REVIEW

The pathogenesis of lung injury following pulmonary resection

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The pathogenesis of lung injury following pulmonary resection. S. Jordan, J.A. Mitchell, G.J. Quinlan, P. Goldstraw, T.W. Evans. ©ERS Journals Ltd 2000.
ABSTRACT: Postpneumonectomy pulmonary oedema (PPO) develops in ~5% of patients undergoing pneumonectomy or lobectomy, and has a high associated mortality (>50%). In its extreme form, PPO follows a clinical and histopathological course indistinguishable from acute respiratory distress syndrome.

Perioperative fluid overload, impaired lymphatic drainage following node dissection and trauma caused by surgical manipulation have been implicated in the pathogenesis of PPO. However, PPO more probably represents the pulmonary manifestation of a panendothelial injury consequent upon inflammatory processes induced by the surgical procedure, which involves collapse and re-expansion of the operative lung to permit hilar dissection and pulmonary resection.

High inspired oxygen concentrations are required to overcome the effects of shunt. Animal studies have shown that pulmonary ischaemia/reperfusion can result in oedema formation, possibly due to the generation of pro-oxidant forces. Moreover, plasma taken from patients undergoing lobectomy or pneumonectomy (but not lesser resections) shows evidence of oxidative damage.

Such evidence suggests either that the high inspired oxygen concentrations associated with one-lung ventilation, or ischaemia/reperfusion injury, may modulate postpneumonectomy pulmonary oedema. Mechanisms by which redox imbalance may result in tissue damage and postpneumonectomy pulmonary oedema are discussed.
Eur Respir J 2000; 15: 790–799.

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Major developments in thoracic surgery have occurred during the twentieth century, facilitated by the advent of safe tracheal intubation and following the widespread availability of positive pressure mechanical ventilation and muscle relaxant. These advances have overcome the hazards of spontaneous ventilation in the open hemithorax and the cardiorespiratory depression associated with deep inhalational anaesthesia. At the beginning of the century, the principle indications for thoracic surgery were empyema, treated by rib resection and drainage, and tuberculosis, managed by creating an artificial pneumothorax. Thoracoplasty was not widely accepted until after the First World War. After 1945, the availability of antibiotics, and antituberculous chemotherapy in particular, revolutionized the management of infective lung disease. Pulmonary malignancy has subsequently become the most common indication for thoracotomy.

The first pneumonectomy was performed by R. Nissen in Germany in 1931 for bronchiectasis. In 1933, E.A. Graham performed the first one-stage pneumonectomy for squamous cell carcinoma. Individual ligation techniques for the hilar structures, developed by W.F. Rienhoff and E.D. Churchill in the 1930s, made lobectomy possible, which came to be seen as a safe or even preferable alternative to pneumonectomy during the 1950s and 1960s. Segmentectomy and wedge resection were later advocated for small or peripheral tumours. Bronchoplastic techniques

or sleeve resections were described in the 1950s and allowed the preservation of normal lung distal to a tumour. Video-assisted thoracoscopic techniques have been used since the 1980s for many procedures, and, although they are now being used to perform lung resections [1], they have not been widely accepted as an adequate alternative to thoracotomy in the management of pulmonary malignancy [2].

Postpneumonectomy pulmonary oedema

Postoperative lung injury or postpneumonectomy pulmonary oedema (PPO) as it has been termed in the USA, complicates a significant number of thoracic surgical procedures involving lung resection. PPO may be regarded as pulmonary oedema and refractory hypoxaemia developing after lung resection, usually defined as pneumonectomy, lobectomy or bilobectomy, although some authors restrict use of the term only to pulmonary oedema formation following pneumonectomy. Lesser procedures, such as wedge resections, are usually excluded. PPO has been defined variably as pulmonary oedema after pneumonectomy with no identifiable cause [3], oedema formation following pneumonectomy characterized by normal cardiac filling pressures (PAPs), high pulmonary artery pressures and high cardiac output [4], the development of severe and often lethal respiratory failure secondary to noncardiac (*i.e.* high permeability) pulmonary oedema after resection of the lung [5], and noncardiogenic pulmonary oedema complicating lung resection [6]. In its

extreme form, PPO follows a clinical and histopathological evolution indistinguishable from that of acute respiratory distress syndrome (ARDS) [3], and might therefore be regarded as a variation of ARDS developing in particular clinical circumstances.

Acute respiratory distress syndrome

The American-European Consensus Committee on ARDS was convened in 1992 to focus upon the lack of uniform definition and the pathophysiological mechanisms. It also aimed to establish guidelines for the conduct and co-ordination of clinical trials. It was recommended that acute lung injury (ALI) be formally defined as a syndrome of inflammation and increased permeability, associated with a constellation of clinical, radiological and physiological abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension, and that the term ARDS should be reserved for the most severe end of this spectrum [7]. ALI and ARDS are acute in onset and persistent, lasting days to weeks, and are associated with a wide variety of pulmonary and nonpulmonary risk factors. Both are characterized by arterial hypoxaemia resistant to oxygen therapy alone in the presence of diffuse radiological infiltrates. These recommended criteria for the definition of ALI and ARDS are summarized in table 1.

