The Pathophysiology, Biomarkers, and Treatment Developments in Acute Respiratory Distress and Acute Lung Injury

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Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are associated with substantial mortality and morbidity. ARDS occurs in association with systemic inflammatory response syndrome (SIRS), sepsis, major trauma, and cardiopulmonary bypass (CPB). SIRS occurs in 33% of patients requiring hospital admission and as many as 70% after CPB [1]. Those who fail to survive often develop multiple organ dysfunction syndrome (MODS), which includes AIL. The incidence of ARDS in SIRS is in patients with sepsis and severe sepsis is 40% and 80%, respectively. Sepsis and severe sepsis together represent the leading cause of death in adult general ICUs, with 30 - 45% associated mortality.

SIRS and ALI are defined by hypoxemia associated with lung inflammation and increased pulmonary vascular permeability. The first widely accepted radiological and physiological criteria were developed by an American-European Consensus Conference [1]. The criteria for SIRS include changes in thermoregulation (body temperature > 38°C or 36°C), the emergence of cardiovascular (heart rate > 90 beats/min) and respiratory (tachypnea > 20 breaths/min or arterial pCO_2 4.3 kP_a) instability, and alterations in white blood cell count (> 12,000 cells/mm^3, < 4,000 cells/mm^3, or the presence of > 10% band neutrophils). Two or more of the following criteria are needed for the diagnosis of ALI: new, bilateral, diffuse, patchy, or homogeneous pulmonary infiltrates consistent with pulmonary edema must be demonstrated on chest radiography; no evidence of heart failure, fluid overload, or chronic lung disease, or the pulmonary artery occlusion pressure is < 18 mmHg; and an arterial PO_2-to-inspired O_2 fraction ratio < 300 mmHg defines ALI, and a ratio < 200 mmHg defines ARDS [1].

Reactive oxygen intermediates (ROS) developed in the lung have the potential to initiate cell signaling processes that cause oxidative damage at sufficient concentrations to characterize oxidative stress [1].

Metal ion catalysts have a role of variable-valence transition in the generation and potentiation of oxidative stress. Among these is iron. These freely donate and accept electrons and overcome stabilization arising in molecular oxygen because of parallel electron spin. In this manner iron allows the activation of a relatively unreactive free radical gas [1]. In this respect, if iron-catalyzed reactions are freed from constraints, the iron catalyzes an array of inorganic and organic electron transfer reactions involving oxygen and/or nitrogen and halogen species that lead to the formation of reactive species capable of modifying biomolecules [1]. These authors suggest that the systemic inflammatory response syndrome (SIRS) and the development of acute lung injury (ALI) feature pronounced systemic and lung specific alterations in iron/heme mobilization which may be of pathological significance.

Classical clinical examination has suggested that the measurement of C-reactive protein (CRP)is sufficient in the evaluation of the patient with SIRS/sepsis. In the most severe cases of SIRS, transthyretin (TTR) values may drop to one-third or one-fourth of the normal level, whereas in the most severe inflammatory conditions CRP values may exceed 100 times the starting level [2]. Nutritional status and hypermetabolism cannot be separated and depressed synthesis of plasma TTR and the exhaustion of body nitrogen stores evolve along parallel curves in stressful conditions due to cytokine driven effects on the hepatic and muscular tissues [2]. The TTR decrease with SIRS, directly influenced by interleukin-6 and tumor necrosis factor a, is proportional to the severity of the inflammatory response, as is the increase in CRP.

Damage the lung by SIRS with ARDS leads to the development of a particular form of lung injury named ventilator-induced lung injury (VILI) [3]. There is a relationship between tidal volume and the development of VILI, the so called volotrauma. This leads to a lung-protective ventilatory strategy based on the use of low tidal volumes scaled to the predicted body weight (PBW) [3]. This has resulted in a concept of the use of airway driving pressure as a surrogate for the amount of ventilatable lung tissue or the concept of strain, i.e. the ratio between the tidal volume delivered relative to the resting condition, that is the functional residual capacity (FRC) [3]. This is related to the concept of an ultra-low tidal volume strategy with the use of extracorporeal carbon dioxide removal (ECCO2R). Tidal volume is limited, high plateau pressures are avoided, and positive end-expiratory pressure (PEEP) are applied minimize VILI [4]. However, increasing inspiratory time and I:E ratio may aggravate VILI. These investigators induced VILI in mice by high tidal-volume ventilation (HVT 34 ml/kg). Low tidal-volume ventilation (LVT 9 ml/kg) was used in controls. PEEP was set to 2 cm H2O, FiO2 was 0.5 in all groups. They measured survival, lung compliance, oxygenation, pulmonary permeability, markers of pulmonary and systemic inflammation (leukocyte differentiation in lung and blood, analyses of pulmonary interleukin-6, interleukin-1β, keratinocyte-derived chemokine, monocyte chemoattractant protein-1), and histopathologic pulmonary changes.

