Review

Tong Wang*

Basic and clinical research progress in acute lung injury/acute respiratory distress syndrome

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Abstract: Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is an acute progressive respiratory failure caused by severe infection, trauma, shock, poisoning, inhaled harmful gas, acute pancreatitis, and pathological obstetrics. ALI and ARDS demonstrate similar pathophysiological changes. The severe stage of ALI is defined as ARDS. At present, a significant progress has been achieved in the study of the pathogenesis and pathophysiology of ALI/ARDS. Whether or not ALI/ARDS patients can recover depends on the degree of lung injury, extra-pulmonary organ damage, original primary disease of a patient, and adequacy in supportive care. Conservative infusion strategies and protective lung ventilation reduce ARDS disability and mortality. In this study, the pathogenesis of ALI/ARDS, lung injury, molecular mechanisms of lung repair, and conservative infusion strategies and pulmonary protective ventilation are reviewed comprehensively.

Keywords: acute lung injury, acute respiratory distress syndrome, conservative infusion strategy, pulmonary protective ventilation

The incidence and mortality of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) are relatively high. In the United States, the number of adult patients with ALI/ARDS is estimated at 190,000–200,000 each year, in addition to many children with ALI/ARDS [1–5]. ALI/ARDS remains to be a major cause of death in critically ill patients. The mortality rate is approximately 30%, and the mortality rate in elderly patients can be 60% [3,6,7]. ARDS is not only a huge social burden but also long-term sequelae among survivors, including various mental disorders, such as depression, cognitive impairment, pulmonary dysfunction, and decreased quality of life [2–4]. The pathogenesis of ALI/ARDS is complex. In terms of its etiology, ALI/ARDS is associated with various clinical diseases, including direct and indirect lung injuries. At present, more than 100 causes of ALI/ARDS are recorded [1,8].

1 Pathogenesis of ALI/ARDS

The human body frequently suffers from invasive endogenous or exogenous pathogenic microorganisms, including viruses, bacteria, fungi, archaea, legionella, actinomycetes, and rickettsia, and their metabolites. Shock, trauma, major surgery, prolonged cardiopulmonary cerebral resuscitation, tumor intervention, chemotherapy, radiotherapy, acute pancreatitis, and pathological obstetrics can lead to inflammation of a body's tissue cells after poisoning, thereby triggering infection, sepsis, and septicemia and further inducing the body to produce many inflammatory cytokines (CKs). The major inflammatory CKs are interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor- α . These factors are called proinflammatory CKs [9]. As a result,

Department of Thoracic Surgery, Peking University Third Hospital, Beijing 100191, China

*Correspondence: Tong Wang, E-mail: wangtongdoctor@sohu.com

inflammatory hyperreactivity occurs, and systemic inflammatory response syndrome is initiated, thereby causing an accumulation of numerous white blood cells and platelets. Activation of the coagulation pathway, increased alveolar permeability, and disruption of the physiological barrier of epithelial cells remain the main features of ALI/ARDS pathophysiology. The currently known mechanisms are microbial products or endogenous molecules associated with cell damage, also known as danger-associated molecular patterns. It is a model of toll-like receptors that bind to the surface of lung epithelial cells and alveolar macrophages. It activates the innate immune response after recognizing the receptor, thus resulting in acute pulmonary inflammation [10]. Recent studies have found that histones released by neutrophils can cause alveolar damage [11]. Signals between inflammation and target cells, such as platelets and neutrophils, may play an important role in several models, including acid-induced ALI, sepsis, and transfusion-induced lung injury [12,13]. In lung infections, acute inflammatory reactions induced by pathogens and their toxins, leukocyte proteases, reactive oxygen species, many chemokines and CKs, toll-like receptors, and lipid mediators can cause ALI [14–19]. The balance-regulatory molecules between angiotensin-converting enzymes 1 and 2 may affect the degree of inflammation of viral lesions and sepsis-induced lung injury. Increased permeability of a microvascular barrier leads to extravascular accumulation of protein-rich edema fluids that are classical pathophysiological changes in ALI/ARDS [20]. Increased permeability is also associated with leukocyte and red blood cell migration to various transmitters in the alveoli. Inflammatory mediators and signaling pathways may be involved in endothelial and alveolar epithelial cell permeability changes [21]. Vascular endothelial cell cadherin (VE-cadherin) and adhesive junction proteins play a key role in maintaining the integrity of endothelial cell barriers [22].

In the ALI/ARDS study, researchers have been extensively aiming to use molecular methods to reverse pulmonary edema caused by increased vascular permeability. A major treatment strategy is using ligands with stable functions. This ligand binds to the corresponding receptor on the surface of endothelial cells and then activates intracellular signaling pathways, thus leading to structural reorganization of the cell and enhancing the interaction between catenin and VE-cadherin. Sphingosine-1-phosphate (S1P) is a lipid that is recognized by G protein-coupled receptors (S1Pr1, S1Pr2, and S1Pr3) on the surface of endothelial cells. *In vitro* cultured human vascular endothelial cells, S1P, and S1Pr1 induce actin cytoskeleton reorganization, thereby resulting in accumulation of α -, β -, γ -catenin, and VE-cadherin at the junction of cells to produce adhesive attachment [23]. S1P enhances the integrity of lung and systemic vascular endothelial barriers, and the small molecule agonists of S1Pr1 in endothelial cells inhibit the release of numerous CKs and exudation of leukocytes in the lung [24,25]. Platelets may produce S1P at the site of vascular injury to reduce alveolar hemorrhage, which is also a consequence of endothelial cell barrier disruption.