Incidence of postpneumonectomy pulmonary oedema

The lack of a consensus definition means that there is wide variation in the reported incidence of PPO. Rates of 4–7% following pneumonectomy and 1–7% after lobectomy [3, 6, 8] have been reported, but may be as high as 12–15% [9, 10] according to authors including cases of mild pulmonary oedema. A study using the Consensus Committee Guidelines for ALI/ARDS found an overall incidence of lung injury of 7%. PPO severe enough to constitute ARDS was recorded in 5.2% of lobectomies and 4.9% of pneumonectomies, and ALI in 2.2% of lobectomies and 1.9% of pneumonectomies, with no cases of either following segmentectomy, wedge resection or open lung biopsy [11]. This was a retrospective investigation and may therefore have underestimated the number of patients who developed ALI postoperatively. Others have found a higher proportion of patients develop lung injury following pneumonectomy compared to lobectomy [6], but again no cases were found after lesser degrees of resection. The annual Thoracic Surgical Register (UK) reported 2,962 pneumonectomies and lobectomies in 1996, suggesting that ~200 cases of PPO might be expected to develop each year in the UK alone.

Outcome of postpneumonectomy pulmonary oedema

The reported mortality rate for PPO varies. Most authors report figures in the range 50–100% [3, 6, 8, 10, 11]. There are no specific data concerning morbidity in survivors after PPO, although the high mortality rates imply that permanently impaired lung function may ensue, especially given the perioperative loss of lung parenchyma and the strong possibility of pre-existing chronic underlying lung disease.

Histopathological changes in postpneumonectomy pulmonary oedema

The histological changes found in PPO are identical to those of ARDS, and the lung tissue can be seen to evolve through three pathological phases. Over the first 5 days, endothelial integrity is lost, with extravasation of oedema fluid, protein and inflammatory cells into the alveolar spaces [8]. There is also haemorrhage from engorged dilated capillaries. Type I pneumocytes undergo necrosis at this stage, and fibrin and platelet microthrombi form in the microvasculature [12]. In those who survive the first few days, organization and repair begin. Marked proliferation of fibroblasts and type II pneumocytes occurs. The type II pneumocyte is the stem cell for epithelial regeneration and first proliferates before differentiating into type I pneumocytes. Squamous metaplasia of the epithelium occurs and hyaline membrane formation can be recognized. After ~10 days, interstitial and intra-alveolar fibrosis begin. Widespread thrombotic, fibroproliferative and finally obliterative changes develop in the vasculature. Extensive remodelling of the pulmonary vascular bed also takes place. An increase in lung collagen levels can be detected in patients with lung injury of >14 days duration, and continue to increase for the duration of the disease [13].

Clinical presentation

Patients who develop PPO do not follow a uniform postoperative course. Some authors report cases presenting in respiratory failure within the first 12 h, others as late as 7 days [8, 10]. Most patients with PPO, however, present between 1 and 3 days postoperatively [3, 6]. This variation in the speed of onset of lung injury is again similar to ARDS, as are the first clinical signs of tachycardia and tachypnoea. In the early stages of ARDS and PPO, clinical examination results may be unremarkable, although low-grade pyrexia can develop. Following the onset of pulmonary oedema, rapidly progressive hypoxaemia ensues, manifest as a widened alveolar/arterial gradient relatively refractory to supplemental oxygen. Later, as lung injury develops, the alveolar dead space increases

Table 1. – Definition of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

	Timing	Oxygenation(Pa,O$_2$/FI,O$_2$)	Chest radiograph	PAOP
ALI	Acute onset	<300 mmHg (Regardless of level of PEEP*)	Bilateral infiltrates seen on frontal radiograph	<18 mmHg, when measured, or no clinical evidence of left atrial hypertension
ARDS	Acute onset	<200 mmHg (Regardless of level of PEEP*)	Bilateral infiltrates seen on frontal radiograph	<18 mmHg, when measured, or no clinical evidence of left atrial hypertension

*: The influence of positive end-expiratory pressure (PEEP) was excluded from the definitions in the interest of practicality. Pa,O$_2$: arterial oxygen tension; FI,O$_2$: inspiratory oxygen fraction; PAOP: pulmonary artery occlusion pressure. (1 mmHg=0.133 kPa.)

with hypercapnia. The radiological changes lag behind the clinical deterioration, but range from signs of diffuse interstitial infiltration to those of gross alveolar oedema. To exclude a cardiac cause for the pulmonary oedema, pulmonary artery catheterization may be required. In such cases a pulmonary artery occlusion pressure (PAOP) of ≤18 mmHg is required to make a diagnosis of ALI or ARDS, although falsely low PAOP readings are known to occur following pulmonary resection [14]. It may be difficult to differentiate between PPO and pneumonia, especially if the onset is delayed. Positive microbiological cultures favour the latter, although the two conditions may coexist.

