Lung injury after thoracotomy

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Postoperative respiratory complications are the commonest problem after all types of thoracic surgery. The exact incidence depends on the type of surgery and the preoperative health and lung function of the patient, but rates of up to 50% are often quoted. Most of these complications are diagnosed as either ‘pneumonia’ or ‘postoperative atelectasis’. However, the role of microbiological pathogens is often uncertain and the diagnosis of atelectasis usually rests on the presence of shadowing on the postoperative chest x-ray.

This article will discuss a specific type of severe respiratory problem that occurs after thoracotomy, namely the syndrome of acute lung injury (ALI). The features of lung injury after thoracotomy for oesophageal and lung resection surgery will be discussed in detail. The review will draw on the extensive experimental and clinical literature on the pathogenesis of the acute respiratory distress syndrome (ARDS) and ALI to suggest possible mechanisms of perioperative lung damage. Finally, the therapeutic implications of this hypothesis of post-thoracotomy respiratory complications will be examined.

Acute lung injury

The pathology of ALI

ARDS and the less severe ALI are acute, diffuse conditions that cause severe disturbances of pulmonary gas exchange. The pathology of ARDS is characterized by diffuse damage to the alveolar–capillary unit. The stimulus for the injury may either be direct (for example, smoke inhalation or bacterial pneumonia) or indirect (sepsis and massive blood transfusion are common causes). Classic descriptions of ARDS, based on lung biopsy and post-mortem specimens, have divided the course into three phases: (i) exudative, up to 1 week from the initiating stimulus; (ii) proliferative, from 1 to 3 weeks; and (iii) fibrotic, from 3 weeks onwards. However, these divisions are artificial and there is significant overlap between the phases. In particular, soluble mediators of early fibroproliferation, including procollagen peptides, occur at an early stage of ARDS.

The initial exudative phase of ARDS corresponds to the clinical period of rapidly worsening respiratory failure. Alveolar flooding occurs because of breakdown of the alveolar capillary barrier. Interstitial and alveolar oedema are marked and alveolar haemorrhage often occurs. Hyaline membranes form in the damaged alveoli, composed of plasma proteins that have leaked from the circulation.

Endothelial injury in the form of swollen endothelial cells is common, but endothelial cell necrosis and detachment is surprisingly unusual. This may be because of the rapid proliferative response of the endothelium to damage. There is exudative type 1 epithelial cell necrosis with evidence of injury to type 2 cells. Neutrophil leucocytes are commonly found, both in pulmonary capillaries and in the alveolar exudate.

The proliferative phase of alveolar repair is observed between 1 and 3 weeks. Type 2 epithelial cells regenerate and begin to cover the damaged alveolar wall. Granulation-like tissue forms in the alveolar spaces with the proliferation and migration of fibroblasts into the exudate. The fibroblasts synthesize and deposit collagen, starting the final, fibrotic stage of lung injury. Lung remodelling with collagenous tissue occurs, which may result in significant scarring and fibrosis. Irregular airspace enlargement occurs and cystic areas may form. However, macroscopic scarring is not inevitable and the degree of permanent structural lung damage after ARDS is very variable.

ARDS also produces widespread pulmonary vascular damage, which commonly produces pulmonary hypertension. There is a marked loss of functional pulmonary vessels from a combination of intense vasoconstriction, interstitial oedema and thromboembolism. The cause of the thrombosis is not known, but it may be from widespread endothelial cell damage. It has been reported to occur in up to 95% of patients in the acute phase of the illness. With the evolution of ARDS, marked remodelling of the pulmonary vascular bed occurs. Small muscular arteries are narrowed.
by both fibrocellular intimal hyperplasia and by hyperplasia of the endothelial cells. In the late proliferative phase, increased numbers of tortuous pulmonary capillaries are observed, with muscularization of pulmonary vessels.

**The physiology of ALI**

In the last few years there has been renewed interest in lung mechanics in ARDS. This interest comes from the suggestion that pressure–volume curves could improve outcome in ARDS through improved control of mechanical ventilation. Measurement of lung mechanics has complemented high-resolution thoracic CT studies to produce what could be described as a standard model of early ALI. The lung mechanics and CT findings will first be briefly described.

