Don’t Make Things Worse with Your Ventilator Settings: How You Manage the Lungs During the Perioperative Period Affects Postoperative Outcomes

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Nonphysiological ventilation in healthy lungs induces acute lung injury (ALI). Protective lung ventilation in patients with ALI improves outcomes. Protective lung ventilation in noninjured lungs and in the absence of a primary pulmonary insult may initiate ventilator-induced lung injury, as evidenced by inflammatory markers. Ventilator-induced lung injury has important implications remote to the lungs and may be associated with significant morbidity and mortality. Volatile anesthetics may have a lung-protective effect. Excess fluids may contribute to perioperative lung injury. Anesthesiologists 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 severe chronic obstructive pulmonary disease. More patients are at risk for ALI during surgery than previously thought. Appropriate perioperative management may prevent or ameliorate this lung injury.

INTRODUCTION
Patients are at risk for several types of lung injury in the perioperative period. These injuries include atelectasis, pneumonia, pneumothorax, broncho-pleural fistula, acute lung injury and acute respiratory distress syndrome (ALI/ARDS). Anesthetic management can cause, exacerbate or ameliorate most of these injuries. Lung-protective ventilation strategies using more physiologic tidal volumes and appropriate levels of positive end-expiratory pressure (PEEP) can decrease the extent of this injury.1 In this review I will discuss the effects of mechanical ventilation and its role in ventilator-induced lung injury (VILI) with specific reference to patients with severe chronic obstructive pulmonary disease (COPD) requiring general anesthesia and surgery.

Chronic Obstructive Pulmonary Disease
The most common chronic respiratory illness in the surgical population is COPD which incorporates three disorders: emphysema, peripheral airways disease and chronic bronchitis. Any individual patient may have one or all of these conditions, but the dominant clinical feature is impairment of expiratory airflow.2 Assessment of the severity of COPD is on the basis of the FEV1% of predicted values. The American Thoracic Society categorizes Stage I >50% predicted stage II: 35-50%, and stage III <35 stage I patients should not have significant dyspnea, hypoxemia or hypercarbia and other causes should be considered if these are present.

Respiratory Drive
Many stage II or III COPD patients have an increased PaCO2 at rest. It is not possible to differentiate these “CO2-retainers” from nonretainers on the basis of history, physical examination or spirometric pulmonary function testing.3 This CO2-retention seems to be more related to an inability to maintain the increased work of respiration (Wexp) required to keep the PaCO2 normal in patients with mechanically inefficient pulmonary function and not primarily due to an alteration of respiratory control mechanisms. It was previously thought that chronically hypoxemic/hypercapnic patients relied on a hypoxic stimulus for ventilatory drive and became insensitive to PaCO2. This explained the clinical observation that COPD patients in incipient respiratory failure could be put into a hypercapnic coma by the administration of a high concentration of oxygen (FiO2). Actually, only a minor fraction of the increase in PaCO2 in such patients is due to a diminished respiratory drive, as minute ventilation is basically unchanged.4 The PaCO2 increases because a high FiO2 causes a relative decrease in alveolar ventilation and an increase in alveolar dead space and shunt by the redistribution of perfusion away from lung areas of relatively normal ventilation/perfusion (V/Q) matching to areas of very low V/Q ratio because regional hypoxic pulmonary vasoconstriction is decreased5 and also due to the Haldane effect.6 However, supplemental oxygen must be administered to these patients postoperatively to prevent the hypoxemia associated with the unavoidable decrease in functional residual capacity (FRC). The attendant increase in PaCO2 should be anticipated and monitored. To identify these patients preoperatively, all stage II or III COPD patients need an arterial blood gas analysis.

Nocturnal Hypoxemia
COPD patients desaturate more frequently and severely than normal patients during sleep.7 This is due to the rapid, shallow breathing pattern that occurs in all patients during rapid eye movement sleep. In COPD patients breathing air, this causes a significant increase in the respiratory dead space/tidal volume (Vd/Vt) ratio and a decrease in alveolar oxygen tension (PaO2) and PaO2. This is not the sleep apnea hypoventilation syndrome (SAHS). There is no increased incidence of SAHS in COPD.