Pathophysiology of postpneumonectomy pulmonary oedema

PPO probably represents only the pulmonary manifestation of a panendothelial inflammatory vascular injury. An initial insult, or perhaps combination of insults, at the endothelial or epithelial barrier, or at a distant site, triggers the release of inflammatory mediators. These, in conjunction with the altered pulmonary haemodynamics consequent upon surgery, act upon the vascular endothelium and underlying smooth muscle, resulting in changes in vascular control and permeability.

Pulmonary vascular control

In contrast to systemic blood vessels, the pulmonary vasculature has the ability to constrict in response to alveolar, and to a small extent arterial, hypoxia. Such hypoxic pulmonary vasoconstriction (HPV) occurs principally at the arteriolar level, although (a lesser degree of venoconstriction has also been identified [15]. The mechanisms underlying the reflex are not entirely understood, but it has long been recognized that the endothelium plays a role in modulating HPV by releasing a variety of vasoactive substances including the vasodilators prostacyclin and nitric oxide, and vasoconstrictor endothelins (ETs). The development of (chronic) primary pulmonary hypertension (PPH) is now thought attributable to an imbalance in the release of these agents consequent upon endothelial damage and favouring vasoconstriction. The release of ETs may also lead to pulmonary vascular remodelling in patients with PPH. By contrast, pulmonary hypertension of acute onset complicates ALI/ARDS, the magnitude of which has been shown to correlate with the severity of the lung injury [16]. HPV is probably responsible for this rapid onset pulmonary arterial hypertension, but, later in the disease process, vascular obstruction by microthrombi of fibrin and hyalin, and extrinsic compression by oedema fluid and positive pressure ventilation, may be relevant. By influencing hydrostatic forces, pulmonary hypertension also contributes to the formation of alveolar oedema leading to right ventricular impairment. HPV has been shown to be disrupted in the presence of ARDS [17], resulting in ventilation/perfusion mismatch, and contributes significantly to the development of refractory hypoxaemia. Similar data are unavailable for PPO. The large number of patients undergoing lung resection with chronic pulmonary pathology suggests that pulmonary hypertension may be relatively common in such patients, although whether this is of prognostic significance is also unclear.

Vascular permeability

High concentrations of protein in alveolar oedema fluid and histological evidence suggest that endothelial integrity is lost in ALI/ARDS. In patients with PPO, this may, in part, be due to stretching of the capillaries by increased pulmonary vascular resistances, or occur through shear stresses acting upon the endothelium due to the hyperdynamic pulmonary circulation caused by single-lung ventilation and resection of lung tissue. Measurements of changes in alveolar capillary permeability have been made in patients with ARDS over protracted periods. An increase in pulmonary vascular permeability has been shown to not only persist throughout the course of ARDS but also correlate with a clinical score of injury severity and the bronchoalveolar lavage fluid neutrophil content [18].

Pathogenesis of postpneumonectomy pulmonary oedema: surgical and perioperative factors

ARDS is usually precipitated by one of many recognized predisposing conditions. However, several factors specific to pulmonary resection have been implicated in the pathogenesis of PPO, particularly related to clinical and perioperative/surgical issues.

Fluid balance

The theory that perioperative fluid overload may precipitate PPO has been suggested previously in a report of 10 cases, although only four were investigated with regard to fluid balance [19]. They were found to have significantly higher fluid inputs and urine outputs, relative to patients not developing PPO. In the same study, a dog pneumonectomy model, in which fluid overload with crystalloid induced pulmonary oedema formation, was used. However, others were subsequently unable to produce PPO in the same model if left heart filling pressures remained normal [20]. In a third study, both the incidence of PPO and a 24-h perioperative fluid balance of >3 L were associated with increased mortality [21]. Finally, an intraoperative fluid input of >2 L has been reported as a risk factor for PPO [9], although, in this series, a positive postoperative fluid balance was not. By contrast, other authors have found no relationship between fluid balance and PPO [3, 6]. The high protein content of the alveolar oedema fluid in PPO, and the frequent delay in presentation, tend to suggest that perioperative fluid overload is not the primary cause of PPO. Clearly, however, increased infusion of fluids following the development of the high permeability that characterizes PPO may be relevant in exacerbating or prolonging the clinical condition.