Pressure–volume curves can be recorded using a number of static and quasi-static methods. Modern intensive therapy unit (ITU) ventilators can either be adapted to use these techniques or increasingly have a built-in function to measure pressure–volume curves. The normal pressure–volume curve of the lung is sigmoidal and reaches the flat, non-compliant portion as volume approaches total lung capacity. At low lung volumes compliance is less because of airway collapse, reducing the number of alveoli participating in ventilation. The normal curve also shows hysteresis, with more pressure needed to inflate than deflate the lung to the same volume. This is a result of collapse of dependent lung units at low volume. Loss or inactivation of surfactant decreases compliance and accentuates the hysteresis.

Changes in the pressure–volume curve occur in ARDS. These changes are variable and are not always detectable, but in the early stages there is often marked hysteresis and inflexion points can be identified on both inflation and deflation points of the curve. At later stages the inflexion points are often lost and a uniform reduction in compliance is seen.

High-resolution CT scanning in early lung injury can explain changes in the pressure–volume curve. Originally performed by Gattinoni’s group and subsequently confirmed by others, these scans show a striking non-uniformity in aerated tissue in the lung. The loss of aerated units is most marked in the dependent, posterior regions of the supine patient, and anterior regions are often normally, or even excessively, aerated. In addition, the non-aerated units can migrate. Moving the patient from supine to prone can change the CT appearance, with inversion of the previous appearance. The conventional interpretation of the CT data is that the weight of the lung is increased by oedema. This causes compression and collapse of the dependent regions and hence the CT appearance. The lower inflation point on the pressure–volume curve is explained by the minimum pressure required to blow open the collapsed, dependent units and recruit these newly aerated alveoli. Once maximum recruitment has occurred, the pressure–volume curve becomes relatively linear. The upper inflexion point occurs as overdistension of lung units commences.

This explanation of CT and pressure–volume curve changes in terms of collapse and atelectasis of alveoli has been challenged recently. Such changes can be explained by loss of gas-exchanging units caused by alveolar flooding and oedema rather than collapse. CT appearances of oedema and collapse are identical at the resolution available to even the best current scanner. Experimental work suggests that, during experimental lung injury, alveolar units do not collapse but are simply filled with fluid. These results are important both from the perspective of ventilator-induced lung injury (see below) and when interpreting other CT studies of lung ‘atelectasis’.

**The cellular and molecular biology of acute lung injury**

Early studies on the pathogenesis of ALI focused on the mechanism of low-pressure pulmonary oedema. Work over the last decade has emphasized that ARDS is also an inflammatory condition involving complex interactions between circulating inflammatory cells, inflammatory mediators and the endothelial–epithelial barrier. The following section will review selected aspects of the inflammatory process.

**Cytokines**

Cytokines are small-molecular-weight peptides which are synthesized and released by many cells, including neutrophils, monocyte/macrophages, pulmonary epithelial and pulmonary endothelial cells. They modify cellular responses and appear central to the control of inflammation, tissue repair, fibrosis and angiogenesis. Physiologically, they probably act over a very short distance, unlike classic hormonal messengers. Most studies of cytokine release in lung injury have examined a small group of proinflammatory cytokines, including interleukin (IL)-8, IL-1, tumour necrosis factor α (TNF-α) and IL-6. More recent studies have focused on anti-inflammatory cytokines (e.g. IL-10) and growth factors [e.g. TGF-β and vascular endothelial growth factor (VEGF)]. The accessibility of the lung to the technique of bronchoalveolar lavage (BAL) has also provided insight into the local changes in cytokines and inflammatory mediators in lung injury.

In 1993 Donnelly and colleagues published a classic paper on the role of the chemotactic cytokine IL-8 in the pathogenesis of ARDS. They performed BAL in 29 patients at high risk of developing ALI at a very early stage in their clinical course and before any of the group had developed frank ARDS. They found no difference in plasma IL-8 concentration, but significantly greater lavage concentrations were detected in patients who subsequently developed clinical lung injury. They also provided evidence that at least some of the IL-8 was being produced locally in the
lung by pulmonary macrophages. The increase in IL-8 also preceded subsequent neutrophil infiltration into the alveolar spaces. This work remains important because it demonstrates that a biologically plausible mediator increases in the lung before the development of lung injury. IL-8 is a prototypical chemokine with specific neutrophil attractant properties. The subsequent increase in alveolar neutrophils observed in lung injury could be explained by the early increase in IL-8.

