Learning Objectives:

1) To understand the risk factors for development of perioperative lung injury in patients having intra-thoracic surgery

2) To develop an anesthetic plan to minimize lung injury during heart, lung or esophageal surgery


Questions:

Further Investigations?

Echocardiography: LVEF 45%, mild MR and TR, Dipyridamole-thallium scan: small fixed anterior wall defect.

Questions:

**Intraoperative:** T6-7 thoracic epidural: bupivicaine plus fentanyl bolus + infusion. Left double-lumen tube, CVP. During laparotomy P 50, BP 90/50, CVP 6. Surgeon refuses vasopressors.

**Questions:**

Treatment of Hypotension? Voluven 1.5L, RL 3L. Management of one-lung ventilation?

Extubation at end of 7h surgery?

**Postoperatively:** persistent hypotension, epidural decreased then d/c’d, IV PCA analgesia, poor pain control. Resp. failure POD 3, bilateral pneumonia, ICU admission. Prolonged PPV, tracheostomy, re-operation for anastomotic dehiscence POD 20.

**Question:**

Could anesthetic management have altered this outcome?

**Case 2:** 72 y.o. male (70kg, 165 cm) with COPD presents for left pneumonectomy for lung Ca. Past medical history: HTN, DM2, paroxysmal AF and renal dysfunction (GFR 50). He has normal exercise tolerance. His investigations showed moderate COPD (FEV₁ 72%, DLCO 67%) and normal room-air blood gas.

**Questions:**

Is he an acceptable risk for a left pneumonectomy?


**Intraoperative course:** Thoracic epidural, a-line, central venous line. During OLV ventilated with pressure-control (30/ 5 cm H₂O, 520 ml x 12, FiO₂ 0.56). Patient stable throughout, surgery completed after 200 min. Blood loss 400 ml., not transfused, 2L RL, urine output 500ml.
**Postoperative Course:** Patient extubated in the OR, and taken to recovery comfortable and stable for overnight observation. PaO₂/FiO₂ ratio in the recovery room was 473. Patient required 3 fluid challenges overnight to maintain blood pressure targets, with temporary decreases in the epidural infusion. Patient was discharged to the thoracic step-down unit POD1 on room air, hemodynamically stable with reasonable analgesia. On POD2 the patient went into hemodynamically stable AF and was treated with rate control. POD4 patient developed severe hypoxemia requiring high flow oxygen and displaying signs of respiratory distress. He was intubated and taken to the ICU. P/F ratio was 78.

**Differential Diagnosis?**

Treated with protective ventilation, steroids, broad spectrum antibiotics. Chest CT demonstrated dense consolidation in the remaining right lung. A TEE showed LV dysfunction (20-35%) and RV failure, inotropic support was initiated with norepinephrine and milrinone. Patient improved rapidly, was extubated on POD 11, however required re-intubation on POD 13. Patient failed another extubation within 48 hrs on POD 15.

**Questions:**

Alternative ICU ventilation strategies in this case? Arrhythmia prevention, management?

Is there an anesthetic technique that may decrease the risk of this complication?

**Discussion**

Patients are at risk for several types of lung injury in the peri-operative 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 PEEP can decrease the extent of this injury\textsuperscript{1}. This PBLD will look at the effects of mechanical ventilation and its role in Ventilator Associated Lung Injury (VILI) with specific reference to Thoracic Anesthesia. Newer work looking at lung protection strategies will briefly be discussed.

