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A primary biomarker examination in preventing progressivity of acute respiratory distress syndrome: the role of surfactant protein-D in sepsis induced ARDS

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Abstract

Sepsis is one of the most unreachable conditions of hospitalization and a major contributor to hospital mortality, representing a major worldwide health burden. Sepsis is a syndrome characterized by an irregular host response to pathogens invasion, which involving hemodynamic changes that lead to multiple life-threatening organ dysfunctions. Among the injured organs, the lung is the first and most frequent organ to fail. Acute respiratory distress syndrome (ARDS) develops with many serious medical disorders. At least, mortality is 40% and there is no specific therapy. ARDS is an acute inflammatory process in the lung caused by infection direct or indirectly to the alveolar-capillary membrane. Currently, ARDS is diagnosed based on a combination of clinical and physiological variables. In this article, we will review the current understanding of surfactant protein-D as one of many biomarkers in ARDS diagnosis.

Key words: ARDS, surfactant protein-D, sepsis induced ARDS, ARDS biomarker, blood biomarker.

Introduction

The acute respiratory distress syndrome (ARDS) is a form of severe hypoxemic respiratory failure that is characterized by inflammatory injury to the alveolar-capillary barrier, with extravasation of protein-rich edema fluid into the airspace. Although many modalities to treat ARDS have been investigated over the past several decades, supportive therapies remain the mainstay of treatment. (1) Sepsis and ARDS are heterogeneous syndromes associated with high mortality rates and substantial healthcare costs in critically ill patients. The clinical manifestations of severe sepsis syndrome involve organ dysfunction including encephalopathy, acute kidney injury, coagulopathy, and acute lung injury (ALI) or ARDS. (2)

Discrimination between ARDS and other similar diseases is very important; however, only a few biomarkers are currently available for diagnostic purposes. In addition, predicting the severity, response to therapy, or outcome of the disease are also important for developing treatment strategies for each patient. (3) Many biomarkers have been tested for the diagnosis and treatment of ARDS. This review article will explore the role of surfactant protein-D (SP-D) as one of the biomarkers that establish the diagnosis of ARDS.

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Surfactant protein-D

SP-D is a 43-kD member of a family of collagenous carbohydrate-binding proteins (C-type lectins), which is called choline. (4,5) In the lung, SP-D is synthesized and secreted primarily by type II cells and other non-ciliated respiratory epithelial cells. SP-D monomers are assembled into dodecamers consisting of four homotrimeric subunits. The

structural motives along with other collection and in vitro studies show that SP-D plays a role in innate immunity against various pulmonary pathogens. (6-8) The receptor of SP-D is Gp340 ad CD14. (9)

The review article by Colmorten, et al (2019) said that surfactant protein-D was a biomarker for the vascular inflammation and cardiovascular disease. They quoted from the article by Wulf-Johansson et al examined the correlation between circulating SP-D levels with total mortality. The twin with the highest-circulating SP-D level had a significantly increased risk of dying before the co-twin during the study follow-up period. (10) Otaki, et al (2018) made a publication about the circulating surfactant protein-D, which was associated with clinical outcomes in peripheral artery disease patients following endovascular therapy. (11) This article was about the role of surfactant protein-D in extrapulmonary disease.

SP-D deficiency has the effect of increasing of macrophage and pulmonary inflammation recruitment in lipopolysaccharide (LPS)-induced lung injury. (12) Serum SP-D level may serve as a good diagnostic indicator of ARDS in cases of sepsis. (13) SP-D serum levels also can be used as a marker of disease activity for interstitial lung disease. Several human lung diseases are characterized by decreased levels of bronchoalveolar SP-D. (14)

In lung diseases such as pulmonary fibrosis and idiopathic interstitial pneumonia, serum surfactant protein levels (especially SP-D) are inversely proportional to their respective levels in bronchoalveolar lavage (BAL). The level of SP-A and SP-D in serum are likely to be good biomarkers for the clinical outcomes of certain disorders. For example, a decrease in the systemic SP-D in chronic obstructive pulmonary disease (COPD) was associated with a better clinical outcome. (15) **Table 2** shows altered levels of SP-A and SP-D in lung tissue, brochoalveolar lavage fluid (BALF) and serum specimens from patients or animal models with a variety of lung disease. ALI and ARDS also show a similar association between SP-D serum level and mortality. Post-mortem subjects in a study showed extremely high levels of circulating SP-D when compared to ALI/ARDS patients in the early stages. (16,17)

