Perioperative Lung Protection Strategies: Are They Worth the Trouble?

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INTRODUCTION

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. This lecture will look at the effects of mechanical ventilation and its role in Ventilator Associated Lung Injury (VILI) with specific reference to Thoracic Anesthesia. The specific clinical scenarios of Chronic Obstructive Pulmonary Disease (COPD), One-lung ventilation, Cardiopulmonary Bypass and Transfusion related lung injury (TRALI) will be examined. Newer work looking at lung protection strategies will briefly be discussed.

MECHANICAL VENTILATION

Historically, Anesthesiologists have been taught to ventilate patients in the peri-operative period with relatively large tidal volumes. Volumes as high as 15ml kg⁻¹ ideal body weight have been suggested to avoid intra-operative atelectasis. This far exceeds the normal spontaneous tidal volumes (6ml.kg⁻¹) common to most mammals. 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. 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 > 30cm H₂O were independently associated with the development of ARDS. An intra-operative study of patients having oesophageal surgery compared the use of tidal volumes of 9 ml.kg⁻¹ without positive end-expiratory pressure (PEEP) during two- and one-lung ventilation vs. 9 ml.kg⁻¹ during two-lung ventilation and 5 ml.kg⁻¹ during one-lung ventilation with PEEP 5 cmH₂O throughout. They found significantly lower serum makers of inflammation (cytokines IL-1β, 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 Oliveira and colleagues randomized patients to ventilation with either 10-12ml.kg⁻¹ or 6-8ml.kg⁻¹ predicted body weight. In both groups a PEEP of 5 cmH₂O was applied and the FiO₂ titrated to keep SpO₂ > 90%. At 12 hours post-ventilation, inflammatory markers in broncho-alveolar lavage fluid (TNFα 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. 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. 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. Work with rodents undergoing mechanical ventilation showed significant gene expression (including genes involved in immunity and inflammation) after only 90 minutes of protective ventilation. Whether this has an impact on clinical outcome is unknown at this time. A pig study suggested that ventilation with 15ml.kg⁻¹ and 3cmH₂O PEEP was less injurious than 6 ml.kg⁻¹ with either 3 or 10 cmH₂O PEEP. ALI is the most common cause of post-operative respiratory failure and is associated with a markedly decreased post op survival. 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 FiO₂ 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⁻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). 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\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-kB (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{15}

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{16} 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{17} These studies go some way as to explain the remote organ dysfunction seen with ALI/ARDS, and the role optimising ventilatory strategies play in ameliorating this.

This leads to the question; are the lung protective strategies in ARDS\textsuperscript{18} applicable to the peri-operative environment, specifically in patients with healthy lungs? A recent paper looking at this question highlights the lack of randomised-controlled trials looking at best intra-operative tidal volume, PEEP, and use of intra-operative lung recruitment.\textsuperscript{19} 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 (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{21,22} Atelectasis occurs frequently following open surgical procedures and in up to 90% of patients undergoing general anaesthesia.\textsuperscript{23} 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{24} While open to debate, retrospective\textsuperscript{25,26} and prospective\textsuperscript{27} 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 undergoing lung disease. Patients with COPD seem to derive the most benefit from epidural analgesia.\textsuperscript{28} Reviews comparing Para-vertebral block (PVB)\textsuperscript{29,30} vs. epidural analgesia in patients undergoing thoracic surgery showed equivalent analgesia efficacy but a better side effect profile and lower complication rate with PVB. 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{31}

**PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

COPD patients are at an increased risk of lung injury in the peri-operative period.\textsuperscript{32} Key concepts that are relevant to anaesthetic management and lung protection include:

**Dynamic hyperinflation:** Emphysema is almost exclusively an expiratory disease, thus during positive pressure ventilation moving gas into the patient’s lungs is easy, but due to intrinsic PEEP (auto-PEEP) it is extremely difficult to move the gas out. This intra-thoracic gas trapping is called dynamic hyperinflation.\textsuperscript{33} Severe hyperinflation impairs cardiac venous return leading to hypotension and in severe cases, cardiac arrest.\textsuperscript{34} This can occur during seemingly low levels of positive airway pressure, such as during bag-mask ventilation at induction. Anaesthesiologists must be very alert to this entity. Thorous pre-oxygenation prior to induction, use of small tidal volumes, slow respiratory rates with long expiratory times, tolerance of hypercarbia and hemodynamic support are key to avoiding hemodynamic collapse in these patients. Acute decompensation during positive pressure ventilation of these patients presents a challenging differential diagnosis between dynamic hyperinflation and tension pneumothorax. Unilateral breath sounds, tracheal shift and presence of bullae favour pneumothorax and the need for urgent decompression. In the absence of these clues it is reasonable to disconnect the patient from the ventilatory circuit and allow passive exhalation to the atmosphere. If there is no improvement with a period
of apnoea, then treatment measures for pneumothorax should be instituted.

**Bullae:** Many patients with moderate to severe COPD develop cystic air spaces in the lung parenchyma. These bullae will tend to be asymptomatic unless occupying more than 50% of the hemi-thorax, in which case patients will have features of restrictive and obstructive lung disease. These bullae are localized areas of loss of structural support tissue in the lung with elastic recoil of surrounding parenchyma. The pressure in the bullae is the mean pressure in the surrounding alveoli averaged over the respiratory cycle. This means that during normal spontaneous ventilation the intra-bulla pressure is slightly negative in comparison to the surrounding parenchyma. When positive pressure ventilation is instituted the pressure in the bulla becomes positive in relation to adjacent structures and the bulla will expand, with the attendant risk of rupture, tension pneumothorax and broncho-pleural fistula. Positive pressure ventilation can be safely used if airway pressures are kept low and there is the expertise and equipment available for chest drain insertion and lung isolation.

Respiratory drive: Determining patient’s PaCO₂ baseline with peri-operative arterial blood gases is important in setting goals for intra- and post-ventilation. It is not possible to predict which patients are CO₂-retainers based on severity of their disease. CO₂ retention seems primarily related not to an alteration of respiratory control mechanisms but due to an inability to maintain the increased work of respiration. In patients receiving supplemental oxygenation the PaCO₂ rises not due to decreased minute ventilation but due to a relative increase in alveolar dead space by the redistribution of lung perfusion and due to the Haldane effect. However, post operative hypoxemia must be prevented with supplemental oxygen; the attendant rise in PaCO₂ must be anticipated and monitored. Arterial blood gases and level of consciousness are the best monitors, with PaCO₂ levels of > 10-13kPa having sedative and anaesthetic effects.

**Nocturnal Hypoxemia:** COPD patients desaturate more frequently and severely than normal patients during sleep. This is related to the rapid shallow pattern of ventilation which occurs in all patients during REM sleep. This tendency to desaturate combined with the postoperative fall in FRC and opioid analgesia places these patients at high risk for severe hypoxemia postoperatively during sleep.

Right ventricular dysfunction: RV dysfunction occurs in up to 50% of COPD patients. A dysfunctional RV is intolerant of sudden changes in afterload associated with switching from spontaneous to controlled ventilation or large pulmonary resections.

**PERI-OPEative TherAPY oF COPD TO DecreASE lUNG INjURY**

**Physiotherapy:** It has been clearly shown that patients with COPD benefit form an intensive program of preoperative chest physiotherapy, with fewer postoperative pulmonary complications. It is possible to improve exercise tolerance in even the most severe COPD patient. However, little improvement is seen before one month. Those COPD patients with excessive sputum production benefit the most from chest physiotherapy.

**Smoking cessation:** A pre-operative smoking cessation program can significantly decrease the incidence of respiratory complications (4-8 weeks abstinence), wound complications (4 weeks abstinence), and intra-operative myocardial ischemia (48h abstinence).