**Mechanical ventilation**

Historically, Anesthesiologists have been taught to ventilate patients in the perioperative period with relatively large tidal volumes. Volumes as high as 15 ml kg\textsuperscript{-1} ideal body weight have been suggested to avoid intra-operative atelectasis\textsuperscript{ii}. This far exceeds the normal spontaneous tidal volumes (6 ml kg\textsuperscript{-1}) common to most mammals\textsuperscript{iii}. Recent studies have identified the use of large tidal volumes as a major risk factor for development of lung injury in mechanically ventilated patients without acute lung injury (ALI). Gajic reported that 25% of patients with normal lungs ventilated in an ICU setting for 2 days or longer developed ALI or ARDS\textsuperscript{iv}. 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 have found that tidal volumes > 700mls and peak airway pressures > 30 cm H\textsubscript{2}O were independently associated with the development of ARDS\textsuperscript{v}. An intra-operative study of patients having oesophageal surgery compared the use of tidal volumes of 9 ml kg\textsuperscript{-1} without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation vs. 9 ml kg\textsuperscript{-1} during two-lung ventilation and 5 ml kg\textsuperscript{-1} during one-lung ventilation with PEEP 5 cm H\textsubscript{2}O throughout\textsuperscript{vi}. They found significantly lower serum makers of inflammation (cytokines IL-1\textbeta, IL-6 and IL-8) in the lower tidal volume plus
PEEP group. The study did not find any major difference in post-operative 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 one-lung ventilation, but not after 18h. In a study looking at conventional vs. protective ventilation in critically ill patients without lung injury, de Olivera and colleagues randomized patients to ventilation with either 10-12ml.kg\(^{-1}\) or 6-8ml.kg\(^{-1}\) predicted body weight\(^{vii}\). In both groups a PEEP of 5 was applied and the FiO\(_2\) titrated to keep SpO\(_2\) > 90%. At 12hours post-ventilation, inflammatory markers in broncho-alveolar lavage fluid (TNF\(_\alpha\) and IL-8) were significantly higher in the larger tidal volume group. Choi and colleagues compared 12ml.kg\(^{-1}\) without PEEP vs. 6ml.kg\(^{-1}\) with 10cm PEEP and showed pro-coagulant changes in lavage fluid of the larger tidal volume group after 5 hours of mechanical ventilation\(^{viii}\). A recent randomised-control trial in 150 critically ill patients without ALI compared tidal volumes of 10ml.kg\(^{-1}\) vs. 6ml.kg\(^{-1}\) predicted body weight\(^{ix}\). The conventional tidal volumes were associated with a sustained plasma increase in inflammatory cytokines.

Of importance is recent work suggesting that non-injurious or so-called protective ventilatory settings can induce lung injury in previously healthy lungs. An animal study using a very elegant murine ‘one hit’ ventilator induced lung injury (VILI) model, showed that even least injurious lung settings induced biochemical and histological changes consistent with lung injury\(^{x}\). Work with rodents undergoing mechanical ventilation showed significant gene expression (including genes involved in immunity and inflammation) after only 90 minutes of protective ventilation\(^{xi}\). Whether this has an impact on clinical outcome is unknown at this time.
ALI is the most common cause of post-operative respiratory failure and is associated with a markedly decreased post-op survival\textsuperscript{xii}. A prospective case controlled study by Fernandez-Perez and colleagues looking at intra-operative ventilator settings and ALI after elective surgery in over 4000 patients showed a 3% incidence of ALI in high-risk elective surgeries. Compared with controls, patients with ALI had significantly lower postoperative survival and increased length of hospital stay. Interestingly in this study, intra-operative peak airway pressure, but not tidal volume, PEEP or FiO\textsubscript{2} were associated with ALI. A retrospective cohort study looking specifically at intra-operative 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{xiii}. 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 were ventilated with a Vt.IBW\textsuperscript{-1} of 8-10ml.kg\textsuperscript{-1} and an intra-operative PEEP of 0.

**Ventilator Induced Lung Injury (VILI)**

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. The deleterious effects of mechanical ventilation may be mediated by localized inflammation and the systemic release of inflammatory cytokines (bio-trauma). 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 nuclear translocation of NF-κB (a key regulator of the expression of multiple genes involved in inflammatory response) and up-
regulation of other pro-inflammatory 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 ischaemia-reperfusion and mechanical stretch\textsuperscript{xiv}.