Right Ventricular (RV) dysfunction
RV dysfunction occurs in up to 50% of COPD patients. The dysfunctional RV is poorly tolerant of sudden increases in
afterload such as the change from spontaneous to controlled ventilation. RV function becomes critical in maintaining cardiac output as the pulmonary artery pressure increases. The RV ejection fraction does not increase with exercise in COPD patients as it does in normal patients. Chronic recurrent hypoxemia is the cause of the RV dysfunction and the subsequent progression to cor pulmonale. Patients who have episodic hypoxemia in spite of normal lungs (e.g., central alveolar hypoventilation, SAHS, etc.) develop the same secondary cardiac problems as COPD patients. The only therapy which has been shown to improve long-term survival and decrease right heart strain in COPD is oxygen. COPD patients who have resting PaO2 <55 mmHg should receive supplemental home oxygen and also those who desaturate to <44 mmHg with exercise. The goal of supplemental oxygen is to maintain a PaO2 60–65 mmHg. Compared to patients with chronic bronchitis, emphysematous COPD patients tend to have a decreased cardiac output and mixed venous oxygen tension while maintaining lower pulmonary artery pressures.

Bullae
Many patients with moderate or severe COPD develop cystic air spaces in the lung parenchyma known as bullae. These bullae will often be asymptomatic unless they occupy more than 50% of the hemithorax, in which case the patient will present with findings of restrictive respiratory disease in addition to their obstructive disease. A bulla is a localized area of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in a bulla is actually the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intra-bulla pressure is actually slightly negative in comparison to the surrounding parenchyma. However, whenever positive-pressure ventilation is used the pressure in a bulla will become positive in relation to the adjacent lung tissue and the bulla will expand with the attendant risk of rupture, tension pneumothorax and bronchopleural fistula. Positive-pressure ventilation can be used safely in patients with bullae provided the airway pressures are kept low and there is adequate expertise and equipment immediately available to insert a chest drain and obtain lung isolation if necessary.

Flow limitation
Severe COPD patients are often “flow-limited” even during tidal volume expiration at rest. Flow limitation is present in normal patients only during a forced expiratory maneuver. Flow limitation occurs when an equal pressure point (EPP) develops in the intrathoracic airways during expiration. During quiet expiration in the normal patient the pressure in the lumen of the airways always exceeds the intrapleural pressure because of the upstream elastic recoil pressure which is transmitted from the alveoli. The effect of this elastic recoil pressure diminishes as air flows downstream in the airway. With a forced expiration the intrapleural pressure may equal the intraluminal pressure at a certain point, the EPP, which then limits the expiratory flow. Then, any increase in expiratory effort will not produce an increase in flow at that given lung volume.

Flow limitation occurs particularly in emphysematous patients, who primarily have a problem with loss of lung elastic recoil and have marked dyspnea on exertion. Flow limitation causes dyspnea because of stimulation of mechanoreceptors in the muscles of respiration, thoracic cage and in the airway distal to the EPP. Any increase in the work of respiration will lead to increased dyspnea. This variable mechanical compression of airways by over-inflated alveoli is the primary cause of the airflow obstruction in emphysema.

Severely flow-limited patients are at risk for hemodynamic collapse with the application of positive pressure ventilation due to dynamic hyperinflation of the lungs. Even the modest positive airway pressures associated with manual ventilation with a bag/mask at induction can lead to hypotension since these patients have no increased resistance to inspiration but a marked obstruction of expiration. In some of these patients this has contributed to the “Lazarus” syndrome in which patients have recovered from a cardiac arrest only after resuscitation and positive-pressure ventilation was discontinued.

Auto-PEEP
Patients with severe COPD often breathe in a pattern that interrupts expiration before the alveolar pressure has decreased to atmospheric pressure. This incomplete expiration is due to a combination of factors which include flow-limitation, increased work of respiration and increased airway resistance. This interruption leads to an increase of the end-expiratory lung volume above the FRC. This PEEP in the alveoli at rest has been termed auto-PEEP or intrinsic-PEEP. During spontaneous respiration the intrapleural pressure will have to be decreased to a level which counteracts auto-PEEP before inspiratory flow can begin. Thus, COPD patients can have an increased inspiratory load added to their already increased expiratory load.

Auto-PEEP becomes even more important during mechanical ventilation. It is directly proportional to tidal volume and inversely proportional to expiratory time. The presence of auto-PEEP is not detected by the manometer of standard anesthesia ventilators. It can be measured by end-expiratory flow interruption, a feature available on the newer generation of intensive care ventilators. Auto-PEEP has been found to develop in most COPD patients during one-lung anesthesia. Paradoxically it has been found that a small amount of added PEEP (e.g. 5cmH2O) can decrease Auto-PEEP and hyperinflation in many ventilated COPD patients.

