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Postperfusion lung syndrome: physiopathology and therapeutic options

Síndrome pós-perfusão pulmonar: fisiopatologia e opções terapêuticas

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Abstract

Postperfusion lung syndrome is rare but can be lethal. The underlying mechanism remains uncertain but triggering inflammatory cascades have become an accepted etiology. A better understanding of the pathophysiology and the roles of inflammatory mediators in the development of the syndrome is imperative in the determination of therapeutic options and promotion of patients' prognosis and survival. Postperfusion lung syndrome is similar to adult respiratory distress syndrome in clinical features, diagnostic approaches and management strategies. However, the etiologies and predisposing risk factors may differ between each other. The prognosis of the postperfusion lung syndrome can be poorer in comparison to acute respiratory distress syndrome due to the secondary multiple organ failure and triple acid-base imbalance. Current management strategies are focusing on attenuating inflammatory responses and preventing from pulmonary ischemia-reperfusion injury. Choices of cardiopulmonary bypass circuit and apparatus, innovative cardiopulmonary bypass techniques, modified surgical maneuvers and several pharmaceutical agents can be potential preventive strategies for acute lung injury during cardiopulmonary bypass.

Descriptors: **Acid-Base Imbalance. Cardiopulmonary Bypass. Multiple Organ Failure. Respiratory Insufficiency. Ventilators, Mechanical.**

Resumo

Síndrome pós-perfusão pulmonar é rara, mas pode ser letal. O mecanismo subjacente permanece incerto, mas desencadear cascatas inflamatórias tornou-se uma etiologia aceita. É imperativo uma melhor compreensão da fisiopatologia e os papéis de mediadores inflamatórios no desenvolvimento da síndrome na determinação de opções terapêuticas e de promoção do prognóstico e sobrevida dos pacientes. Síndrome pós-perfusão pulmonar é semelhante à síndrome da angústia respiratória do adulto em características clínicas, métodos diagnósticos e estratégias de gestão. No entanto, as etiologias e fatores de risco predisponentes podem ser diferentes entre si. O prognóstico da síndrome pós-perfusão pulmonar pode ser mais pobres em comparação com síndrome da angústia respiratória aguda, devido à falência de múltiplos órgãos secundária e desequilíbrio ácido-base triplo. Estratégias de gestão atuais centram-se em atenuar reações inflamatórias e impedir lesão pulmonar de isquemia-reperfusão. Escolhas do circuito de circulação extracorpórea e aparelhos, técnicas inovadoras de circulação extracorpórea, manobras cirúrgicas modificadas e vários agentes farmacêuticos podem ser potenciais estratégias preventivas para lesão pulmonar aguda durante a circulação extracorpórea.

Descritores: **Desequilíbrio Ácido-Base. Ponte Cardiopulmonar. Insuficiência de Múltiplos Órgãos. Insuficiência Respiratória. Ventiladores Mecânicos.**

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Abreviations, acronyms & symbols	
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CPB	Cardiopulmonary bypass
ECMO	Extracorporeal membrane oxygenation
EVLWI	Extravascular lung water index
HMGB1	High-mobility group box 1
IL	Interleukin
$P(A/a)O_2$	Arterial/alveolar oxygen tension ratio
$P(A-a)O_2$	Alveolar-arterial oxygen pressure difference
PaO_2/FiO_2	Arterial oxygen tension/fractional inspired oxygen
PEEP	Positive end-expiratory pressure
RI	Respiratory index
TNF	Tumor necrosis factor

INTRODUCTION

Acute respiratory distress syndrome (ARDS), also known as respiratory distress syndrome, adult respiratory distress syndrome, or shock lung, is a fatal pulmonary parenchymal disorder as sequelae of respiratory infection, trauma, or stress triggered by pulmonary cytokine release, impaired endothelial barriers and surfactant deficiency resulting in fluid accumulation in the distal airspaces, fibrotic changes and eventually impaired gas exchange. The ARDS that develops early after cardiopulmonary bypass (CPB) is known as postperfusion or post-pump syndrome, which remains a significant clinical problem on those patients receiving heart operations under CPB[1]. In the early years, postperfusion lung syndrome was taken as a prerequisite condition of cardiac surgical patients that may develop into ARDS if it is not properly treated[2]. However, this argument is not supported by modern theories. Postperfusion lung syndrome is rare but refractory. It was reported that the incidence of postperfusion lung syndrome was 1-2%[3], but the mortality could be as high as 91.6%, with 70% patients developing multiple organ failure[4]. An early diagnosis and timely treatment are crucial for the patients' outcomes.

