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Introduction

Respiratory failure frequently happens in acute respiratory distress syndrome (ARDS) which is a multi-factorial syndrome with high morbidity and mortality rates. ARDS is characterized by deficiency in gas exchange and lung mechanics which lead to hypoxemia, dyspnea and respiratory failure. Histologically, ARDS is characterized by an acute, exudative phase, combining diffuse alveolar damage and noncardiogenic edema, followed by a later fibroproliferative phase. Although there is a better understanding of ARDS pathogenesis, the ability to predict the development of ARDS and to risk-stratify patients with the disease remains limited. Biomarkers are believed to help identify patients at the greatest risk of developing ARDS, to evaluate response to therapy, to predict outcome, and to improve clinical trials.[1] In this article, the ARDS etiology, pathogenesis, concepts and information on biomarkers that are currently used clinically and experimentally are presented.

Etiology of ARDS

Etiology of ARDS can be divided into pulmonary (direct) and extrapulmonary (indirect) injuries. (Table 1).[1]

Table 1. Etiology of ARDS

Direct (pulmonary injury)	Indirect (extrapulmonary injury)
• Pneumonia • Aspiration of gastric contents • Fat emboli • Pulmonary contusion • Inhalation injury • Near drowning • Reperfusion pulmonary edema after transplantation or pulmonary embolectomy	• Sepsis • Cardiopulmonary bypass • Severe trauma with shock and multiple transfusions • Acute pancreatitis • Transfusion of blood products • Drug overdose

Direct injuries to lung parenchyma usually arise from infection, aspiration, adverse drug reactions and autoimmune inflammatory injury. Less-common causes are pulmonary

contusion, near-drowning events, fat emboli, toxic inhalation injury, pulmonary thromboembolism and reperfusion edema following lung transplantation.[1]

Common etiology of indirect lung injury are sepsis and shock (often related to severe trauma requiring multiple transfusions). Less-common etiology are cardiopulmonary bypass, drug overdoses, blood-product transfusions and acute pancreatitis. Regardless of the etiology of injury, epithelial damage stimulates macrophage activation and an inflammatory response. The consequence of the disruption of endothelial and epithelial integrity is the flooding of the alveolar airspaces by edema fluid from the plasma.[1]

Pathogenesis of ARDS

Effective gas exchange in the lung requires thin alveolar septa with a minimum distance between the alveolar epithelium and the endothelium of the microvasculature to facilitate simple diffusion of those gases.[2] When there is injury to the endothelial-epithelial barrier, interstitial and alveolar edema may develop, which in turn, has a fundamental role in the development of ARDS.[1]

Because of overlapping criteria applied to the definition of acute lung injury (ALI) and ARDS, the Berlin definition of ARDS emphasizes 3 ARDS categories – mild, moderate and severe – based on the degree of hypoxemia.[1]

The pathogenesis of ARDS is characterized by two phases that may sometimes overlap temporarily and spatially: exudative and proliferative.

Exudative phase is characterized by alveolar-capillary barrier dysfunction resulting in altered permeability of epithelial and endothelial alveolar cells. Due to loss of cellular integrity, alveoli are filled with proteinaceous edema fluid that results in impaired gas exchange. Initially, there is an early exudative phase associated with diffuse alveolar damage, microvascular injury with subsequent pulmonary edema, alveolar type 1 (AT1) epithelial cell necrosis, and influx of inflammatory cells which then release active mediators.[3] In the early exudative phase, alveolar inflammation is mainly mediated by polymorphonuclear neutrophils (PMN), monocytes and macrophages.[3] There is also proinflammatory mechanism involved, characterized by the release of proinflammatory cytokines by lung cells, inflammatory cells and fibroblasts.[3]

Proliferative phase is characterized by persistent injury and failure to repair lung damage in a timely manner, which contributes to the fibroproliferative response during which there are proliferation of fibroblasts, hyperplasia of alveolar type 2 (AT2) cells and lung repair. The repair of the injured alveolar epithelium remains incompletely understood; it involves hyperplasia of AT2 (and may be AT1) cells, to perform a new epithelial barrier, and complex interactions with epithelial cell membrane and other cells, including alveolar macrophages. In the absence of recovery, processes leading to fibrosing alveolitis may occur during a fibrotic phase, resulting in some cases, marked changes of lung structure and function.[2]

Biomarkers in ARDS

Pathophysiologic changes can be used as a framework to better understand various biomarkers that have been studied in ARDS, including the cellular injury pathway that are central to lung injury which is consist of endothelial injury, epithelial injury, proinflammatory injury, coagulation, fibrosis, and apoptosis.[4]

Biomarkers can be used as: 1. To identify patients with risk factors of ARDS, who are most likely to develop the syndrome, 2. To improve risk stratification once ARDS criteria are present, 3. To design future clinical trials by the identification of patients at high risk of poor outcome, thus decreasing the required sample size needed to show a therapeutic benefit, 4. To evaluate the response to therapy.[5]

Exudative phase of ARDS.

