Lung injury after cardiopulmonary bypass

Stephen C Clark

Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne, UK

Pulmonary injury during cardiopulmonary bypass is common as patient factors (smoking, pain, pneumonia) and the effects of cardiopulmonary bypass combine to compromise lung function after cardiac surgery. Lung injury follows the propagation of an inflammatory response involving cytokines, complement, neutrophils, monocytes, activated endothelial cells and platelets. Neutrophils sequester in the lung in response to chemotactic agents and release injurious oxygen free radicals and specific enzymes resulting in widespread pulmonary injury.

To alleviate this lung injury a number of possible interventions exist. Off pump surgery may reduce the degree of systemic inflammation but respiratory impairment still occurs and the clinical advantage is uncertain. The use of leukocyte filtration can attenuate the acute inflammatory response with encouraging though variable results. Aprotinin, Pentoxyfilline, Nitric oxide, Aspirin and other agents have shown benefits in lung function after cardiopulmonary bypass induced lung injury. Given the magnitude and diversity of the inflammatory response to cardiopulmonary bypass many possible interventions exist to attenuate lung injury resulting from extracorporeal circulation. Immediate clinical benefits are likely to result from successful amelioration of the processes involved. Perfusion (2006) 21, 225–228.

Introduction

Pulmonary dysfunction is very common after operations involving cardiopulmonary bypass (CPB). This may present as a spectrum of manifestations, from mild postoperative dyspnoea to florid adult respiratory distress syndrome (ARDS) in 2% of cases, which, in itself, carries a 50% mortality rate. Up to 20% of patients need to be ventilated for more than 48 h following cardiac surgery involving CPB.1

It is important to accept that the cause of lung failure after operations involving CPB is multifactorial and patient factors combine with the direct effects of CPB to compromise pulmonary function in the early postoperative phase.

Undoubtedly, patients presenting for cardiac surgery will often be current or ex-smokers and the prevalence of preoperative chronic obstructive airways disease or occult pneumonia is high. In the early postoperative period, pain, low spontaneous tidal volumes, poor expectoration and reduced pulmonary compliance add to the injury inflicted on the lung from the effects of CPB.

The lung injury caused by CPB has been extensively investigated and manifests itself with many physiologic characteristics. Separating the dysfunction caused by CPB and that arising from patient factors and the general consequences of major surgery and anaesthesia is difficult.

Indeed, some impairment of lung function occurs after any form of major surgery, usually due to atelectasis, but there is little doubt that CPB causes additional injury.2 The development of off-pump surgical techniques for coronary artery bypass (CAB) surgery has provided an excellent opportunity to study the impact of CPB on pulmonary function in this specific context.

In patients operated on without CPB, the inflammatory cascade is certainly attenuated compared to those operated upon with extracorporeal circulation and, therefore, one might expect an improvement in pulmonary function in those individuals. The level of neutrophil elastase is undoubtedly reduced, along with lipid hydroperoxides and nitrotyrosines, suggesting lower levels of oxidative stress in patients receiving off-pump operations.3

However, both groups seem to have similar levels of respiratory impairment, and no differences can be elucidated in alveolar–arterial oxygen pressure or intrapulmonary shunt fraction4,5 in clinical practice when directly comparing patients having similar operations with and without CPB.

There seems to be no difference in postoperative ventilation times in primary CABG patients, whether they are performed on- or off-pump.5,6 A number of clinical studies have demonstrated little clinical benefit as pertains to postoperative pulmonary function.7,8 Despite this apparent similarity in physiological terms, it has been demonstrated that...
off-pump patients exhibit shorter times to extubation in high-risk patients having re-do surgery.9

Mechanism of lung injury after CPB

The contact of blood elements with the artificial surfaces of the CPB machine primes and activates neutrophils (polymorphonucleocytes; PMN). This activation is accentuated by proinflammatory mediators, eg, IL-1, -2, -6, -8 and TNFα. Complement (especially C3 and C5a), platelet activating factor (PAF), and LTB4 are also important mediators in this process. The roles of various mediators are very complex, inter-related and their influences may change under different circumstances.

