasma TNFα and IL6 from 6 to 48 h postoperatively ($P < 0.01$). Preconditioning reduced plasma MDA levels during OLV and for 30 min after OLV ($P < 0.05$)	Reduced ALI after preconditioning (4.6% vs 12%; $P = 0.04$)
Lee et al.[121]	RCT	Lobectomy	16	IV Sivelestat (neutrophil elastase inhibitor) versus placebo	Sivelestat: reduced neutrophil cytoskeletal rearrangement at the end of OLV and post-lung re-expansion ($P = 0.0061$)	NS
Shyamsundar et al.[122]	RCT	Esophagectomy	31	Oral Simvastatin for 4 days before and 7 days after surgery versus placebo	Reduced plasma MCP-1 on POD3 in intervention group ($P = 0.003$). Abolished EBC acidification in intervention group versus control ($P = 0.008$). Attenuated levels of plasma RAGE in intervention group ($P = 0.02$)	Nonsignificant decrease in ALI in the intervention group

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ARM = alveolar recruitment maneuver; BAL = bronchoalveolar lavage; BP = blood pressure; CPAP = continuous positive airway pressure; CRP = C-reactive protein; CV = conventional ventilation; EBC = exhaled breath condensate; EVLWI = extravascular lung water index; F_{IO_2} = fraction of inspired oxygen; IH = inhalational anesthesia; IL = interleukin; MCP = monocyte chemoattractant protein; MDA = malondialdehyde; MIP-1α = macrophage inflammatory protein 1α; NS = not studied; OLV = 1-lung ventilation; PCV = pressure-control ventilation; PEEP = positive end-expiratory pressure; POD = postoperative day; PV = protective ventilation; RAGE = receptor for advanced glycation end products; RCT = randomized control trial; RR = respiratory rate; sICAM-1 = soluble intercellular adhesion molecule 1; SIRS = systemic inflammatory response syndrome; TIVA = total intravenous anesthesia; TLV = 2-lung ventilation; TNFα = tumor necrosis factor α; VCV = volume-control ventilation; Vt = tidal volume.

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procedures, low-level CPAP of 2 cm H_2O has been shown to be feasible without impairing surgical exposure.[139] This approach has been shown to reduce HPV and attenuate inflammatory cytokine release in models of animal OLV [89] and during clinical esophagectomy (Fig. 7).[98] The use of an air–oxygen mixture before OLV will delay lung collapse,[140] which may be preferable in cases in which incomplete lung collapse is not detrimental. It would appear sensible to minimize active suctioning of the lung, which may produce negative pressure trauma, although this has never been formally investigated.

Lung recruitment at the end of OLV harms the collapsed lung because of volume, pressure, and oxygen effects. The impact of recruitment maneuvers on the alveolar–capillary membrane may be minimized by the use of slow airway pressure increases[83] and cycling maneuvers.[85] The use of lower F_{IO_2} during recruitment maneuvers may reduce the creation of reactive oxygen species, but this has not been studied in the OLV setting.[93]

During OLV: Ventilated Lung

Protective ventilation is essential to reduce lung injury. Low Vt ventilation based on predicted body weight should be routine. Predicted body weight is readily calculated on the basis of existing formulas[13] and is crucial to avoid the use of excess Vt, which is common particularly in women and patients with obesity.[141,142] Vts should be restricted to 4 to 5 mL/kg predicted body weight, with the acknowledgment that lung strain may still be excessive depending on the end-expiratory lung volume. We previously considered Vt 6 mL/kg to be protective[2,115] and still believe that this is preferable to 10 mL/kg. However, Vt 6 mL/kg corresponds to the same harmful lung stretch observed during 2-lung ventilation at 12 mL/kg[143] and should therefore likely be avoided particularly during OLV of the smaller left lung.

PEEP must be routine for lung injury prevention to restore end-expiratory lung volume toward FRC and minimize tidal recruitment and lung strain. The most appropriate PEEP level depends on individual respiratory mechanics and is ideally chosen based on optimal lung compliance. In a recent PEEP decrement trial, optimal PEEP during OLV with Vt 5 to 7 mL/kg averaged 10 cm H_2O in patients with relatively normal lung function.[117] This illustrates that the stabilization of the end-expiratory lung volume in the ventilated lung likely requires greater PEEP levels than commonly used in clinical practice. Lung recruitment and PEEP titration should be repeated in case of deteriorating oxygenation or lung compliance.[52,59]

Respiratory rate and minute ventilation targets should be relaxed to allow mild hypercapnia, which attenuates ALI primarily by reducing mechanical stress, and also appears to down-regulate cytokine release in animal models.[144,145] Extreme hypercapnia ($Paco_2$ >70) may be associated with impaired right ventricular function and cardiovascular instability.[146,147] Mild hypercapnia ($Paco_2$ 40–60), however, is well tolerated,[148–150] unless there is preexisting marked right ventricular dysfunction or primary pulmonary arterial hypertension. High F_{IO_2} may be necessary at the onset of OLV but should be reduced after approximately 20 to 30 minutes of OLV, when the nadir in oxygenation has been reached.[151] Further reductions may be possible, as shunt decreases with the strengthening of HPV and the resection of lung tissue. Oxygen fractions as low as 0.4 have been shown to provide adequate oxygenation for OLV in the lateral decubitus position.[152]

After OLV

Histologic and biochemical lung injury is invariably present after OLV, which necessitates the avoidance of additional iatrogenic injury. Because of the presence of reactive oxygen species, hyperoxia must be avoided and oxygen titrated to effect on resumption of 2-lung ventilation and continuing into the postoperative period.[93,94] Protective 2-lung ventilation should be instituted after OLV to attenuate the inflammatory changes associated with early lung injury.[153] Post-extubation noninvasive pressure ventilation has been shown to improve lung mechanics, and oxygenation and may be warranted in patients at high risk for respiratory dysfunction. Whether noninvasive ventilation is capable of reducing lung injury or progression to respiratory failure in this setting is unclear.[154]

CONCLUSIONS

The lung injury of OLV involves the entire alveolar–capillary unit, with trauma to both the alveolar epithelium and the vascular endothelium. Lung injury occurs in both lungs but for different reasons. The ventilated lung is primarily affected by hyperperfusion and ventilator-induced lung injury, whereas the collapsed lung is exposed to ischemia–reperfusion injury and shear stress on reventilation. There appears to be substantial crosstalk because of reactive oxygen species and cytokines released into the circulation, which may cause injury in the contralateral lung. Multiple pathways appear to converge in damage to the endothelial glycocalyx which, in turn, facilitates vascular leakage and cell migration. Given the multifactorial nature of ALI creation, it is not surprising that no single intervention has proven beneficial. Any OLV is nonphysiologic and will result in histologic lung injury. Protective OLV should be routine and consists of Vt 4 to 5 mL/kg predicted body weight and PEEP 5 to 10 cm H_2O, with an emphasis on open lung ventilation with lung recruitment preceding OLV and repeated as necessary. Protective ventilation with volatile agents may reduce the risk of ALI and appears to improve patient outcomes but cannot eliminate the risk completely. Research on anti-inflammatory agents and glycocalyx stabilizers holds promise for future prophylactic interventions.

DISCLOSURES

Name: Jens Lohser, MD, MSc, FRCPC.
Contribution: This author helped write the manuscript.
Attestation: Jens Lohser approved the final manuscript.
Name: Peter Slinger, MD, FRCPC.
Contribution: This author helped write the manuscript.
Attestation: Peter Slinger approved the final manuscript.
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