Review Articles

Prevention of Lung Injury in Cardiac Surgery: A Review

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Abstract: Inflammatory lung injury is an inevitable consequence of cardiac surgery with cardiopulmonary bypass. The lungs are particularly susceptible to the effects of the systemic inflammatory response to cardiopulmonary bypass. This insult is further exacerbated by a pulmonary ischemia–reperfusion injury after termination of bypass. Older patients and those with pre-existing lung disease will clearly be less tolerant of any lung injury and more likely to develop respiratory failure in the postoperative period. A requirement for prolonged ventilation has implications for morbidity, mortality, and cost of treatment. This review contains a summary of recent interventions and changes of practice that may reduce inflammatory lung injury after cardiac surgery. The review also focuses on a number of general aspects of perioperative management, which may exacerbate such injury, if performed poorly. **Keywords:** inflammatory lung injury, respiratory failure, cardiac surgery, cardiopulmonary bypass, ultrafiltration, autotransfusion, leucocyte depletion, transfusion, hyperoxia. *JECT. 2014;46:130–141*

THE INCIDENCE OF RESPIRATORY FAILURE IN CARDIAC SURGERY

Filsoufi and colleagues (1) retrospectively analyzed the New York State Department of Health database to determine the incidence of respiratory failure after cardiac surgery. The database included 5798 patients who underwent cardiac surgery between January 1998 and December 2005. Respiratory failure was defined as pulmonary insufficiency requiring intubation and ventilation for 72 hours or more. The overall incidence of respiratory failure was 9.1%. The mortality rate among those patients who developed respiratory failure was 15.5% compared with 2.4% in those who did not develop respiratory failure.

Impairment of respiratory function occurs for many reasons. It is a risk with any form of major surgery under general anesthesia. This is predominantly the result of alveolar collapse leading to reduced gas exchange and retention of respiratory secretions and reduced sensitivity to both hypoxia and hypercapnia in the postoperative period. Intrathoracic surgery is associated with the further problems of reduced chest wall compliance, diaphragmatic dysfunction, and the potential for trauma to both the lungs and phrenic nerves. Finally, and most importantly, cardiac surgery with cardiopulmonary bypass leads to inflammation of the lung parenchyma (2).

Acute respiratory distress syndrome (ARDS) is the extreme form of inflammatory lung injury. It is clearly defined as respiratory failure occurring within a week of a known clinical insult together with the presence of pulmonary edema not explained by heart failure or fluid overload. The degree of respiratory failure is quantified on the basis of the ratio of arterial oxygen tension to inspired fraction of oxygen (PaO_2/FiO_2). ARDS has been demonstrated to be associated with an increased mortality (3). It may occur as an isolated lung pathology or as one facet of multiorgan failure. There has been a number of studies of the incidence of ARDS after cardiac surgery with attempts made to identify risk factors (4–6). The incidence is typically .5% with mortality rates varying widely between 15% and over 90%.

THE INFLAMMATORY PROCESS

The inflammatory response is triggered by a number of factors during cardiac surgery. These include the exposure of blood to artificial surfaces during cardiopulmonary bypass (CPB), the recirculation of blood recovered through cardiotomy suction, endotoxemia resulting from splanchnic hypoperfusion, ischemia–reperfusion of the lung, surgical tissue trauma, and the use of protamine (7). The effects of inflammatory lung damage can be further exacerbated by inappropriate oxygenation, ventilation, and fluid administration.

The inflammatory response is a highly complex and dynamic one. Our understanding of it is incomplete. Key features early in the process are the generation of proinflammatory cytokines and the activation of the complement system. This leads, among other things, to the attraction, sequestration, and activation of neutrophils within the pulmonary circulation (8). Pulmonary endothelial cells are stimulated to express adhesion molecules on their luminal surface. Neutrophils bind to and migrate across the pulmonary endothelium. Activated neutrophils secrete both reactive oxygen species and various proteinases leading to structural damage and the influx of protein-rich fluid into the alveolar airspaces.

The lungs are susceptible to inflammatory damage during cardiac surgery for a number of reasons. First, the lungs are the only organ to receive the entire cardiac output. Second, the pulmonary capillaries have a diameter of only 2–15 µm. Neutrophils must deform as they pass through these vessels leading to an increase in transit time (1). Finally, the lungs are the only organs, with the exception of the heart, to suffer a significant ischemia–reperfusion injury around the period of CPB (9).

STUDY RESULTS AND THEIR INTERPRETATION

Attenuation of the inflammatory response to cardiac surgery and the protection of the lungs and other vital organs has excited much interest and led to the publication of a large number of studies.

Studies of the effect of an intervention on the inflammatory process are often difficult to interpret. The factors assayed vary widely and the implication of a change in absolute levels of certain inflammatory mediators is not clear. Indeed, it may be that changes in relative concentrations of the different pro- and anti-inflammatory mediators are of more consequence. Meta-analysis of studies is often hindered by the high degree of heterogeneity of the included studies. An attempt has been made to better focus the research effort by the recent publication of recommendations for study design in this field of investigation (10).