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 looking at 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\textsuperscript{xv}. 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\textsuperscript{xvi}. 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\textsuperscript{xvii} applicable to the peri-operative environment, specifically in patients with healthy lungs? A recent paper looking at this question highlights the lack of randomized-controlled trials looking at best intra-operative tidal volume, PEEP, and use of intra-operative lung recruitment\textsuperscript{xviii}. 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 peri-operative practice.
**Peri-operative 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\textsuperscript{xix} (any surgery approaching the diaphragm). A decrease in respiratory complications has been documented if major cavity procedures can be done with minimally invasive vs. open techniques\textsuperscript{xx xxi}. Atelectasis occurs frequently following open surgical procedures and in up to 90\% of patients undergoing general anaesthesia\textsuperscript{xxii}. 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\textsuperscript{xxiii}. While open to debate, retrospective\textsuperscript{xxiv xxv} and prospective\textsuperscript{xxvi} 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\textsuperscript{xxvii}. Reviews comparing Para-vertebral block (PVB) vs. epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with PVB\textsuperscript{xxviii xxix}. Aggressive physiotherapy with CPAP in the post-operative period in patients after major abdominal surgery who develop early desaturation leads to lower rates of major respiratory complications\textsuperscript{xxx}

**One-Lung Ventilation (OLV)**
Anesthesiologists are faced with a heterogeneous patient group, in terms of underlying pathology and surgical procedure, requiring one-lung ventilation. Both the patient’s pathology and the surgical procedure can predispose to or cause ALI. ALI following pulmonary resection has been described since the beginning of OLV for thoracic surgery. The most publicized report is a compilation of 10 pneumonectomy cases published in 1984xxxii, which focused on the role of intravenous over-hydration as a cause of post-pneumonectomy pulmonary oedema. Much work has subsequently followed and our understanding of 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 a 100% mortality in affected patientsxxxii. There was no difference in peri-operative fluid balance between post-pneumonectomy ALI cases (24 hr fluid balance 10ml.kg\(^{-1}\)) vs. matched pneumonectomy controls (13ml.kg\(^{-1}\)). Authors used rigorous fluid restriction compared to other reportsxxxiii, suggesting that limiting intra-operative fluids might decrease but not eliminate ALI. Post-pneumonectomy pulmonary ALI has been shown to have a bimodal distribution of onsetxxxiv. Late cases presented 3-10 days post-operatively and were secondary to obvious causes such as bronchopneumonia, aspiration etc. Early or “primary” ALI presented on post-operative days 0-3. Four factors were independent significant predictors of primary ALI: high intra-operative ventilation pressures, excessive intravenous volume replacement, pneumonectomy, and pre-operative alcohol abuse. Looking specifically at ventilation pressures, Licker and colleagues used a baro-trauma index taking into account both the duration of OLV and the use of increased inspiratory pressure. This index represented the strongest risk factor
for ALI (approximately threefold increase risk if PIP ≥ 25cm H₂O vs. PIP = 15cm H₂O). The known facts about ALI following lung surgery include: an incidence following pneumonectomy of 2-4%, greater frequency of right vs. 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 8/9 cases who developed unilateral ALI following lobectomy, the ALI was in the non-operated (i.e. the ventilated) lung. While there is an association between postoperative ALI and fluid overload, the non-cardiogenic nature of the pulmonary oedema (low/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. Post-operative increases in lung permeability of the non-operated lung have been demonstrated after pneumonectomy but not lobectomy. This capillary-leak injury may be due to an inflammatory cascade affecting even the non-operative lung that is triggered by lung resection and is proportional to the amount of lung resected. Free oxygen radical generation in lung cancer patients is related to the duration of OLV. 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 post-operative injury. End-inspiratory lung volume is a key factor in VILI. Many patients, especially emphysema patients, develop auto-PEEP with OLV, thus inspiration begins at a lung volume above functional residual capacity (FRC). Using large tidal volumes (10-12ml.kg⁻¹) during OLV in such patients produces end-inspiratory volumes at levels that may cause or contribute to ALI. The effects of PEEP during OLV are variable and
very much dependant on the lung mechanics of the individual patient, with initial studies suggesting that it leads to a deterioration of arterial oxygenation\textsuperscript{xlii}. Most COPD patients develop auto-PEEP during OLV, leading to hyperinflation and increased shunt\textsuperscript{xliii}. 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 avoiding setting up a pre-inflammatory state leading to injury in both the atelectatic lung and the ventilated portions of the lung, which become hyper-inflated\textsuperscript{xliv}. 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 (8ml.kg\textsuperscript{-1}) ventilation produced a picture of ALI absent in animals randomized to a lung-protective ventilation pattern (4ml.kg\textsuperscript{-1} plus PEEP)\textsuperscript{xlv}. Large pulmonary resections (pneumonectomy or bi-lobectomy) should be considered to be associated with some degree of ALI. 42% of pneumonectomy patients who had been ventilated with peak airway pressures > 40cm H\textsubscript{2}O had ALI diagnosed radiographically\textsuperscript{xlvi}. A retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intra-operative tidal volumes (8.3ml.kg\textsuperscript{-1} vs. 6.7ml.kg\textsuperscript{-1} in those patients who did not develop respiratory failure)\textsuperscript{xlvii}. Thus our current understanding of post-thoracotomy ALI supports applying the management strategies of least injurious lung ventilation: FiO\textsubscript{2} as low as acceptable, variable tidal volumes\textsuperscript{xlviii}, beginning inspiration at FRC and avoiding atelectasis with frequent recruitment maneuvers\textsuperscript{xlix}. An observational study in patients undergoing lung cancer surgery by Licker and workers would seem to confirm this\textsuperscript{1}. Using a protective lung ventilation strategy (Vt < 8ml.kg\textsuperscript{-1} predicted body weight, pressure control ventilation, Peak
inspiratory pressures < 35cm H₂O, external PEEP 4-10cm H₂O and frequent recruitment maneuvers) in a protocol group (558 patients) vs. conventional ventilation in an historical group (533 patients). They showed a decreased incidence of ALI (3.7% to 0.9%, p < 0.01), atelectasis (8.8 to 5.0, p = 0.018), fewer ICU admissions (2.5% vs. 9.4% p < 0.001) and shorter hospital stay.