Impaired lymphatic drainage

The lymphatic system drains fluid filtered by the pulmonary capillaries, and transports it out of the thorax. Pulmonary lymph flow can increase seven to ten-fold over baseline levels in response to increased filtration forces [22]. Ipsilateral lymphatic vessels are necessarily damaged during lobectomy and pneumonectomy, especially

as it is now standard practice to sample the ipsilateral and subcarinal lymph node stations during surgery for pulmonary malignancy. In a series of patients with bronchogenic carcinoma, the incidence of contralateral, intrathoracic, metastatic spread was far higher for primary tumours of the left lung (percentage of superior mediastinal metastases found on contralateral side: 6% for right lung tumours, 56% for left lung tumours and 78% for left lower lobe tumours) [23]. This suggests that, for the left lung, lymphatic drainage is to a considerable extent *via* the contralateral lymphatic channels. This theory is supported by a study in nine subjects who underwent transthoracic injection of the left lower lobe with a coloured pigment. Left and right prescalene lymph nodes were then excised. Traces of the pigment were found in eight of the nine ipsilateral nodes and three of the nine contralateral nodes [24]. Contralateral lymph vessels therefore play an important role in draining intrathoracic fluid, especially in the case of the left lung. However, although some reports have detected a higher incidence of PPO following right, compared to left, pneumonectomy [3, 19], others have not [6, 9, 11]. It is probably reasonable to assume that lymphatic disruption may play some role in the clinical manifestation or severity of PPO, although unlikely that this alone would be sufficient to induce its onset.

Surgical technique

To perform either lobectomy or pneumonectomy, considerable surgical manipulation is necessary to carry out hilar and mediastinal dissection. Given the delicate structure of the lung, it is possible that some degree of parenchymal injury, similar in nature to contusion, occurs, following which an inflammatory reaction develops, although duration of surgery does not appear to be implicated [11].

One-lung ventilation

During pulmonary resection, the patient relies on the ventilation of one lung for adequate oxygenation. This is made more difficult as some blood is still shunted through the nonventilated lung. Consequently, the single ventilated lung may be subjected to a combination of hyperoxia, volotrauma and hyperinflation.

Hyperoxia may result from the need to increase inspired oxygen concentrations in the contralateral lung to sustain arterial oxygenation during one-lung ventilation. The threshold level above which oxygen toxicity and lung damage may ensue is unknown, but hyperoxia *per se* represents a potential source of oxidative stress (see *Pathogenesis of postpneumonectomy pulmonary oedema: biomedical and inflammatory factors* section).

During single-lung ventilation, an initial tidal volume of 10 mL·kg^{-1} is used customarily, using a peak inspiratory pressure of $\leq$30 cmH$_2$O [25], and this normally provides adequate ventilation. However, pre-existing lung disease or poor lung compliance may necessitate the application of a higher tidal volume or peak inspiratory pressure for a short time [25]. Following lung resection (especially pneumonectomy), there is often some degree of mediastinal shift, and an increase in functional residual capacity (FRC) has also been described [26]. It has been reported

that there is a correlation between the development of PPO and both mediastinal shift and the use of intercostal drainage connected to an underwater seal [27]. Hyperinflation may thereby result in parenchymal trauma by direct or indirect means.

Recent work evaluating the possible benefits of socalled "protective" mechanical ventilatory techniques in the support of patients with ARDS may therefore also be relevant to PPO. A number of recent clinical trials have suggested that the adoption of low-tidal-volume pressure-limited techniques can improve outcome with established ARDS [28–30]. It has been suggested that this approach modulates the increase in alveolar capillary permeability that is the hallmark of lung injury, diminished exudation of inflammatory cytokines from the alveoli into the pulmonary and systemic circulation may ensue, thereby reducing the incidence of associated distant organ failure to which many such patients succumb [31–33].

In summary, the type and intensity of mechanical ventilation applied during one-lung anaesthesia may contribute to the development of PPO, but a causal link has not been established.

Other factors

Most patients do not require blood supplementation during or after lung resection, but massive transfusion is occasionally necessary. This in itself is a recognized precipitating factor for ARDS. Age and preoperative lung function do not appear to correlate with the development of PPO [11]. Aspiration of gastric contents in the postoperative period and early-onset postoperative infection may mimic PPO, but are not in themselves risk factors.

Pathogenesis of postpneumonectomy pulmonary oedema: biochemical and inflammatory factors

ARDS is precipitated by a wide variety of clinical conditions, and is unlikely to be the result of a single process. It is more likely that the co-ordinated interaction of immune and nonimmune cells and the effects of activation of a diverse range of pro- and anti-inflammatory mediators are involved (table 2). How these processes might be implicated in the pathogenesis of PPO is less clear, but the surgical technique required exposes the patient to biochemical/inflammatory processes that are relatively specific to lung resection. First, oxidative stress may arise

Table 2. – Major groups of pro- and anti-inflammatory mediators involved in the pathogenesis of acute respiratory distress syndrome

Pro-inflammatory mediators	Anti-inflammatory mediators
Cytokines (TNF-α, IL-1β and IL-8)	Cytokines (IL-10)
	Endogenous cytokine antagonists (IL-1RA)
Eicosanoids	
Complement factors	
Endotoxin	Prostacyclin
Reactive oxygen and nitrogen species	

TNF-α: tumour necrosis factor-α: IL: interleukin; IL-1RA: IL-1 receptor antagonist.

