

## Are lung-protective ventilation strategies worth the effort?

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### Abstract

Nonphysiological ventilation in healthy lungs induces acute lung injury (ALI). Protective lung ventilation in patients with ALI improves outcome. Protective lung ventilation in noninjured lungs and in the absence of a primary pulmonary insult may initiate ventilation-induced lung injury (VILI), as evidenced by inflammatory markers. VILI has important implications that are remote to the lungs and may be associated with significant morbidity and mortality. Volatile anaesthetics can have a lung-protective effect. Excess fluids may contribute to perioperative lung injury. Anaesthesiologists manage a heterogeneous group of patients in the perioperative period, from patients with healthy lungs and patients with at-risk lungs through to patients with established ALI. More patients are at risk for ALI during surgery than previously thought. Appropriate perioperative management may prevent or ameliorate this lung injury. Although evidence is lacking from randomised controlled trials, applying protective ventilatory strategies seems to be a reasonable approach, based on the current understanding of mechanical ventilation and lung injury.

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### Introduction

Patients are at risk of acquiring several types of lung injury in the perioperative period. These injuries include atelectasis, pneumonia, pneumothorax, bronchopleural fistula, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Anaesthetic management can cause, exacerbate or ameliorate most of these injuries. Lung-protective ventilation strategies that use more physiological tidal volumes and appropriate levels of positive end-expiratory pressure (PEEP) can decrease the extent of this injury.<sup>1</sup> This lecture will examine the effects of mechanical ventilation and its role in ventilator-induced lung injury (VILI), with specific reference to thoracic anaesthesia. The specific clinical scenarios of one-lung ventilation, cardiopulmonary bypass and transfusion-related lung injury (TRALI) will be examined. Newer work that includes lung protection strategies will be discussed briefly.

### Mechanical ventilation

Historically, anaesthesiologists have been taught to ventilate patients in the perioperative period with relatively large tidal volumes. Volumes as high as 15 ml/kg ideal

body weight have been suggested to avoid intraoperative atelectasis.<sup>2</sup> This far exceeds the normal spontaneous tidal volumes (6 ml/kg) that are common to most mammals.<sup>3</sup> Recent studies have identified the use of large tidal volumes as a major risk factor for the development of lung injury in mechanically ventilated patients without ALI. Gajic reported that 25% of patients with normal lungs who were ventilated in an intensive care unit (ICU) setting for two days or longer developed ALI or ARDS.<sup>4</sup> The main risk factors for ALI were use of large tidal volumes, restrictive lung disease and blood product transfusion. A prospective study from the same group found that tidal volumes > 700 ml and peak airway pressures > 30 cmH<sub>2</sub>O were independently associated with the development of ARDS.<sup>5</sup>

An intraoperative study of patients who had oesophageal surgery compared the use of tidal volumes of 9 ml/kg without PEEP during two- and one-lung ventilation vs. 9 ml/kg during two-lung ventilation and 5 ml/kg during one-lung ventilation with PEEP 5 cmH<sub>2</sub>O throughout.<sup>6</sup> Significantly lower serum markers of inflammation [cytokines interleukin (IL)-1 $\beta$ , IL-6 and IL-8] were found in the lower tidal volume plus PEEP group. The study did not find any major difference in postoperative outcome between the

two groups. However, it was not powered to do this. Better oxygenation was demonstrated in the lower tidal volume group during and immediately after one-lung ventilation, but not after 18 hours.

In a study that considered conventional versus protective ventilation in critically ill patients without lung injury, de Olivera et al randomised patients to ventilation with either 10-12 ml/kg or 6-8 ml/kg of predicted body weight.<sup>7</sup> In both groups, a PEEP of 5 was applied and the fraction of inspired oxygen (FiO<sub>2</sub>) titrated to keep oxygen saturation > 90%. At 12 hours post ventilation, inflammatory markers in bronchoalveolar lavage fluid [tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) and IL-8] were significantly higher in the larger tidal volume group.