Many groups have confirmed and extended these observations in man and animals. In general, concentrations of all proinflammatory acute-phase cytokines (IL-1, TNF-α, IL-6, IL-8) are high in lavage samples from patients with established ARDS. However, absolute concentrations do not necessarily correlate with the degree of lung injury as assessed physiologically. In patients who recover, cytokine concentrations fall over time, but remain persistently high in those where ARDS progresses. The increase in pulmonary cytokines is not found in classic high-pressure pulmonary oedema after left-ventricle failure. The appearance of pulmonary oedema alone is therefore not sufficient to cause an inflammatory response in the lung.

A number of cytokines, in particular IL-8, have been the subject of blockage experiments in animals with ALI. In some, but not all, of these studies IL-8 antagonists have been shown to protect against the development of lung injury when given before the initiating insult. These results support the view that cytokines have a key role in the development of ARDS.

**Cellular mediators**

Histological and lavage studies indicate that neutrophils are important in lung injury. In both animals and man with lung injury, there are increased numbers of activated neutrophils in BAL samples, with some correlation between increased numbers and poor outcome. Neutrophils remain increased in progressive disease, with evidence of the release of destructive degranulation products and the production of reactive oxygen species (ROS) in the alveolar spaces. Neutrophil elastase, collagenase and myeloperoxidase are all found in lavage fluid from patients with lung injury. The lung has many macrophages, in both the alveolar and the interstitial spaces. Activated macrophages are potent producers of cytokines and are likely to be an important cause of ALI. BAL studies show IL-8 production in macrophages from patients with lung injury and hypoxia induces IL-8 gene expression in macrophages.

**Other mediators**

The growth of knowledge in molecular and cell biology has provided clinical scientists with an almost unmanageable list of potential targets for research and a clear picture has yet to emerge. A wide range of other inflammatory mediators has been implicated in causing ARDS. These include leukotrienes, complement, platelet-activating factor, endotoxin, coagulation components and growth factors. The clinical significance of many of the studies is difficult to interpret. Inflammation and the acute-phase response constitute a generalized and rather non-specific reaction to tissue injury. Separating causal factors from dependent variables has proved difficult.

**Surfactant**

The key role of surfactant in the neonatal respiratory distress syndrome is well established and replacement treatment is effective. Abnormalities of surfactant have also been reported in ARDS and include: (i) reduced surfactant production; (ii) change in composition of surfactant; (iii) the presence of surfactant inhibitors; and (iv) the alteration and destruction of surfactant in the alveolar space by other mediators. These observations led to a number of surfactant replacement trials in ARDS, all with negative results. Important practical issues in terms of effective surfactant delivery to adults remain to be solved and future trials may yet show replacement to be effective in adults.

**Lung injury after elective oesophagectomy**

Elective oesophagectomy for cancer is a major surgical procedure with a hospital mortality often >10%. In England approximately 2000 oesophagectomies are performed each year. A recent confidential enquiry into perioperative deaths (CEPOD) found that postoperative respiratory problems were the commonest cause of postoperative morbidity. Comparison of the incidence of respiratory problems between CEPOD reports is complicated by the lack of a standard definition. Muller and colleagues published a review of 1201 papers on surgical treatment of oesophageal cancer between 1980 and 1988. Median hospital mortality was 11% and pneumonia complicated 26% of transthoracic procedures; respiratory insufficiency occurred in 27% of cases and atelectasis in 23% of patients. Single-centre figures from the UK confirm these findings. In total, 523 patients underwent elective oesophagectomy in Nottingham between 1987 and 1997. Patients were divided into three groups depending upon age (<70, 70–79, 80–86 yr). Respiratory complications occurred in 16.3, 24.7 and 17.4% respectively. More recent data from Newcastle upon Tyne reported on 193 patients with elective operations between 1996 and 1999. This showed a 23.8% incidence of postoperative respiratory failure, defined as the presence of ALI, and the need for invasive ventilatory support for more than 48 h after surgery.