from the application of high inspired oxygen concentrations to the contralateral lung. Secondly, ischaemia/reperfusion injury (I/R) sustained by the operative lung may play an important role. Thus, during pulmonary resection, the operative lung is excluded from the ventilatory circuit and collapsed in order to allow surgical access to the hilum and mediastinal structures. It is thereby exposed to relative ischaemia, although there is still some degree of perfusion. In the case of lobar resection, the relative ischaemia of collapse is followed by re-expansion of the lung and, thus, reperfusion. In fact, in the case of both lobectomy and pneumonectomy, this process of collapse and re-expansion may need to be carried out several times in order to facilitate the resection. Finally, mechanical forces may also be relevant to PPO developing after pneumonectomy (see also *One-lung ventilation* section). In these circumstances, the contralateral lung is hyperperfused as it receives the majority of right ventricular output. This increase in blood flow is likely to increase the shear stress on the pulmonary vascular endothelium, particularly in patients with chronic obstructive pulmonary disease in whom the pulmonary vasculature displays reduced compliance. This unfavourable change in hydrostatic forces may exacerbate pulmonary oedema formation.

Oxidative stress

Although more efficient in terms of energy utilization, aerobic metabolism imposes what is collectively termed oxidative stress. This results from the actions of reactive oxygen (ROS) and reactive nitrogen species (RNS) produced during the redox processes associated with this form of metabolism. ROS is a term used to describe oxygen free radicals and other oxygen-containing species that are oxidants or lead to the production of more aggressive oxidants (for an up-to-date review, see [34]). RNS is an analogous term used to describe nitrogen-centred free radicals and associated oxidants. The formation of these reactive species (ROS and RNS) at toxic levels *in vivo* can lead to deleterious consequences including molecular damage, and, at subtoxic levels, altered cellular signal transduction processes. Under normal circumstances, these deleterious effects are balanced by the protective effects of endogenous antioxidant systems and removal and repair mechanisms. However, if these defence mechanisms become overwhelmed, as is the case during certain disease processes, measurable oxidative damage ensues.

Redox balance

The oxidation/reduction (redox) balance of a biological system is governed by the redox status of its environment. The tendency of species within a given environment to become oxidized (lose electrons) is known as their redox potential and is measured in electronvolts. Normally cellular biological systems exist under predominantly reducing (negative) conditions. Such so-called redox balance is maintained by numerous agents including the glutaredoxin and thioredoxin systems [35, 36] that maintain cellular thiols in the reduced state. Under such conditions, normal cellular function and metabolism are maintained. By contrast, the redox balance can be shifted (positive) under conditions of oxidative stress over and above that which can be contained by endogenous protective mechanisms. Thiol oxidation ensues and a range of cellular processes are altered that may result in metabolic dysfunction, altered cellular fate, molecular damage and an amplified inflammatory response (for reviews see [37, 38]).

Oxidative stress in the pathogenesis of lung injury

ROS formation and oxidative damage have been implicated in the onset and progression of ARDS, both in animal models and in observational clinical studies in which markers of oxidative damage have been identified [39]. Thus, increased levels of the products of lipid peroxidation [40], and protein oxidation [41, 42], and increased levels of xanthine oxidase (XO) [43] and substrates of this enzyme have been found in the plasma of patients with ARDS [44]. Secondly, redox active iron acts as a catalyst for hydroxyl radical ($OH^{\cdot}$) formation, and, in patients with ARDS, aberrant iron turnover and control have been identified [45], raising the possibility of additional pro-oxidant effects. Finally, decreased levels of both primary [46] and secondary [47] antioxidant systems have been demonstrated in patients with ARDS. Elevated levels of markers of oxidative damage have also been detected in bronchoalveolar lavage fluid from these patients, including oxidized α_1-antiprotease [42], oxidized glutathione [48], and markers of peroxynitrite [49, 50], hydroxyl radical and hypochlorous acid [50] formation. The formation of some markers of pro-oxidant forces appears to be dependent upon neutrophil activation [50]. Neutrophils are implicated as key sources of reactive species, but, as ARDS may develop in neutropenic patients, the possible relevance of other factors including other inflammatory cell types, and the possible influence of nonbiochemical factors (see *Pathogenesis of postpneumonectomy pulmonary oedema: surgical and periobronchial factors* section), should not be ignored.

Ischaemia/reperfusion injury and oxidative stress

The need for hyperoxic ventilation and the specific operative techniques employed during lung resection are likely to lead to increased oxidative stress. Thus, patients undergoing lobectomy are subjected to ipsilateral lung hypoperfusion. When tissues are made ischaemic for any length of time, tissue injury ensues [51], but, following reoxygenation (as occurs when the operative lung is re-expanded), additional damage can occur. Such I/R injury has been attributed, at least in part, to the production of ROS during re-oxygenation [51]. How ROS production occurs during I/R remains unclear. Increased leakage of ROS from mitochondria through alterations in the electron transport chain may be responsible, together with depletion of manganese superoxide dismutase (SOD, a mitochondrial antioxidant), which is known to occur during ischaemia [52, 53]. Secondly, the electron transfer reaction involved in the release and metabolism of arachidonic acid to prostagladins during ischaemia can lead to ROS formation, a process that is amplified when more oxygen becomes available (reviewed in [54]). Thirdly, although most experimental studies suggest that this is