Choi et al compared 12 ml/kg without PEEP vs. 6 ml/kg with 10 cm PEEP and showed procoagulant changes in lavage fluid of the larger tidal volume group after five hours of mechanical ventilation.<sup>8</sup> A recent randomised control trial of 150 critically ill patients without ALI compared the tidal volumes of 10 ml/kg vs. 6 ml/kg of predicted body weight.<sup>9</sup> The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines.

Of importance is recent work that suggests that noninjurious or so-called protective ventilatory settings can induce lung injury in previously healthy lungs. An animal study that used a very elegant murine "one-hit" VILI model showed that even least injurious lung settings induced biochemical and histological changes that were consistent with lung injury.<sup>10</sup> Work with rodents who underwent mechanical ventilation showed significant gene expression, including genes involved in immunity and inflammation, after only 90 minutes of protective ventilation.<sup>11</sup> Whether this has an impact on clinical outcome is presently unknown.

ALI is the most common cause of postoperative respiratory failure and is associated with markedly decreased postoperative survival.<sup>12</sup> A prospective controlled case study by Fernandez-Perez et al that examined intraoperative ventilator settings and ALI after elective surgery in over 4 000 patients showed a 3% incidence of ALI in high-risk elective surgeries. Patients with ALI had significantly lower postoperative survival and increased length of hospital stay compared with controls. Interestingly in this study, intraoperative peak airway pressure, but not tidal volume, PEEP or FiO<sub>2</sub> was associated with ALI. A retrospective cohort study that specifically assessed for intraoperative risk factors for ARDS in critically ill patients found that for patients who received fluid resuscitation > 20 ml/kg/hour, the odds of developing ARDS were three times greater than if < 10 ml/kg/hour was given [odds ratio 3.1, 95% confidence interval (CI) = 1.0-9.9, p-value = 0.05].<sup>13</sup> Vt/IBW (ml/kg) and number of blood products were not associated with ARDS in this study. It is of interest that the majority of patients were ventilated with a Vt/IBW of 8-10 ml/kg and an intraoperative PEEP of 0.

## Ventilator-induced lung injury

The phenomenon of VILI is well recognised and can be particularly significant in surgical specialties that require large transfusions, cardiopulmonary bypass and associated lung ischaemia-reperfusion injury (IRI). The deleterious effects of mechanical ventilation may be mediated by localised inflammation and the systemic release of inflammatory cytokines (biotrauma). Mechanical stretch from cyclical alveolar opening and closing sets up an inflammatory response in the alveolar epithelial cells and the vascular endothelial cells. Hyperinflation causes the nuclear translocation of nuclear factor-kappa B (NF- $\kappa$ B) (a key regulator of the expression of multiple genes involved in inflammatory response), and upregulation of other proinflammatory cytokines. Polymorphonuclear leukocyte recruitment and activation appear to be a key component of the mechanical stretch-induced inflammatory response. The balance between apoptosis and necrosis is unfavourably altered by both ischaemia-reperfusion and mechanical stretch.<sup>14</sup>

Biotrauma not only aggravates ongoing lung injury, but also has important systemic consequences because of the spillover of these inflammatory mediators into the systemic circulation, inducing remote organ dysfunction. A study that examined the novel mechanisms of remote organ injury resulting from VILI showed that mechanical ventilation can lead to epithelial cell apoptosis in the kidney and the small intestine, with accompanying biochemical evidence of organ dysfunction.<sup>15</sup> Alveolar stretch-induced adhesion molecules were found in the lung and the liver and kidneys of mice who underwent injurious mechanical ventilation. In addition, cytokine and chemokine expression in pulmonary, hepatic and renal tissue after mechanical ventilation was accompanied by enhanced recruitment of granulocytes to these organs.<sup>16</sup> These studies go some way in explaining the remote organ dysfunction that is noted with ALI and ARDS and the role that optimising ventilatory strategies play in ameliorating this.

This leads to the question: are lung-protective strategies in ARDS<sup>17</sup> applicable to the perioperative environment, specifically in patients with healthy lungs? A recent paper that examined this question highlighted the lack of randomised, controlled trials that focus on best intraoperative tidal volume, PEEP and use of intraoperative lung recruitment.<sup>18</sup> While outcome studies are lacking, based on what is known about the effects of mechanical ventilation, it is reasonable to aim for protective ventilatory strategies in perioperative practice.