Preoperative therapy of COPD
There are four treatable complications of COPD that must be actively sought and therapy begun at the time of the preanesthetic assessment. These are: atelectasis, bronchospasm, respiratory tract infections and pulmonary edema. Atelectasis impairs local lung lymphocyte and macrophage function predisposing to infection. Pulmonary edema can be very difficult to diagnose by auscultation in the presence of COPD and may present very abnormal radiological distributions (unilateral, upper lobes, etc.). Bronchial hyper-reactivity may be a symptom of congestive failure or may be an exacerbation of reversible airways.
obstruction. All COPD patients should receive maximal bronchodilator therapy as guided by their symptoms. Only 20–25% of COPD patients will respond to corticosteroids. In a patient who is poorly controlled on sympathomimetic and anticholinergic bronchodilators, a trial of corticosteroids may be beneficial.

Physiotherapy: Patients with COPD have fewer postoperative pulmonary complications when a perioperative program of intensive chest physiotherapy is initiated preoperatively. Among the different modalities available (cough and deep breathing, incentive spirometry, PEEP, continuous positive airway pressure [CPAP] etc.) there is no clearly proven superior method. Family members or nonphysiotherapy hospital staff can easily be trained to perform effective preoperative chest physiotherapy and this should be arranged at the time of the initial preoperative assessment. Even in the most severe COPD patient, it is possible to improve exercise tolerance with a physiotherapy program. Little improvement is seen before one month. Among COPD patients, those with excessive sputum benefit the most from chest physiotherapy.

A comprehensive program of pulmonary rehabilitation involving physiotherapy, exercise, nutrition and education can improve functional capacity for patients with severe COPD. These programs are usually several months duration and are generally not an option in resections for malignancy although for nonmalignant resections in severe COPD patients, rehabilitation should be considered. The benefits of short duration rehabilitation programs before malignancy resection have not been fully assessed. Smoking: Pulmonary complications are decreased in thoracic surgical patients who cease smoking for > 4 weeks before surgery. Carboxyhemoglobin concentrations decrease if smoking is stopped >12 hr. It is extremely important for patients to avoid smoking postoperatively. Smoking leads to a prolonged period of tissue hypoxemia. Wound tissue oxygen tension correlates with wound healing and resistance to infection. There is no rebound increase in pulmonary complications if patients stop for shorter (< 8 week) periods before surgery.

Postoperative Analgesia: It was initially theorized that thoracic epidural analgesia (TEA) could diminish the diaphragmatic inhibition, which is known to occur after thoracotomy. Such disinhibition was shown for TEA after upper abdominal surgery. Indeed a postthoracotomy animal model demonstrated similar disinhibition, however, a postthoracotomy study of patients with moderate COPD failed to show any improvement of diaphragmatic contractility by TEA even though respiratory function (tidal volume) was improved. This is not easy to explain but it may be similar to the concept of increasing cardiac output without increasing myocardial contractility by changing loading conditions for the ventricle. The diaphragm inserts on the chest wall, and by decreasing chest splinting the diaphragm may be returned to a mechanically more efficient position on its force-length (Starling) contraction curve without affecting its actual contractility.

In patients with severe emphysema it has been shown that analgesic doses of TEA bupivacaine do not cause any significant reduction in lung mechanics or increase in airway resistance. In volunteers a thoracic level of epidural blockade increased FRC. This increase is largely due to an increase in thoracic gas volume caused by a decrease in the resting level of the diaphragm without a decrease in tidal volume. This contradicts earlier studies, which found no change in FRC with TEA. However, different results are probably related to the more advanced methodology of the more recent work. FRC is considered the most important determinant of oxygenation in the postoperative period. Although it is possible to deliver an opioid to the spinal cord receptors via a lumbar catheter in adequate amounts for analgesia, the beneficial effects of local anesthetics on respiratory mechanics require a thoracic catheter.