Clinical outcomes are of more interest to those involved in perioperative patient management. Parameters most often measured are the oxygenation index, respiratory index, and pulmonary shunt fraction. It is not clear which of these best reflects the effect of inflammation on lung function. In many cases, these measurements are only taken in the first few hours after surgery. The impact on functional recovery is not apparent. A commonly used indicator of sustained effect is the duration of postoperative ventilation. However, although this is a useful marker of resource use and cost of treatment, it is relatively nonspecific as a measure of respiratory function. Many factors can affect time on a ventilator and the potential for bias is great.

Finally, lung protection does not occur in isolation. The benefits or otherwise of a given intervention with regard to lung function must be assessed in the context of overall effect in other areas such as cardiac, neurological, and renal function.

THE IMPACT OF CARDIOPULMONARY BYPASS

The inflammatory response to cardiac surgery is driven by several factors. A key element, and one that is amenable to intervention, is the exposure of circulating blood to the artificial surfaces of the CPB circuit. This exposure leads to complement activation, triggering of the coagulation cascade, and activation of neutrophils and platelets (11).

Attempts have been made to attenuate the inflammatory response by changing the nature of the materials within the CPB circuit, by reducing the total surface area of the circuit that is in contact with blood, or by avoiding CPB altogether.

BIOCOMPATIBLE CARDIOPULMONARY BYPASS CIRCUITS

Biocompatible circuits have been available for over 20 years. Early circuits were heparin-bonded. Over time a variety of different molecules have been used including poly2-methoxyethylacrylate, polyethylene oxide chains, and phosphorylcholine. Numerous studies have demonstrated a beneficial effect of such circuits in terms of attenuation of the inflammatory response (12,13). The clinical benefits including preservation of lung function have been less clear.

Ranucci and colleagues (14) undertook a meta-analysis of trials looking at various clinical outcomes with biocompatible circuits. All included trials were prospective and randomized. Trials with pediatric patients were excluded. Thirty-six trials were included with a total number of 4360 patients. Seventy-eight percent of trials used heparin-bonded circuits. Only outcome variables reported in at least eight studies were analyzed. These included the incidence of postoperative lung dysfunction as defined by the authors and mechanical ventilation time. Unfortunately,

the latter measure was later excluded from the analysis as a result of the presence of publication bias. Analysis demonstrated a reduction in red cell transfusion, incidence of atrial fibrillation, and shorter intensive care unit (ICU) stay. There was no difference in the incidence of lung dysfunction.

The authors pointed to a number of limitations to the review. First, a great majority of the studies involved heparin-bonded circuits and so little can be surmised with regard to other types of biocompatible circuits. Second, the investigators were unable to stratify studies based on preoperative risk, and so no assessment could be made of respiratory outcomes in patients with pre-existing lung disease.

There is currently no compelling evidence that the use of biocompatible bypass circuits reduces lung injury after cardiac surgery. Further investigation is required into the newer biocompatible circuits, particularly with regard to higher risk patients and those with pre-existing respiratory disease.

MINIATURIZED EXTRACORPOREAL CIRCULATION

In recent years there has been much interest in miniaturizing cardiopulmonary bypass circuits to reduce the area of interface between blood and foreign surfaces and thus attenuate the inflammatory response. A variety of circuit configurations has been developed. Common features include greatly reduced tubing length, the use of biocompatible surfaces, removal of the venous reservoir and cardiotomy suction, and the use of centrifugal pumps. The blood–air interface is eradicated. Circuit priming volumes are greatly reduced, being typically 450–500 mL.

A majority of studies have demonstrated a reduction in various inflammatory mediators with the use of miniaturized extracorporeal circulation (MECC) when compared with conventional extracorporeal circuits (CECC) (15). The most recent meta-analysis of clinical trials included 24 studies comprising a total of 2770 patients (16). All studies were randomized and contained at least 40 patients in each treatment group (MECC versus CECC). Use of MECC was associated with a reduced duration of mechanical ventilation. Other significant findings were a reduction in red cell transfusion and overall mortality.

OFF-PUMP CORONARY ARTERY BYPASS SURGERY

The avoidance of CPB should, intuitively, lead to a reduction in the overall inflammatory response to cardiac surgery. Indeed, a number of studies have demonstrated significant reductions in levels of proinflammatory cytokine levels, activated complement, leukocyte numbers, and neutrophil elastase production (17).

Perhaps not surprisingly, studies into the effect of off-pump coronary artery bypass (OPCAB) on lung function in low-risk patients have failed to show a benefit over on-pump surgery (18–20). Of more interest are those studies in high-risk patients, the elderly, and those with pre-existing lung disease.

