

REVIEWS

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Pulmonary Dysfunction and Acute Respiratory Distress Syndrome After Cardiopulmonary By-pass – Mechanisms and Prevention

Niewydolność układu oddechowego i ostry zespół niewydolności oddechowej po operacjach z zastosowaniem krążenia pozaustrojowego – mechanizmy powstawania i zapobieganie

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Abstract

Postoperative lung injury is one of the most frequent complications of cardiac surgery. It mostly results from the use of cardiopulmonary bypass (CPB). However, recent comparative studies between conventional and off-pump coronary artery bypass grafting have indicated that CPB itself may not be the major contributor to the development of postoperative pulmonary dysfunction. Thus the pathophysiology of this complication is not clearly defined. This article summarizes the molecular and cellular mechanisms involved in pulmonary dysfunction after cardiopulmonary by-pass. The associated physiological, biochemical, and histological changes are reviewed with reference to the current understanding of the underlying mechanisms. Reports on the prevalence and mortality of acute respiratory distress syndrome after cardiac surgery are summarized. Therapeutic interventions and modifications which are helpful in the prevention of the described adverse results of cardiopulmonary bypass are also presented (*Adv Clin Exp Med* 2007, 16, 5, 683–688).

Key words: cardiac surgery, cardiopulmonary bypass, cytokine, inflammatory response, lung injury, neutrophils, ventilation.

Streszczenie

Pooperacyjne uszkodzenie płuc jest częstym powikłaniem operacji kardiochirurgicznej i jest często związane z zastosowaniem krążenia pozaustrojowego (KPU). Kilka współczesnych badań porównujących konwencjonalną rewaskularyzację mięśnia sercowego i metodę rewaskularyzacji naczyń wieńcowych bez zastosowania maszyny płucoserce wskazało, że samo krążenie pozaustrojowe może nie być najważniejszym czynnikiem odpowiedzialnym za powstanie pooperacyjnego zaburzenia czynności oddechowej. Na tej podstawie można wnioskować, że patofizjologiczne mechanizmy odpowiedzialne za uszkodzenie układu oddechowego nie są ostatecznie wyjaśnione. Artykuł przedstawia molekularne i komórkowe mechanizmy odpowiedzialne za opisywane powikłanie. Przedstawiono zmiany z punktu widzenia fizjologii, biochemii i histologii. Szczególny nacisk położono na zespół ostrej niewydolności oddechowej. Zaprezentowano też metody stosowane w kardiochirurgii w celu zmniejszenia ryzyka wystąpienia opisanych powikłań (*Adv Clin Exp Med* 2007, 16, 5, 683–688).

Słowa kluczowe: kardiochirurgia, krążenie pozaustrojowe, cytokiny, odpowiedź zapalna, uszkodzenie płuc, neutrofile, wentylacja oddechowa.

Postoperative pulmonary dysfunction in patients undergoing cardiopulmonary by-pass (CPB) has long been recognized by cardiac surgeons and anesthetists as a significant clinical problem. Pulmonary dysfunction after CPB was first described 40 years ago [1] and it continues to

be the subject of a considerable amount of clinical research. The most severe form is acute (or adult) respiratory distress syndrome (ARDS) [2]. Since the early days of cardiac surgery it has been known that cardiopulmonary bypass (CPB) is associated with systemic inflammation. It can lead to major

organ dysfunction. When organ dysfunction cannot be directly attributed to a specific cause, such as infection or ischemia, the terms “post-pump syndrome” or “systemic inflammatory response syndrome to CPB” are used as an explanation [3]. Lung injury after CPB is evident by the presence of postoperative pulmonary functional, physiological, biochemical, and histological changes.

Physiological Changes

The physiologic disturbance after CPB can be summarized as abnormal gas exchange and poor lung mechanics. These functions are measured by such parameters as the alveolar-arterial oxygen pressure difference ($P[A-a]O_2$), intrapulmonary shunt function, and the degree of pulmonary edema. There are also such parameters as lung compliance and pulmonary vascular resistance. Increased $P(A-a)O_2$ and pulmonary shunt fraction and decreased residual functional capacity have been observed in patients after CPB [4, 5]. In addition to these abnormalities, lung function tests after CPB in children and neonates have shown lower FVC levels and inspiratory capacity [6]. Lung disturbances after CPB include increased lung permeability [7] and pulmonary vascular resistance [8]. Surfactant changes are also observed. Pulmonary epithelial-capillary endothelial permeability is related to alveolar protein accumulation and the facilitation of inflammatory cell sequestration. Increased pulmonary permeability after CPB has been shown by the increased rate of transfer of Tc 99m-labeled diethylenetriamine pentaacetate [9] and the increased level of radio-labeled transfer [10]. CPB could affect pulmonary surfactant activity, particularly in infants and neonates [11].