The only large randomized prospective study of epidural versus systemic analgesia was the MASTER trial performed in Australia, mainly for upper abdominal surgery. Postoperative respiratory failure was significantly reduced in the epidural group (23% vs. 30%) with no differences in other types of complications or mortality. This beneficial effect of thoracic epidural analgesia seems to be most pronounced in patients with underlying lung disease such as COPD. In a retrospective propensity-based analysis of patients with COPD who had major abdominal surgery, the use of TEA was associated with a lower incidence of postoperative pneumonia (11% vs. 16%) and a lower 30-day mortality (5% vs. 9%). This trend also seems to apply to thoracic surgery where a retrospective analysis found TEA was associated with a three-fold decrease in respiratory complications in COPD patients after lung resection. A large retrospective review of more than 80,000 surgical patients in the Ontario Health Insurance database found a small significant reduction in overall mortality related to the use of epidural anesthesia and analgesia (1.7% vs. 2%) and this difference was most notable in thoracic and orthopedic surgery.

Mechanical ventilation

Historically, anesthesiologists have been taught to ventilate patients’ lungs in the perioperative period with relatively large tidal volumes. Volumes as high as 15ml.kg⁻¹ ideal body weight have been suggested to avoid intraoperative atelectasis. This far exceeds the normal spontaneous tidal volumes (6ml.kg⁻¹) common to most mammals. Several studies have identified the use of large tidal volumes as a major risk factor for development of lung injury in mechanically ventilated patients without ALI. Gajic et al. reported that 25% of patients with normal lungs ventilated in an intensive care unit setting for 2 days or longer developed ALI or ARDS. 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 has found that tidal volumes > 700mls and peak airway pressures > 30cm H2O were independently associated with the development of ARDS. An intraoperative study of patients having esophageal surgery compared the use of tidal volumes of 9 ml.kg⁻¹ without PEEP during two- and one-lung ventilation (OLV) versus 9 ml.kg⁻¹ during two-lung ventilation and 5 ml.kg⁻¹ during OLV with PEEP 5 cmH2O throughout. They found significantly lower serum makers of inflammation (cytokines interleukin (IL)-1β, IL-6 and IL-8) 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. The study did demonstrate better oxygenation in the lower tidal volume group during and immediately after OLV, but not after 18h. In a study looking at conventional versus protective ventilation in critically ill patients without lung injury, de Olivera et al. randomized patients to ventilation with either 10-12ml.kg⁻¹ or 6-8ml.kg⁻¹ predicted body weight. 38 In both groups a PEEP of 5 was applied and the FiO₂ titrated to keep SpO₂ > 90%. At 12 hours after ventilation, inflammatory markers in bronchoalveolar lavage fluid (tumor necrosis factor α and IL-8) were significantly higher in the larger tidal volume group. Choi et al. compared 12ml.kg⁻¹ without PEEP versus 6ml.kg⁻¹ with 10cm PEEP and showed procoagulant changes in lavage fluid of the larger tidal volume group after 5 hours of mechanical ventilation. 39 A randomized-control trial in 150 critically ill patients without ALI compared tidal volumes of 10ml.kg⁻¹ versus 6ml.kg⁻¹ predicted body weight. 40 The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines.

Of importance is work suggesting that noninjurious or so-called “protective ventilatory settings” can induce lung injury in previously healthy lungs. An animal study using a very elegant murine “one hit” VILI model, showed that even the least injurious lung settings induced biochemical and histological changes consistent with lung injury. 41 Work with rodents undergoing mechanical ventilation showed significant gene expression (including genes involved in immunity and inflammation) after only 90 minutes of protective ventilation. 42 Whether this has an impact on clinical outcome is unknown at this time.

ALI is the most common cause of postoperative respiratory failure and is associated with markedly decreased postoperative survival. 43 A prospective case controlled study by Fernandez-Perez et al. looking at intraoperative ventilator settings and ALI after elective surgery in more than 4000 patients found a 3% incidence of ALI in high-risk elective surgeries. Compared with controls, patients with ALI had significantly lower postoperative survival rates and increased length of hospital stay. Interestingly in this study, intraoperative peak airway pressure, but not tidal volume, PEEP or FiO₂ were associated with ALI. A retrospective cohort study looking specifically at intraoperative risk factors for ARDS in critically ill patients found that for patients receiving fluid resuscitation > 20ml.kg⁻¹.hr⁻¹ the odds of developing ARDS were 3 times greater than if < 10ml.kg⁻¹.hr⁻¹ was given (odds ratio 3.1, 95% CI = 1.0-9.9 p = 0.05). 44 Tidal Volume.Ideal Body Weight⁻¹ (Vt.IBW⁻¹) (ml.kg⁻¹) and number of blood products were not associated with ARDS in this study. Of interest the majority of patients’ lungs were ventilated with a Vt.IBW⁻¹ of 8-10ml.kg⁻¹ and an intraoperative PEEP of 0.