Compared with the information available in sepsis and trauma-associated ARDS, less is known about the cause and pattern of lung injury after elective oesophageal surgery. Definition of lung injury in this context is difficult. Most now use the joint North American–European consensus
conference definitions (Table 1), but these are based only on gas exchange and radiology criteria. While gas exchange measures are reliable, thoracotomy inevitably causes radiological change and the interpretation of plain chest films becomes subjective. Definitions based on permeability and inflammatory changes would improve diagnosis, but are not routinely available in most units.

The incidence of lung injury after oesophagectomy
Oesophagectomy is mentioned as a risk factor for ARDS in most review articles, but the precise incidence of lung injury after elective oesophageal surgery is less well defined. Few studies have used the North American–European definitions and most contain only small numbers of patients (Table 2). Published incidence varies from 14.5 to 33% of all cases, the lowest figure being from a recent large series that used current definitions. In the same report, ALI occurred in 23.8% of cases. Lung injury is a serious complication, with a mortality of 50% reported.

There is substantial evidence that the pathophysiology of lung injury after oesophagectomy is similar to that of classic ARDS. Changes in pulmonary vascular permeability, peripheral and alveolar inflammatory mediator production and cellular infiltration all appear similar to those in other cases of lung injury. These will be briefly summarized.

Pulmonary permeability changes
An increase in pulmonary permeability to proteins is a defining characteristic of classic ARDS. Lavage studies demonstrate increased protein concentrations in BAL fluid and radioisotope methods show greater movement of tagged plasma proteins into the lung. A number of studies have measured pulmonary vascular permeability after oesophageal surgery. Rocker and colleagues detected an increase in pulmonary vascular permeability to transferrin in both lungs 8 h after surgery. Permeability was greater on the thoracotomy side than on the dependent side. By 24–48 h, permeability was no longer significantly greater. However, a further study of 20 patients using radioisotopes early after surgery found no difference in permeability compared with healthy volunteers. The serial approach in Rocker’s study is the more powerful method to detect significant change, as the ‘normal range’ of permeability in the second study was very large. Real changes in permeability may therefore have been masked.

Plasma cytokine and inflammatory mediators
Several studies have reported increases in plasma cytokines and other inflammatory mediators after oesophagectomy. These include IL-1, IL-1ra, IL-8, IL-6, neutrophil elastase, soluble P- and E-selectin, thrombomodulin, TNF-α and IL-10. In general, these mediators increase rapidly after surgery (within 6–8 h), peak by 24 h and return to baseline by 48–72 h. These findings are similar to findings in other patients at high risk of developing ALI.

Pulmonary cytokine and inflammatory mediators
There is less information on alveolar concentrations of inflammatory mediators after oesophagectomy. Sato and colleagues performed postoperative BALs on the thoracotomy lung in 10 patients. Lavage concentrations of IL-8 and IL-1ra were at least one order of magnitude higher than concentrations in plasma samples obtained simultaneously. Okawa and colleagues measured TNF-α, IL-6 and IL-8 in BAL samples in 16 patients after oesophagectomy, half of whom were given methylprednisolone before surgery. IL-8 concentrations in BAL were greater than plasma concentrations. High IL-8 BAL concentrations after surgery were also reported by Tsukada and colleagues in 17 patients, with higher IL-8 concentrations in patients who subsequently developed postoperative pulmonary complications. Neutrophil elastase was also high in the group that developed pulmonary complications. Kooguchi and colleagues also found

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<th>Table 1</th>
<th>1994 consensus conference definition of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)</th>
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<tr>
<td>Onset Oxygenation criteria</td>
<td>Acute and persistent</td>
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<td>$P_{aO_2}/F_{IO_2} &lt; 300$ for ALI</td>
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<td>$P_{aO_2}/F_{IO_2} &lt; 200$ for ARDS</td>
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<tr>
<td>Exclusion criteria</td>
<td>Pulmonary artery occlusion pressure $&gt; 18$ mm Hg (if measured)</td>
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<td>Clinical evidence of left atrial hypertension</td>
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<td>Radiographic criteria</td>
<td>Bilateral opacities consistent with pulmonary oedema</td>
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<th>Table 2</th>
<th>Incidence of lung injury after elective oesophagectomy</th>
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<tr>
<td>Study</td>
<td>Year</td>
</tr>
<tr>
<td>Schilling and colleagues</td>
<td>1998</td>
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<td>Duprat and colleagues</td>
<td>1987</td>
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<td>Millikan and colleagues</td>
<td>1995</td>
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<td>Tandon and colleagues</td>
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increases in IL-8 in BAL samples in four patients after oesophagectomy. IL-6 and nitrogen-free radicals were also increased.