A consensus committee has provided objective criteria for the diagnosis of ARDS, and has defined acute lung injury (ALI) as a less severe form of ARDS[5]. In 1994, the American-European Consensus Conference on ARDS set the criteria for the diagnosis of ALI and ARDS[6]. Both ALI and ARDS were characterized by an acute onset, bilateral pulmonary infiltrations on chest X-ray and pulmonary wedge pressure <18 mmHg. The only differential criterion for both disorders was arterial oxygen tension (PaO_2)/fractional inspired oxygen (FiO_2) <300 mmHg in ALI, but PaO_2/FiO_2 <200 mmHg in ARDS. In 2012, the Berlin Definition was developed, focusing on feasibility, reliability, validity and objective evaluation of the performances. ARDS was classified into 3 levels based on degree of hypoxemia: mild (200 mmHg < PaO_2/FiO_2 ≤300 mmHg) moderate (100 mmHg <PaO_2/FiO_2 ≤200 mmHg) and severe (PaO_2/FiO_2 ≤100 mmHg); and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤40 mL/cmH_2O), positive end-expiratory pressure (≥10 cmH_2O) and corrected expired volume per minute (≥10 L/min)[7]. The pulmonary inflammatory responses subsequent to CPB mostly result in subclinical symptoms, but may lead to major organ dysfunction and multiple organ failure including ARDS in only 2% of the patients[4]. In spite of rarity, ALI/ARDS remains the important cause leading to patients' death[8]. CPB may be of considerable pulmonary pathophysiological consequences in terms of the alveolar-arterial oxygenation gradient [$P(A-a)O_2$], intrapulmonary shunt, degree of pulmonary edema, pulmonary compliance and pulmonary vascular resistance, and may eventually lead to pulmonary dysfunction[7]. The respiratory dysfunction can be a result of pulmonary ischemia-reperfusion injury, interstitial edema and impaired microcirculation induced by CPB with activated cytokines, enhanced reactive oxygen species and reduced endogenous nitric oxide production[9,10]. At present, the underlying mechanisms of postoperative ALI/ARDS still remain uncertain and the pathophysiological aspects have not been comprehensively stated. A better understanding of the pathophysiology and roles of inflammatory mediators in the development of the syndrome is imperative in the determination of therapeutic options and promotion of patients' prognosis and survival[11]. This article aims to highlight postperfusion lung syndrome in terms of the pertinent pathophysiological changes, mechanisms and risk factors as well as the potentially effective management and preventive strategies.

MAJOR DIFFERENTIATIONS BETWEEN ACUTE RESPIRATORY DISTRESS SYNDROME AND POSTPERFUSION LUNG SYNDROME

Both ARDS and postperfusion lung syndrome have similar mechanisms of triggering inflammatory processes. They also share similar clinical features, diagnostic approaches and management strategies. However, their etiologies and predisposing risk factors differ between each other. As the pulmonary pathologies are more severe in the patients with postperfusion lung syndrome, the prognosis of these patients are always poorer than those with ARDS. The multiple organ failure rate was likely to be higher in the patients with postperfusion lung syndrome than with ARDS. Ge et al.[12] reported 15 patients with ARDS, the extrapulmonary organ failure involving 0, 1, 2 and 3 organs were found in 20% (3/15), 20% (3/15), 26.7% (4/15) and 33.3% (5/15) patients, respectively with the heart being the most involved organ followed by kidney, digestive tract, central nervous system, hematological system and liver. The mortalities were respectively 0% (0/3), 33.3% (1/3), 50% (2/4) and 100% (5/5) with an

overall mortality of 53.3% (8/15). The major similarities and differences between the two syndromes are listed in Table 1.

Pathophysiology

Respiratory indicators

PaO_2/FiO_2, PaO_2 and arterial/alveolar oxygen tension ratio [$P(A/a)O_2$] are all simple and noninvasive indicators of pulmonary gas exchange impairment. PaO_2 is easily influenced by mechanical ventilation and FiO_2 and also influenced by geographic diversity and patient's age. As PaO_2 decreases in all types of respiratory failure, it cannot reflect the actual respiratory function and may therefore be less reliable, but leading to a delayed diagnosis if taken for an early diagnosis of ARDS[17]. $P(A\text{-}a)O_2$ is an indicator of gas exchange (oxygen intake) impairment. Increase of $P(A\text{-}a)O_2$ mean deficiency of gas exchange and is likely to be more sensitive than the

Table 1. Major differentiations between acute respiratory distress syndrome and postperfusion lung syndrome.

Variable	Acute respiratory distress syndrome	Postperfusion lung syndrome
Alias	Respiratory distress syndrome, adult respiratory distress syndrome, or shock lung	Pump lung, or systemic inflammatory response syndrome to CPB
Incidence	1.5-8.3 cases per 100,000 population per year[3]	0.4-2.0% of the patients[4]
Etiology	Trauma, operation, stress, shock, infection, inflammation, fat embolism, massive blood transfusion and drug interaction	Cardiac operation under CPB
Mechanism	Complement activation and organ neutrophil sequestration	Complement activation, organ neutrophil sequestration and circulating endotoxin activation during CPB
Pathology	Alveolar-capillary membrane damage due to direct toxicity, prolonged hypoperfusion, or direct cellular damage[13]	Same
Predisposing risk factor	>65 years old, smoking cigarettes, chronic lung disease and a history of alcoholism[14]	Cardiac and pulmonary ischemia/reperfusion, hypothermic cardioplegic arrest and heparin-protamine interactions
Clinical manifestation	Tachypnea, tachycardia and respiratory alkalosis (12-24 hours after onset); respiratory failure (48 hours)	Breathing problems, weakness, anorexia, fever and hypoventilation
Diagnosis	Chest radiographs: diffuse interstitial infiltrates to diffuse, fluffy, alveolar opacities (acute phase) and reticular opacities (fibroproliferative stage); chest computed tomography: bilateral alveolar opacities (acute phase) and bilateral reticular opacities, reduced lung volumes and occasionally large bullae (fibroproliferative stage)[3]	Same
Differential diagnosis	Cardiogenic pulmonary edema	Postoperative atelectasis
Management	Etiological therapy, ventilatory support, pharmacologic treatment, extracorporeal membrane oxygenation support, long-term supportive care and tracheostomy	Same
Subsequent multiple organ failure (%)	53.4-80[12,15]	63.2-91.6[8]
Mortality (%)	67[16]	50-91.6[8]

CPB=cardiopulmonary bypass

decrease of PaO_2. As $P(A\text{-}a)O_2$ is affected by FiO_2, its use in patients with oxygen therapy is limited. It is also affected by patient's age, position, cardiac output, oxygen dissociation curve and closing capacity. PaO_2/FiO_2, also termed as oxygenation index, shows a good correlation with intrapulmonary shunting, and can better reflect anoxia even in the condition of oxygen therapy. PaO_2/FiO_2 is affected by methods of oxygen supply and oxygen concentration, and hence it is an indicator of impairments of the pulmonary vascular beds and alveoli, irrelevant to extrapulmonary organ failure[18].

