Review

Additional Lung-Protective Perfusion Techniques during Cardiopulmonary Bypass

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Postoperative cardiopulmonary bypass (CPB)-induced lung dysfunction still remains as a serious complication that could lead to life-threatening problems. CPB is associated with a whole-body inflammatory response. The contact of blood components with the artificial surface of the bypass circuit causes activation of complements, upregulation of cytokines and adhesion molecules, and induction of oxygen-free radicals. The pathogenic consequences are adhesions of complement-activated neutrophils to endothelial cells, neutrophil migration into the extravascular spaces, and free-radical mediated pulmonary damage. Injured endothelial cells are vulnerable to the cytokine-mediated inflammatory cascade. Moreover, CPB renders the lung being at risk for ischemic insults because lung perfusion is maintained solely by the bronchial arterial system. Postischemic reperfusion of the lung upregulates adhesion molecules and enhances neutrophil-endothelial cell adhesion and extravascular neutrophil sequestration, thereby aggravating further structural and functional abnormalities of pulmonary endothelial cells. Thus the systemic inflammatory response and ischemia-reperfusion during CPB constitute a vicious network in the pathogenesis of CPB-derived lung injury. Accordingly, it is postulated that additional pulmonary perfusion could alleviate CPB-induced lung damage. This review article summarizes recent literature on the mechanisms involved in lung dysfunction after CPB, and it also summarizes current reports on lung-protective perfusion techniques. (Ann Thorac Cardiovasc Surg 2010; 16: 150–155)

Introduction

Although the technical refinement of cardiopulmonary bypass (CPB) has progressively improved the surgical outcomes of heart diseases, postoperative CPB-induced lung dysfunction still remains as a serious complication that could lead to a life-threatening problem. CPB provokes systemic cytokine-mediated inflammatory reaction, and it renders the lung being at risk for ischemic insults. The systemic inflammatory response and postischemic reperfusion of the lung play a pivotal role in the pathogenesis of CPB-derived lung damage. Accordingly, it is postulated that controlled pulmonary perfusion could alleviate CPB-induced lung injury. Current knowledge of the issue is reviewed in this manuscript.

Etiology of Pulmonary Dysfunction after Cardiac Surgery

In cardiac surgery, postoperative systemic inflammatory response syndrome is a hazardous complication that is presumed to relate to the contact of blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia, and operative trauma, solely or in combination. It is thought that the syndrome develops through cytokine-mediated inflammation. Several studies reveal that off-pump coronary artery bypass grafting (CABG)

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provides a reduction of cytokine response and complements activation, fewer circulating neutrophils and monocytes, and a significantly lower level of neutrophil elastase, as compared with on-pump CABG.[1,2] The pathogenic relation between the cytokine-induced inflammation and CPB has been clearly elucidated. Several reports have emphasized that direct contact of blood with the synthetic surface of the CPB circuit activates complements,[3] which induce inflammatory cytokines that exert activating stimuli on pulmonary endothelial cells.[4,5] The activated endothelial cells promote widespread expression of a variety of adhesion molecules, which facilitate the adhesion of complement-activated neutrophils to endothelial cell surfaces and cause neutrophil migration into the extravascular spaces.[6–8] A progressive accumulation of neutrophils in the pulmonary circulatory system is presently known to result in tissue injury mediated by oxygen-derived free radicals.[9–11]

Furthermore, the lung is at risk for ischemic insults during total CPB because lung perfusion is maintained solely by the bronchial arterial system. Schlensak et al. demonstrated that CPB lessens even bronchial arterial blood flow in a neonatal pig model.[12] It is thought that the ischemic and reperfusion insults play a critical role in the development of CPB-derived lung damage. Horgan and associates endorsed this concept, and they claimed that postischemic reperfusion of the lung causes upregulation of adhesion molecules on the endothelial cell surface, which enhances neutrophil-endothelial cell adhesion and neutrophil sequestration, thereby aggravating further structural and functional abnormalities of pulmonary endothelial cells.[13] Intrapulmonary neutrophil sequestration that occurs during CPB is especially prominent at the moment of lung reperfusion.[14–17] The endothelial injury and neutrophil sequestration induced by ischemia and reperfusion fall into the category of a cytokine-mediated lung injury. Several experimental studies exhibited that the lung injury was not nearly as severe in the lesser deprivation of blood flow in the pulmonary arteries during CPB.[18,19] Kuratani et al. demonstrated that total CPB decreases pulmonary regional blood flow to 11% and adenosine triphosphate (ATP) in the lung tissue to 50%, as compared with those of the prebypass status, and partial CPB reduces blood flow to only 41% and does not alter ATP in the experimental model.[20] Therefore it is highly probable that additional pulmonary perfusion throughout the period of total CPB may minimize the ischemic insult and can eventually prevent lung injury.