Arachidonic acid metabolites have also been implicated in the pathogenesis of ARDS. In a study of 18 patients undergoing oesophagectomy, a rise in postresection plasma concentrations of thromboxone B₂ was associated with the development of ARDS.59

**Cellular changes**

There is little information on cellular changes in oesophagectomy-related lung injury. Peripheral activation of neutrophils has been reported with increased concentrations of plasma elastase⁶³ ⁶⁴ and upregulation of the integrin surface receptor CD11b.⁶⁰ Monocyte activation also occurs with CD11b upregulation,⁶⁰ increased in vitro TNF-α production⁶⁰ ⁶¹ and IL-1β production.⁶¹ No separate studies have been published of lavage findings in established postoesophagectomy ARDS. Cytocfluorometric increases in macrophage IL-6, IL-8 and inducible nitric oxide synthase (iNOS) after oesophagectomy have been reported.⁵⁷ Increases in neutrophil numbers in BAL samples 24 h after oesophagectomy have also been found.⁵⁵

Cytokine upregulation also occurs in the lung after surgery. Abe and colleagues⁶² compared IL-6 mRNA expression in lung biopsy samples taken before and after oesophagectomy. IL-6 mRNA increased in both alveolar and bronchial epithelial cells after operation.

In summary, both peripheral and pulmonary inflammatory changes occur after oesophagectomy. These are similar to changes reported in both established ARDS and in high-risk patients. However, a causal role of these changes has not been fully established, as a marked acute-phase response appears to be a universal consequence of oesophagectomy. A few studies suggest that patients with a more marked inflammatory response develop clinical lung injury, but numbers reported are small.

**Prediction of lung injury after oesophagectomy**

The relationship between preoperative testing and the development of postoperative respiratory problems and general mortality in oesophageal surgery is well described (Table 3). Preoperative respiratory function tests predict complications in some, but not all, studies. Even when there is a link, the ability of preoperative static lung function testing to predict complications appears poor. Patients with significantly reduced preoperative lung function are unlikely to be considered for surgery, and this probably explains the poor association.

A few studies have reported associations between intraoperative instability and postoperative respiratory problems.⁴⁴ ⁶³ ⁶⁴ In a recent study, the degrees of intraoperative hypotension and hypoxaemia during one-lung ventilation (OLV) were significantly associated with postoperative lung injury. Static preoperative tests of cardiac and respiratory function are unlikely to be good predictors of postoperative problems. Oesophageal surgery is a major stressor and dynamic tests of function may be more discriminating. Dynamic respiratory exercise testing was performed on 91 patients before oesophagectomy, using expired gas analysis.⁶⁵ Static preoperative respiratory function tests did not predict postoperative cardiorespiratory complications, but maximum oxygen uptake did correlate with problems. Further work on preoperative risk assessment and evaluation is needed, both to improve patient selection and to stratify patients for possible pre- and perioperative interventions designed to improve outcome.

**Lung injury after pulmonary resection**

Respiratory complications are common after pulmonary resection. These occur in 5–14% of all patients and account for approximately 50% of all major postoperative complications.⁶⁶–⁶⁸ Respiratory complications have a major impact on outcome, with mortality rates of 40–70% after major postoperative respiratory problems.⁶⁹

Respiratory complications after pulmonary resection have several causes. Risk factors include preoperative lung function, the extent of lung resection, other medical problems and increasing age. However, a number of case studies have described what appears to be a specific syndrome of postpneumonectomy pulmonary oedema (PPO).⁷⁰–⁷₂ In 1984, Zeldin and colleagues described 10
cases of PPO. The syndrome consisted of the onset of severe respiratory failure, within 48 h of operation, associated with diffuse radiographic changes on plain chest films consistent with pulmonary oedema. However, central pressure measurements showed no evidence of left ventricular failure or cardiogenic pulmonary oedema. In 1993, Turnage and colleagues published a large retrospective case series of PPO from a single centre in North America. They reported 21 cases of PPO in 806 patients after pneumonectomy. All the patients who developed PPO died. Post-mortem data were available for 17 of the patients, and 15 of these showed classic features of ARDS with hyaline membrane formation and, in a number of cases, thromboemboli in the pulmonary vessels.