There are 4 pathways that contribute to making ARDS: epithelial, endothelial, inflammatory, and coagulation and fibrinolysis pathways. Respiratory epithelium markers include surfactant proteins (SP), Krebs von den Lungen-6 (KL-6) protein, vascular endothelial growth factor (VEGF), and soluble receptor for advanced glycation end-products (sRAGE). SPs are generally increased in ARDS, and SP-B can cross damaged alveolocapillary membranes. (18) Blood SP-D levels have been shown to correlate with ARDS mortality. (19,20) Systemic levels of SP-D and KL-6 are associated with mortality, duration of mechanical ventilation, and length of stay in hospital. (21)

The hallmark of the ARDS is an increase in the alveolocapillary permeability arising from insults via the airways or the blood. The barrier between air and blood is formed by three main layers, namely the alveolar epithelium, the interstitial space including the basement membrane, and finally, the blood vessels including the endothelium. Some lung diseases have, as a characteristic, damage to this barrier. In the later years, specific biomarkers for lung injury have been identified with the intention to guide a more pathophysiological stratification of patients, in turn, allowing a personalized treatment for patients with lung injury. The most promising markers include SP-D, club cell secretory protein 16 (CC16), and actin-scavenger gelsolin specific for alveolar, bronchial and endothelial damage to the lungs, respectively. (22) The route where the protein enters the circulation is unknown; however, there is strong evidence that bidirectional plasma protein flux occurs in the lungs, the magnitude of which depends on the severity of the disease. SP-D is easier to circulate into circulation because of hydrophilicity. (23)

Sepsis and ARDS

ARDS is one of the most critical prognostic factors for death in patients with sepsis, which is a clinical term for ALI. (24) A major complication in sepsis is progressively impaired lung function and susceptible to intrapulmonary infection. ARDS induced by sepsis has a high level of morbidity and mortality and occurs after lung infection or infection at the extrapulmonary site. Lung injury to ARDS is caused by damage to the pulmonary vessels and alveoli, which is mediated in part by activated neutrophils, which results in massive pulmonary edema, neutrophilia, and surfactant dysfunction. (25) The disruption of the pulmonary alveolar-capillary barrier is caused by an aberrant host response to infection, resulting in lung injury characterized by hypoxemia, inflammation, and non-cardiogenic pulmonary edema. Although ARDS induced by sepsis is based on an increasing understanding of molecular biology, no pharmacological therapy is targeted for this devastating condition.

(26) Increased pulmonary injury is associated with increased accumulation of neutrophils in the lungs, increased production of CXC chemokines (not tumor necrosis factor-α) in bronchoalveolar lavage fluid, and increased expression of pulmonary intracellular adhesion molecules (ICAM-1). (27)

ARDS is a common cause of respiratory failure in critically ill patients, which is defined by acute onset of noncardiogenic pulmonary edema, hypoxemia, and the need for mechanical ventilation. ARDS most often occurs in the regulation of pneumonia, sepsis, aspiration of gastric contents or severe trauma, and is present in ~10% of all intensive care unit (ICU) patients worldwide. Despite some improvements over the past few decades, mortality rates remain high at 30-40% in most studies. (28) Diffuse alveolar damage most commonly occurs in pathological specimens from patients with ARDS, which results in the accumulation of protein-rich inflammatory edema fluid in the alveolar space, is an injury to the alveolar epithelium and pulmonary endothelium, which has been demonstrated by laboratory studies. (29)

Despite some recent modifications, the clinical definition of ARDS remains non-specific, which causing under-diagnosis and under-treatment. Biomarkers are potentially useful as guides to clinical management and as research tools. (30) The key factors for preventing ARDS are identifying patients at risk and implementing prevention strategies in this group. (31) Abnormal levels of five plasma biomarkers (SP-D, Interleukin-6 [IL-6], Interleukin-8 [IL-8], the receptor for advanced glycation end products [RAGE], and CC-16) provided excellent discrimination for diagnosis of ARDS in patients with severe sepsis. The rate of change in plasma biomarkers can be a useful biological confirmation for the diagnosis of ARDS in patients with sepsis, selecting patients for clinical trials designed to reduce lung epithelial injury. (32) Three of five biomarkers were caused by the lung epithelium injury. The injury of lung epithelial is a critical determinant of alveolar flooding and the subsequent arterial hypoxia and bilateral opacities. Its clinical condition refers to the definition of ARDS.