## Perioperative surgical environmental factors

There are multiple factors in the surgical environment which can contribute to lung injury. The most obvious is the

surgical approach. Site of operation is an important predictor of pulmonary complications, with upper abdominal and thoracic incisions being the most important<sup>19</sup> (any surgery that approaches the diaphragm). A decrease in respiratory complications has been documented when major cavity procedures are carried out with minimally invasive versus open techniques.<sup>20,21</sup> Atelectasis occurs frequently following open surgical procedures and in up to 90% of patients who undergo general anaesthesia.<sup>22</sup> It is a pathological state that can contribute to or attenuate lung injury. Thus, anaesthesiologists must be aware of techniques to avoid or treat it.<sup>23</sup> While open to debate, retrospective<sup>24,25</sup> and prospective<sup>26</sup> studies have shown that appropriate thoracic epidural analgesia reduces the incidence of respiratory complications (atelectasis, pneumonia and respiratory failure) after major abdominal and thoracic surgery. The benefits of epidural analgesia seem to be in direct proportion to the severity of the underlying lung disease in the patients. Patients with chronic obstructive pulmonary disease seem to derive the most benefit from epidural analgesia.<sup>27</sup> Reviews that compared paravertebral block (PVB) with epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy, but a better side-effect profile and lower complication rate with PVB.<sup>28,29</sup> In the postoperative period, aggressive physiotherapy with continuous positive airway pressure in patients who develop early desaturation after major abdominal surgery leads to lower rates of major respiratory complications.<sup>30</sup>

## One-lung ventilation

Anaesthesiologists are faced with a heterogeneous patient group, in terms of underlying pathology and surgical procedure that requires one-lung ventilation. Both the patient's pathology and the surgical procedure can predispose to, or cause ALI. ALI has been described since one-lung ventilation (OLV) was first employed in thoracic surgery. The most publicised report is a compilation of 10 pneumonectomy cases published in 1984<sup>31</sup> which focused on the role of intravenous overhydration as a cause of post-pneumonectomy pulmonary oedema. Considerable work has subsequently followed, and understanding the risk factors, mechanisms of injury and management strategies for (what is now termed) post-thoracotomy ALI has greatly advanced.

A thorough retrospective study of 806 pneumonectomies found a 2.5% incidence of post-pneumonectomy pulmonary oedema, with 100% mortality in affected patients.<sup>32</sup> There was no difference in perioperative fluid balance between post-pneumonectomy ALI cases (24-hour fluid balance 10 ml/kg) versus matched pneumonectomy controls (13 ml/kg). Authors used rigorous fluid restriction, compared to other reports,<sup>33</sup> suggesting that limiting intraoperative fluids might decrease, but not eliminate ALI. Post-pneumonectomy pulmonary ALI has been shown to have a bimodal distribution of onset.<sup>34</sup> Late cases presented

3-10 days postoperatively and were secondary to obvious causes, such as bronchopneumonia and aspiration. Early or "primary" ALI presented on postoperative days 0-3. Four factors were independent significant predictors of primary ALI: high intraoperative ventilation pressures, excessive intravenous volume replacement, pneumonectomy and preoperative alcohol abuse. Looking specifically at ventilation pressures, Licker et al used a baro-trauma index that took into account both the duration of OLV and the increased inspiratory pressure. This index represented the strongest risk factor for ALI (an approximately three-fold increase risk if positive inspiratory pressure (PIP)  $\geq 25$  cmH<sub>2</sub>O vs. PIP = 15 cmH<sub>2</sub>O).