The incidence and outcome of PPO depends on the various definitions used. Between 4 and 7% of patients after pneumonectomy and 1–7% after lobectomy develop PPO. Using the American Thoracic Society/European Respiratory Society (ATS/ERS) definitions of ALI/ARDS, Hayes reported an overall incidence of post-thoracotomy lung injury of 7%. ARDS developed in 5.2% of lobectomy patients and 4.9% of pneumonectomies. ALI developed in 2.2% of lobectomies and 1.9% of pneumonectomies. No cases developed after more minor thoracic procedures. Mortality in the ARDS group was 88% and in the ALI group 29%. There was no correlation between preoperative lung function, blood gases or duration of anaesthesia and the development of lung injury.

Mechanisms of lung injury after thoracotomy

ALI after oesophagectomy and lung resection surgery suggests that common mechanisms may be responsible. An obvious candidate is prolonged OLV during both surgical procedures. This period of OLV could cause lung injury by a number of mechanisms (Fig. 1).

(i) During lung collapse, blood flow to the lung is significantly reduced and lung ischaemia–reperfusion injury could occur with subsequent spread to the dependent lung.

(ii) It is common practice to ventilate the dependent lung with a high $F_{\text{O}_2}$, usually 100%. This could lead to the generation of ROS that could injure both the ventilated and the collapsed lung.

(iii) Mechanical ventilation can cause lung injury. The use of normal or near-normal tidal volumes during OLV could damage the ventilated lung.

(iv) Pulmonary capillary stress failure occurs when the pulmonary microvascular bed is subjected to increased pressure. During OLV most pulmonary blood flow enters the ventilated lung and could produce capillary injury.

The following section will consider each of these mechanisms and the evidence for their involvement in post-thoracotomy lung injury.

Ischaemia–reperfusion injury in the lung

Tissue ischaemia occurs once the oxygen supply to a tissue falls below a threshold concentration. Both microcirculatory and intracellular changes occur rapidly as a defensive response, but prolonged ischaemia results in cell damage and death. Tissue reperfusion is necessary for cell recovery, but paradoxically can worsen tissue injury. Systemic injury to distant organ systems can also occur, mediated by the release of toxic metabolites from the reperfused tissue. For example, muscle reperfusion after
severe crush injury can produce the syndrome of rhabdomyolysis and renal failure.

ALI occurs frequently in animals with experimental ischaemia–reperfusion injury of the gut.\textsuperscript{81–83} This injury resembles ARDS, with increased lung permeability and inflammatory cell infiltrate into the alveolar spaces. It is mediated by a complex combination of cellular and soluble factors, including ROS, activated neutrophils, cytokines, arachidonic acid metabolites and complement.

Such an indirect mechanism of lung injury could occur during and after oesophageal surgery. Boyle and colleagues\textsuperscript{84} assessed gastric and jejunal perfusion during oesophageal resection, using scanning laser Doppler fluorimetry and intraluminal gas tonometry in 16 patients. They found evidence of significant gastric and jejunal ischaemia during the operations, which improved towards the end of the procedure.

Ischaemia–reperfusion injury to the non-ventilated collapsed lung could also produce lung dysfunction after surgery. Several groups have shown that even relatively short periods of lung ischaemia, produced by pulmonary artery banding in animals, causes ALI if followed by reperfusion with oxygenated blood.\textsuperscript{85} The key role of oxygen in producing reperfusion injury suggests that ROS may mediate the damage. In some experimental ischaemia–reperfusion injury models, free radical scavengers and blockers prevent damage.\textsuperscript{81}

Lack of ventilation to the collapsed lung may also exacerbate the reperfusion injury. De Leyn and colleagues\textsuperscript{86} found greater lactate concentrations and lower ATP concentrations in isolated ischaemic rabbit lungs that were deflated rather than inflated with either air or 100% oxygen. Hamvas and colleagues\textsuperscript{87} studied ischaemia–reperfusion lung injury in dogs. They found that ventilation or static inflation protected against lung injury. Only the combination of lung ischaemia (produced by pulmonary artery occlusion) and absence of ventilation resulted in lung injury.