**Bronchodilation:** Broncho-constriction is assessed by history, physical examination and evaluation of pulmonary function response to bronchodilators. Patients should receive maximal bronchodilator therapy as guided by their symptoms. It is not clear if corticosteroids are as beneficial as they are in asthma, but in patients poorly controlled on sympathomimetic and anticholinergic bronchodilators a trial of corticosteroids may be beneficial. Pulmonary function tests are not useful screening tools for all patients, but are valuable in assessing flow rates in symptomatic patients, to confirm the diagnosis and to assess adequacy of treatment. Incidence of intra-operative life-threatening bronchospasm has become very low. The principles for managing patients with reactive airways remains the same however: preoperative optimizing of bronchodilation, avoiding instrumentation of the airway, airway instrumentation at an adequate depth of anaesthesia, use of bronchodilating anaesthetics (volatile, propofol, ketamine) and appropriate warming and humidification of gases. In patients with bronchial hyperactivity on regular bronchodilator therapy, post-intubation wheezing can be significantly reduced by a 5-day preoperative course of corticosteroids.

**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 1984 which focused on the role of intravenous overhydration 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 patients. 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 reports, 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 onset.\textsuperscript{34} Late cases presented 3–10 days post-operatively and were secondary to obvious causes such as broncho-pneumonia, 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 duration of OLV and increased inspiratory pressure. This index represented the strongest risk factor for ALI (approximately threefold increase risk if PIP \(\geq 25\) cm H\(_2\)O vs. PIP = 15 cm H\(_2\)O). 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.\textsuperscript{55} 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.\textsuperscript{56} 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.\textsuperscript{37,56} Free oxygen radical generation in lung cancer patients is related to the duration of OLV.\textsuperscript{59} 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.\textsuperscript{50} Many patients, especially emphysema patients, develop auto-PEEP with OLV,\textsuperscript{61} 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 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{52} Most COPD patients develop auto-PEEP during OLV, leading to hyperinflation and increased shunt.\textsuperscript{53} 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{64} 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\(^{-1}\)) ventilation produced a picture of ALI absent in animals randomized to a lung-protective ventilation pattern (4ml.kg\(^{-1}\) plus PEEP).\textsuperscript{65} Large pulmonary resections (pneumonectomy or bilobectomy) 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\(_2\)O had ALI diagnosed radiographically.\textsuperscript{46} A retrospective study found that post-pneumonectomy respiratory failure was associated with the use of higher intra-operative tidal volumes (8.3ml.kg\(^{-1}\) vs. 6.7ml.kg\(^{-1}\) in those patients who did not develop respiratory failure).\textsuperscript{67} Thus our current understanding of post-thoracotomy ALI supports applying the management strategies of least injurious lung ventilation: \(\text{FiO}_2\) as low as acceptable, variable tidal volumes,\textsuperscript{68} beginning inspiration at FRC and avoiding atelectasis with frequent recruitment manoeuvres.\textsuperscript{69} An observational study in patients undergoing lung cancer surgery by Licker and workers would seem to confirm this.\textsuperscript{70} Using a protective lung ventilation strategy (\(V_t < 8\)ml.kg\(^{-1}\) predicted body weight, pressure control ventilation, Peak inspiratory pressures < 35cm H\(_2\)O, external PEEP 4–10cm and frequent recruitment manoeuvres) 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.\textsuperscript{71} 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 centres.\textsuperscript{72}

**ROLE OF VOLATILE ANES THETIC 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\textsuperscript{73} 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. Post-conditioning with sevoflurane attenuated lung damage and preserved lung function in an in vivo rat ALI model. In a prospective study, patients undergoing thoracic surgery with OLV were randomised to either propofol or sevoflurane anaesthesia. 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-1) with desflurane vs. propofol anaesthesia looked at the inflammatory response in the ventilated lung. The inflammatory markers IL-8, IL-10, PMN elastase and TNF were significantly lower in the desflurane group. Sevoflurane has been shown to be lung protective in a pig lung autotransplant model. 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.