**Ventilator Induced Lung Injury**

The phenomenon of VILI is well recognized, and can be particularly significant in surgical specialties that require large transfusions, cardiopulmonary bypass and associated lung ischemia-reperfusion injury (IRI). The deleterious effects of mechanical ventilation may be mediated by localized inflammation and the systemic release of inflammatory cytokines (bio-trauma). Mechanical stretch from cyclic alveolar opening and closing sets up an inflammatory response in the alveolar epithelial cells and the vascular endothelial cells. Hyperinflation causes nuclear translocation of Nuclear Factor-κB (a key regulator of the expression of multiple genes involved in inflammatory response) and up-regulation of other proinflammatory cytokines. Polymorphonuclear leukocyte recruitment and activation appear to be key component of the mechanical stretch induced inflammatory response. The balance between apoptosis and necrosis is unfavourably altered by both ischemia-reperfusion and mechanical stretch. 45

Bio-trauma not only aggravates ongoing lung injury but also has important systemic consequences due to the spill over of these inflammatory mediators into the systemic circulation, inducing remote organ dysfunction. A study evaluating 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. 46 In mice undergoing injurious mechanical ventilation, alveolar stretch induced adhesion molecules not only in the lung but also in the liver and kidney. 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. 47

These studies go some way to explain the remote organ dysfunction seen with ALI/ARDS, and the role optimizing ventilatory strategies play in ameliorating this.

This leads to the question; are the lung-protective strategies in ARDS 48 applicable to the perioperative environment, specifically in patients with healthy lungs? A study analyzing this question highlights the lack of randomized controlled trials looking at best intraoperative tidal volume, PEEP, and use of intraoperative lung recruitment. 49 While outcome studies are lacking, based on what we know about the effects of mechanical ventilation, it seems not unreasonable to aim towards protective ventilatory strategies in perioperative practice.

**Perioperative surgical environment factors**

There are multiple factors in the surgical environment that can contribute to lung injury. The most obvious being the surgical approach. Site of operation is an important predictor of pulmonary complications, with upper abdominal and thoracic incisions being the most important (any surgery approaching the diaphragm). A decrease in respiratory complications has been documented if major cavity procedures can be done with minimally invasive versus open techniques. 50 Atelectasis occurs frequently after open surgical procedures and in up to 90% of patients undergoing general anesthesia. 51 It is a pathological state that can contribute to or attenuate lung injury. Thus anesthesiologists must be aware of techniques to avoid or treat it. 52 While open to debate, retrospective 53 and prospective 54 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 patients’ underlying lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia. Reviews comparing paravertebral block versus epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with paravertebral block.\textsuperscript{59,60} Aggressive physiotherapy with CPAP in the postoperative period in patients after major abdominal surgery who develop early desaturation leads to decreased rates of major respiratory complications.\textsuperscript{61}

\textbf{Role of Volatile Anesthetic Drugs in Lung Protection}

Volatile anesthetics have immune-modulatory effects. Much work has been done, especially in the cardiac setting, on the role of volatiles in IRI and in pre- and postconditioning. Studies in models of ALI, during OLV and in cases of lung ischemia-reperfusion suggest that volatile anesthetics may act as pre- and postconditioning drugs inducing 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 reduction of polymorphonuclear recruitment and microvascular protein leakage.\textsuperscript{63} Postconditioning with sevoflurane attenuated lung damage and preserved lung function in an \textit{in vivo} rat ALI model.\textsuperscript{64} In a prospective study, patients undergoing thoracic surgery with OLV were randomized to either propofol or sevoflurane anesthesia.\textsuperscript{65} Observing inflammatory markers in the nonventilated lung, they found an attenuated inflammatory reaction. Significantly, the sevoflurane group had improved outcome and significantly lower overall number of adverse events. A study comparing OLV (Vt 10ml.kg\textsuperscript{-1}) with desflurane versus propofol anesthesia observed the inflammatory response in the ventilated lung.\textsuperscript{66} The inflammatory markers IL-8, IL-10, PMN elastase and TNF\textalpha were significantly lower in the desflurane group.