ARDS by definition is heterogeneous, including lung injury in the regulation of the underlying illnesses that may cause either direct injury to the lung (e.g., pneumonia, aspiration of gastric contents) or indirect one (e.g., non pulmonary sepsis, massive transfusion, pancreatitis). A study by Calfee, et al (2015) showed that patients with direct ARDS had significantly higher rates of pulmonary epithelial injury (surfactant protein-D) and significantly lower levels of endothelial injury biomarkers (angiopoietin-2) than patients with indirect ARDS. (33)

The role of surfactant protein-D in ARDS

Pulmonary SP-D is expressed in type II alveolar and bronchiolar epithelial cells and is secreted into alveoli and conducting airways. However, SP-D has also been measured in serum and is increased in patients with acute respiratory distress syndrome, pulmonary fibrosis, and alveolar proteinosis. (34-36) Fujita, et al (2004) showed the data that clarified the profile of SP-A and SP-D in acute and chronic inflammation, and indicated that serum SP-D can serve as a biomarker of lung inflammation in both acute and chronic lung injury in mice. (37)

Pulmonary surfactant prevents alveolar collapse and maintains gas exchange in the lungs. Apoproteins are essential for the manifestation of pulmonary surfactant function. They are divided into four types of surfactant protein (SP-A, SP-B, SP-C, and SP-D). All are synthesized and secreted by type II cells. SP-A and SP-D are hydrophilic glycoproteins. Together with the mannan-binding protein, they are referred to as the glycoprotein-collecting family. They bind to bacteria, fungi, and viruses, and are involved in host defence mechanisms. Since the surface activity function of the pulmonary surfactant collected from bronchoalveolar lavage fluid (BALF) of ARDS patients is very low, damage to type II alveolar cells and surfactant inactivation are considered to occur in the presence of ARDS and the associated alveolar pulmonary edema. A quantitative surfactant abnormality is also observed in ARDS. (38) The previous study by Nakae, et al (2004) reported SP-A and SP-D blood will increase in the presence of septic ARDS.

SP-D has a role as a surfactant homeostatic, in addition, SP-D also contributes to the regulation of lung inflammation. Inflammation and injury to the lungs affect the synthesis and secretion of SP-D from pulmonary epithelial cells into the systemic circulation. (39) These SP-D characteristics provided a reason for its examination as a biomarker in human lung disease, such as ARDS. Using data from two US and one Asian cohort of critically ill patients, which were treated in a medical ICU, Park, et al (2017) had found that SP-D plasma levels within 48 hours after ICU admission were significantly higher in patients with ARDS compared to patients without ARDS. His research found that plasma SP-D levels provided sufficient discrimina-

tion for the diagnosis of ARDS in medical ICU patients. Park, et al (2017) validated those reported by Ware, et al who identified SP-D as an important component of the biomarker panel provides good discrimination for the diagnosis of ARDS in patients with severe sepsis. In addition, although SP-D may be better than other epithelial injury markers for the diagnosis of ARDS, it may useful as a biomarker panel component rather than a single biomarker for the diagnosis of ARDS. (40) The other previous research by Delgado, et al (2014) strengthen the role of SP-D circulation as a biomarker of lung injury. Delgado, et al conducted a study of 37 patients with ARDS due to A/H1N1 virus infection and 40 healthy people as controls.
The results showed that higher SP-D circulating levels are associated with higher mortality risk in critically ill A/H1N1 patients. SP-D might be a predictive factor of poor outcomes in viral pneumonia. (41)
The previous literature by Jensen, et al (2016) said that early profound alveolar damage in intubated patients could be identified by SP-D blood measurement at intensive care admission, and high SP-D level was a strong independent predictor that the patient suffered from ARDS, and will not recover independent respiratory function within one month. (42)