The known facts about ALI following lung surgery include an incidence following pneumonectomy of 2-4%, greater frequency of right versus left pneumonectomy, symptom onset 1-3 days post surgery, high associated mortality (25-50%), and resistance to standard therapies. While ALI occurs after lesser resections, e.g. lobectomy, it has a much lower mortality rate. Of note, in eight out of nine cases which developed unilateral ALI following lobectomy, the ALI was in the nonoperated, i.e. the ventilated, lung.<sup>35</sup> While there is an association between postoperative ALI and fluid overload, the noncardiogenic nature of the pulmonary oedema (low and normal pulmonary occlusion pressures) and the protein-rich oedema fluid is much more in keeping with an ARDS-type picture, with endothelial damage playing a key role. Postoperative increases in lung permeability of the nonoperated lung have been demonstrated after pneumonectomy, but not lobectomy.<sup>36</sup> This capillary-leak injury may be because of an inflammatory cascade that affects even the nonoperative lung that is triggered by lung resection and is proportional to the amount of lung resected.<sup>37,38</sup> Free radical oxygen generation in patients with lung cancer relates to the duration of OLV.<sup>39</sup> While there is no single mechanism to explain ALI post lung resection, a unifying hypothesis is that there is a spectrum of ALI that occurs during all lung resections. The more extensive the resection, the more likely there is to be postoperative injury. End-inspiratory lung volume is a key factor in VILI.<sup>40</sup> Many patients, especially emphysema patients, develop auto-PEEP with OLV,<sup>41</sup> thus inspiration begins at a lung volume above functional residual capacity (FRC). Using large tidal volumes (10-12 ml/kg) during OLV in such patients produces end-inspiratory at levels that may cause or contribute to ALI. The effects of PEEP during OLV are variable and very much dependent on the lung mechanics of the individual patient. Initial studies suggest that it leads to a deterioration of arterial oxygenation.<sup>42</sup> Most COPD patients develop auto-PEEP during OLV, leading to hyperinflation and increased shunt.<sup>43</sup> However, patients with normal lung parenchyma, or those with restrictive lung diseases, tend to fall below their FRC at end-expiration during OLV and benefit from external PEEP.

Avoiding atelectasis is important in preventing setting up a pre-inflammatory state that leads to injury in both the

atelectatic lung and the ventilated portions of the lung which become hyper-inflated.<sup>44</sup> Just as in two-lung ventilation, high tidal volumes in OLV cause or contribute to ALI. In a rabbit model of OLV during isolated perfusion, large tidal volume (8 ml/kg) ventilation produced a picture of ALI that was absent in animals randomised to a lung-protective ventilation pattern (4 ml/kg plus PEEP).<sup>45</sup> Large pulmonary resections (pneumonectomy or bi-lobectomy) should be considered to be associated with some degree of ALI. ALI was diagnosed radiographically in 42% of pneumonectomy patients who had been ventilated with peak airway pressures > 40 cmH<sub>2</sub>O.<sup>46</sup> A retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intraoperative tidal volumes (8.3 ml/kg vs. 6.7 ml/kg in those patients who did not develop respiratory failure).<sup>47</sup> Thus, current understanding of post-thoracotomy ALI supports applying the management strategies of least injurious lung ventilation: keeping FiO<sub>2</sub> as low as acceptable, varying tidal volumes,<sup>48</sup> beginning inspiration at FRC and avoiding atelectasis with frequent recruitment manoeuvres.<sup>49</sup> An observational study by Licker et al in patients who underwent lung cancer surgery would seem to confirm this.<sup>50</sup> Using a protective lung ventilation strategy (Vt < 8 ml/kg predicted body weight, pressure control ventilation, peak inspiratory pressures < 35 cmH<sub>2</sub>O, external PEEP 4-10 cm and frequent recruitment manoeuvres) in a protocol group (558 patients) versus conventional ventilation in a historical group (533 patients). A decreased incidence of ALI (3.7% to 0.9%, p-value < 0.01), atelectasis (8.8 to 5.0, p-value = 0.018), fewer ICU admissions (2.5% vs. 9.4%, p-value < 0.001) and shorter hospital stay was shown.