Respiratory index (RI) is the ratio of $P(A\text{-}a)O_2$ to PaO_2, less affected by ventilation method or FiO_2. Therefore, it may reflect the actual pulmonary function and is helpful in the early diagnosis of ARDS. The normal range of RI is 0.1-0.3. RI ≥2.5 represents a high risk for the development of ARDS, and RI ≥3.0 is a diagnostic indicator of ARDS[19]. RI <2.5 as shown in daily repeated blood-gas analysis can be an indicator for safe extubation[20]. ARDS patients with sustained RI elevation may eventually develop multiple organ failure[21].

Lung compliance

Type II cells are thicker, square-shaped cells and their main function is to produce surfactant. Surfactant plays an essential role in preventing the alveoli from collapsing. Increase in capillary endothelial and/or alveolar epithelial permeability and pulmonary surfactant deficiency from type II cell impairment may inevitably result in pulmonary compliance reduction. The inflammatory process and alveolar flooding lead to severe ventilation-perfusion mismatch and intrapulmonary shunt, which are manifested clinically as severe hypoxia with a decrease in the PaO_2/FiO_2 ratio. Generally, with a marked reduction in lung compliance, the work of breathing and the physiologic dead space increase. Mechanical ventilation may reverse hypoxemia of ALI and prevent from developing into ARDS. However, airway injury and hypokinemia may occur under the treatment of a high positive end-expiratory pressure (PEEP) and positive pressure support. This may in turn worsen the systemic inflammatory reactions and lead to extrapulmonary organ dysfunction or failure[22]. With increasing PEEP, PaO_2/FiO_2 increases and static lung compliance stabilizes. However, a 20-cmH_2O PEEP can be a turning point of PaO_2/FiO_2 and static lung compliance fall[23].

Clinical studies revealed close positive correlations between PEEP, cardiac output or peak pressure of airway and PaO_2/FiO_2, and weak correlations between PaO_2/FiO_2 and oxygen supply or static lung compliance (Figure 1)[23]. Pulmonary dynamic compliance and oxygenation index correlated significantly in ARDS patients irrespective of patients' outcome (Figure 2)[24]. In ALI models, RI correlated positively, but PaO_2/FiO_2 correlated negatively to plasma soluble intercellular adhesion molecule-1, showing a significant correlation in the experimental other than in the control group (Figure 3)[25].