The CD18 and CD11b surface adhesion molecules on the neutrophil cell surface increase in their expression after activation and promote neutrophil adhesion to specific ligands (eg, ICAM-1) on the pulmonary endothelium, which are themselves up-regulated by CPB. Neutrophils adhere and transmigrate into the lung parenchyma under the influence of IL-8 to sequester in the lung.

Activated neutrophils release specific proteolytic enzymes (elastase, collagenase) and oxygen free radicals, which enter both the systemic circulation and mediate lung parenchymal damage locally through cellular and tissue injury.

Systemic neutrophil elastase levels reach a peak at the end of CPB and, as such, this is a useful marker of pulmonary injury and of neutrophil activation.

The resulting pulmonary injury destroys the ultrastructure of the lung, increasing alveolar–endothelial permeability, leading to functional sequelae.

In addition to the role of inflammatory mediators in lung injury, there are a number of indirect indications that lung ischaemia may contribute to the injury seen after CPB. During bypass, pulmonary blood flow is limited to flow through the bronchial arteries and studies have shown that this is significantly diminished during CPB.10 This leads to the metabolic and pathological features of ischaemia of the lung. Indeed, intermittent lung perfusion during CPB improves lung function following surgery.11 In experimental studies in neonatal swine, perfusion of the lung via the pulmonary artery while on bypass ameliorates the level of inflammatory mediators, suggesting that a systemic response to the bypass circuit materials is not entirely responsible for the lung injury observed.

Sequelae

CPB itself causes a reduction in lung compliance (static and dynamic) and an increase in the alveolar–arterial oxygen pressure difference. The intrapulmonary shunt fraction and pulmonary vascular resistance are also elevated and there is an increase in lung permeability with interstitial oedema. The transfer factor declines and lung surfactant is also affected after CPB.12 Reduced levels of exhaled nitric oxide (NO) have been detected after CPB and appear to be a result of epithelial dysfunction in the bronchial tree rather than indicating injury to the pulmonary endothelium.

The injury to the lung can be clearly seen histologically as alveolar oedema with neutrophil extravasation. Pneumocytes and endothelial cells are necrotic and swollen.

Methods of amelioration

As alluded to earlier, the obvious question is, with the advent of off-pump CAB techniques, how much lung injury is actually directly related to CPB? Can lung injury be circumvented by off-pump surgery?

Certainly, reduced cytokine responses in an attenuated inflammatory reaction have been demonstrated in off-pump surgery compared to those patients operated on with CPB. Less neutrophil sequestration in the lung and attenuated oxidative stress have been shown in such cases, but does this translate into a clinical advantage?

A number of clinical studies have been performed looking specifically at pulmonary haemodynamics and gas exchange in off-pump CAB grafting. Although results have sometimes been contradictory, it appears that the differences in PaO2 and C(a–v)O2/dL of blood show no significant differences between cases performed on and off bypass over the first 24 h after surgery. Similarly, functional indices, such as the FEV1 and FVC show no statistically significant changes irrespective of the technique used for surgery over 6 postoperative days.13 It would seem, therefore, that significant and clinically relevant reductions in pulmonary injury are not necessarily to be expected by avoiding CPB altogether.

The continuation of ventilation during CPB is another simple measure thought to have benefit. The avoidance of microatelectasis was reasonably felt to have advantageous effects, but most studies have concluded that the benefits are inconsistent with no improvements in pulmonary vascular resistance, endothelial permeability or oxygenation. The addi-
tion of pulmonary artery perfusion may, however, have advantageous effects.

The modification of the extracorporeal circuit with heparin coating can reduce neutrophil activation and lower cytokine release. Studies have shown that there can be transient improvements in lung function and in intrapulmonary shunting with heparin-bonded circuits, but this appears to have little clinical significance in practice.

Given the pathophysiology of lung injury after CPB, an obvious intervention to ameliorate injury would be the removal of neutrophils from the perfusate altogether.

Leucocyte-depleting filters can be incorporated into the arterial return line of the extracorporeal circuit and, with modern 40 µm polyester screen media, flow rates of >6 L/min can be achieved with 95–99% efficiency in neutrophil and microaggregate removal.

The clinical effectiveness of leucocyte depletion in ameliorating lung injury is, however, debatable, with many conflicting studies.