While much work remains to be done, this exciting work does point towards a role for volatile anesthetics in attenuating the proinflammatory response in the lungs to a host of insults, whether this is pre, during or postinsult.

\textbf{Ultra-protective Lung ventilation}

Following along the continuum of lung-protective ventilation in ALI/ARDS is the concept of ultra-protective ventilation. This concept uses pumpless extracorporeal lung assist, specifically the Novalung\textsuperscript{\textregistered} ILA membrane ventilator, and near static ventilation. A brief description of the Novalung\textsuperscript{\textregistered} is appropriate; it is a membrane ventilator that allows O\textsubscript{2} and CO\textsubscript{2} gas exchange via simple diffusion.\textsuperscript{67} The membranes are biocompatible and provide a non-thrombogenic surface. It is designed to work without a mechanical pump in an arteriovenous configuration, thus requiring an adequate mean arterial blood pressure to drive flow. Flow rates are typically 1-2l.min\textsuperscript{-1}, or approximately 15% of cardiac output. CO\textsubscript{2} 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. As compared with conventional extracorporeal membrane oxygenation, the Novalung\textsuperscript{\textregistered} is a simple, pumpless portable device. Anticoagulation requirements are much reduced with an activated partial thromboplastin time target of 55s. Bleeding complications and blood product requirements are significantly less.

ARDN\textsuperscript{\textregistered}net and animal data demonstrate that lower tidal volumes (3ml.kg\textsuperscript{-1}) compared with 6-12ml.kg\textsuperscript{-1} significantly reduce endothelial and epithelial injury.\textsuperscript{68,69} In other words “protective” tidal volumes can still induce VILI. However clearance of CO\textsubscript{2} and oxygenation become an issue at these lower minute volumes. The Novalung\textsuperscript{\textregistered} allows for this marked reduction in minute volumes and the simultaneous correction of PaCO\textsubscript{2} and pH. An animal model of post-pneumonectomy ARDS using the Novalung\textsuperscript{\textregistered} and tidal volumes of 2.2mls.kg\textsuperscript{-1} and respiratory rate of 6 showed significantly better outcomes compared with conventional lung-protective strategies.\textsuperscript{70} Case reports in humans in a variety of clinical scenarios have been encouraging.\textsuperscript{71} Tidal volumes \textless{} 3ml kg\textsuperscript{-1}, low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung\textsuperscript{\textregistered} \textit{in situ}, causing less VILI and subsequent remote secondary organ failure. The use of extracorporeal membrane oxygenation in combination with protective ventilation has been shown in a randomized trial to significantly increase the survival rate to 63% versus 47% with conventional ventilation strategies, in patients with severe ARDS.\textsuperscript{72}

\textbf{Fluids, Inflammation and the Glycocalyx}

A retrospective cohort study looking specifically at intraoperative risk factors for ARDS in critically ill patients found that for patients receiving fluid resuscitation > 20ml.kg\textsuperscript{-1}hr\textsuperscript{-1} the odds of developing ARDS were 3 times greater than if < 10ml.kg\textsuperscript{-1}hr\textsuperscript{-1} was given (odds ratio 3.1, 95\% CI = 1.0–9.9 p = 0.05).\textsuperscript{73} Vt.IBW\textsuperscript{-1} (ml.kg\textsuperscript{-1}) and number of blood products were not associated with ARDS in this study. Of interest the majority of patients’ lungs were ventilated with a Vt.IBW\textsuperscript{-1} of 8-10ml.kg\textsuperscript{-1} and an intraoperative PEEP of 0. It has long been a concern that excess amounts of IV fluids predispose patients to develop ALI.

However, it has been a conflicting concern for anesthesiologists that fluid restriction in thoracic surgery may contribute to postoperative renal dysfunction which was reported to be associated with a very high (19\%) mortality.\textsuperscript{74} In a review of >100 pneumonectomies at our institution, acute kidney injury (AKI) as defined by the RIFLE classification\textsuperscript{75} occurred in 22\% of patients.\textsuperscript{76} However, there was no association of AKI with fluid balance and there was no increased 30-day mortality in the AKI patients. AKI was associated with preoperative hypertension and complex surgical procedures such as extrapleural pneumonectomy. A similar retrospective study looking at all pulmonary resection patients found that AKI, as defined by the Acute Kidney Injury Network criteria, which occurred in 67/1129 (6\%) patients was not associated with a statistically significant increase in mortality versus non-AKI patients (3\% vs. 1\%).\textsuperscript{77}