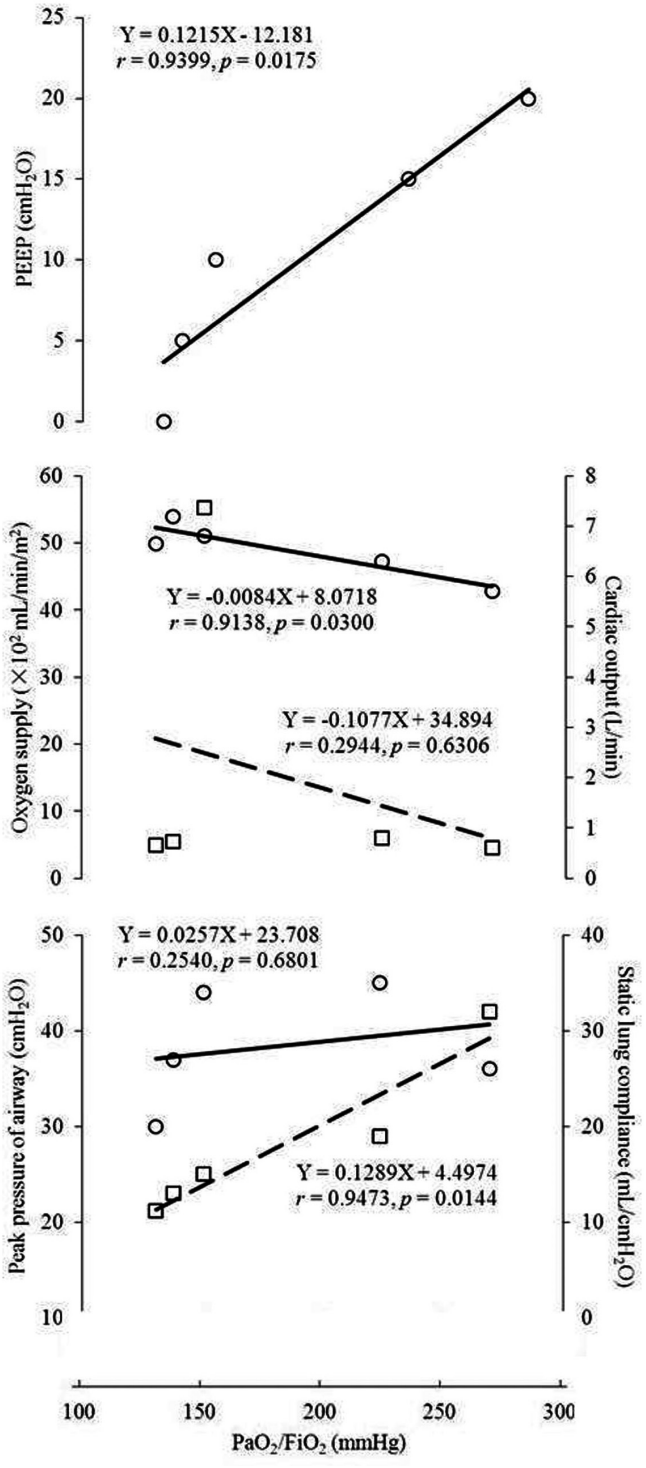

Fig. 1 - Linear correlations between respiratory mechanics and PaO_2/FiO_2[23].
PaO_2/FiO_2=arterial oxygen tension/fractional inspired oxygen; PEEP=positive end-expiratory pressure

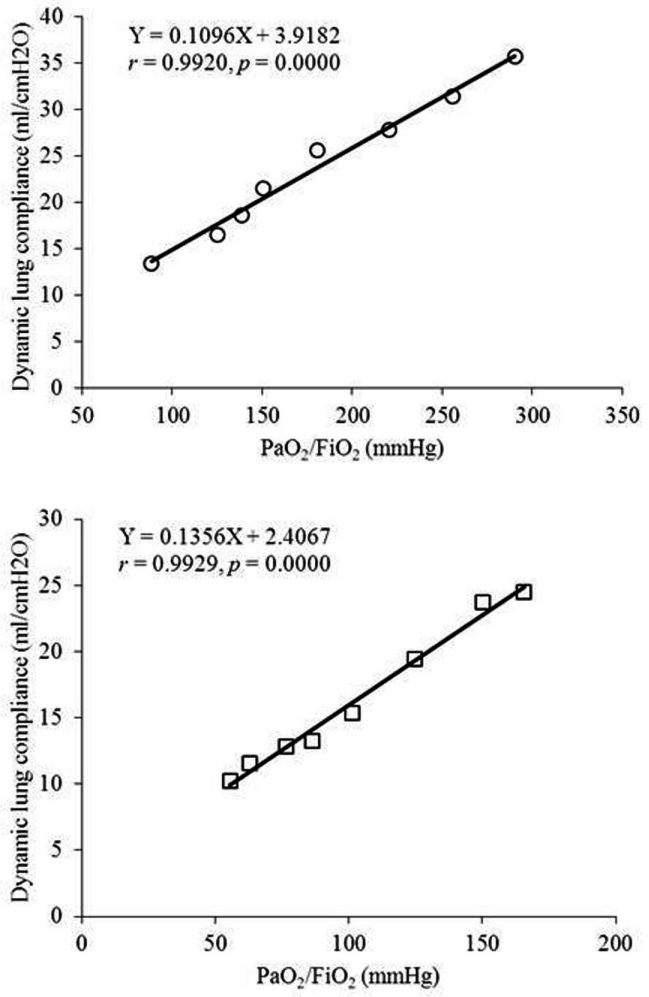

Fig. 2 - Linear correlations between pulmonary dynamic compliance and oxygenation index in patients with acute respiratory distress syndrome[24]. Upper panel=cured patients; Lower panel=dead patients. PaO_2/FiO_2=arterial oxygen tension/fractional inspired oxygen

Extravascular lung water

Extravascular lung water is the fluid distributed beyond the pulmonary vessels. It is composed of intracellular, intra-alveolar and alveolar interstitial fluid. Little intracellular fluid change stands out the effects of intra-alveolar and alveolar interstitial fluid in the formation of pulmonary edema. Increase of extravascular lung water is a prominent feature of ARDS and the actual reason for refractory hypoxemia. Clinically, extravascular lung water index (EVLWI) is an indicator for the description of extravascular lung water. The normal range of EVLWI is 3.0-7.0 mL/kg. An EVLWI >7.0 mL/kg suggests the presence of pulmonary edema[26]. Extravascular lung water positively correlated with lung injury severity and oxygenation but negatively correlated pulmonary compliance[27]. Stratified analysis illustrated a strong negative correlation between EVLWI and PaO_2/FiO_2 when EVLWI ≥12 mL/kg and also a strong negative correlation between pulmonary vascular permeability index and PaO_2/FiO_2 when pulmonary vascular permeability index ≥5[28]. Kushimoto et al. [29] found, in a multicenter retrospective study, that the severity of ARDS closely correlated with increase of EVLWI and pulmonary vascular permeability index. A report also stressed on that EVLWI may be associated with severity of ARDS, ventilation duration, Intensive Care Unit stay and mortality[30]. EVLWI is therefore a useful tool for the evaluation of pulmonary function, superior to PaO_2/FiO_2 and chest roentgenogram.