Lung Perfusion during Cardiopulmonary Bypass

Biventricular bypass

Drew and Anderson formulated the first trial of CPB with continuous pulmonary perfusion in 1959.[21] They introduced biventricular bypass using patients' own lungs as the oxygenator because the use of an artificial lung had not been well established at that time. The technique had a theoretical advantage of eliminating direct contact between blood and the synthetic surface of the oxygenator. However, the procedure failed to show any biochemical or clinical benefits for the prevention of CPB-induced lung injury. Since then this work had gone unrecognized. In the late '80s, Drew and Anderson's method was successfully revisited by Glenvile et al. for patients who underwent CABG.[22] In the late '90s, its potential benefits for the prevention of CPB-induced lung injury attracted the attention of several investigators. They showed that the procedure provided attenuated cytokine response and improved respiratory index in animal model[23] and a favorable clinical outcome.[24] However, the drawback was that the technique was applicable to only closed-heart procedures, as with uncomplicated coronary surgery.

Additional lung perfusion

Serraf and associates reported an experimental work of a neonatal piglet model in 1997, which first showed the potential capability of supplementary pulmonary perfusion to alleviate CPB-induced lung injury. They showed that additional low-flow continuous perfusion of the lung during total CPB resulted in better preservation of tissue ATP stores and arterial oxygen tension.[25] The lung was perfused with venous blood during CPB using an independent pump at the flow rate of 35 ml/min. Mean perfusion pressure was 14 mmHg. They also developed the single dose of pulmonary artery perfusion with protective solution as a concept of pneumoplegia during total CPB, and showed that the procedure prevents hemodynamic alteration after CPB. Following their successful experimental report, additional lung perfusion techniques became applicable to any sort of open-heart surgery in regard to technical aspects.

Chai and associates demonstrated in an experimental model using neonatal piglets that exposure to CPB alone was enough to cause pulmonary injury, but cessation of pulmonary artery flow during CPB significantly exacerbated the pulmonary dysfunction.[26] In this study, pulmonary vascular resistance, A-a gradient, and pulmonary compliance were all adversely affected by the absence of antegrade

flow to the lungs during CPB. Based on these results, they drew particular attention to ischemic lung damage as a result of extracorporeal membrane oxygenator therapy (ECMO) in the management of congenital heart diseases in 2000.[26] They demonstrated that a patent aortopulmonary shunt during ECMO maintaining pulmonary blood flow improved the outcome of patients with single ventricle physiology. In patients with shunt-dependent pulmonary circulation, survival became significantly better in patients with the aortopulmonary shunt left open.

Continuous lung perfusion during total CPB

After the accumulation of preliminary knowledge, we began on the clinical application of additional lung perfusion with promising results in the practice of cardiac surgery. We first reported our experiences that continuous lung perfusion was able to reduce postoperative lung injury in children with congenital heart diseases in 2000.[28] The patients underwent continuous perfusion of oxygenated blood to the pulmonary arteries with a nonpulsatile flow of 30 ml/kg/min during total CPB. The mechanical ventilation was arrested at positive end-expiratory pressure (PEEP) of 5 cmH_2O. Our method gave rise to a well-preserved PaO_2/FiO_2 ratio and reduced the duration of postoperative mechanical ventilation. Furthermore, this procedure lessened the elevation of plasma levels of circulating adhesion molecules, including intercellular adhesion molecule 1 (ICAM-1) and soluble granule membrane protein 140 after cessation of CPB.[29]

An experimental work of Siepe and associates exhibited that continuous pulmonary perfusion during CPB reduced apoptosis and inflammatory response in the lung, preventing expressions of interleukin-1, interleukin-6, and tumor necrosis factor (TNF-α). Moreover, they demonstrated that the alleviative effect was greater in the continuous pulmonary perfusion using pulsatile flow of 20% of systemic circulation compared with nonpulsatile flow perfusion.[30] In this study, mechanical ventilation was executed and continuous positive airway pressure to the lungs was kept at 5 mbar during CPB. They speculated that the reduction in cytokine expression by pulsatile pulmonary perfusion might be mediated by nuclear factor [NF]-κB and activating protein [AP]-1.

Most recently, Gabriel and his associates reported experimental results of variable methods of continuous lung perfusion.[31] Lasting 30 min, the experiment was carried out with arterial or venous blood. Mechanical ventilation was executed once CPB was established. Mean lung perfusion pressure and mean lung perfusion flow rate were equivalent to 24.6 mmHg and 200 ml/min, respectively. They demonstrated that continuous lung perfusion with arterial blood provided lower mean pulmonary artery pressure and pulmonary vascular resistance (PVR) and a well-preserved PaO_2/FiO_2 ratio. Lung perfusion with venous blood also made PVR markedly lower and preserved good PaO_2/FiO_2 ratio. There were no histological differences between lungs perfused with venous and arterial blood. Nevertheless, they speculated that a duration of lung perfusion for 30 min was not enough to promote substantial modifications in the expressions of TNF-α, interleukin-4, and ICAM-1.