The mechanism of ARDS in sepsis

Disruption of the alveolar-capillary barrier is the pathophysiologic hallmark of sepsis-induced ARDS. Initiation of the host response to infection and subsequent dysregulation of that response drives barrier disruption. Repair of the epithelium and endothelium are essential for the resolution of sepsis-induced ARDS. (23) During acute lung injury induced by environmental factors, allergens, infectious organisms or non-infectious inflammatory stimuli, the alveolar-capillary barrier permeability increases and damages the endothelium and/or alveolar lining cells. Damage to this layer leads the entry of edema fluid, which is rich in protein and inflammatory cells, into the alveoli. The influx of cells, chemotaxis factors, enzymes, and cytokines further injure the alveolar epithelium. This type II epithelial cell injury directly leads to a decrease in surfactant production with the resulting alveolar collapse. The alveolar septal damage causes leakage of SP-A and SP-D into the blood. Overall, significant reductions in SP-A and SP-D alveolar lavage pools and elevated serum SP-A and SP-D are considered typical for lung damage in various conditions, such as asthma, ARDS, and bronchopulmonary dysplasia (BPD). Also, a number of proinflammatory cytokines and growth factors are released during the inflammatory phase of lung injury, which can adversely affect surfactant synthesis and secretion without disturbing the integrity of the epithelium. For example, keratinocyte growth factor and vascular endothelial growth factor increase surfactant synthesis. In addition, tumour necrosis factor-α (TNF-α), hepatocyte growth factor, and their intermediates in the signalling pathway can inhibit surfactant synthesis. The signal-transduction pathways induced by growth factors, cytokines, and regulatory mechanisms involved in surfactant synthesis and secretion have been reviewed elsewhere. (43)
The surface of the airways and the alveoli are protected by an epithelial cell layer. This epithelium forms the first line of defence against airborne noxae and prevents an invasion of the organism by infectious particles. It also traps airborne particulate matter and removes them from the airways. Furthermore, it feels disturbed so that it can regulate the immune response.
Epithelial barrier damage is characteristic in respiratory distress syndrome and can be identified through the appearance of high molecular weight serum proteins in bronchoalveolar lavage from patients. The function of the lung epithelial barrier depends on so-called tight junctions (TJ). This heteromeric protein is complex from the sealing interface between adjacent epithelial cells. TJ damage is the major cause breakdown to the epithelial barrier during lung inflammation. Even though the damage to lung epithelial barrier is life-threatening, TJs of the lung epithelium and their regulation/disruption in health and disease are less elaborated. (44)
There is a role for cytokines in the tight junction condition. Especially, TNF-α plays a major role in disrupting tight junctions in the airway epithelium. TNF-α works via nuclear factor-kappa B (NFκB), which is considered as a major regulator of tissue inflammation. In the resting phase, NFκB dimers bind proteins of the NFκB inhibitor family of inhibitor kappa B (IκB). Activation of NFκB signalling induces expression and release of pro-inflammatory factors such as IL-1, IL-2, IL-6, IL-8, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), TNF-α, TNF-β, and interferon beta (IFN-β). This pro-inflammatory effect of NFκB is also shown for airway epithelial cells. In airway epithelium, TNF-α decreases paracellular epithelial barrier function. Transforming growth factor beta (TGF-β) can play an important role in the tight interruption of the epithelial and endothelial junc-

tion. Since TGF-β is an important mediator of lung injury and pulmonary fibrosis, changes in tight junctions due to lung injury may be partially mediated by TGF-β. Previous study by Ohta, et al (2012) showed that TGF-β activity increased in BAL after bleomycin-induced lung injury. (45) Furthermore, Kaminski, et al showed that TGF-β expression was upregulated in pulmonary fibrosis from acute to chronic stage. (46) Although some studies have indicated that TGF-β upregulated the expression of tight junction, proteins, and strengthens the function of epithelial cell barrier, others have reported that TGF-β downregulated tight junction molecules by apoptosis or epithelial-to-mesenchymal transition (EMT) in cultured epithelial cells. The effects of TGF-β depends on cell types and context. Undevia, et al showed that TGF-β could protect human airway epithelial cells from apoptosis and this antiapoptotic pathway was mediated by the Smad pathway involving the cyclin-dependent p21 kinase inhibitor. Considering these findings, we speculate that TGF-β functions as an antiapoptotic and protective cytokine. (45)

Lung injury can be caused by lipopolysaccharide (LPS). Although the surfactant molecule contains effective protection mechanisms, under certain circumstances pulmonary surfactant may be damaged by excessive amounts of LPS. High dose LPS induces IL-1β and TNF production, leading to inflammation. Neutrophil influx into the alveoli further worsens the lung damage by increasing pulmonary permeability, edema formation, and cell death. LPS interferes with all major components of pulmonary surfactant. It occurs even directly by interaction with surfactant specific proteins and incorporation into the phospholipid layers, or indirectly through alveolar type II cells. (47,48)

Surfactant protein-D as biomarkers choice in blood

The lack of a specific biomarker for ARDS is arguably one of the most important obstacles to progress in developing new treatments for ARDS. (49) Blood is the most common biological sample used to check the presence of biomarkers candidates. Blood is easy to collect, process, and make serial measurements during disease progression. However, the use of blood as a sample source implies the measurement of circulating biomarkers, which may be caused by other processes, such as coagulation, response to infection, and inflammation.