Meharwal and colleagues (21) reviewed 1075 patients undergoing OPCAB who were categorized as being high risk. Inclusion criteria were age older than 70 years, left main coronary artery stenosis, acute myocardial infarction, redo surgery, or a left ventricular ejection fraction of less than 30%. The comparison group consisted of 2312 patients undergoing on-pump surgery over the same 5-year period (October 1996 to June 2001). Intubation time was significantly lower in the OPCAB group (19 ± 5 hours versus 24 ± 6 hours, $p < .001$). Incidence of prolonged postoperative ventilation, defined as greater than 48 hours, was also lower (4.6% versus 7.6%, $p = .002$).

In contrast, Moller and colleagues (22) performed a prospective randomized trial—the Best Bypass Surgery Trial. The trial included 341 patients with Euroscores of ≥ 5 and three-vessel coronary disease randomized to on-pump or off-pump surgery. There was no significant difference in time to extubation, incidence of prolonged ventilation, defined as greater than 24 hours, or the incidence of pneumonia.

The benefits of OPCAB in elderly patients (>80 years) have also been studied. LaPar and colleagues (23) undertook a retrospective analysis of 1993 patients undergoing surgery at one of 16 centers between 2003 and 2008. The incidence of prolonged ventilation, defined as longer than 24 hours, was significantly lower in the OPCAB group (11.4% versus 14.7%, $p = .05$). By contrast, Sarin and colleagues (24), in a retrospective analysis of 937 patients older than 80 years of age, found no difference in the duration of postoperative ventilation, although 30-day mortality was significantly reduced.

A recently published meta-analysis of trials of OPCAB in octogenarians showed that respiratory failure requiring ventilation lasting over 24 hours was 30% less likely with OPCAB and lasting over 48 hours, 70% less likely (25).

Patients with chronic lung disease (CLD) are a high-risk group for coronary artery surgery. Kerendi and colleagues (26) undertook a retrospective analysis of 7060 patients undergoing isolated coronary artery bypass grafting (CABG) in a single institution between 2002 and 2007 with a particular focus on patients with chronic lung disease. Overall, CLD was associated with a greater incidence of prolonged ventilation, pneumonia, and mortality. Those patients with CLD who underwent off-pump surgery had a significantly reduced incidence of all these parameters when compared with those undergoing on-pump surgery.

The subject of OPCAB versus conventional on-pump surgery is a controversial one. The demonstrated advantages of

ULTRAFILTRATION

Conventional ultrafiltration during CPB may benefit the lungs in several ways. Removal of plasma water will maintain or improve plasma oncotic pressure, preventing interstitial and alveolar edema (27). Hemoconcentration with the retention of plasma clotting factors has been shown to reduce postoperative blood transfusion requirements, thus avoiding the associated increase in pulmonary morbidity (28).

A number of studies have demonstrated a reduction in various proinflammatory cytokines with the use of ultrafiltration (29,30). It is not clear, however, whether these reductions are clinically significant.

Zero-balance ultrafiltration (Z-BUF) is a technique whereby blood is filtered and an equal volume of crystalloid or colloid-containing physiological concentrations of various electrolytes returned to the circulation. Any benefit in terms of lung protection would be accrued by a reduction in inflammatory mediators rather than plasma volume control. A recent meta-analysis of trials of Z-BUF showed no benefit in terms of duration of postoperative ventilation or length of ICU stay in adult patients (31).

Modified ultrafiltration (MUF) occurs immediately after the cessation of CPB typically for a period of 20 minutes or until a target hematocrit is achieved. This technique was initially used in pediatric cardiac surgery but is now increasingly used in adult surgery. Studies of the effect of MUF on lung function in pediatric patients have shown only transitory improvements in lung function (32,33). Studies in adults are scarce. Of note is a large prospective, randomized trial of MUF in 573 consecutive adult cardiac surgical cases. The investigators demonstrated a significantly lower incidence of respiratory insufficiency, defined as a $PaO_2 < 60$ mmHg or $PaCO_2 > 50$ mmHg on room air, in the group receiving MUF (11 of 284 [3.9%] versus 20 of 289 [6.9%], $p = .005$). The timing and duration of arterial blood gas sampling is not stated. The difference in time on assisted ventilation between the two groups did not reach statistical significance (34).

Ultrafiltration appears to modulate the inflammatory response to cardiopulmonary response and to reduce blood loss. However, there is currently little evidence of a sustained benefit with regard to lung function.

AUTOTRANSFUSION DEVICES

Autotransfusion of shed blood is now routinely used in many centers (35). Blood is collected by cardiotomy suction and the red blood cells are separated by centrifugation and suspended in .9% saline before transfusion. Residual circuit blood can be processed in the same way. The putative benefit is the preservation of autologous blood and the reduction in the requirement for allogeneic blood transfusion. A recent meta-analysis of 31 randomized controlled trials demonstrated a decrease in the odds of exposure to red blood cells of 40% and to any blood product of 37% (36). The benefit in terms of lung function lies in the avoidance of allogeneic blood (37). There may be an additional benefit in the net removal of fluid during processing.