Hypercarbia resulting 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 hypercarbia. Minimizing pulmonary capillary pressure by avoiding over-hydration for patients undergoing pneumonectomy is reasonable while acknowledging that not all peri-operative increases in pulmonary artery pressures are due to intravascular volume replacement. Finally it must be appreciated that not all hyper-inflation 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 to contribute to a decrease in ALI in some centers.

Role of Volatile Anesthetic Agents in Lung Protection.

Volatile agents have immune-modulatory effects. Much work has been done, especially in the cardiac setting, on the role of volatiles in Ischemia-Reperfusion Injury (IRI) and in pre- and post-conditioning. Recent studies in models of ALI, during OLV and in cases of lung ischemia-reperfusion suggest that volatiles may act as pre- and post-conditioning agents inducing lung protection by inhibition of the expression of pro-inflammatory mediators. Isoflurane pre-treatment in an endotoxin mediated animal model of lung injury exerted protective effects, as evidenced by reduction of polymorphonuclear recruitment
and microvascular protein leakage\textsuperscript{lv}. Post-conditioning with sevoflurane attenuated lung damage and preserved lung function in an \textit{in vivo} rat ALI model\textsuperscript{lv}. In a prospective study, patients undergoing thoracic surgery with OLV were randomized to either propofol or sevoflurane anesthesia\textsuperscript{lvii}. Looking at inflammatory markers in the non-ventilated lung, they showed an attenuated inflammatory reaction. Significantly, the sevoflurane group had an improved outcome and significantly lower overall number of adverse events. A study comparing OLV (Vt 10ml.kg\textsuperscript{-1}) with desflurane vs. propofol anesthesia looked at the inflammatory response in the ventilated lung\textsuperscript{lvii}. The inflammatory markers IL-8, IL-10, PMN elastase and TNF\alpha were significantly lower in the desflurane group.

While much work remains to be done, this exciting work does point towards a role for volatiles in attenuating the pro-inflammatory response in the lungs to a host of insults, whether this is pre, during or post insult.