Intrapulmonary shunting

The major etiology of hypoxia in ARDS patients is functional intrapulmonary shunting. A pulmonary shunt is a condition of ventilation-perfusion mismatch with normal blood perfusion but insufficient ventilation of the lungs. Intrapulmonary shunting has a close relation negative to PaO_2/FiO_2, but positive to $P(A\text{-}a)O_2$[31], and is also affected by pulmonary artery wedge pressure and cardiac index[32]. Normally, pulmonary shunt is 2-5%[33]. The intrapulmonary shunt is optimal in assessing the severity of hypoxemia. An intrapulmonary shunt <15% as well as $P(A\text{-}a)O_2$ difference <75 mmHg is helpful for the exclusion of ARDS[34]. A shunt of 10-19% usually does not need ventilation support; whereas a shunt of 20-29% can be a fatal sign in patients with impaired cardiac function, and a shunt >30% requires circulatory support[35]. In normal subjects and experimental animals with ARDS, PEEP did not alter the distribution of blood flow; the apparent perfusion ratio remained constant when PEEP was increased from 5 to 10 cmH_2O[36]. However, when a positive end-expiratory plateau was added to intermittent positive pressure ventilation, intrapulmonary shunting may decrease and the disrupted surfactant production may take into action[37].

Acid-base imbalances

In the early stage of ARDS, respiratory alkalosis is the most common type of acid-base imbalance followed by metabolic acidosis and combined respiratory alkalosis and metabolic alkalosis. In its late stage, patients may develop respiratory acidosis, respiratory acidosis-associated with metabolic acidosis and even triple acid-base imbalance. The triple acid-base imbalance can be a respiratory alkalosis or a respiratory acidosis type. The respiratory alkalosis type is respiratory alkalosis associated with metabolic acidosis and metabolic alkalosis, which is often developed from uncorrected primary respiratory alkalosis, while using diuretics and glucocorticoids (for metabolic alkalosis), or in the presence of severe hypoxia, renal dysfunction, or shock (for metabolic acidosis) and electrolyte imbalance (hypokalemia, normal or high blood chloride, and normal or reduced blood

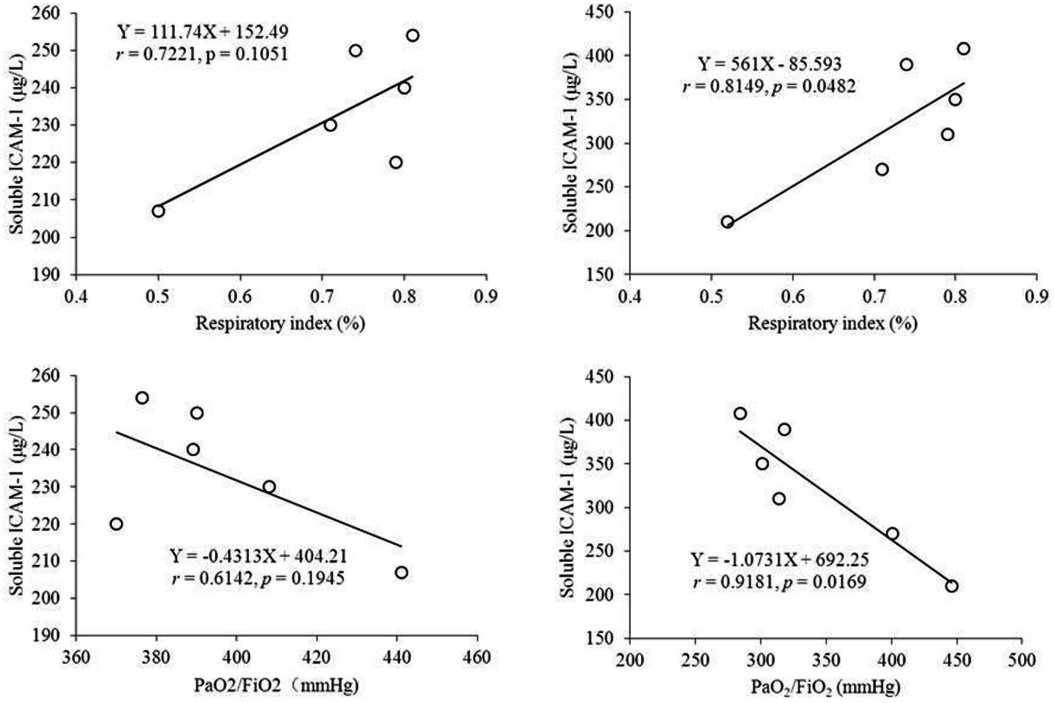

Fig. 3 - Linear correlations between soluble intercellular adhesion molecule-1 and respiratory index or PaO_2/FiO_2[25]. Left panel=control group; Right panel=experimental group with intercellular adhesion molecule-1 antibody 2 mg/kg was given to the rabbit; PaO_2/FiO_2=arterial oxygen tension/ fractional inspired oxygen; ICAM=intercellular adhesion molecule