Both the coagulation and inflammatory cascades are activated in shed pericardial and mediastinal blood. Cardiotomy suction blood has been shown to contain elevated levels of various inflammatory mediators such as tumor necrosis factor-α, interleukin (IL)-6, and IL-8 (38) as well as debris such as fat and air microemboli (39).

The washing of cardiotomy suction blood has been demonstrated to significantly reduce levels of various proinflammatory cytokines (40,41). Damgaard and colleagues (42) randomized 29 patients undergoing CABG to receive processed or unprocessed blood from both cardiotomy suction and the residual circuit volume. They demonstrated significant reductions in the levels of proinflammatory cytokines IL-6 and IL-8 at 6 hours post-CPB. These differences were lost at 24 hours.

Activated neutrophils play a key role in lung injury. There is significant variation between devices with regard to the efficiency of leukocyte removal. Serrick and colleagues (43) compared five different autotransfusion devices and found that leukocyte removal rates ranged between 30% and 78%.

In a clinical trial, Boodhwani and colleagues (44) randomized patients undergoing CABG or aortic valve surgery to receive processed or unprocessed shed blood during surgery. Various parameters of lung function were measured before and immediately after CPB and 2 hours later. They found no difference between the two groups in mechanical function or gas exchange. The meta-analysis of trials of intraoperative cell salvage by Wang and colleagues (35) showed no difference in postoperative ventilation time or ICU length of stay.

There is evidence that processing of salvaged blood reduces levels of various proinflammatory mediators. In addition, levels of anti-inflammatory proteins are also altered. There is variable removal of leukocytes, platelets, and debris, depending on the device used. However, there is currently no evidence of clinical benefit with regard to lung function.

LEUKOCYTE DEPLETION

Activated leukocytes play a key role in inflammatory lung damage (45). Leukocyte filters have been added to

both the arterial and venous sides of the CPB circuit in an attempt to ameliorate the inflammatory response. Filters have also been used to process salvaged and residual circuit blood. More recently blood added to the cardioplegia solution has been filtered with the aim of reducing myocardial reperfusion injury.

The use of leukocyte filters in cardiac surgery has been widely investigated. Study endpoints have included change in leukocyte counts, changes in levels of substances released from activated leukocytes such as neutrophil elastase, and changes in other proinflammatory proteins. In addition, there have been a few clinical trials of pulmonary function with the use of leukocyte filters.

Warren and colleagues (46) published an excellent review in 2007 of the effects of the various leukocyte filtration strategies used in cardiac surgery. The reviewers identified 26 studies in which pre- and postoperative white cell counts were recorded with and without the use of leukocyte filtration. Of these, there was no difference in 15 studies. In the remainder, the reduction in white cell count was short-lived, tending to disappear post-CPB. A great majority of studies into plasma levels of various cytokines showed no difference with systemic leukofiltration.

Neutrophil elastase is an enzyme released by activated neutrophils. It acts to hydrolyze protein and plays a key role in inflammatory lung tissue injury. Six studies were identified by Warren and colleagues, in which neutrophil elastase levels were assayed. In three of these, no difference was found with leukofiltration. In the remaining three, elastase levels were elevated with leukofiltration, leading to the suggestion that trapped neutrophils released increased levels of elastase into the circulation.

The effects of leukocyte filters on postoperative lung function have been investigated in a number of trials. Generally, numbers of patients in these trials have been small and they have been of limited quality. Results are conflicting. A further meta-analysis by Warren and colleagues (47) identified 21 clinical studies with a total of 996 patients. Analysis demonstrated an improvement in oxygenation index up to 12 hours postoperatively in the leukofiltration-treated patients. In addition, ventilation time was significantly reduced. However, in a subgroup analysis of trials with greater than 25 patients per group (seven from 21 trials), no benefit was demonstrated with leukofiltration. Subgroup analysis of higher quality trials (Jadad score >2) also revealed no benefit with leukofiltration either in terms of oxygenation index within the first 12 hours or the duration of postoperative ventilation.

There has been a small number of relevant trials published since Warren's meta-analysis. Of note, Bechtel and colleagues (48) undertook the largest investigation to date. The study was a retrospective one. During a 10-week period, leukocyte filters were used in the arterial side of the CPB circuit and in the cardioplegia delivery line for all patients undergoing cardiac surgery at their institution. The total number of patients was 266. The control group was constructed of an equal number of patients who underwent surgery immediately before or after this period. The two groups were well matched for multiple characteristics including history of smoking and presence of chronic lung disease. The number of patients extubated within 12 hours was significantly greater in the leukofiltered group ([182 [68.4%] versus 159 [59.8%]). The incidence of reintubation and pneumonia was similar in the two groups.

Leukofiltration would, in theory, be an effective way to reduce lung injury in cardiac surgery given what is known about the generation and effects of activated neutrophils in this setting. However, the studies to date have not been convincing. There is a high degree of heterogeneity in studies with variation in the positioning of filters and the timing and duration of their use. Clinical trials have generally been small and of limited quality.