In the pathogenesis of ALI/ARDS, the relationship between the integrity of vascular endothelial barriers and the damage and protection of inflammatory factors is complex [1]. Inflammation is expressed in VE-cadherin, thereby producing an inflammatory and an immune response [26]. In contrast to vascular endothelial cells, alveolar epithelial cells play an important role in pulmonary edema, leukocyte accumulation, alveolar fibrin deposition, and hyaline membrane formation. However, disrupting the function of VE-cadherin in endothelial cells can lead to alveolar epithelial leakage and cell damage in certain conditions. Experimental studies have indicated that mesenchymal stem cells (MSCs) can restore the barrier function of human alveolar epithelial cells to CK destruction. This mechanism involves the release of angiopoietin-1, which induces S1P production and inhibits the inward migration of endothelial VE-cadherin [27–29].

2 ALI/ARDS conservative infusion strategy

In a previous study, reducing lung vascular hydrostatic pressure was found to decrease pulmonary edema in the case of increased pulmonary vascular permeability. This experimental result has been confirmed by subsequent clinical trials [30]. Therefore, clinical attention is accorded to the input of appropriate restrictive fluids, which are called conservative infusion strategies. Conservative infusion strategy significantly averaged 2.5 days of mechanical ventilation, and this difference was unaffected by pulmonary artery cannulation [31].

The mechanism of conservative infusion strategy can be explained by the principle of Starling mechanics, which states the following: in the condition of increased pulmonary vascular permeability, reducing intravascular pressure can decrease intravascular leakage of fluid, thereby reducing pulmonary edema. In addition, reducing pulmonary vascular pressure can decrease P-selectin turnover and neutrophil accumulation in the pulmonary vascular endothelium. Plasma levels of angiopoietin-2 are lower in patients who are conservatively treated with liquids than with non-liquids, hence supporting the hypothesis of anti-inflammatory mechanisms [32].

In the study and clinical treatment of ALI/ARDS, the content of the pulmonary surfactant is frequently decreased, the phospholipid composition is changed, and the function of surface-active substances is inhibited by exuded plasma proteins, oxygen-free radicals, and proteases. All these abnormalities can lead to atelectasis. No convincing evidence in clinical trials has confirmed that granulocyte-macrophage colony-stimulating factor, glucocorticoids, antioxidants, or anti-CKs can reduce the mortality of patients with sepsis, although several studies have suggested that anti-inflammatory therapy can potentially reduce lung injury [33–35]. Anticoagulation is considered effective in treating ALI/ARDS, given the close relationship between coagulation mechanisms and inflammatory pathways [36,37]. Recent clinical trials have indicated that activated protein C is ineffective in treating severe sepsis, which is the deadliest cause of ALI and ARDS [36]. Therefore, anticoagulation strategies for ALI/ARDS must be reassessed.

3 ALI/ARDS pulmonary protective ventilation

Many randomized, controlled clinical trials have demonstrated that small tidal volume mechanical ventilation can reduce the mortality of ALI/ARDS [38]. The absorption of pulmonary edema was increased by a factor of three when the tidal volume was reduced from 12 mL/kg to 6 mL/kg in part, given a reduced epithelial cell damage. The absolute risk of ARDS decrease was 10.9% when the tidal volume was 6 mL/kg, and the risk of deterioration and progression to ARDS was much lower in patients with low tidal volume ventilation than that in ICU patients [39]. Simultaneously, markers of lung epithelial cell damage were also reduced in patients with low tidal volume ventilation [40]. Pulmonary protective ventilation also reduced the mechanosensitivity of the proinflammatory response pathway, thereby inhibiting the accumulation of alveolar neutrophils and reducing the plasma levels of IL-6, IL-8, and soluble tumor necrosis factor receptor 1 [41]. Small tidal volume mechanical ventilation also has the function of protecting extra-pulmonary organs. In the acid-induced rabbit ALI model, a large tidal volume mechanical ventilation can cause tubular cell apoptosis, but using small tidal volumes can avoid this effect. Small tidal volume ventilation can also delay the onset of renal failure in ARDS patients. Prone ventilation, optimization of positive end expiratory pressure (PEEP) levels, high-frequency oscillatory mechanical ventilation, neuromuscular blockade, monitoring of esophageal pressure, and extracorporeal lung-induced CO₂ excretion have also been tested in clinical trials [42–47]. These therapies may provide a certain clinical value in several cases of refractory hypoxia but are insufficient to be the main treatment strategies for ARDS [48].

4 Research on ALI/ARDS and future development directions

The use of human MSCs to treat ALI and ARDS is gradually becoming a promising treatment [49–54]. These MSCs can secrete various effector molecules, including anti-inflammatory CKs, growth factors, and antimicrobial peptides. These molecules can reverse the major lung injury of ALI/ARDS, including restoring impaired pulmonary vascular endothelial and alveolar epithelial cell permeability, promoting the absorption of pulmonary edema, regulating inflammation, and controlling infection. The MSCs attach to alveolar epithelial cells and transfer their mitochondria to endotoxin-damaged alveolar epithelial cells via a connexin-43-gap junction to restore alveolar energy and surfactant production, thereby repairing the barrier function of epithelial cells [55]. In addition, cell-free lung tissue can restore short-term function after treatment with

MSCs. This finding helps in understanding the mechanisms of lung regeneration, including signals produced by lung interstitial cells [56], and may help in discovering new strategies for treating severe lung injury. An efficient extracorporeal circulation system is also developed to provide an effective gas exchange for patients with severe lung injury [57,58]. Current evidence supports small tidal volume mechanical ventilation as the optimal ventilation strategy for ALI/ARDS [59].

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