not a feature of the initial phase of injury [55–57], neutrophil activation may induce ROS release and I/R (see also *Animal-based studies* section). Finally, increased ROS flux may centre around the enzyme xanthine dehydrogenase (XD)/XO. This enzyme is involved in purine catabolism and exists predominantly as a dehydrogenase. In this form, it utilizes nicotinamide adenine dinucleotide (NAD^+) as a cofactor for the conversion of hypoxanthine to xanthine and then uric acid. However, the enzyme can become modified by limited proteolysis or redox- based mechanisms to form an oxidase. Ischaemia is known to cause this conversion to take place, when the enzyme utilizes molecular oxygen as a cofactor in preference to NAD^+ to catalyse essentially the same reaction. However, the superoxide anion radical ($O_2 \cdot^-$) and hydrogen peroxide are formed as byproducts of this process, particularly on reoxygenation. Additionally, during ischaemia aberrant adenosine triphosphate metabolism leads to increased production of hypoxanthine and xanthine, substrates for XD and XO, a situation with potential pro-oxidant implications [58]. XD and XO have therefore been identified as the most likely source of damaging ROS, and this has been reinforced by the localization of the enzyme to endothelial cells [59], thereby explaining how organs such as the heart and the lungs, which contain little XD, can still manifest I/R injury. Furthermore, XO has a heparin-like binding site [60] and can be translocated from organs rich in the enzyme such as the gut and the liver to binding sites on endothelial cells in distant organs [61, 62]. Moreover, recent evidence suggests that both XD and XO may use reduce NAD^+ (NADH) as a substrate, in addition to or instead of hypoxanthine and xanthine, to generate ROS under hypoxic or ischaemic conditions [63, 64]. This may have implications for I/R injury as NADH would be expected to accumulate under these conditions (fig. 1).

Biochemical influences in the pathogenesis of postpneumonectomy pulmonary oedema

Animal-based studies. What is known of the role of these processes in modulating the lung injury that characterizes

PPO? Several authors have used isolated blood-perfused rodent lungs to investigate the role of I/R injury in these circumstances. A study of endothelial integrity using this model [65] investigated the effects of I/R on HPV and albumin escape as markers of changes in endothelial function and integrity respectively. A 30-min period of ischaemia caused no increase in permeability to albumin unless it was followed by reperfusion. This suggests that short periods of ischaemia followed by reperfusion may cause as much damage as much longer periods of ischaemia alone. HPV was significantly enhanced following lung reperfusion, when compared with baseline levels, suggesting that endothelially derived NO release might have been impaired [65]. In a second study using a similar model, a small rise in extravascular albumin accumulation seen after ischaemia alone was greatly increased by periods of reperfusion of varying duration [55]. Following neither ischaemia nor I/R was there evidence of disruption of tissue architecture using either light or electron microscopy [55]. In a third investigation, using blood-perfused rodent lungs, administration of SOD, a scavenger of ROS, immediately before reperfusion prevented changes in vascular control and permeability to albumin, together with rises in circulating markers of oxidative stress. Superoxide may therefore play a part in modulating I/R in these models, possibly *via* its interaction with NO and consequent formation of peroxynitrite, a known initiator of lipid peroxidation [66]. Circulating neutrophils are a potential source of ROS, but neutrophil-depleted rodents seem to respond identically to controls to I/R-mediated lung injury [55]. It is therefore unlikely that neutrophil recruitment and activation contribute to the immediate onset of I/R, other sources of ROS production mentioned above being more likely candidates.

Few investigations have been designed specifically to investigate the effects of lung resection. However, evidence of hydroxyl radical-like damage to marker molecules was identified in plasma from animals undergoing pneumonectomy or one-lung ventilation followed by lung reinflation, compared to controls. Maximal rises in plasma markers of ROS damage were observed following reperfusion in both test groups. Superoxide and nitric oxide
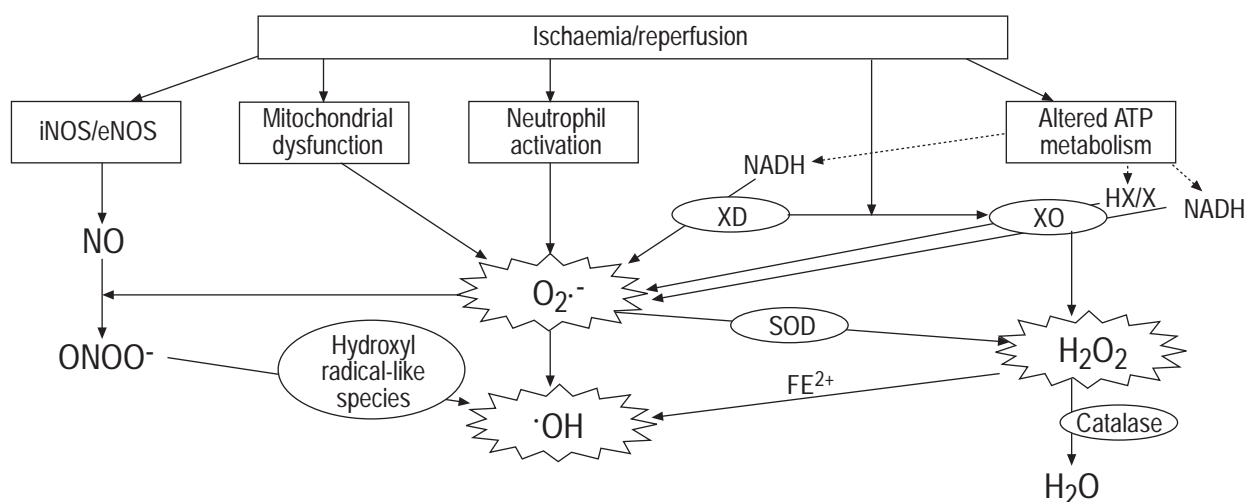