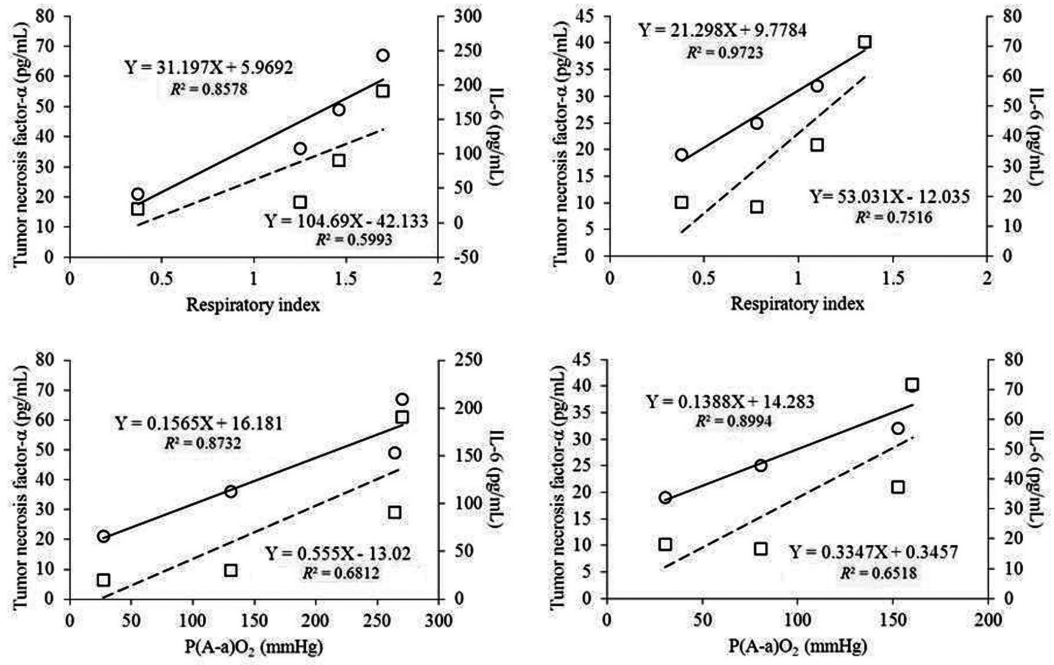

Fig. 4 - Linear correlations between tumor necrosis factor-α or interleukin-6 and respiratory index or $P(A\text{-}a)O_2$[68]. Left panel=control group; Right panel=penehyclidine hydrochloride; $P(A\text{-}a)O_2$: alveolar-arterial oxygen pressure difference.

sodium). Patients with this type triple acid-base imbalance are often with a poor outcome[38].

The respiratory acidosis type triple acid-base imbalance is respiratory acidosis associated with metabolic acidosis and metabolic alkalosis, which is less common but may occur in the condition of reduced ventilation and carbon dioxide retention, often associated with normal or high blood potassium and normal or reduced blood chloride and sodium [38].

MECHANISMS

The exact mechanism of postperfusion lung syndrome remains uncertain, but it may probably be due to the inflammatory cascade induced by contact between blood and CPB circuit and the subsequent activations of leukocytes, platelets, coagulation and fibrinolysis system and kallikrein-bradykinin and complement system. After crossclamp removal, joint actions of protease release by leukocytes in the pulmonary vascular beds, production of oxygen free radicals and intestinal endotoxin translocation lead to increased pulmonary microvascular permeability, microthrombus formation in the pulmonary vessels and the quality and quantity changes of pulmonary surfactant predispose to the development of postperfusion lung syndrome[39]. The significant complement activation and organ neutrophil sequestration contribute to vascular injury, and hence patients undergoing cardiac operation under CPB showed increased circulating endotoxin and tumor necrosis factor (TNF) levels[40,41].

Alveolar macrophages are prone to be activated, releasing many inflammatory mediators including TNF-α, interleukin (IL)-6 and IL-8 and superoxide dismutase, etc., and damaging vascular endothelium and alveolar epithelium, thus making the lungs being the first target organ of insult. TNF-α and IL-6 may cause direct lung injury effects by inducing early inflammatory reactions, releasing toxic products and increasing pulmonary permeability[42]. In the lung, TNF-α is generated by activated pulmonary macrophages and accumulates in the bronchoalveolar lavage fluid of ALI patients[43]. The pathogenesis of TNF-α with receptors in neutrophil activation and infiltration of lung injury remain unclear. However, it has been noted that neutrophil accumulation and lung leak were abrogated in mice lacking the p55 TNF-α receptor[44]. TNF-α also stimulates the adhesions of the endothelial cells and neutrophils, and impacts a toxic effect by release of proteases, oxygen free radicals and superoxide dismutase. Productions of ILs including ILs-1, -2, -6 and -8 would be increased by stimulations of mon-macrocytes strengthening the lung injury. Accordingly, an early appearance of TNF-α may herald the development of ARDS and the synthesis and secretion of ILs.

RISK FACTORS

Both direct and indirect lung injuries can be predisposing risk factors leading to ARDS. Surgical trauma and CPB are among indirect risk factors[13]. Christenson et al.[2] reported insufficient perfusion of visceral organs caused by low output syndrome and prolonged hypotension might be responsible for the development of postperfusion lung syndrome. Rady et al.[45] observed that early postoperative pulmonary dysfunction was associated with preoperative (age ≥75 years, body mass index ≥ 30 kg/m^2, mean pulmonary arterial pressure ≥ 20 mmHg, stroke volume index ≥30 mL/m^2, serum albumin and history of cerebral vascular disease), operative (emergency surgery and CPB duration ≥140 min) and postoperative variables (hematocrit ≥30%, mean arterial pressure ≥90 mmHg and cardiac index ≥3.0 L/min/m^2). Besides, preoperative cardiac function impairment, bloodstream infection, prolonged crossclamp and operation durations, hypotension episodes and hypogammaglobulinemia can be risk factors of postperfusion lung syndrome[46].