Karaiskos et al. compared cases with and without filtration and showed reductions in the respiratory index and intubation time in those patients treated with filtration, but ITU stay was not significantly different. Alexiou, in a randomized study, showed a rise in exhaled NO in the control group, which was ameliorated in the filtered patients. The respiratory index was significantly lowered in the treatment group though the intubation time and frequency of respiratory complications was similar between the groups.

Other studies have variously demonstrated little impact, or modest improvement in respiratory function postoperatively from the inclusion of a leucocyte filter in the extracorporeal circuit, so the impact of this intervention is perhaps less impressive than might have been anticipated from our knowledge of the pathophysiology.

Pharmacological interventions to ameliorate lung injury have great potential and, from our understanding of the mechanisms involved, there are a variety of drugs that may be used, ranging from agents which act at various levels in the inflammatory cascade, to very specific agents perhaps targeting neutrophil adhesion molecules or selective endothelial cell activation inhibitors.

It is beyond the scope of this article to cover all potential interventions that have been the subject of clinical investigations, but some are noteworthy.

Aprotinin, well known for its anti-fibrinolytic effects, has numerous other actions as a protease inhibitor. Apart from the inhibition of plasmin and kallikrein, and the preservation of GPIIb, GPIIIb and IIa receptors on platelets, aprotinin reduces TNFα, IL-6, -8 and elastase levels. Adhesion molecule up-regulation, crucial in the initial phase of neutrophil adhesion to pulmonary endothelium prior to transmigration into the lung, is also inhibited by aprotinin. Complement activation is also curtailed. It is, therefore, reasonable to believe that this agent may have a beneficial effect on postoperative lung injury after CPB. Rahman et al. studied this by giving study group patients 2 million units of aprotinin in the pump prime and examining its effects on lung function postoperatively. Malondialdehyde (MDA) levels, glutathione peroxidase activity levels and neutrophil numbers in lung biopsy specimens were taken before CPB and 5 min after removing the crossclamp. In addition, the alveolo–arterial oxygen difference (AaDO₂) was calculated. There was a significant and favourable effect on these parameters by administering aprotinin. Under histopathological examination, it was observed that neutrophil counts in the lung parenchyma rose significantly following removal of the crossclamp in both groups. However, the increase in the untreated group was significantly larger than in those receiving aprotinin.

Pentoxifylline has also been investigated in relation to lung injury after CPB. Pentoxifylline is a methylxanthene derivative, which inhibits cytokine-activated neutrophils and prevents degranulation and endothelial activation. Cellular deformability is enhanced, TNFα and IL-1 are inhibited and cAMP increased. It has been shown to effectively ameliorate reperfusion injury after lung transplantation.

Butler et al. investigated this agent by administering 1 mg/kg/h during surgery, but found no differences in neutrophil elastase, IL-1 or -6 at the dose given between controls and the treatment group of patients. Indeed, no difference in postoperative PO₂ was shown. However, a study comparing the effects of pentoxifylline, aprotinin and placebo by Ege et al. showed a difference at 12 h postoperatively compared to controls, though aprotinin and pentoxifylline were equally efficacious.

Simpler agents have been examined and promising results have been obtained with aspirin. Gerrah et al. investigated the effects of aspirin administration on postoperative lung injury. Intubation times were significantly reduced and PO₂ was improved in the treatment group. Thromboxane A₂ was significantly lower in the group receiving aspirin. However, postoperative blood loss was significantly greater. Clearly, thromboxane A₂ release by platelets is important in lung injury, but though the ability of
aspirin administration to ameliorate lung injury is promising in reducing lung injury, there is a trade-off with increased postoperative blood loss and its inevitable sequelae.20

Summary

The continuing refinement of CPB techniques, materials and postoperative recovery techniques have limited the clinical effects of lung injury following CPB, though significant respiratory failure still complicates the recovery of many patients postoperatively. Respiratory impairment is clearly multifactorial and, in part, occurs independently of CPB. Neutrophils are important mediators of lung injury and physical interventions (such as filters and heparin-bonded circuits) and pharmacological agents have the potential to ameliorate significant injury.

References

Copyright of Perfusion is the property of Arnold Publishers and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.