It would seem that three factors are important in maximizing any potential benefit from leukodepletion in the future. First there needs to be further investigation into the optimal deployment of these filters for maximum effect. Second, attention should be paid to patient selection, because benefit may only be significant in those with pre-existing lung disease. Finally, filter design is likely to improve with time leading to greater efficiency and capacity. This may lead to improved clinical outcomes in the future.

Finally, it is worth noting that the use of leukocyte filters is not recommended in the current clinical practice guidelines for blood conservation produced by the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists (Class 3 recommendation, level of evidence B). The authors state that their use may prove harmful as a result of the activation of leukocytes during CPB (49).

VENTILATION

Inappropriate positive pressure ventilation can lead to overdistension of the alveoli (volutrauma), overpressurization (barotrauma), and repeated collapse and reinflation (atelactotrauma). Shear stress leads to the generation of cytokines and activation of neutrophils. Lung injury has been confirmed by microscopy in animal studies (50). Ventilator-induced lung injury is a well-recognized phenomenon.

Studies of ventilation strategies in critically ill patients without lung injury have demonstrated that larger tidal volumes lead to increased levels of proinflammatory cytokines in both bronchoalveolar lavage fluid and blood together with a significantly higher incidence of lung injury (51,52). In the landmark paper produced by the Acute Respiratory Distress Syndrome Network (ARDSNet) (53), patients

with existing lung injury were randomized to receive initial tidal volumes of either 12 mL/kg of predicted body titrated to maintain plateau airway pressure below 50 cm H_2O or 6 mL/kg with a plateau pressure at or below 30 cm H_2O. The study was terminated early as a result of recognition of a significantly lower mortality in the low tidal volume group. The number of days without ventilator use in the first 28 days after randomization was also significantly lower in this group.

The lungs of patients undergoing cardiac surgery are already at risk as a result of the inevitable systemic inflammatory response. Mechanical ventilation may exacerbate this injury. Zupancich and colleagues compared a strategy of high tidal volumes (10–12 mL/kg) and low positive end expiratory pressure ([PEEP] 2–3 cm H_2O) with one of a low tidal volume (6–8 mL/kg) and high PEEP (10 cm H_2O). Inflammatory cytokines in blood and bronchoalveolar lavage fluid were significantly higher in the high tidal volume group at 6 hours postseparation from CPB (54). A similar study by Wrigge and colleagues (55) found no difference in levels of inflammatory cytokines at 6 hours postoperatively when tidal volumes of 6 or 12 mL/kg were used. It should be noted that in the latter study, the different ventilation strategies were only used once the patient reached the ICU and not immediately on recommencing ventilation after separation from CPB, as was the case in the Zupancich study.

Chaney and colleagues performed a small prospective randomized trial of ventilation with different tidal volumes (6 mL/kg versus 12 mL/kg) in low-risk patients undergoing CABG. Various parameters of lung function were measured at 60 minutes after arrival in the ICU and compared with measurements taken soon after initial intubation (56). Both groups were ventilated with a FiO_2 of 1.0 and PEEP of 5 cm H_2O. The group with the higher tidal volume demonstrated significantly greater increases in peak airway and plateau pressures. The decrease in lung compliance was significantly greater in the high tidal volume group. Significant decreases in static lung compliance and increases in shunt occurred in the high tidal volume group but not the low tidal volume group.

A recent meta-analysis of studies of different lung protective strategies during CPB reported some benefit in oxygenation immediately postbypass with the use of continuous positive airway pressure or alveolar recruitment maneuvers, that is to say the application of a brief period of high airway pressure in an attempt to reopen collapsed alveoli (57). However, there was no evidence for sustained benefit. The authors reported that the overall quality of studies was poor and that there was a high degree of heterogeneity with regard to study protocols and measured endpoints.

Absence of ventilation during CPB leads to lung collapse and increased resistance to blood flow through the bronchial arteries. This reduction in flow is likely to cause ischemic damage. Okuda and colleagues subjected rat lungs to 90 minutes of ischemia and measured lung edema after 60 minutes of reperfusion. Continuous ventilation of the lungs during the period of ischemia led to a significant reduction in lung edema. This reduction was seen when ventilating with 21% oxygen or 100% nitrogen (58). Imura and colleagues subjected pigs to CPB. Those pigs that were ventilated at low tidal volumes during CPB were better oxygenated with lower alveolar–arterial oxygen gradients and less histological evidence of lung injury post-CPB (59).

There are currently few trials of ventilation during CPB. John and colleagues randomized 23 low-risk patients undergoing CABG to receive either ventilation or no ventilation during CPB. Ventilated patients had tidal volumes of 5 mL/kg (60). The FiO_2 was not stated in the paper. Extravascular lung water postbypass was significantly reduced as was time to extubation. There was no significant difference in lung compliance or alveolar–arterial oxygen difference. Gagnon and colleagues (61) found no statistically significant improvement in oxygenation, pulmonary vascular resistance, or length of hospital stay when patients were ventilated with tidal volumes of 3 mL/kg during CPB. The authors noted that five patients in the ventilated group received blood transfusion during surgery. No patients in the control group were transfused.