Hypercapnia that results from smaller minute volumes should be tolerated. Permissive hypercapnia has become a central component of protective ventilatory strategies and humans have been shown to be remarkably tolerant of even extreme hypercapnia.<sup>51</sup> Minimising pulmonary capillary pressure by avoiding overhydration for patients undergoing pneumonectomy is reasonable, while it should be acknowledged that not all perioperative increases in pulmonary artery pressures are owing to intravascular volume replacement. Finally, it must be appreciated that not all hyperinflation of the residual lung occurs in the operating room. The use of a balanced chest drainage system, following pneumonectomy, to keep the mediastinum in neutral position and avoid hyperinflation of the residual lung, has been suggested as a way of contributing to a decrease in ALI in some centres.<sup>52</sup>

### The role of volatile anaesthetic agents in lung protection

Volatile agents have immune-modulatory effects. Considerable work has been carried out, especially in the cardiac setting, on the role of volatiles in IRI and in pre- and

post-conditioning. Recent studies of models of ALI during OLV and in cases of lung ischaemia reperfusion<sup>53</sup> suggest that volatiles may act as pre- and post-conditioning agents that induce lung protection by inhibition of the expression of proinflammatory mediators. Isoflurane pretreatment in an endotoxin-mediated animal model of lung injury exerted protective effects, as evidenced by the reduction of polymorphonuclear recruitment and microvascular protein leakage.<sup>54</sup> Post-conditioning with sevoflurane attenuated lung damage and preserved lung function in an in vivo rat ALI model.<sup>55</sup>

In a prospective study, patients undergoing thoracic surgery with OLV were randomised to either propofol or sevoflurane anaesthesia.<sup>56</sup> An attenuated inflammatory reaction was shown when assessing inflammatory markers in the nonventilated lung. Significantly, the sevoflurane group had an improved outcome and a significantly lower overall number of adverse events.

A study which compared the OLV (Vt 10 ml/kg) with desflurane versus propofol anaesthesia examined the inflammatory response in the ventilated lung.<sup>57</sup> The inflammatory markers IL-8, IL-10, polymorphonuclear elastase and TNF $\alpha$  were significantly lower in the desflurane group.

While considerable work remains to be carried out, this exciting work indicates a role for volatiles in attenuating the proinflammatory response in the lungs to a host of insults, whether this is pre-, during or post-insult.

### Transfusion-related lung injury

TRALI has emerged as a leading cause of transfusion morbidity and mortality.<sup>58</sup> A disproportionate number of cases have occurred in the perioperative period.<sup>59</sup> Anaesthesiologists are routinely involved in transfusion decisions and are well placed to decrease the incidence and the morbidity and mortality of TRALI. Diagnostic criteria consist of hypoxia or bilateral pulmonary oedema during or within six hours of transfusion, in the absence of circulatory overload.<sup>60</sup>

Difficulties lie when patients have other risk factors for ALI, pre-existing ALI and in subtle cases which may not meet current criteria. The exact pathogenesis is not completely understood.<sup>61,62</sup> While an immune antibody-mediated mechanism is implicated in most cases, with good supporting experimental and clinical evidence, supporting antibodies are not found in 15% or more of cases. Thus, an antibody independent two-hit model has been proposed. The antibody-mediated mechanism is primarily due to leukoagglutinating antibodies in the transfused plasma binding to recipient neutrophils. These antibody-bound neutrophils are activated and sequestered in the lung where complement activation and the release of neutrophil bioactive products results in endothelial damage, capillary leak and ALI. Implicated antibodies are human leukocyte antigens class I and II and neutrophil-specific antibodies.

The two-hit model postulates that an initial insult, e.g. sepsis, surgery and trauma, to the vascular endothelium results in endothelial activation, causing the release of cytokines and adhesion molecules. Neutrophils are then attracted, primed and sequestered in the lung in this proinflammatory milieu. A second hit, by the transfusion of biological response modifiers, activates these sequestered neutrophils, resulting in the release of oxidases and proteases, and causing endothelial damage and subsequent ALI.