Oxidative stress injury to the lung

 Reactive oxygen species (ROS) are short-lived but highly toxic free radicals and molecules that cause cell damage by modifying body substances such as lipids, proteins and DNA.\textsuperscript{77,88} Cellular organisms have developed enzymic and non-enzymic defences against oxidative stress and it is only when these defences are overwhelmed that cellular damage occurs.

ROS have been detected indirectly in the alveolar spaces of patients with established ARDS. Depletion of circulating ROS scavengers also occurred in high-risk patients who subsequently developed lung injury. In adult rats, ventilation with high $P_{\text{FiO}_2}$ alone produces severe lung injury.\textsuperscript{89} In man, the role of oxygen in the development of lung injury is less clear. High $P_{\text{FiO}_2}$ is required in patients with established lung injury and no randomized, controlled trial has compared different $P_{\text{FiO}_2}$ levels against outcome. There is some evidence of ROS production after pulmonary resection in man. Williams and colleagues\textsuperscript{90} measured changes in plasma indices of oxidative damage in 28 patients after pulmonary surgery. Significant changes in these indices occurred after major pulmonary resections, but not after minor procedures. The contribution, if any, that ventilation with high $P_{\text{FiO}_2}$ during thoracic surgery makes to the development of lung injury is unknown. Most patients do not develop clinically important lung dysfunction despite this practice. However, the additive effect of high $P_{\text{FiO}_2}$ in a lung being injured by other stimuli cannot be discounted.

Ventilator-induced lung injury

In 1974, Webb and Tierney published a seminal paper on ventilator-induced lung injury (VILI).\textsuperscript{91} Rats that were ventilated for 1 h at 45 cm H$_2$O without PEEP all died of fulminating lung injury. Ventilation at 14 cm H$_2$O did not produce lung damage, while 30 cm H$_2$O resulted in mild injury. These results have been confirmed and extended by many groups.\textsuperscript{78,92–94} In experiments dissociating lung pressure from volume, it has been established that large lung volume is the main determinant of damage. Rapid upregulation of proinflammatory mediator production in lung epithelial and endothelial cells also occurs after ventilation.\textsuperscript{94}

The relevance of the experimental studies on VILI to man have been confirmed by four recent randomized, controlled trials.\textsuperscript{93} In all four studies, patients were randomized to either a low-pressure–volume lung protection strategy or a higher pressure–volume conventional strategy group. Patients in these studies differed, three trials studying patients with established ARDS\textsuperscript{14,95,96} and one studying high-risk patients.\textsuperscript{97} Two studies\textsuperscript{14,95} reported significantly lower mortality in the protective ventilation group, while the other two studies\textsuperscript{96,97} found no difference in outcome. The ARDSnet study was the largest and most recent of the trials.\textsuperscript{95} It randomized 861 patients with established ARDS from 10 North American centres. The mortality of 31.0% in the lung protection group was significantly reduced compared with the mortality of 39.8% in the control group.

A likely explanation for the different outcomes in the trials is the level of ventilation in the control group. In the two positive studies, plateau airway pressures in the control patients exceeded 30 cm H$_2$O. In addition, mean $P_{\text{aCO}_2}$ in the control patients was in the lower part of the normal range, suggesting that control patients were overventilated. The trial results therefore broadly support the experimental work on VILI. Patients ventilated at plateau airway pressures exceeding approximately 30 cm H$_2$O are likely to develop worse lung injury.

In established ARDS, the increase in proinflammatory cytokines in the plasma may be caused by spillover of alveolar mediators into the circulation. Ranieri and colleagues randomized 44 patients with ARDS to either conventional or lung-protection ventilation and measured...
inflammatory cytokines at entry and 36 h in BAL and plasma. BAL and plasma mediators increased in the control group but decreased in the lung protection group, suggesting that low-volume ventilation causes less lung inflammation. The considerably higher BAL than plasma concentrations of cytokines also suggest that the lung is the source of cytokine production. These ideas were extended to the study of healthy patients undergoing elective surgery with ventilation. Wrigge and colleagues randomized 39 patients to the three ventilation (V_T) settings of 15 ml kg\(^{-1}\) with 0 cm PEEP, 6 ml kg\(^{-1}\) with 0 cm PEEP, and 6 ml kg\(^{-1}\) with 10 cm PEEP. No significant change in plasma cytokine concentration occurred after 1 h of ventilation. However the lack of direct alveolar sampling of cytokines limits the study and it cannot be concluded that mild lung injury (insufficient to produce cytokine spillover to the systemic circulation) did not occur.