**Cardio-pulmonary Bypass (CPB)**

Pulmonary dysfunction post CPB is a well-described but poorly understood phenomenon\textsuperscript{lviii}. While the incidence of ARDS post CPB is low (<2\%) the mortality associated with it is high (>50\%)\textsuperscript{lix}. While the Systemic Inflammatory Response Syndrome (SIRS) initiated by CPB plays a major role, the pulmonary insult is multifactorial and not all related 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, ischemia-reperfusion injury, administration of blood products and ventilatory arrest.

It must be emphasized that the above strategies, while having good theoretical basis, have showed inconsistent results in the literature in terms of improving pulmonary
outcome. Protective post-operative ventilation of these “at risk” lungs is key. A randomized-control trial compared the use of non-protective high tidal volumes (10-12 ml.kg$^{-1}$) plus low PEEP (2-3 cm H$_2$O) vs. lung protective low tidal volumes (8 ml.kg$^{-1}$) plus high PEEP (10 cm H$_2$O) in patients ventilated for 6h following cardiopulmonary bypass for coronary artery bypass surgery$^{18}$. Serum and bronchiolar lavage levels of the inflammatory cytokines IL-6 and IL-8 were significantly increased at 6h only in the non-protective ventilation group.

**Ultra-protective Lung ventilation.**

Following along the continuum of lung protective ventilation in ALI/ARDS is the concept of ultra-protective ventilation. This concept utilizes pumpless extracorporeal lung assist, specifically the Novalung® ILA membrane ventilator, and near static ventilation. A brief description of the Novalung® is appropriate; it is a membrane ventilator that allows O$_2$ and CO$_2$ gas exchange via simple diffusion$^{18i}$. The membranes are biocompatible and provide a non-thrombogenic surface. It is designed to work without a mechanical pump in an Arterio-Venous configuration, thus requiring an adequate mean arterial pressure to drive flow. Flow rates are typically 1-2l.min$^{-1}$, or approximately 15% of cardiac output. CO$_2$ 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 ECMO, the Novalung® is a simple, pumpless portable device. Anti-coagulation requirements are much reduced with an aPTT target above or equal 55s. Bleeding complications and blood product requirements are significantly less.
ARDSnet and animal data demonstrates that lower tidal volumes (3ml.kg\(^{-1}\)) compared with 6-12ml.kg\(^{-1}\) significantly reduces endothelial and epithelial injury\(^{\text{lxii} \text{ lxiii}}\). In other words “protective” tidal volumes can still induce VILI. However clearance of CO\(_2\) and oxygenation become an issue at these lower minute volumes. The Novalung\(^{\text{\textregistered}}\) allows for this marked reduction in MV and the simultaneous correction of PaCO\(_2\) and pH. An animal model of post-pneumonectomy ARDS using the Novalung\(^{\text{\textregistered}}\) and tidal volumes of 2.2mls.kg\(^{-1}\) and respiratory rate of 6 showed significantly better outcomes compared with conventional lung protective strategies\(^{\text{lxiv}}\). Numerous case reports in humans in a variety of clinical scenarios have been encouraging\(^{\text{lxv lxxvi lxxvii lxxviii}}\). Tidal volumes \(\leq 3\text{ml.kg}\(^{-1}\), low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung\(^{\text{\textregistered}}\) in situ, causing less VILI and subsequent remote secondary organ failure. While by no means standard of care at this time, this technique 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 looking specifically at intra-operative 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)\(^{\text{lxix}}\). 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 were ventilated with a Vt.IBW\(^{-1}\) of 8-10ml.kg\(^{-1}\) and an intra-operative 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 Anesthesiologists that fluid restriction in thoracic surgery may contribute to postoperative renal dysfunction, which previously was reported to be associated with a very high (19%) mortality\textsuperscript{xx}. In a recent review of >100 pneumonectomies at our institution, acute kidney injury (AKI) as defined by the RIFLE classification\textsuperscript{xxi} occurred in 22% of patients\textsuperscript{xxii}. 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 extra-pleural pneumonectomy. A similar retrospective study looking at all pulmonary resection patients found that acute kidney injury (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 vs. non-AKI patients (3% vs. 1\%)\textsuperscript{xxiii}.