Both mechanisms have their limitations, but it seems reasonable that both may occur and that TRALI may represent the final common pathway of neutrophil activation and subsequent endothelial injury. True incidence is unknown because of the fact that standardised definitions have only recently been developed, but a prospective cohort study that examined an ICU population that used current definitions reported an 8% incidence (901 patients). Plasma and platelets had the highest associations.<sup>63</sup> Mortality was estimated at 5-10%. All blood products were implicated. Most of the products contained more than 50 ml of plasma. Data suggest that plasma and apheresis platelets have the highest component risk.<sup>64</sup>

Strategies to prevent transfusion services include, but are not limited to, fresher products, washed components and plasma that derives primarily or exclusively from male donors (donations from multiparous females should be avoided). The appropriate use of blood products and avoiding further lung injury are of the utmost importance for the anaesthesiologist. Transfusion triggers must be individualised for each patient and aimed at clinical endpoints. Prothrombin complex concentrates may have a future role in place of fresh frozen plasma. There is certainly a sound theoretical basis for this.

### Cardiopulmonary bypass

Pulmonary dysfunction post cardiopulmonary bypass (CPB) is a well described but poorly understood phenomenon.<sup>65</sup> While the incidence of ARDS post CPB is low (< 2%), the mortality associated with it is high (> 50%).<sup>66</sup> While the systemic inflammatory response syndrome that is initiated by CPB plays a major role, the pulmonary insult is multifactorial and does not relate to the bypass itself. Extra CPB factors are general anaesthesia, sternotomy and breaching of the pleura. Intra-CPB factors include but are not limited to hypothermia, blood contact with artificial surfaces, IRI, administration of blood products and ventilatory arrest.

It must be emphasised that the above strategies, while having good theoretical basis, have showed inconsistent results in the literature in terms of improving pulmonary outcome. Protective postoperative ventilatory strategies of these at-risk lungs is key.

A randomised, control trial compared the use of nonprotective high tidal volumes (10-12 ml/kg) plus low PEEP (2-3 cmH<sub>2</sub>O), versus lung-protective low tidal volumes (8 ml/kg) plus high PEEP (10 cmH<sub>2</sub>O), in patients ventilated for six hours following cardiopulmonary bypass for coronary artery bypass surgery.<sup>67</sup> Serum and bronchiolar lavage levels of the inflammatory cytokines IL-6 and IL-8 were significantly increased at six hours only in the nonprotective ventilation group.

### Ultra-protective lung ventilation

The concept of ultra-protective ventilation is next on the continuum of lung-protective ventilation in ALI and ARDS. This concept utilises pumpless extracorporeal lung assist, specifically the Novalung<sup>®</sup> iLA Membrane Ventilator and near-static ventilation. A brief description of the Novalung<sup>®</sup> is appropriate. It is a membrane ventilator that allows O<sub>2</sub> and CO<sub>2</sub> gas exchange via simple diffusion.<sup>68</sup> The membranes are biocompatible and provide a nonthrombogenic surface. It is designed to work without a mechanical pump in an arteriovenous configuration, thus requiring an adequate mean arterial pressure to drive flow. Flow rates are typically 1-2 l/minute, or approximately 15% of cardiac output. CO<sub>2</sub> clearance is controlled by varying the oxygen flow rate. It must be noted that oxygenation may be variable and may not be sufficient in severe hypoxic disorders. Compared with conventional extracorporeal membrane oxygenation, the Novalung<sup>®</sup> is a simple, pumpless portable device. Anti-coagulation requirements are considerably reduced with a partial thromboplastin time target of 55 seconds. Bleeding complications and blood product requirements are significantly less.

ARDSNet and animal data demonstrate that when compared with 6-12 ml/kg, lower tidal volumes of 3 ml/kg, significantly reduce endothelial and epithelial injury.<sup>69,70</sup> In other words, "protective" tidal volumes can still induce VILI. However, clearance of CO<sub>2</sub> and oxygenation become an issue at these lower minute volumes. The Novalung<sup>®</sup> allows for this marked reduction in minute ventilation and the simultaneous correction of PaCO<sub>2</sub> and pH. An animal model of post-pneumonectomy ARDS using the Novalung<sup>®</sup> and tidal volumes of 2.2 ml/kg and a respiratory rate of 6, showed significantly better outcomes than that of conventional lung protective strategies.<sup>71</sup> Numerous case reports in humans in a variety of clinical scenarios have been encouraging.<sup>72-75</sup> Tidal volumes ≤ 3 ml/kg, low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung<sup>®</sup> in situ, causing less VILI and subsequent remote secondary organ failure. While this technique is not currently the standard of care, it represents an exciting area for further clinical research, with significant benefits for patients with respiratory failure refractory to conventional therapy and potential application for use as part of an ultra-protective lung protection strategy.