Fluid requirements vary widely among patients and procedures and ultimately represent the sum of preoperative deficits, maintenance requirements, and ongoing losses. Fluid management for major esophageal surgery is particularly challenging. Preoperative fluid deficits in patients with severe esophageal disease may be substantial, though they have not been well defined.\textsuperscript{78} Fluid requirements in patients

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undergoing esophageal procedures may be complicated by the fact that patients may be relatively hypovolemic after long preoperative fasts, particularly if esophageal obstruction or dysphagia limit fluid intake. Perioperative losses occur via a number of mechanisms including urinary, gastrointestinal, 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 thus considered to be a “nonfunctional” extracellular 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 of the fluid compartments in the body.89

One of the factors complicating fluid management for esophageal resection is that thoracic epidural analgesia has been shown to improve outcome for these patients80 but its use tends to contribute to hypotension. Hypotension is well known to contribute to ischemia of the gut anastomosis81 and treatment with excessive fluids is likely to exacerbate the problem.82 Many surgeons are concerned about the effects of vasopressors on the anastomotic gut blood flow.83 However, several animal studies suggest that treatment of intraoperative hypotension with norepinephrine does not cause any reduction of gut blood flow in the presence of normovolemia.84,85

An ideal fluid regimen for major surgeries, including esophageal surgery, is individualized and optimizes cardiac output and oxygen delivery while avoiding excessive fluid administration. There is some evidence that fluid therapies which are designed to achieve individualized and specific flow-related hemodynamic endpoints 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, such as central venous pressure which does not predict fluid responsiveness or correlate with circulating blood volume after transthoracic esophagectomy.86,87

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.88 Intravascular colloid retention during treatment of hypovolemia may approach 90% versus 40% when administered during normovolemia.102

The relationship of hydrostatic and oncotic pressure to determine fluid flux across a semi-permeable membrane was described in a classic equation developed in 1896 by Starling.89 Several clinical observations such as the relative resistance of the intact organism to develop edema 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.90 This discrepancy is now attributed to the glycocalyx, a micro-cilial 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 seen 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 seen with colloid boluses. Protecting the glycocalyx may be among the anesthesiologist’s most important duties perioperatively. Volatile anesthetics may have a protective effect on the glycocalyx.91

Other therapies for lung protection
Beyond those already discussed, there are several therapies that may play a future role in lung protection. Permissive hypercapnia’s place in protective ventilation has been alluded to earlier, but as found in the original ARDSnet data, may be protective in the presence of higher tidal volumes.52 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.93 Inhaled hydrogen sulfide shows beneficial effects in a model of VILI via the inhibition of inflammatory and apoptotic responses, independent of its effects on body temperature.94 Inhaled aerosolized activated protein C in a sheep model of ALI demonstrated improved oxygenation as well as lung aeration (as assessed by computed tomography scan).95 β-adrenergic agonists have potential benefits by increasing the rate of alveolar fluid clearance by increasing cellular cyclic adenosine monophosphate and have antiinflammatory properties.96 A randomized controlled trial in 40 patients with ALI showed a decrease in extravascular lung water and plateau airway pressure with IV salbutamol, although it showed no differences in outcome.97 A randomized placebo-controlled trial of several different therapies including surfactant, prone positioning, inhaled nitric oxide and antiinflammatories has not shown significant clinical benefits in patients with established ALI.98 While it is unreasonable to expect there to be a single therapy (or “magic bullet”) that will prevent ALI, the above exciting research does hold promise in both furthering our understanding and management of injured or at risk lungs.

Summary
To summarize what we know:

1. Nonphysiological ventilation in healthy lungs induces ALI.
3. Protective lung ventilation in noninjured lungs and in the absence of a primary pulmonary insult may initiate VILI (as evidenced by inflammatory markers).
4. VILI has important implications remote to the lungs and may be associated with significant morbidity and mortality.
5. Volatile anesthetics may have a lung-protective effect.
6. Excess fluids may contribute to perioperative lung injury.
Anesthesiologists 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 severe COPD. More patients are at risk for ALI based on our current understanding of mechanical ventilation and lung injury. Applying protective ventilatory strategies seems reasonable based on our current understanding of mechanical ventilation and lung injury.

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