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 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{xxiv}. Fluid requirements in patients 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, 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 non-interstitial extra-cellular spaces, which are not in equilibrium with the vascular compartment and thus considered to be a “non-functional” 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 of the fluid compartments in the body.

One of the factors complicating fluid management for esophageal resection is that thoracic epidural analgesia has been shown to improve outcome for these patients but it use tends to contribute to hypotension. Hypotension is well known to contribute to ischemia of the gut anastomosis and treatment with excessive fluids is likely to exacerbate the problem. Many surgeons are concerned about the effects of vasopressors on the anastomotic gut blood flow. However, several recent animal studies suggest that treatment of intraoperative hypotension with nor-epinephrine does not cause any reduction of gut blood flow.

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\textsuperscript{lixxii,lixxiii}. 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\textsuperscript{lixxxiv}. Intravascular colloid retention during treatment of hypovolemia may approach 90% vs. 40% when administered during normovolemia\textsuperscript{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\textsuperscript{lixxxv}. 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\textsuperscript{lixxxvi}. 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 ischemia-reperfusion injury 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.

\textbf{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 $V_t^{lxxxvii}$. Hypercapnic Acidosis (HCA) 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$^{lxxxviii}$. 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$^{lxxix}$. Inhaled aerosolized activated protein C in a sheep model of ALI demonstrated improved oxygenation as well as lung aeration (as assessed by CT scan)$^{xc}$.

β-adrenergic agonists have potential benefits by increasing the rate of alveolar fluid clearance by increasing cellular cAMP and have anti-inflammatory properties$^{xci}$. A randomized-control trial in 40 patients with ALI showed a decrease in extra-vascular lung water and plateau airway pressure with intravenous salbutamol, although it showed no differences in outcome$^{xcii}$ Randomized placebo-controlled trial of several different therapies including surfactant, prone positioning, inhaled nitric oxide and anti-inflammatories have not shown significant clinical benefits in patients with established ALI$^{xciii}$. 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**

1) Non-physiological ventilation in healthy lungs induces ALI.

2) Protective lung ventilation in patients with ALI/ARDS improves outcome.
3) Protective lung ventilation in non-injured 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.

---


de Oliveira RP, Hetzel MP, Silva M, Dallegrave D, Friedman G. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Critical Care 2010; 14: R39


Determann R, Royakkers A, Wolthuis EK et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Critical Care 2010; 14: R1


Ng CSH, Song Wan, Ho AMH, Underwood MJ. Gene expression changes with a “non-injurious’ ventilation strategy. Critical Care 2009; 13: 403


xviii Beck-Schimmer B, Schimmer RC. Perioperative tidal volume and intraoperative open lung strategy in healthy lungs: where are we going? Best Practice and Research Clinical Anaesthesiology 2010; 24: 199-210


Tusman G, Bohm SH, Suarez-Shipman F. Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Canadian Journal of Anaesthesia 2004; 51: 723-727


Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side effects of paravertebral vs. epidural blockade for thoracotomy – a systematic review and meta-analysis of randomized trials. BJA 2006; 96: 418-426


Slinger PD, Kruger M, McRae K, Winton T. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation. Anesthesiology 2001; 95: 1096-1102


Gama de Abreu M, Heintz M, Heller A, Széchényi R, Albrecht DM, Koch T. One-lung ventilation with high tidal volumes and zero positive end-expiratory pressure is injurious in the isolated rabbit lung model. Anesthesia & Analgesia 2003; 96: 220-228


Apostolakis EE, Koletsis EN, Baikoussis NG, Siminelakis SN, Papadopoulos GS. Strategies to prevent intraoperative lung injury during cardiopulmonary bypass. Journal of Cardiothoracic Surgery 2010; 5: 1

Ng CS, Wan S, Yim AP, Arifi AA. Pulmonary dysfunction after cardiac surgery. Chest 2002; 121: 1269-1277


The Cardiothoracic Surgery Network website.


Frank JA, Gutierrez JA, Jones KD, Allen L, Dobbs L, Matthay MA. Low tidal volume


Starling EH. On the absorption of fluids form the connective tissue spaces. J Physiol 1896, 19: 312-26