Initial exudative phase of ARDS is characterized by diffuse alveolar damage associated with the formation of lung inflammatory edema. Alveolar injury is predominant during this phase, and various proteins that are specific to lung injury are released in both the blood and the alveolar compartment, which serving as markers of the disease or of its resolution.[3]

Experimental models provide insight into the molecular basis of ARDS and have suggested several biomarkers that may be prognostically useful in ARDS. Table 2 summarizes the major biomarkers of inflammation in experimental models of ARDS.[1]

Biomarkers of inflammation

Meduri et al[6] found that unfavorable outcomes in acute lung injury (ALI) were related to the degree of inflammatory response early in, and throughout the course of ARDS. Patients with higher plasma levels of TNF-α, IL-1β, IL-6 and IL-8 on day 1 of ARDS seemed to have persistently elevated levels of those inflammatory cytokines during the disease course and ultimately passed away from the disease. In contrast, surviving patients tended to have a lesser elevations of plasma inflammatory cytokines on day 1 of ARDS and a rapid reduction over time.

Table 2. Summary of biomarkers testing in clinical and experimental ARDS.[1]

Biomarkers	Experimental	Clinical	BAL	Plasma	Lung tissue
Inflammation	IL-6, IL-8, TGF-β	TNF-α, IL-1β, IL-6	^	^	^
Endothelial cell damage	VEGF	Von-Willebrand Factor	^	^	^
		E-selectin, ICAM-1		^	
		Protein C		^	
		Plasminogen Activator Inhibitor1		^	
		Thrombomodulin		^	
Epithelial cell damage	PTEN deficiency	RAGE		^	^
		KL-6		^	^
		SP-D		^	
		CC16		^	
Fibrogenesis	Versican	Procollagen III		^	^
	Decorin	Myofibroblasts		^	^
		Fibrocytes		^	^

Abbreviations: BAL, bronchoalveolar lavage; CC16, Clara cell secretory protein; IL, interleukin; KL-6, Krebs von den Lungen-6; PTEN, phosphatase and tensin homolog; RAGE, receptor of advanced glycation end products; SP-D, surfactant protein -D, TGF, transforming growth factor; VEGF, vascular endothelial growth factor.
^ indicates the increase in the biomarker according to the investigation in routine laboratory testing.
Empty cells indicate that the biomarker was not investigated as routine laboratory testing.

Biomarkers of endothelial damage

Vascular endothelial growth factor (VEGF) is one of the most extensively studied biomarker in endothelial damage. VEGF play important role in the regulation of angiogenesis and lymphangiogenesis.[7] The expression of VEGF in ARDS varies, depending on the degree of epithelial and endothelial damage. Many lung cells release VEGF, for example, AT2 cells, neutrophils, alveolar macrophages, and activated T cells. VEGF increases microvascular permeability. Over expression of VEGF induces pulmonary edema in animal models.[8]

Kayal et al[9] found higher plasma levels of E-selectin, ICAM-1, and vWF in non-survivors of septic shock and sepsis. Initial plasma levels of E-selectin, ICAM-1, and vWF could predict survival with high sensitivity and specificity.

Sapru et al[10] demonstrated that increased levels of plasma soluble thrombomodulin (sTM) were associated with increased mortality, probably reflecting an increased degree of inflammation in the lungs and systemic endothelial damage.

Activated protein C controls coagulation and fibrinolysis and also decreases the levels of proinflammatory cytokines. Ware et al[11] found that low plasma levels of protein C were associated with mortality and increased risk of multiple organ failure compared to control subjects.

Plasminogen activator inhibitor-1 (PAI-1) activates fibrinolysis through the conversion of plasminogen to plasmin, a fibrinolytic enzyme. During ARDS, activated macrophages over-expressed PAI-1, decreasing fibrinolytic activity. Ware et al[12] showed that higher levels of PAI-1 were independently associated with higher mortality, poor survival and more organ failure.

Biomarkers of epithelial cell damage

Phosphatase and tensin homolog (PTEN) are multifunctional phosphatases that negatively regulate the PI3K/Akt pathway and exerts tumor suppression. Previous studies reported the regulatory role of PTEN on fibroblasts in lung fibrosis and have shown that deletion of PTEN confers resistance to airway injury.[1]

Clinical studies in ARDS patients have suggested biomarkers of epithelial cell damage that may be useful for determining prognosis such as RAGE (receptor of advanced glycation end products), KL-6 (Krebs von den Lungen-6), SP-D (surfactant protein -D), and CC16 (Clara cell secretory protein).[1]

Calfee et al[13] demonstrated that higher baseline plasma RAGE was associated with increased lung injury severity and increased mortality.