## Fluids, inflammation and the glycocalyx

A retrospective cohort study that specifically examined intraoperative risk factors for ARDS in critically ill patients found that for patients receiving fluid resuscitation > 20 ml/kg/hour, the odds of developing ARDS were three times greater than if < 10 ml/kg/hour was given (odds ratio 3.1, 95% CI = 1.0-9.9, p-value = 0.05).<sup>76</sup> In this study, Vt/IBW (ml/kg) and number of blood products were not associated with ARDS. Of interest is the fact that the majority of patients were ventilated with a Vt/IBW of 8-10 ml/kg and an intraoperative PEEP of 0. It has long been a concern that excess amounts of intravenous fluids predispose patients to develop ALI.

However, it has been a conflicting concern for anaesthesiologists that fluid restriction in thoracic surgery may contribute to postoperative renal dysfunction, which was previously reported to be associated with a very high (19%) mortality.<sup>77</sup> In a recent review of > 100 pneumonectomies at our institution, acute kidney injury (AKI), as defined by the RIFLE classification (risk, injury, failure, loss of kidney function, and end-stage kidney disease),<sup>78</sup> occurred in 22% of patients.<sup>79</sup> However, there was no association of AKI with fluid balance and there was no increased 30-day mortality in AKI patients. AKI was associated with preoperative hypertension and complex surgical procedures, such as extra-pleural pneumonectomy. A similar retrospective study that observed pulmonary resection patients found that AKI, as defined by the Acute Kidney Injury Network criteria, which occurred in 67 out of 1 129 (6%) patients, was not associated with a statistically significant increase in mortality versus that found in non-AKI patients (3% vs. 1%).<sup>80</sup>

Fluid requirements vary widely between patients and procedures, and ultimately represent the sum of preoperative deficits, maintenance requirements and ongoing losses. Fluid management for major oesophageal surgery is particularly challenging. Preoperative fluid deficits in patients with severe oesophageal disease may be substantial, though they have not been well defined.<sup>81</sup> Fluid requirements in patients undergoing oesophageal procedures may be complicated by the fact that they may be relatively hypovolaemic after long preoperative fasts, particularly if oesophageal obstruction or dysphagia have limited fluid intake. Perioperative losses occur via a number of mechanisms, including urinary, gastrointestinal and evaporative losses, bleeding and interstitial fluid shifting. This shift of fluid from the vascular compartment into the interstitial space accompanies surgical trauma and is likely to reflect vascular injury and loss of endothelial integrity. So called third-space losses describe fluid loss into noninterstitial extracellular spaces which are not in equilibrium with the vascular compartment and are thus considered to be a "nonfunctional" extra-cellular fluid compartment. However, it is very possible that

the "third space" does not exist and was described as a result of measurement errors in early studies on the fluid compartments in the body.<sup>82</sup>

One of the factors which complicates fluid management during oesophageal resection is that thoracic epidural analgesia has been shown to improve outcome for these patients,<sup>83</sup> but its use tends to contribute to hypotension. Hypotension is well known to contribute to ischaemia of the gut anastomosis<sup>84</sup> and treatment with excessive fluids is likely to exacerbate the problem.<sup>85</sup> Many surgeons are concerned about the effects of vasopressors on the anastomotic gut blood flow.<sup>86</sup> However, several recent animal studies have suggested that treatment of intraoperative hypotension with norepinephrine does not cause any reduction in gut blood flow.<sup>87,88</sup>

An ideal fluid regimen for major surgeries, including oesophageal surgery, is individualised and optimises cardiac output and oxygen delivery, while avoiding excessive fluid administration. There is some evidence that fluid therapies which are designed to achieve individualised and specific flow-related haemodynamic end-points, such as stroke volume, cardiac output or measures of fluid responsiveness, such as stroke volume variation (collectively referred to as goal-directed fluid therapy), may provide a superior alternative to fixed regimens or those based on static measures of cardiac filling. For example, central venous pressure does not predict fluid responsiveness or correlate with circulating blood volume after transthoracic oesophagectomy.<sup>89,90</sup>