In summary, care should be taken in the setting of ventilatory parameters to avoid exacerbating inflammatory lung injury in the post-CPB period. Further investigation is required to determine whether there is any sustained benefit from ventilation during CPB.

LUNG PERFUSION DURING CARDIOPULMONARY BYPASS

During total CPB, pulmonary blood flow is arrested. The lungs are perfused through the bronchial arteries. Schlensak and colleagues (62,63) have demonstrated in animal studies that bronchial blood flow is greatly reduced during CPB. This finding raises the possibility of an inflammatory ischemia–reperfusion injury to the lungs. This is supported by initial animal studies (64) and later investigations in patients undergoing cardiac surgery (65).

Pulmonary perfusion during CPB has been shown to reduce the levels of various proinflammatory proteins after 2 hours of reperfusion in animal studies (66). In a clinical trial, Suzuki and colleagues (67) randomized 30 infants undergoing open cardiac surgery to standard CPB or CPB with continuous pulmonary perfusion. The perfusion group received pulmonary perfusion with oxygenated blood at 30 mL/kg/min during the period of CPB. Patients were electively ventilated for 24 hours postoperatively. The oxygenation index was significantly higher in the perfusion group

at all time points up to 24 hours. The duration of ventilator support was significantly shorter in the perfusion group (67.2 ± 13.8 hours versus 183.8 ± 56.5 hours, $p = .049$).

Santini and colleagues (68) randomized 30 low-risk patients undergoing CABG to either conventional CPB or CPB with pulsatile pulmonary perfusion. Oxygenated blood was infused through a cannula into the pulmonary artery and drained from the left atrium. A pulsatile pump was used at a rate of 60 beats per minute. Various measures of lung function were made on admission to ICU, at 3 hours postsurgery and after extubation. Alveolar–arterial oxygen gradient, oxygenation index, and lung compliance were significantly better in the perfusion group across all three time points. Mean pulmonary arterial pressures and pulmonary vascular resistance were significantly lower in the perfusion group. Analysis of bronchoalveolar lavage samples collected on admission to ICU and 4 hours later showed a reduced absolute white cell count and lower percentage of neutrophils in the perfusion group.

An alternative to continuous pulmonary perfusion is single-shot pulmonary perfusion with a protective solution at the commencement of CPB. In an animal study, Liu and colleagues (69) demonstrated a reduction in lung injury with perfusion of the lungs with a single dose of cold protective solution containing glucose–insulin–potassium, L-arginine, aprotinin, anisodamine (an anti-inflammatory agent), and phosphate buffer.

Sievers and colleagues (70) investigated the effects of single-shot pulmonary perfusion at the commencement of CPB in adult patients undergoing scheduled coronary bypass or aortic valve surgery. Study numbers were small, and no indication of preoperative risk was given. Lung perfusion consisted of arterial blood cooled to 15°C at 1 L/min for 10 minutes. The lungs were ventilated for the duration of perfusion. Alpha-2 macroglobulin levels increased significantly in bronchoalveolar lavage (BAL) samples from the control group but not in the perfused group. Alpha-2 macroglobulin is a large plasma protein and elevated BAL levels are taken to indicate increased leakiness of the capillary endothelium. The alveolar–arterial oxygenation gradient was significantly lower in the perfused lungs. The oxygenation index did not differ significantly.

Drew and Anderson (71) first described the use of a separate pulmonary extracorporeal circulation with ongoing ventilation in 1959. Using this system the lungs continue their function as physiological oxygenators removing the requirement for a mechanical oxygenator in the systemic bypass circuit. The primary benefit was the avoidance of the complications associated with early oxygenators. This technique was revisited by Richter and colleagues to determine if it led to a reduction in systemic inflammatory response to CPB and improved clinical outcomes. They randomized 30 low-risk patients undergoing CABG to receive conventional CPB or bilateral extracorporeal circu-

lation as described by Drew and Anderson (72). Peak concentrations of proinflammatory cytokines IL-6 and IL-8 were significantly lower in the Drew–Anderson group. Oxygenation index was significantly higher in the Drew–Anderson group at 30 minutes and 2 hours postbypass. The difference was lost at 4 hours. A similar pattern, favoring the Drew–Anderson group, was demonstrated for the alveolar–arterial oxygen gradient. Shunt fraction was significantly greater in the standard CPB group at 30 minutes post-CPB. This difference was lost at 4 hours. Time to extubation was significantly shorter in the Drew–Anderson group (5.2 ± .4 hours versus 9.5 ± 1.2 hours, $p = .0025$).

The perfusion of the lungs with protective solutions during CPB may ameliorate inflammatory injury. Studies of clinical benefit are few and show only short-term benefit. Far more investigation would be required to justify the use of pulmonary artery cannulation and pneumoplegia in routine practice.