Fig. 1. – Probable pathways for the generation of reactive oxygen species following ischaemia/reperfusion injury. XD: xanthine dehydrogenase; XO: xanthine oxidase; X: xanthine; HX: hypoxanthine; SOD: superoxide dismutase; iNOS: inducible nitric oxide synthase; eNOS: endothelial nitric oxide synthase; ATP: adenosine triphosphate; NADH: reduced nicotinamide adenine dinucleotide.

synthase (NOS) inhibitors both prevented the formation of hydroxyl (OH·⁻)-like damage, suggesting that peroxynitrite was formed in this model. Lung injury measured as rises in PAP and vascular permeability to albumin, both of which were attenuated in the presence of SOD and NOS inhibition, was detectable in both test groups post reperfusion. It would seem, therefore, that the formation of reactive oxidants, including NO, occurs in this model of I/R in association with the development of lung injury. Indeed, NO generation may contribute to I/R, in that inducible NOS (iNOS) messenger ribonucleic acid (mRNA) expression increases progressively in rodent lungs with the duration of reperfusion, becoming maximal after 180 min [67]. In this study, although total NOS activity was not different following I/R, iNOS activity was significantly increased. A transient rise in PAP was seen, unaffected by either nonselective or selective NOS blockade. Moreover, neither form of NOS inhibition affected vascular permeability, unless 30 min of ischaemia was followed by a 180-min period of reperfusion, in which case blockade significantly increased the permeability index. These data suggest that the constitutive form of NOS may be protective in I/R, supporting the hypothesis that an imbalance between impaired NO production and ROS generation may induce adhesion molecule expression and local entrapment of neutrophils within the pulmonary capillary bed [68].

A rise in PAP is frequently seen in both animal models of I/R [55] and human lung transplantation recipients [69], and it has been suggested that this may exacerbate the extravascular accumulation of protein seen following an I/R injury through changes in hydrostatic forces. Further, although addition of the pressor agent angiotensin II to rodent lungs fails to induce lung injury in the absence of I/R, reducing PAP to baseline (*i.e.* preischaemic) levels using vasodilators reduces albumin extravasation post I/R.

Clinical investigations. I/R injury is known to occur after rapid re-expansion of a collapsed lung, following lung transplantation and after thrombectomy in massive pulmonary embolus [70–75]. ROS production during I/R may therefore contribute to this form of lung injury. However, few studies regarding the association of oxidative stress and the pathogenesis of PPO have been published. In one such investigation, subjects were divided into three groups according to surgical procedure: pneumonectomy, lobectomy and "lesser resections" (wedge resection or open lung biopsy) [70]. In this last group, patients were not subjected to one-lung ventilation and the ipsilateral lung was not collapsed. Oxidative damage to proteins was quantified by means of loss of plasma thiols through the process of oxidation and formation of protein-associated carbonyl groups. Albumin levels remained constant throughout and therefore had no bearing on the results. Plasma myeloperoxidase (MPO) was also assayed as an indicator of neutrophil activation. Samples were collected and analysed immediately after induction of anaesthesia and after the operation, before the patient was extubated. The carbon monoxide transfer coefficient (KCO), transfer factor of the lung for carbon monoxide, end-expiratory lung volume and FRC were also measured or calcuated. The KCO fell in the pneumonectomy and lobectomy patients but more markedly in the lobectomy group, indicating that damage to the remaining lung

parenchyma on the operated side was sustained. No significant difference was seen in the lesser resection group. Evidence of oxidative damage was detected only in the pulmonary resection groups, as measured by a perioperative fall in plasma thiol and a rise in plasma protein carbonyl group levels; again, no change was found in patients undergoing more minor resections. No significant rise in MPO levels was seen in any group; nor was any correlation found between MPO levels and either KCO or markers of oxidative damage. These clinical data reinforce the impression from animal studies that neutrophils are not a major factor in the injury process, at least at this early stage.