PREVENTION

Apostolakis et al.[47] summarized preventive strategies for operative lung injury, which included choices of CPB circuit (use of miniaturized circuits of CPB and circuit with biocompatible surfaces ultrafiltration) and apparatus (leukocyte depletion filters and ultrafiltration), innovative CPB techniques (partial restoration of pulmonary artery perfusion during CPB), modified surgical maneuvers (reducing the use of cardiotomy suction device and reducing the contact-time between free blood and pericardium) and medicinal agents (corticosteroids and aprotinin) as preventive strategies for ALI during CPB, which were proved to be of satisfactory outcomes on improving the lung function. Moreover, hyperonocotic CPB-prime with hydroxyethyl starch 10% (200:0.5) may improve cardiac function and reduce pulmonary water content in the early postoperative period[48]. Studies have shown that Travenol bubble oxygenator was associated with significant increases of EVLWI and pulmonary vascular resistance and greater blood component trauma than the membrane[49], and bubble oxygenators caused more leukocyte sequestrations[50]. Care has to be taken with choice of oxygenator in risky patients.

MANAGEMENT

Ventilatory treatment

Mechanical ventilation remains the primary support technique for ARDS. New ventilation strategies, such as high-frequency oscillatory ventilation appear to be promising[51]. However, in patients with ALI/ARDS, mechanical ventilation with a lower tidal volume (6 mL/kg) than is traditionally used[52]. Low tidal volume ventilation reduces volutrauma, and is the standard care for ARDS patients with mechanical ventilation. A strategy of low tidal volume ventilation of 6-8 mL/kg reduces absolute mortality by about 7-9% in compar-

ison to using ≥10 mL/kg tidal volumes. Mechanically ventilated patients with ARDS appear to tolerate very low blood pH and very high carbon dioxide partial pressure without any adverse sequelae. Based on this theory, permissive hypercapnia can be attempted in ARDS patients in order to achieve normal blood gas values.

Adequate PEEP levels avoid alveolar collapse and maintain sufficient pulmonary volume at the end of expiration. Excessive PEEP increases the risk of pneumothorax and airway impairment, causing adverse hemodynamic effects by increasing intra-thoracic pressure and reducing venous return. Meanwhile, inadequately low PEEP level provokes cyclic alveolar collapse and re-opening, resulting in atelectrauma[51]. Most ventilation modes used in ARDS are those cycled by time and controlled by volume or pressure. In ARDS patients randomized to high frequency oscillatory ventilation, mortality was significantly reduced and so was the treatment failure rate comparing to conventional ventilation[53]. Recruitment is a strategy aimed at re-expanding collapsed lung tissue, and then maintaining high PEEP to prevent subsequent "de-recruitment". Various ventilation modes such as inverse ratio pressure-controlled ventilation, airway-pressure release ventilation and even high-frequency oscillatory ventilation have been used to promote recruitment [54].

Prone positioning improves gas exchange and has long been used as an adjunct or salvage therapy for severe or refractory ARDS. A strategy employing higher PEEP along with low tidal volume ventilation should be considered for ARDS patients receiving mechanical ventilation. ARDS patients receiving higher PEEP had a strong trend toward improved survival. However, higher PEEP had a strong trend toward harm as higher PEEP can conceivably cause ventilator-induced lung injury by increasing plateau pressures, or cause pneumothorax or decreased cardiac output[55].

Pharmaceutical treatment

Surfactant

Surfactant therapy has shown beneficial effects on oxygenation and survival of children with ALI/ARDS, however, no effect or even adverse effects of exogenous surfactant has been shown on survival in adult patients[56-58]. Instillation of a natural lung surfactant (calfactant) contains high levels of surfactant-specific protein B. Calfactant (2 doses of 80 mL/m^2 calfactant, 12 hours apart) acutely improved oxygenation and significantly decreased mortality in infants, children and adolescents with ALI[59].

Vasodilators

Nitric oxide is a powerful endogenous vasodilator. A placebo-controlled study demonstrated that the ARDS patients receiving 5 ppm inhaled nitric oxide showed significantly improved oxygenation parameters with better survival comparing with placebo[60]. Some authors suspected the role of inhaled nitric oxide in ARDS. They found by incorporating the results of 14 randomized clinical trials that inhaled nitric oxide resulted in a transient improvement in oxygenation without reducing mortality but was probably harmful[61]. Therefore physicians have to take care when using this agent for ARDS.

Prostaglandins are endogenous derivatives of arachidonic acid with properties of vasodilation, platelet aggregation inhibition and anti-inflammation. Inhaled prostacyclins cause selective pulmonary vasodilation, thereby enhancing lung function by improving ventilation-perfusion mismatch and oxygenation and by reducing pulmonary vascular resistance[62]. Inhaled prostaglandin E_2 had a comparable effect to nitric oxide on pulmonary vasculature and oxygenation with minimal systemic effects[62]. Continuous infusion of prostaglandin E_1 may induce oxygen delivery and obtain better tissue oxygenation, while increasing cardiac output[63]. Prostacyclin is also a promising vasodilator in decreasing pulmonary artery pressure and improving PaO_2/FiO_2[64], but it may cause compromised hemodynamics[65].

Glucocorticoids

Glucocorticoids can reduce inflammation and fibrosis through inhibition of several cytokines including ILs-1, -3, -5, -6 and -8, TNF-α and granulocyte macrophage-colony stimulating factor[66]. Lisofylline, like pentoxifylline, has been shown to diminish proinflammatory cytokine expressions of TNF-α, IL-1 and IL-6 and to inhibit neutrophil accumulation and edema formation. Unlike pentoxifylline, lysofylline partly exerts its anti-inflammatory properties by inhibiting the release of oxidized free fatty acids from cell membranes under oxidative stress[62].