PHARMACOLOGICAL INTERVENTIONS

In recent years, a large number of drugs have been shown to alter the inflammatory response during cardiac surgery. These include phosphodiesterase inhibitors (73), ketamine (74), aminophylline (75), free radical scavengers such as n-acetylcysteine (76), and antioxidants (77). However, adequately powered clinical trials demonstrating a beneficial effect on postoperative lung function are few. An exception are the corticosteroids, which have been studied more extensively.

Two recent meta-analyses of trials investigating the clinical benefits of steroids have demonstrated no reduction in the duration of postoperative ventilation (78,79). In contrast, Dieleman and colleagues (80) recently published the results of a large multicenter, randomized double-blind placebo-controlled trial. A total of 4494 patients were randomized to receive high-dose dexamethasone (1 mg/kg) or placebo intraoperatively. A total of 10.9% of patients in the dexamethasone group and 11.9% of the placebo group were being treated for chronic lung disease before the surgery.

The primary endpoint was a composite of death, myocardial infarction, stroke, renal failure, and respiratory failure within 30 days of surgery. There was no significant difference demonstrated between the steroid-treated cases and the control subjects. However, the duration of mechanical ventilation was significantly shorter in the dexamethasone group. The incidence of postoperative pneumonia was also significantly reduced. Respiratory failure, defined as a period of ventilation for an uninterrupted period of greater than 48 hours, occurred in significantly fewer cases in the dexamethasone group (67 [3%] versus 97[4.3%], $p = .02$). This prompted the authors to

recommend further study of the effects of dexamethasone on pulmonary outcomes.

OXYGENATION

A high inspired fraction of oxygen (FiO_2) leads to alveolar collapse with the extent of collapse being related to both the FiO_2 and duration of exposure (81). There is radiological evidence of basal atelectasis after only brief exposure to 100% oxygen (82). The effect is magnified in lungs already made susceptible by the inflammatory response to CPB (83).

Hyperoxia causes increased production of reactive oxygen species (ROS) by mitochondria (84). Hyperoxia also increases pulmonary sequestration and activation of neutrophils with further ROS production (85). Hyperoxia has been shown to exacerbate lung injury caused by high tidal volume ventilation (86) and to worsen ischemia–reperfusion injury of the lung (87).

Ihnken and colleagues (88) demonstrated a significantly greater decrease in vital capacity and forced expiratory volume over one second (FEV_1) postoperatively in patients rendered hyperoxic during CPB (PaO_2 = 400 mmHg) when compared to a normoxic control group (PaO_2 = 140 mmHg).

Reber and colleagues (89) randomized 20 low-risk cardiac surgical patients to receive either 100% or 35% oxygen after separation from CPB. Venous admixture, a measure of pulmonary shunt, was significantly increased in the hyperoxic group when compared with the level before CPB. There was no such difference in the control group.

In a study by Pizov and colleagues (90), 30 patients were randomized to receive either 50% or 100% oxygen throughout their cardiac surgery. They were able to demonstrate that gas exchange was impaired in both groups immediately postoperatively. However, by 6 hours post-surgery, although the efficiency of gas exchange had returned to prebypass levels in the 50% group, it remained significantly reduced in the 100% group.

Many of the studies into the effects of hyperoxia on lung function after cardiac surgery are small and there remains much to be elucidated. However, anesthesiologists and perfusionists should be aware of the possible adverse effects when considering oxygen management during cardiac surgery.

FLUID MANAGEMENT

It has long been recognized that administration of excessive volumes of isotonic crystalloid solutions leads to the development of interstitial edema. More recently, there has been work to indicate that the administration of colloidal solutions to euvolemic patients also leads to interstitial edema (91). The lungs are rendered highly susceptible to edema during cardiac surgery as a result of increased capillary permeability, elevated pulmonary arterial vascular resistance, and reduced myocardial diastolic function after reperfusion.

Hemodilution of the blood at the commencement of CPB leads to a reduction in colloid osmotic pressure and risks the development of pulmonary edema. This effect can be attenuated either by the use of colloids in the bypass prime (92) and by the use of retrograde autologous priming (93).

The administration of excessive volumes of fluid in the pre- and postbypass period can be avoided by using goal-directed therapy. Fluids are given based on the measurement of a parameter that has been demonstrated to accurately indicate fluid responsiveness in the form of an increase in cardiac output. Numerous parameters have been assessed. Static measures of pressure such as central venous pressure and pulmonary artery occlusion pressure have been shown repeatedly to be of no use in this regard (94,95). Dynamic interactions between intrathoracic pressures during positive pressure ventilation and left ventricular output such as pulse pressure variation and stroke volume variation more accurately reflect fluid responsiveness (96,97).