The pathogenesis of postpneumonectomy pulmonary oedema: a hypothesis

A schematic representation of the possible routes to the development of PPO and ARDS is shown in figure 2. The clinical and histopathological parallels between ALI/ARDS and PPO are clear, although the lack of a standard definition of the latter has meant that epidemiological data are difficult to interpret. Nevertheless, in that PPO complicates ~5% of pulmonary resections and has a high
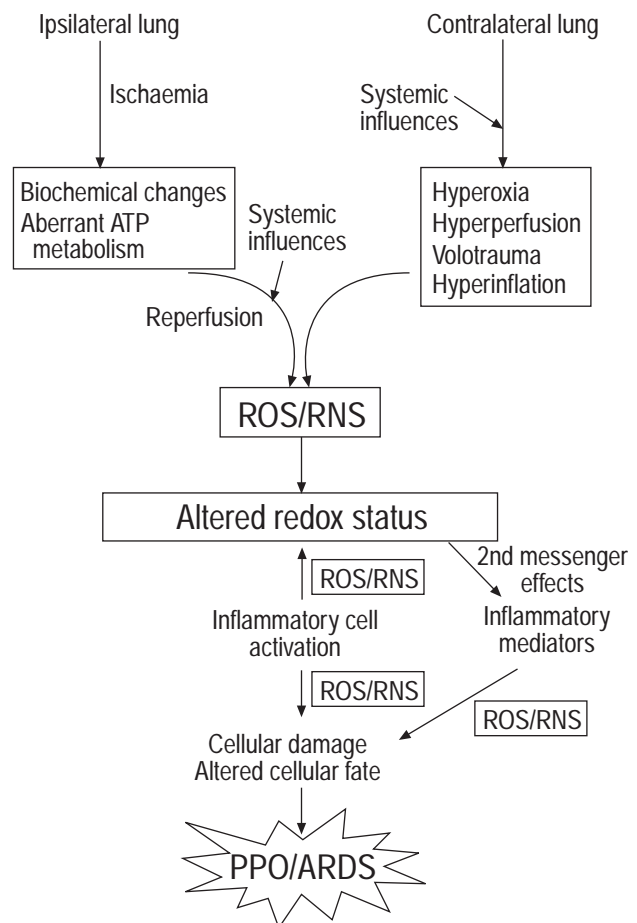

Fig. 2. – Schematic representation showing the possible routes for the generation of reactive oxygen (ROS) and nitrogen species (RNS) as a result of one-lung ventilation, including the cell signalling functions of these species, and the possible implications for the development of postpneumonectomy pulmonary oedema (PPO) and acute respiratory distress syndrome (ARDS). ATP: adenosine triphosphate.

associated mortality rate (>50%), it clearly represents a problem of considerable clinical and fiscal significance. Insults that may be implicated in the pathogenesis of PPO are received by patients undergoing lung resection. First, perioperative single-lung ventilation, during which the contralateral lung may sustain damage through volotrauma, as a result of either high applied tidal volumes or hyperexpansion following postoperative mediastinal shift, may be significant. Secondly, during this period, the ipsilateral lung is relatively hypoperfused because of the effects of HPV and physical collapse. This also results in the contralateral pulmonary endothelium being subjected to an increase in blood flow and increased shear stress. This relative ischaemic insult is followed by reperfusion. Ischaemia/reperfusion injury is accompanied by ROS generation that may contribute to tissue damage and alter redox status, possibly exacerbated by oxidative stress resulting from the high inspired oxygen concentrations which these patients often require. Animal studies suggest that the period of reperfusion does not appear to be important, at least beyond 15 min, but the length of time the tissue is left ischaemic before reperfusion does seem to correlate with the degree of injury sustained. Reperfusion is associated with a rise in PAP, which may exacerbate the extent and duration of lung injury through adverse changes in hydrostatic forces.

Initially, the generation of lung injury seems to be independent of neutrophil recruitment and activation. Longer periods of reperfusion result in increased iNOS activity and iNOS mRNA expression, although the constitutive form of NOS may play a protective role. Clinically, a tendency towards developing PPO may be exacerbated by virtue of operative technique. Limited evidence suggests that ROS generation occurs even in patients undergoing uncomplicated procedures necessitating resection of at least a lobe. Excessive fluid overload may exacerbate a tendency towards alveolar oedema formation, especially in cases in whom lymphatic drainage is impaired postoperatively. It is likely that once the damaging train of events is initiated, inflammatory pathways are activated subsequently that are self-fuelling.

In patients undergoing lung resection there is a significant risk of the development of severe lung injury. If preoperative screening tests could identify the patients at greatest risk, perhaps based on an appropriate measurement of redox status and endogenous antioxidant capacity, a pharmacological antioxidant therapy may be developed to help protect against this condition. Alternatively, the augmentation of endogenous antioxidant systems using genetic manipulation may eventually be possible.

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