Biochemical Changes

Various biochemical changes can elucidate the presence of lung injury after CPB. These include substances responsible for lung injury (e.g. neutrophil elastase) and products released from injured lung tissue (e.g. the 7S protein fragment of collagen and procalcitonin). Neutrophil elastase, a proteolytic enzyme, has been measured as a marker of pulmonary injury after CPB in the systemic circulation. Tonz et al. detected a correlation between systemic elastase peak concentrations and intrapulmonary shunt [12]. However, the results of other studies suggested that neutrophil elastase may not be a consistent marker of lung injury because no correlation between elastase concen-

tration and gas exchange was found [13]. Products associated with a breakdown of type IV collagen, such as the 7S protein fragment of collagen, have been used to mark lung injury. Increased 7S protein levels have been shown to be associated with high neutrophil concentrations in the BAL fluid of patients after CABG [14]. The lung is also a source of procalcitonin. The plasma concentration of procalcitonin can increase dramatically during pulmonary inflammation [15]. Positive correlation between high procalcitonin levels and post-CPB lung injury has been observed [16]. Decreased levels of exhaled NO were detected after CPB. It was proposed that the production of NO decreases after CPB because of pulmonary vascular endothelial injury [17]. Pearl et al. correlated reduced exhaled NO level to elevated airway resistance after CPB [18].

Histological Changes

Alveolar edema and extravasation of erythrocytes and neutrophils following CPB have been confirmed by intra-operative lung biopsy [19]. Pneumocytes and endothelial cells appeared necrotic in electron microscopy. Similar structural lung damage and changes after CPB were also observed in electron microscopy in canine models [20].

Pulmonary Dysfunction After Cardiopulmonary By-pass

On a molecular level, the mechanisms leading to acute lung injury and ARDS are not fully clarified. The relationship between inflammatory response and CPB-related lung injury was still unclear [21]. Acute respiratory distress syndrome is an inflammatory response of the lung to a variety of insults and, therefore, its pathophysiology may be explained by the complement and neutrophil-based inflammatory theory described for lung injury. Increased concentrations of neutrophils and neutrophil-derived proteases were found in the bronchoalveolar lavage fluid of patients with ARDS. The percentage of neutrophils correlated directly with the severity of lung injury [22]. The role of activated neutrophils in ARDS was established through studies that showed increased elastase activity in plasma and the alveoli before and during ARDS [23]. Furthermore, the importance of mechanisms suggestive of systemic inflammation has been demonstrated by studies showing that plasma and lavage fluid levels of inflammatory

mediators such as TNF, IL-1, IL-6, and, in particular, IL-8 increase during ARDS and correlate with adverse outcomes [24].

A crucial step in neutrophil-initiated pulmonary dysfunction is the release of free radicals. These damage the endothelium and put it under significant oxidative stress and contribute to the endothelial disruption which is characteristic of ARDS [25]. A similar subpopulation of neutrophils with an increased capacity to generate the oxygen free radical hydrogen was found in patients with severe pneumonia or ARDS [26]. It has also been shown that animals depleted of neutrophils may also suffer acute lung injury and that complement infusion does not cause severe lung injury. At the clinical level, ARDS is often only one part of multiorgan failure [27]. Lung injury should be seen as part of a more general state of systemic inflammation. Furthermore, despite our improved understanding of the pathophysiology of lung injury, the exact mechanisms involved in the progression from acute lung injury to ARDS in some individuals is still uncertain.

Treating ARDS in the adult is very problematic. The mechanism of the lung injury is well understood and specific treatment can be effective. On the other hand, ARDS in the adult is often only one part of a complex multiorgan failure in which death is not necessarily primarily related to pulmonary damage. Several multicenter randomized trials of specific treatment in ARDS have been conducted, none of which showed a definite survival benefit [28].

In patients undergoing uncomplicated CPB, the use of investigational techniques that can differentiate cardiac from noncardiac pulmonary edema revealed changes in the integrity of the alveolar endothelium that resembled ARDS-type lung injury (on a smaller scale). It is not clear why this low-grade lung injury, detectable in the majority of patients undergoing cardiac surgery, is followed by severe lung injury only in a very small number of cases. It has also not been shown whether ARDS after CPB is an extreme form of the spectrum of CPB-related lung injury or occurs after cardiac surgery through a CPB-unrelated mechanism.

Therapeutic Interventions and Pharmaceutical Modifications

The commonly scrutinized pharmacological agents to treat pulmonary dysfunction are corticosteroids and aprotinin. Corticosteroid administration

before CPB has been shown to reduce the release of proinflammatory mediators such as IL-6, IL-8, and TNF- α . In addition, methylprednisolone therapy can inhibit neutrophil CD11b expression and neutrophil complement-induced chemotaxis, thereby decreasing neutrophil activation and post-CPB neutropenia. Furthermore, methylprednisolone therapy was unable to prevent poor postoperative lung compliance [29]. Aprotinin has also been shown to limit TNF- α and neutrophil elastase release and complement activation as well as neutrophil CD11b up-regulation following CPB. IL-8 levels in BAL fluid and pulmonary neutrophil sequestration after CPB were inhibited after the use of aprotinin [30].