Is there evidence that less prolonged ventilation in patients with relatively normal lungs causes lung injury? A number of studies have shown that perioperative ventilation can cause ‘atelectasis’ over a short period of time. These studies used lung CT scanning to show progressive changes during operation, which can often be reversed by lung recruitment manoeuvres. Although described as atelectasis, the true cause of the CT changes is not known. The CTs show small dependent areas of high attenuation, but give no information on the pathology of the process. These changes could represent early, subclinical lung injury that, in most cases, resolves spontaneously soon after operation.

There is also some indirect evidence that high-pressure ventilation is associated with lung injury after thoracic surgery. In a retrospective analysis of risk factors and PPO in 197 patients, van der Werff and colleagues found that high perioperative ventilation pressures were associated with the development of PPO (relative risk of 3.0).

**Pulmonary capillary stress failure**

During OLV most pulmonary blood flow passes through the ventilated lung. Pulmonary artery pressures therefore increase and could cause pulmonary capillary stress failure. This concept was originally developed by West after investigations into the causes of high-altitude pulmonary oedema (HAPE). Intense pulmonary vasoconstriction occurs in HAPE, causing permeability oedema characterized by the appearance of red cells and high-protein exudate in the lungs. West argued that the high pulmonary capillary pressures caused mechanical failure of the epithelial/endothelial interface in the lung.

In a series of experiments on isolated lung preparations, West and his group found that some damage to the capillary endothelium and alveolar epithelium occurred at capillary transmural pressures as low as 24 mm Hg, although consistent failure required pressures in the region of 40 mm Hg. Whether such pressures occur during OLV is unknown. However, pulmonary artery wedge pressures of over 20 mm Hg have been recorded in healthy volunteers during severe exercise, indicating that capillary transmural pressures at the base of the lung exceed 25 mm Hg.

Pulmonary capillary stress failure occurs more commonly at higher than lower lung volumes. Fu and colleagues examined stress failure in anaesthetized rabbits at low and high transpulmonary inflation pressures. They found significantly more epithelial and endothelial damage at the higher lung volumes. OLV using conventional tidal volumes may therefore cause stress failure.

**Conclusions**

Between 5 and 10% of patients undergoing elective thoracotomy as part of oesophageal or lung resection surgery will develop an ALI syndrome characterized by high-permeability pulmonary oedema. The mortality associated with the syndrome exceeds 50%. The pathophysiology is similar, if not identical, to that reported in ARDS after sepsis and major trauma.

The mechanisms causing post-thoracotomy lung injury are unknown, but appear to originate during surgery. The increasing body of evidence showing that ventilation can cause lung damage suggests that the management of ventilation during and after anaesthesia for thoracotomy requires further debate and investigation. The clear anaesthetic priority is to achieve ventilatory stability during the operation. To this end, large tidal volumes and high F\(_{1}\)\(_{O_2}\) values are standard during OLV, the collapsed lung being effectively abandoned during the operation. However, other ventilatory and respiratory strategies could be used, including lower tidal volumes, PEEP and the use of continuous positive airway pressure on the collapsed lung. All these approaches need investigating.

Another approach that should be considered is the use of anti-inflammatory agents during operation. Studies in ARDS of anti-inflammatory agents have been disappointing. However, many of these agents appear to be effective in experimental studies if given before the initiating insult. If lung injury after thoracotomy starts during surgery, anti-inflammatory agents might well be effective.

Finally, post-thoracotomy lung injury may be just the tip of the iceberg. Perhaps micro-atelectasis, which is almost universal after anaesthesia, is really a form of subclinical lung injury. If this is the case, then operative ventilatory management may have a greater effect on pulmonary complications after surgery than is currently appreciated.

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