SP-D is a biomarker of lung epithelial injury. This glycoprotein is mainly produced by type-II cells, which play a crucial role in maintaining the integrity of the alveolar-capillary interface. In addition to reducing the surface tension at the alveoli, SP-D also has a role in innate immunity, acting as an inflammatory molecule and having anti-microbial functions. Several studies have found an association with increased plasma SP-D levels and diagnosis and/or worse clinical outcomes of ARDS. SP-D seems to be a good diagnostic indicator of ARDS in septic patients. An increase of SP-D plasma level has been found after 48 hours in patients with ARDS; smaller improvements occured in patients who were ventilated by the lung-protective ventilation approach. This same study showed increased levels of SP-D in non-survivors. Eisner, et al (2003) showed the relationship between higher plasma l SP-D levels and a higher risk of death; they found a relationship between higher SP-D levels and worse clinical outcome, in terms of ventilation and fewer organ failure-free days. (16) They also showed that a lower tidal volume strategy attenuated the rise in plasma levels of SP-D. Although some authors have reported no relevant association of SP-D with the development of ARDS, a meta-analysis included SP-D in the list of clinically relevant biomarkers, although it appears not to be strongly associated with the diagnosis of ARDS. However, SP-D has been included in several biomarker panel studies for diagnosis and mortality prediction. Specific markers with a predictive value for development and/or outcome of ARDS are shown in the **Table 1**. (49)

The expression of SP-D in the lung and the circulating levels of SP-D during malaria infection have received limited attention. A study by Punsawad, et al (2019) supports that the elevation of the plasma SP-D level may provide useful biological confirmation of the diagnosis of ALI/ARDS during malaria infection. (50)

Based on literature review by Hartl and Griese (2006), they summarized that the mechanisms of how pulmonary SP-D comes into the circulation were unclear and there were several hypotheses, such as: (51)

- In inflammatory conditions, as in ARDS, increased permeability of lung vessels may result in an alveolar-to-vascular leakage of SP-D; (52)
- The integrity of epithelial secretory cells may be damaged in pulmonary inflammation, resulting in an efflux of SP-D from epithelial cells into the alveoli and in alveolar vessels; (53)
- As SP-D is less tightly associated with surfactant lipids than the other surfactant

proteins, SP-D may reach the bloodstream easily, (54) resulting in higher SP-D levels in serum compared with SP-A despite higher SP-A levels in BALF;

- In inflammatory states, high levels of SP-D in serum may be owing to a decreased clearance rate of SP-D from the circulation; (55) and
- Epithelial surfaces of several organs secrete SP-D and are potential sources of SP-D in the circulation. (56)

Conclusion

Research focusing on preventing ARDS and identifying patients at risk of developing ARDS is necessary to develop strategies to alter the clinical course and progression of the disease. Early identification of lung epithelium damage is a way to detect early acute lung injury before becoming ARDS. Plasma surfactant protein-D is a biomarker to detect lung epithelium injury.

Table 1. Specific markers with a predictive value for development and/or outcome of ARDS

Biological compartment and markers	Cell injury/inflammation
Plasma	
- Receptor for advanced glycation end products (RAGE)	Epithelium
- Angiopoletin-2	Endothelium
- Surfactant protein-D (SP-D)	Epithelium
- Interleukin-8 (IL-8)	Acute inflammation
BALF	
- Fas, Fas ligand	Epithelium
- Procollagen peptide I (PCP I)	Fibroproliferation
- Procollagen peptide III (PCP III)	Fibroproliferation
Exhaled air	
- Octane	Lipid peroxidation
- Acetaldehyde	Bacterial metabolism, inflammation
- 3-methylheptane	Lipid peroxidation

Legend: ARDS=acute respiratory distress syndrome; BALF=bronchoalveolar lavage fluid.

Table 2. Altered levels of SP-A and SP-D in lung tissue, bronchoalveolar lavage fluid (BALF), and serum specimens from patients or animal models with a variety of lung disease (43)

Disease condition	SP-A	SP-D	References
Chronic obstructive pulmonary disease	↓lung, ↑serum	↓lung, ↑serum	57,58
Lung emphysema	↓BALF	↓BALF	59,60
Asthma	↓↑BALF	↑BALF	61-63
Lung transplant	↓BALF	↓BALF	64,65
Cystic fibrosis	SP-A oxidation, ↓lung		51,66-70
Acute respiratory distress syndrome	↓lung	↑serum	34,51,71-74
Bronchopulmonary dysplasia	↓lung	↓BALF	51,75-79

Legend: SP-A=surfactant protein-A; SP-D=surfactant protein-D.

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