Leukocyte Depletion

Leukocyte depletion during CPB may limit the postoperative inflammatory response, as measured by reduced IL-8 production. In some studies, leukocyte depletion did not significantly improve postoperative PaO₂ levels and pulmonary hemodynamics [31].

Modification of the Artificial Circuit

Heparin-coated circuits are associated with reduced activation of leukocytes and the release of cytokines. However, such benefits can be transient and may not be clinically significant [32].

Continuous Hemofiltration

High-volume continuous hemofiltration can significantly reduce systemic edema and pulmonary hypertension and improve lung function (e.g. pulmonary vascular resistance, lung dynamic compliance and P(A-a)O₂) after CPB. Continuous hemofiltration may also reduce lung tissue malondialdehyde levels [33].

Maintaining Mechanical Ventilation During CPB

There is a common practice of stopping ventilation during CPB, as blood oxygenation by the lungs is no longer required because movement from mechanical ventilation may interfere with the surgery. It is known that hypoventilation during CPB is associated with the development of microatelectasis, hydrostatic pulmonary edema, poor

compliance, and a higher incidence of infection. Mechanical ventilation during CPB may limit postoperative lung injury by preventing these complications. The lungs are totally dependent on oxygen supply from the bronchial arteries in the period of cardiac arrest. The effects of ventilation during CPB have been tested using the vital capacity maneuver (VCM, i.e. a peak airway pressure of 40 cm H₂O) and continuous positive airway pressure (CPAP). VCM at the end of CPB resulted not only in improved gas exchange, but also reduced the incidence of atelectasis, as determined by a CT scan soon after CPB [34]. Better postoperative gas exchange and less pulmonary shunting were observed in patients who received CPAP during CPB [34]. To date, evidence for the benefits of maintaining ventilation alone during CPB is inconsistent, with most studies showing no significant preservation of lung function. Continuous ventilation during CPB was shown to provide no significant improvement in pulmonary vascular resistance, cardiac index, or oxygen tensions in a pig model [35].

Maintaining Lung Perfusion During CPB

CPB is associated with pulmonary ischemic-reperfusion injury. However, as far as preventing tissue ischemia during CPB is concerned, the lungs are one of the least protected organs. The lungs have a bimodal blood supply from the PAs and the bronchial arteries. The bronchial arteries contribute about 1 to 3% of the total blood flow to the lungs. The relative contributions of the bronchial arteries and PAs and of alveolar ventilation in delivering oxygen to maintain lung tissue viability are still unclear. The lungs are dependent on the bronchial arteries during CPB to provide the 5% of the whole-body oxygen that is necessary under hypothermic condition. It has been demonstrated, for example, that several proinflammatory cytokines which are released from the heart during CPB could be cleared in the lungs. Hence it would be interesting to study whether maintaining PA perfusion during CPB can attenuate the deterioration of lung function [36].

A number of therapeutic strategies for lung ischemia-reperfusion injury have been tested. Improved lung function was seen after CPB with PA perfusion compared with non-PA perfusion in animals, demonstrating the potential beneficial role for maintaining PA perfusion during CPB [37]. In animal models, CPB without PA perfusion resulted in higher pulmonary vascular resistance and P(A-a)O₂ levels, with lower pulmonary compliance [37]. In infants undergoing CPB, better-preserved lung function was observed in a PA perfusion group compared with control subjects [38]. A recent study in a canine model demonstrated that the use of biventricular CPB helped in preserving lung function (i.e. reduced pulmonary vascular resistance) compared with conventional heart-lung by-pass, which may represent further supportive evidence for maintaining PA perfusion during CPB [39].

In conclusion, the author suggest that severe lung injury after CPB is uncommon. It is a significant cause of morbidity and mortality and has a major impact on healthcare costs. There is little doubt that CPB is associated with pulmonary dysfunction, as supported by the ample experimental and clinical evidence of chemical, cellular, and pulmonary functional disturbances after CPB. However, whether CPB itself is directly responsible for postoperative lung dysfunction is still controversial. Only a small minority of cases demonstrate an intermediate degree of pulmonary impairment and an even smaller minority have ARDS. Thus the incidence of ARDS after CPB in current practice is about 1–2%. The mortality of ARDS is extremely high, in particular when ARDS is part of multiorgan failure. Some studies have shown an attenuated inflammatory response following off-pump CABG compared with on-pump CABG, with a similar degree of postoperative lung dysfunction. Increased understanding of the mechanisms that regulate the inflammatory response to CPB has already allowed the development of several potentially therapeutic techniques that try to inhibit the adverse effects of inflammation. Definite clinical benefit has yet to be demonstrated, but results from animal studies are promising. Further research in cardiac surgery can help in the development of promising therapeutic strategies.

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