**TRANSFUSION RELATED LUNG INJURY (TRALI)**

Transfusion related acute lung injury has emerged as a leading cause of transfusion morbidity and mortality, with a disproportionate number of cases occurring in the peri-operative period. Anaesthesiologists are routinely involved in transfusion decisions and are well placed to both decrease the incidence, and the morbidity and mortality of TRALI. Diagnostic criteria consist of hypoxia or bilateral pulmonary oedema during or within 6 hours of transfusion, in the absence of circulatory overload. Difficulties lie in patients with other risk factors for ALI, pre-existing ALI and subtle cases that may not meet current criteria. The exact pathogenesis is not completely understood. 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 release of neutrophil bioactive products results in endothelial damage, capillary leak and ALI. Antibodies implicated 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, trauma) to the vascular endothelium results in endothelial activation resulting in release of cytokines and adhesion molecules. Neutrophils are then attracted, primed and sequestered in the lung in this pro-inflammatory milieu. A second hit, by transfusion of biologic response modifiers, activates these sequestered neutrophils resulting in the release of oxidases and proteases, resulting in 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 due to the fact that standardized definitions have only recently been developed, but a prospective cohort study looking at an ICU population using current definitions reported an 8% incidence (901 patients), with plasma and platelets having the highest associations. Mortality is estimated at 5-10%. All blood products have been implicated, with most of the products containing more than 50mls of plasma. Data suggest plasma and apheresis platelets have the highest component risk.

Strategies for prevention for transfusion services include, but are not limited to; fresher products, washed components and plasma primarily or exclusively from male donors (avoiding multiparous females). More importantly for the anaesthesiologist is the appropriate use of blood products and to avoid further lung injury. Transfusion triggers must be individualized for each patient and aimed at clinical endpoints. Prothrombin complex concentrates may have a future role in place of FFP and there is certainly a sound theoretical basis for this.

**CARDIO-PULMONARY BYPASS (CPB)**

Pulmonary dysfunction post CPB is a well described but poorly understood phenomenon. While the incidence of ARDS post CPB is low (<2%) the mortality associated with it is high (>50%). While the Systemic Inflammatory response syndrome initiated by CPB plays a major role, the pulmonary insult is multi-factorial 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 ventilatory strategies 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 H2O) vs. lung protective low tidal volumes (8 ml.kg-1) plus high PEEP (10 cm H2O) in patients ventilated for 6h following cardiopulmonary bypass for coronary artery bypass surgery. 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 O₂ and CO₂ gas exchange via simple diffusion.³⁹ 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. CO₂ 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 aPPT target of 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.⁶⁰,⁹¹ In other words “protective” tidal volumes can still induce VILI. However clearance of CO₂ and oxygenation become an issue at these lower minute volumes. The Novalung® allows for this marked reduction in MV and the simultaneous correction of PaCO₂ and pH. An animal model of post-pneumonectomy ARDS using the Novalung® and tidal volumes of 2.2mls.kg⁻¹ and respiratory rate of 6 showed significantly better outcomes compared with conventional lung protective strategies.⁹² Numerous case reports in humans in a variety of clinical scenarios have been encouraging.⁹³,⁹⁴,⁹⁵,⁹⁶ Tidal volumes ≤ 3ml.kg⁻¹, low inspiratory plateau pressure, high PEEP and low respiratory rates are all possible with the Novalung® 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.

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 VT.⁹⁷ 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.⁹⁸ 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.⁹⁹ Inhaled aerosolized activated protein C in a sheep model of ALI demonstrated improved oxygenation as well as lung aeration (as assessed by CT scan).¹⁰⁰ β-adrenergic agonists have potential benefits by increasing the rate of alveolar fluid clearance by increasing cellular cAMP and have anti-inflammatory properties.¹⁰¹ 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.¹⁰² 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.¹⁰³ 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) 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.

Anesthesiologists manage a heterogeneous group of patients in the peri-operative period; from patients with healthy lungs, patients with “at risk” lungs through to patients with established ALI/ARDS. More patients are at risk for ALI during surgery than previously thought. Appropriate peri-operative management may prevent or ameliorate this lung injury. Although lacking evidence from randomized controlled trials, applying protective ventilatory strategies seems reasonable based on our current understanding of mechanical ventilation and lung injury.

REFERENCES
