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Biomarkers in acute lung injury☆

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ABSTRACT

Acute respiratory distress syndrome (ARDS) and its milder form acute lung injury (ALI) may result from various diseases and situations including sepsis, pneumonia, trauma, acute pancreatitis, aspiration of gastric contents, near-drowning etc. ALI/ARDS is characterized by diffuse alveolar injury, lung edema formation, neutrophil-derived inflammation, and surfactant dysfunction. Clinically, ALI/ARDS is manifested by decreased lung compliance, severe hypoxemia, and bilateral pulmonary infiltrates. Severity and further characteristics of ALI/ARDS may be detected by biomarkers in the plasma and bronchoalveolar lavage fluid (or tracheal aspirate) of patients. Changed concentrations of individual markers may suggest injury or activation of the specific types of lung cells—epithelial or endothelial cells, neutrophils, macrophages, etc.), and thereby help in diagnostics and in evaluation of the patient's clinical status and the treatment efficacy. This chapter reviews various biomarkers of acute lung injury and evaluates their usefulness in diagnostics and prognostication of ALI/ARDS.

1. Introduction

Acute respiratory distress syndrome (ARDS) or the older term adult respiratory distress syndrome usually expresses a serious response to various forms of injuries or acute infection to the lung—in contrast with idiopathic respiratory distress syndrome (IRDS) or respiratory distress syndrome (RDS), which is caused by insufficient production of surfactant by immature lung.

ARDS may result from direct lung injury, e.g., pneumonia, aspiration of gastric contents, inhalational injury etc. or from indirect lung injury, e.g., sepsis, severe trauma with shock, acute pancreatitis etc. There are also several preexisting conditions, such as chronic lung disease, chronic alcoholism or age >65 years, that may increase the risk of developing ARDS (Dushianthan et al., 2011; Matthay et al., 2012).

Besides clinical signs and risk factors, various markers reflecting the complex pathogenesis of ARDS have been used as biomarkers. This chapter reviews biomarkers of acute lung injury and evaluates their usefulness in diagnostics and prognostication of ARDS.

2. Definition, incidence and clinical picture of ARDS

The American-European Consensus Conference (AECC) characterized ARDS by acute onset, bilateral infiltrates on chest radiography, pulmonary artery wedge pressure ≤18 mm Hg or the absence of clinical evidence of left atrial hypertension. Acute lung injury (ALI) was considered to be present if PaO_2/FiO_2 is ≤300 mm Hg, whereas for ARDS the values of PaO_2/FiO_2 should be ≤200 mm Hg (Bernard et al., 1994). Recently, the Berlin Definition of ARDS has proposed three categories of ARDS based on the degree of hypoxemia: mild (PaO_2/FiO_2 200–300 mm Hg), moderate (PaO_2/FiO_2 100–200 mm Hg), and severe (PaO_2/FiO_2 ≤100 mm Hg) (ARDS Definition Task Force, 2012).

The incidence of ARDS varies between 50 and 70 per 100,000 person-years with an overall mortality around 30–40%, depending on the geographical and methodological differences in the

Abbreviations: Ang, angiopoietin; AP, activator protein; ALI/ARDS, acute lung inury/acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CCSP, club cell secretory protein; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; HCl, hydrochloric acid; HGF, hepatocyte growth factor; HMGB, high mobility group box nuclear protein; IL, interleukin; IL-1ra, IL-1 soluble antagonist; LBP, lipopolysaccharide binding protein; KGF, keratinocyte growth factor; KL, Krebs von den Lungen protein; NF-κB, nuclear factor-kappa B; NO, nitric oxide; N-PCP-III, N-terminal procollagen peptide-III; 3-NT, 3-nitrotyrosine; PAI, plasminogen activator inhibitor; RAGE, receptor for advanced glycation end products; RDS, respiratory distress syndrome; RNA, ribonucleic acid; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; sICAM, soluble intercellular adhesion molecule; sIL-1RII, soluble IL-1 receptor II; SP, specific surfactant protein; sRAGE, soluble receptor for advanced glycation end products; sTNF-R, soluble TNF receptor; TAS, total antioxidant status; TBARS, thiobarbituric acid-reactive substances; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor.

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observational studies (Seeley, 2013). Beside mortality, attention should be paid also to the long-term consequences of ARDS, as many patients who survived ARDS continue to suffer physical, psychological, and cognitive dysfunction (Herridge et al., 2011).

In clinical observations, tachypnea, tachycardia, and respiratory alkalosis usually develop within the first 12–24 h after the insult and may precede the appearance of diffuse alveolar infiltrates on the chest X-ray. Lung edema formation and inflammation promote severe ventilation-perfusion mismatch, increase dead space and intrapulmonary shunt, and reduce lung compliance, finally leading to severe hypoxia. Most patients progress to respiratory failure within 48 h after the onset of symptoms (Mortelliti and Manning, 2002).

Nevertheless, variability in both pathology and patients may be responsible for contradictory results from various ARDS clinical trials, particularly in adult patients (Dushianthan et al., 2011).

3. Pathophysiological features of ARDS

Although the exact sequence of individual events in ARDS has not been completely elucidated, dysfunction of normal endothelial–epithelial barriers is thought to play a fundamental role in the development of acute lung injury (Cross and Matthay, 2011).