In ARDS patients, plasma and serum KL-6 levels reflect the severity of lung injury and neutrophilic inflammation which was associated with poor prognosis.[14]

Surfactant-associated protein D (SP-D) play a role in the lung immune system which improve phagocytosis of bacteria and virus. Reduced SP-D in pulmonary edema fluid at the onset of ARDS was associated with poor prognosis.[1]

CC16 which is an anti-inflammatory protein secreted by the Clara cells of the distal respiratory epithelium, is a biomarker of lung epithelial injury. Decreased plasma levels of CC16 was found in ARDS patients.[1]

Biomarkers of fibrogenesis

Injury to the lung parenchyma and loss of alveolar epithelial cells (AEC) lead to deposition of temporary extracellular matrix (ECM) which is favorable to the growth of fibroblasts. Repeated injury to AEC causes the loss of basal membrane (BM) integrity and activation of myofibroblasts, which results in abnormal remodelling processes leading to scarring.[1]

Tissue stiffness is determined by collagen and elastin fibers, the main mechanical load-bearing components of the ECM (extra cellular matrix). Those fibers are embedded in a matrix of PGs which are composed of glycosaminoglycan (GAG) chains covalently linked to a protein core. The negatively charged GAGs generate repulsive electrostatic forces, which contribute to the compressive bearing and shear resistance of the ECM. During tissue deformation, collagen and elastin fibers unfold and reorient; that process is opposed by the PGs surrounding fibers.

Therefore, PGs contribute to the stress-strain properties of the ECM, by preventing the alveolar structure from collapse in the healthy lung.[1]

Pulmonary fibroblasts produce procollagen III peptide (PCP-III), that is, a precursor of collagen. The NT part of procollagen III is regarded as a marker of collagen synthesis. Plasma and alveolar levels of procollagen III are higher in ARDS patients, as compared to controls.[15]

Fibrocytes can be quantified in broncho alveolar lavage (BAL) of ARDS patients. Fibrocytes percentages greater than 6% was related to highest risk of mortality.[16]

Additional biomarkers of fibrogenesis are laminins, elastin and matrix metalloproteinase (MMP). Laminins are ECM proteins with high molecular weights that are deposited in basal membranes, involved in cellular adhesion, growth, differentiation, and remodeling of epithelial tissue. Higher levels of laminins were found in the plasma and lung edema fluid in ARDS patients and lower levels in survivors. Elastin is a protein of the ECM responsible for lung elastic recoil. During lung endothelial and epithelial injury, elastin can be broken down by neutrophil elastase and excreted in the urine. Elastin levels can be measured in urine, which is lower in patients ventilated with lower tidal volumes. The MMP are involved in degradation, turnover, and remodeling of the ECM, digesting type 1 collagen. Elevated levels of MMP-2, MMP-8, and MMP-9 in the BAL fluid from ARDS patients were associated with acute inflammation and poor outcome.[17]

Combining biomarkers

Although there are advances in the identification of biomarker candidate and better understanding of ARDS pathogenesis, no single clinical or biological marker that can reliably predicts clinical outcomes in ARDS. The combination of clinical and biology marker is attractive in order to improve the sensitivity and/or the specificity of the test, especially through a recent approach aimed at measuring 8 biological markers that reflect endothelial and epithelial injury, inflammation, and coagulation: vWF, TNF-R1, SP-D, IL-6, IL-8, ICAM-1, protein C, and PAI-1 which has a better clinical predictor of ARDS.[3]

Conclusion

Biomarker research provides a better understanding of lung pathobiology. We have got insight into the pathogenic importance of inflammation, endothelial cell damage, epithelial cell damage and fibrogenesis in ARDS. Biomarker studies may help us to explore the cellular and molecular mechanisms of various therapeutic strategies for ARDS. Given the clinical heterogeneity of patients with ARDS and the complexity of the underlying pathobiology, it is unlikely that a single biomarker will emerge for ARDS, as cardiac specific troponin did for myocardial infarction, but the development of small biomarker panels reflecting each important lung injury pathway would provide valuable predictive and prognostic information

for clinicians and researchers. Although biomarkers are currently not recommended for use in clinical practice in ARDS, biomarker discovery may give significant promise in order to develop and apply targeted therapy and to identify candidates for enrollment in patient-tailored clinical trials of novel therapies in ARDS.

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