Anti-inflammatory agents

High-mobility group box 1 (HMGB1) is a critical mediator in the pathogenesis of many inflammatory diseases. Penehyclidine hydrochloride inhibits the translocation of release of HMGB1 from the nucleus to the cytoplasm and the expression of HMGB1 messenger ribonucleic acid in a dose-dependent manner[66]. Administration of penehyclidine hydrochloride reduces lung water gain, bronchoalveolar lavage protein content, infiltration of neutrophils, malondialdehyde content and lactate dehydrogenase activity and enhances superoxide dismutase activity[67]. Penehyclidine hydrochloride also significantly reduces $P(A\text{-}a)O_2$ and RI as well as TNF-α and IL-6 of lung injury, and both RI and $P(A\text{-}a)O_2$ shows a close correlation with TNF-α and IL-6 (Figure 4)[68]. Ulinastatin decreases free radical productions, lowers ratio of physiological dead space to tidal volume and improves respiratory function after CPB[69]. Induction of anesthesia with ulinastatin 10,000 units/kg inhibits the excessive release of serum HMGB1, TNF-α and IL-8 concentrations[70]. Ulinastatin was shown in a systematic review to have a significant effect on improv-

ing oxygenation and shortening the length of Intensive Care Unit stay[71]. The large dose of propofol (15 mg/kg/hour) attenuated lung leukocyte sequestration, pulmonary edema and pulmonary hyperpermeability and resulted in better oxygenation, lung mechanics and histological changes; while the small dose (4 mg/kg/hour) did not, in endotoxin-induced ALI rabbit model[72]. Treatment with propofol by intravenous infusion (6 mg/kg/min for 5 min) abrogated or reversed the oleic acid-induced ALI changes in rats[73]. However, the use of propafol may induce ALI in particular in the presence of an increased alveolar-capillary permeability, which allowed the propofol emulsion to leak into the alveoli[74].

Studies have suggested activation of adenosine receptors may enhance alveolar fluid clearance and regulate the fluid transport in the lung. The adenosine 2A receptor agonist GW328267C improves lung function of ALI rats[75]. A randomized clinical trial of simvastatin in ALI patients revealed the simvastatin-treated group had improvements in nonpulmonary organ dysfunction on day 14 of treatment. Simvastatin was well tolerated, with no increase in adverse events. Simvastatin improved oxygenation and respiratory mechanics, and decreased bronchoalveolar lavage IL-8 by 2.5-fold[76]. Experimental studies on rats revealed that endothelin-1 inhibited alveolar fluid clearance by inhibition of amiloride-sensitive epithelial Na^+ channels. Endothelin-1 may increase capillary pressure and contribute to pulmonary edema formation[77]. The endothelin-1 receptor subtype blockers significantly prevented the pulmonary vasoconstriction induced by endothelin-1[78]. Atrial natriuretic peptide had a protective effect in the lipopolysaccharide-induced ALI model[79]. H_2 treatment markedly attenuated lipopolysaccharide-induced lung neutrophil recruitment and inflammation and intraperitoneal injection of 10 mL/kg hydrogen-rich saline also significantly attenuated the lipopolysaccharide-induced ALI[80].

Extracorporeal membrane oxygenation (ECMO)

ECMO is a therapeutic option for patients with severe ARDS. The indications for ECMO use in ARDS patients are failed conventional therapy for 24-96 hours and the conformity of two of the three required slow-entry criteria for ECMO including PaO_2/FiO_2 <150 mmHg at PEEP >5 cmH_2O, semistatic compliance <30 mL/cmH_2O and right-left shunt >30%. Only in the patients with life-threatening hypoxemia (PaO_2<50 mmHg at FiO_2 1.0 and PEEP>5 cmH_2O for>2 hours (fast-entry criteria) is immediate ECMO commenced[81]. Mols et al.[82] reported one-quarter of their 245 ARDS patients received ECMO treatment. The survival rate was 55% in ECMO patients and 61% in non-ECMO patients. However, the role of ECMO in the treatment of ARDS is controversial[83]. In neonates treated with ECMO, a survival rate of 80% was achieved. In adult patients with ARDS, two randomized controlled trials revealed the survival rates were 10% and 33%, respectively, in the ECMO groups[84]. Meta-analysis of 9 studies on a total of 1,058 patients with 386 of them treated with ECMO revealed ECMO increased the mortality of ARDS patients. Therefore, it seems that ECMO is not beneficial in adult patients with ARDS as in neonates[85].

CONCLUSIONS

Postperfusion lung syndrome is rare but can be refractory. Both ARDS and postperfusion lung syndrome have similar mechanisms of triggering inflammatory processes. They also share similar clinical features, diagnostic approaches and management strategies. However, their etiologies and predisposing risk factors differ between each other. Inflammatory cascade induced by CPB has been an acceptable mechanical hypothesis. The prognosis of the postperfusion lung syndrome can be poorer than that of the ARDS. The potential sequelea of postperfusion lung syndrome such as multiple organ failure and triple acid-base imbalance can be the principle causes of poor outcome rather than the lung disorder itself. Choices of CPB circuit and apparatus, innovative CPB techniques, modified surgical maneuvers and some medicinal agents can be potential preventive strategies for ALI during CPB. Mechanical ventilation (with low tidal volume and proper PEEP), pharmaceutical agents and ECMO can be therapeutic options of postperfusion lung syndrome. With the mature therapeutic options, the survival rate of the patients with postperfusion lung syndrome and ARDS would be further improved.

Author roles & responsibilities	
SMY	Main author

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