Three stages of ARDS may be distinguished that overlap temporally and spatially. In an exudative phase, diffuse alveolar damage causes that epithelial and endothelial cells produce factors reacting to injury and death. Due to loss of cellular integrity the alveoli are filled with proteinaceous edema fluid what results in impairment of gas exchange. Dilution and dysfunction of pulmonary surfactant lead to collapse of alveoli and decrease in lung compliance. Within several days, edema fluid is gradually cleared and proliferative phase follows, with proliferation of type II alveolar cells and fibroblasts. In the absence of recovery, some patients may progress to a fibrotic stage characterized by diffuse fibrosis and other changes in the lung structure (Cross and Matthay, 2011).

4. Biomarkers of acute lung injury

Severity and further characteristics of ALI may be detected by variety of biomarkers. As recently postulated (Cross and Matthay, 2011; Bhargava and Wendt, 2012), an ideal biomarker should indicate a clear relationship to the pathophysiological event, needs to be reliable, reproducible, disease specific and sensitive, should be sampled by simple methods, relatively inexpensive, with little or no diurnal variation. Concentrations of these substances are detected in exhaled breath condensate, urine, blood or plasma (serum), bronchoalveolar lavage fluid (BALF) or tracheal aspirate. Increased or decreased levels of the individual markers may indicate injury or activation of the specific type of lung cells—epithelial or endothelial cells, bronchiolar exocrine cells (also called club cells), neutrophils, macrophages etc., and thereby may be useful for diagnosis and prediction of mortality, or for monitoring the response to treatment.

In addition, time of sampling is important. In the initial (or exudative) phase of ALI/ARDS, acute lung injury is caused by a complex interaction of inflammation, injury of alveolar cells types I and II, injury of bronchiolar and endothelial cells, and activation of coagulation. On the other hand, the proliferative phase is characterized by a proliferation of epithelial and endothelial cells and fibroblasts. In these processes, different substances are released from the cells and might be detected in variable concentrations according to the time course of ARDS. In Table 1, we provide a list of biomarkers of ALI according to their origin or characteristics, which are discussed more in detail in the further subsections.

Table 1
Biomarkers of exudative and proliferative phases of ALI/ARDS (adapted from Cross and Matthay, 2011; Bhargava and Wendt, 2012).

Pathophysiological feature of ALI/ARDS	Source of biomarker/biomarker
Exudative phase of ALI/ARDS (days 0–7)	
Lung injury	
Alveolar cells type I	RAGE
Alveolar cells type II	Surfactant proteins (SP-D, SP-A, SP-B), KL-6
Bronchiolar club cells	club cell secretory protein (CCSP)
Endothelial cells	vWF, sICAM-1, Ang-1 and Ang-2, E-selectin
Lung matrix	Laminin, desmosine
Inflammation	
	Cytokines (IL-1β, IL-6, IL-8, IL-10, IL-13, TNFα)
	CRP, HMGB1, LBP
	Markers of oxidative stress (NO, TBARS, 3-NT, TAS)
Pulmonary vascular permeability	
	Mini-BALF protein, plasma protein (albumin and transferrin)
Activation of coagulation	
	PAI, protein C, thrombomodulin, urokinase
Proliferative phase of ALI/ARDS (since day 7)	
Epithelial cells	KGF, HGF
Endothelial cells	VEGF, Ang-2
Fibroblasts	N-PCP-III

4.1. Markers of exudative phase of ALI/ARDS

4.1.1. Lung injury

The exudative phase of ALI/ARDS is characterized by formation of lung edema due to diffuse alveolar damage. Injury to type I alveolar cells covering majority of alveolus and break-down of the epithelial barrier promote fluid accumulation in the alveolar space and interstitium and predispose to bacteriemia and sepsis. On the basal surface of type I cells, receptor for advanced glycation end products (RAGE) was identified, responsible for propagation of inflammatory response via nuclear factor-kappa B (NF-κB), thus increasing production of proinflammatory cytokines, reactive oxygen species (ROS) and proteases (Uchida et al., 2006). Besides acute lung injury, sepsis and end-organ injury without sepsis, soluble RAGE (sRAGE) has been implicated also in atherogenesis and cardiovascular diseases (Chiang et al., 2009; Raposeiras-Roubín et al., 2013). In patients with ALI/ARDS, plasma sRAGE levels peaked at day 1 and decreased over time, whereas higher levels were detected in patients with more severe lung dysfunction (Mauri et al., 2010). In another study, baseline plasma levels of sRAGE were significantly higher in patients with ALI/ARDS, with or without severe sepsis, than in patients with severe sepsis only and in mechanically ventilated controls. Levels of sRAGE correlated with severity of ALI/ARDS and decreased over time but were not associated with outcome (Jabaudon et al., 2011).

Injury to type II cells impairs synthesis and metabolism of surfactant, what finally results in an increased alveolar surface tension and alveolar collapse. Therefore, increase or decrease of specific surfactant proteins (SP), products of the type II cells, may have prognostic value for ALI/ARDS (Ware and Matthay, 2000). Although baseline plasma SP-A levels did not predict outcome of ARDS patients, higher baseline plasma SP-D levels were associated with a greater risk of death, fewer ventilator-free days, and fewer organ failure-free days. Additionally, increased plasma SP-D early in the course of ALI/ARDS was associated with a worse clinical outcome (Eisner et al., 2003). On the other hand, Cheng et al. (2003) found that reduced pulmonary edema fluid SP-D and elevated plasma SP-A concentrations at the onset of acute lung injury were associated with more severe disease and worse clinical outcome. Injury to the