In addition to the potential importance of the amount and timing of fluid administration, there is some clinical evidence that the choice of fluid type may be important in affecting clinical outcomes.<sup>91</sup> Intravascular colloid retention during the treatment of hypovolaemia may approach 90% vs. 40% when administered during normovolaemia.<sup>92</sup>

The relationship of hydrostatic and oncotic pressure to determine fluid flux across a semi-permeable membrane was described in a classic equation that was developed by Starling in 1896.<sup>92</sup> Several clinical observations, such as the relative resistance of the intact organism to develop oedema and the inability of therapy with hyperoncotic agents to draw fluid from the pulmonary interstitium into the vascular compartment, are not explained by the Starling formula.<sup>93</sup> This discrepancy is now attributed to the glycocalyx, a microcilial layer that lines the endothelium and acts as a molecular sieve. This layer tends to increase the oncotic pressure on the inner surface of the endothelium and decrease leukocyte and platelet adhesion to the endothelium. The glycocalyx deteriorates during IRI and in the presence of a wide variety of inflammatory mediators, such as cytokines, and probably contributes to the increased vascular permeability that is observed in these situations. Also, the glycocalyx deteriorates in the presence of atrial natriuretic peptide and may explain the increase in

plasma protein filtration that has been noted with colloid boluses. Protecting the glycocalyx may be one of the anaesthesiologist's most important duties perioperatively.

### Other therapies for lung protection

Beyond those already discussed, several therapies may play a future role in lung protection. The place of permissive hypercapnia in protective ventilation has been alluded to earlier, but as found in the original ARDSNet data, may be protective in the presence of higher  $V_t$ .<sup>94</sup> Hypercapnic acidosis is protective in a variety of models of ALI. Beneficial effects include attenuation of lung neutrophil recruitment, pulmonary and systemic cytokine concentrations, cell apoptosis and free radical injury.<sup>95</sup> Inhaled hydrogen sulphide shows beneficial effects in a model of VILI via the inhibition of inflammatory and apoptotic responses, independent of its effects on body temperature.<sup>96</sup> Inhaled aerosolised activated protein C in a sheep model of ALI demonstrated improved oxygenation, as well as lung aeration, as assessed by computed tomography scan.<sup>97</sup>  $\beta$ -adrenergic agonists have potential benefits as they increase the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophosphate and have anti-inflammatory properties.<sup>98</sup>

A randomised control trial in 40 patients with ALI showed a decrease in extravascular lung water and plateau airway pressure with intravenous salbutamol, although it showed no difference in outcome.<sup>99</sup> Randomised placebo-controlled trials on several different therapies, including surfactant, prone positioning, inhaled nitric oxide and anti-inflammatories, have not shown significant clinical benefits in patients with established ALI.<sup>100</sup> While it is unreasonable to expect there to be a single therapy or "magic bullet" that will prevent ALI, the above exciting research holds promise in furthering the understanding and management of injured or at-risk lungs.

### Summary

To summarise what is known:

- Nonphysiological ventilation in healthy lungs induces ALI.
- Protective lung ventilation in patients with ALI and ARDS improves outcome.
- Protective lung ventilation in noninjured lungs, and in the absence of a primary pulmonary insult, may initiate VILI, as evidenced by inflammatory markers.
- VILI has important implications that are remote to the lungs and may be associated with significant morbidity and mortality.
- Volatile anaesthetics may have a lung-protective effect.
- Excess fluids may contribute to perioperative lung injury.

Anaesthesiologists manage a heterogeneous group of patients in the perioperative period, from patients with healthy lungs and patients with at-risk lungs, to patients

with established ALI and ARDS. More patients are at risk of acquiring ALI during surgery than previously thought. Appropriate perioperative management may prevent or ameliorate this lung injury. Although evidence is lacking from randomised controlled trials, applying protective ventilatory strategies is a reasonable approach, based on the current understanding of mechanical ventilation and lung injury.

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