The use of transesophageal echocardiography during cardiac surgery is now widespread. Static measurements such as left ventricular end diastolic area (LVEDA) are often used to reflect cardiac preload. However, these measurements do not take into account changes in ventricular compliance. It is, therefore, not surprising that studies into LVEDA measurement as a predictor of fluid responsiveness have produced mixed results (97,98). Possibly the most sensitive echocardiographic parameter for the prediction of fluid responsiveness is the superior vena cava (SVC) collapsibility index. Collapse of the SVC by more than 36% has been shown to predict fluid responsiveness with 90% sensitivity and 100% specificity (99).

TRANSFUSION OF BLOOD PRODUCTS

Koch and colleagues (100) reviewed 16,847 cases of on-pump cardiac surgery undertaken over an 8-year period at the Cleveland Clinic, Cleveland, Ohio. Patients who received transfusion of red cells or plasma had a significantly increased incidence of respiratory distress, respiratory failure, and ARDS. Intubation times were significantly longer and the incidence of reintubation higher.

The requirement for allogeneic blood in cardiac surgical patients can be minimized by the use of various techniques for the preservation of blood intraoperatively. These techniques include cell salvage and autologous transfusion, the

use of ultrafiltration, and miniaturized extracorporeal circuits. In addition, any intervention that attenuates the inflammatory response to cardiac surgery may also reduce the incidence of coagulopathy and postoperative blood loss. Other important aspects of patient management include the identification and treatment of preoperative anemia, the avoidance of excessive hemodilution by the injudicious use of intravenous fluids, and scrupulous surgical technique. Finally, appropriate triggers for transfusion should be used (101,102).

SUMMARY AND FUTURE DIRECTIONS

There has been much recent interest in the attenuation of the inflammatory response to cardiac surgery and the resulting reduction in lung injury. Studies are many but definitive answers currently few. The avoidance of allogeneic blood transfusion is clearly beneficial. Scrupulous perioperative management of oxygenation, ventilation, and intravenous fluids is also important. The evidence of benefit with interventions such as the use of biocompatible circuits, leukocyte filters, and cell salvage is currently weak. However, ongoing improvements in technology may lead to more obvious benefit.

Off-pump cardiac artery bypass surgery has been associated with a reduction in inflammatory lung injury and it has become the procedure of choice for high-risk patients in many centers. However, it has not been universally embraced and recent investigations have failed to show a benefit at 30 days (103). In addition, the recently published Randomised On/Off Bypass (ROOBY) trial demonstrated less effective revascularization in those patients randomized to off-pump surgery (104). The adverse cardiac event rate at 1 year was also significantly greater (16.4% versus 5.9%, $p < .001$).

There is now interest in alternative strategies to OPCAB in high-risk patients such as CPB with concurrent ventilation or bilateral perfusion with or without ventilation. There are currently few trials, and the body of evidence will need to increase substantially before these approaches are adopted.

It is clear that the greatest benefit from the various interventions discussed in this review will accrue in those patients at most risk of pulmonary morbidity. Identifying these patients is therefore important. Kor and colleagues (105) recently published an evaluation of a scoring system for the identification of patients at risk of acute lung injury after surgery—the surgical lung injury prediction (SLIP) score. Important surgical predictors included high-risk cardiac, thoracic, and vascular procedures. High-risk cardiac procedures included CABG, valve replacement, multiple valve repairs, aortic repair, congenital heart repair, pericardial resection, transplantation, and any reoperation.

Significant comorbidities included chronic obstructive pulmonary disease (COPD), gastroesophageal reflux disease, and diabetes mellitus. The single modifying factor found to be significant was alcohol abuse. The score is calculated out of a possible total of 101 with high-risk patients (SLIP score >27) having a combined risk of acute lung injury of 12.2%.

Risk estimates will only be of use if the data that are included are accurate. Adabag and colleagues (106) performed pulmonary function tests in 1169 patients undergoing cardiac surgery at the Minneapolis Veterans Affairs Medical Center between 2000 and 2007. They defined airway obstruction as a FEV_1 to forced vital capacity ratio of <.7. Four hundred eighty-three patients had a recorded history of COPD. Of these, 178 had no airway obstruction on testing. One hundred eighty-six patients without a diagnosis of COPD had evidence of airway obstruction. When the investigators analyzed outcomes, they found that the mortality risk was 10 times higher in those patients with moderate to severe airway obstruction together with a diffusion capacity of less than 50% of predicted value. The documented causes of death were varied and included multiorgan failure, cardiogenic shock, respiratory failure, stroke, and infection.

Finally, there is emerging evidence of genetically determined variation in susceptibility to lung injury. Dodd-o and colleagues (107) demonstrated strain-specific differences in sensitivity to ischemia–reperfusion lung injury in mice. The investigators found that multiple genes were involved and that differences were not explained by differences in the production of ROS. Chen and colleagues (108) demonstrated a link between polymorphisms of the gene coding for interleukin 18 and the risk of developing an acute lung injury after CPB surgery. Over time, genetic screening may become an additional method for the identification of those at high risk of lung injury after cardiac surgery.

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