Single or multidose of lung perfusion with protective solution

Wei and associates formulated another method of additional lung perfusion. They reported clinical and experimental works of a single dose or multidoses of lung perfusion with a protective solution, such as pneumoplegia. They demonstrated that a single dose of lung perfusion with hypothermic protective solution during CPB reduced lung injury and preserved lung compliance, gas exchange ability, and low vascular resistance during experimental study.[32]

They then reported their successful clinical experiences that intermittent lung perfusion was advantageous to relieve lung injury in the surgical correction of tetralogy of Fallot.[33] In this clinical practice, their procedure was composed of a single dose of lung perfusion with cold (4°C) protective solution following aortic cross-clamp. The solution (20 ml/kg) was infused into the main pulmonary artery with flow rates ranging 70 to 80 ml/min. The perfusion was repeated when cross-clamp time exceeded 70 minutes. The solution comprised a basic solution of dextran (7 to 8 ml/kg) with additives of anisodamine (1 mg/kg), L-arginine (0.2 g/kg), aprotinin (50,000 KIU/kg), 5% sodium hydrogen carbonate (1 ml/kg), and methylprednisolone (30 ml/kg). Oxygenated blood (10 ml/kg) was added to the solution. Oxygen index and alveolar-arterial O_2 gradient were better preserved in children who underwent the procedure than in those in the control group. The durations of mechanical ventilation and stay in the intensive care unit were also shorter. The method suppressed plasma levels of the TNF-α, malondialdehyde, von Willebrand factor, and endothelin. Concentrations of interleukin-6 and interleukin-8 in bronchoalveolar lavage fluid was also reduced. Histopathological examination revealed no capillary hyperemia or hemorrhage, intra-alveolar edema, leukocyte accumulation, mitochondria swelling or vacuolation, or gas-blood barrier broadening. Histochemical examination showed a suppression of ICAM-1 in lung vascular

endothelial cells. Recently, they yield further benefits of clarithromycin-added single doses of hypothermic protective solution for inhibition of inflammatory responses.[34] Histological analyses showed that intra-alveolar hemorrhage and neutrophil accumulation were not found in the experimental group using clarithromycin-added solution. The apoptosis rate of accumulated neutrophils was significantly lower in the control group.

Although experimental investigation and clinical trial of additional lung perfusion during CPB have developed mainly in the field of pediatric cardiac surgery, lung-protective effects have also been investigated currently in the field of adult cardiac surgery. Sievers and associates reported their experiences in adult cases of single-shot hypothermic lung perfusion with oxygenated blood at the beginning of CPB; pulmonary artery perfusion was maintained for 10 minutes with 1 L/min of arterial blood cooled to 15℃. They showed that alveolar-arterial oxygen gradient and oxygenation index were well preserved in patients who underwent the additional lung perfusion technique, especially when combined with ultrafiltration.[35] However, they reported that the technique yielded no differences in postoperative pulmonary artery pressure, weaning time from respiratory support, or duration of stay in the intensive care unit. Therefore doubt remains about the clinical efficacy of additional pulmonary perfusion in adult cardiac surgery.

Other measures with lung perfusion

Recent clinical and experimental works have consistently shown protective effects of supplementary lung perfusion on CPB-induced lung injury. Goebel and associates reported the combination of pulmonary perfusion and inhalative carbon monoxide. The lung was continuously perfused by oxygenated blood at a flow rate of 20% of the systemic flow with pulsatility. This hybrid technique inhibited CPB-mediated pulmonary inflammation with lower levels of TNF-α and interleukin-6 in the lung and hindered pulmonary apoptosis when compared with pulmonary perfusion or carbon monoxide inhalation alone.[36]

Lastly we would like to draw special attention to the work of Badellino et al., which described the potential capability of continuous ventilation to reduce lung ischemia during CPB and eventually hinder CPB-derived lung injury.[37] The lung is uniquely oxygenated through alveolar diffusion and vascular perfusion; thus ventilation during total CPB with lung perfusion may be more helpful for lung protection than lung perfusion alone.

Future Perspective in Lung Perfusion

It remains controversial whether the procedure provides significant clinical benefits in the adult cardiac surgery, as discussed by Sievers et al.[35] On the contrary, the advantageous effects on postoperative lung function of additional lung perfusion have been definitively proven in the practice of pediatric cardiac surgery. However, a question remains whether the continuous perfusion technique with blood would protect the lung much better than the intermittent perfusion technique with protective solution. Another question is what flow rate in the continuous perfusion technique is appropriate for lung protection and whether perfusion with arterial or venous blood is much better. In normal individuals, the bronchial blood flow is nearly 8%–10% of systemic blood flow. Kuratani and associates demonstrated that impairment of postoperative pulmonary function and ultrastructural derangement of lung tissues are less severe in patients whose bronchial blood flow exceeded 25% of systemic blood flow.[20] The experience implies that more-than-normal bronchial blood flow is the prerequisite to protect the lung during CPB.

The cause of CPB-derived lung injury is multifactorial. Additional lung perfusion may not be enough to prevent postperfusion lung injury. Ventilatory factor may play a crucial role in lung-protective additional perfusion techniques. Other additional methods may contribute to further protection of the lung during CPB. More investigative work is required to determine the precise role of lung-protective pulmonary perfusion techniques.

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