LVT 1:2 or LVT 1:1 did not result in VILI, and all individuals survived the ventilation period. HVT 1:2 decreased lung compliance, increased pulmonary neutrophils and cytokine expression, and evoked marked histologic signs of lung injury. Moreover, HVT 1:1 caused further significant worsening of oxygenation, compliance and increased pulmonary proinflammatory cytokine expression, and pulmonary and blood neutrophils. Thus, the increase of inspiratory time and I:E ratio aggravated VILI in mice by the impact of a "stress/strain × time product" for the pathogenesis of VILI [4]. However, while PLV improved gas exchange and reduced inflammation in experimental models of ALI, a systematic review was inconclusive with respect to its use in humans with ALI and ARDS [5]. Another study found that bronchoalveolar lavage (BAL) fluids from 24 patients with ARDS, leukocytic elastase and/or al-PI exist and a complex of elastase and alpha1-proteinase inhibitor (al-PI) was observed [5]. The significance of this is not clear.

A large Cochrane trial was conducted to better understand the variables most strongly associated with ARDS and ARDS mortality [6]. They found that the biomarkers most strongly associated with acute respiratory distress syndrome diagnosis in the at-risk population, when increased, were Krebs von den Lungen-6 (odds ratio [95% CI], 6.1 [3.0 - 12.1]), lactate dehydrogenase (5.7 [1.7 - 19.1]), soluble receptor for advanced glycation end products (3.5 [1.7 - 7.2]), and von Willebrand Factor (3.1 [2.0 - 5.2]). The biomarkers most strongly associated with acute respiratory distress syndrome mortality, when increased, were interleukin-4 (18.0 [6.0 - 54.2]), interleukin-2 (11.8 [4.3 - 32.2]), angiopoietin-2 (6.4 [1.3 - 30.4]), and Krebs von den Lungen-6 (5.1 [3.0 - 12.2]). Decreased levels of Protein C were associated with increased odds for acute respiratory distress syndrome diagnosis and mortality. This study provided a ranking of plasma biomarkers associated with ARDS or ARDS mortality [6].

Endotoxin has effects that include diffuse lung inflammation and injury of pulmonary vascular endothelium. The effects caused by endotoxin on lung are partly dependent on the presence of granulocytes, and both lymphocytes and macrophages may also participate in the response [7].

Changes in lung mechanics and pulmonary vasoconstriction associated with endotoxemia appear to be mediated by cyclooxygenase metabolites of arachidonic acid. This is mediated in part by generation of free radicals, but inflammatory cells, especially neutrophils, are a source of these toxic oxygen species.

Endotoxin may also cause intracellular generation of free radicals within lung cells, and inflammatory-cell-derived proteinases may also mediate the injury of lung cells, while antiproteinases can act as free radical scavengers.

In another study [8] investigators found that the percentage of granulocytes in BAL correlated significantly and inversely with the PaO_2/FiO_2 ratio (r = -0.98), and in ARDS it was significantly higher after septic than after traumatic shock (89 +/- 14 vs. 55 +/- 12). Myeloperoxidase, a specific constituent of neutrophils, was significantly and inversely correlated with PaO_2/FiO_2 ratio (r = -0.62). Furthermore,

it has been reported that interleukin-8 (IL-8) was present in the pulmonary edema fluid of all patients with ARDS [9], and was higher in the edema fluid of patients with ARDS associated with sepsis (84.2 ng/mL, n = 16) than without sepsis (14.8 ng/mL, n = 11) (p < 0.05). In patients with cardiogenic edema, IL-8 concentration (5.0 ng/mL, n = 8, p < 0.05) was significantly lower than those values in patients with ARDS. Ware., *et al.* [10] found that von Willebrand factor antigen released into the circulation and pulmonary edema fluid is a measure of the severity of ARDS or ALI. The degree and duration of thrombocytopenia, as well as the net change in the platelet count are known determinants for survival in organ failure in sepsis [11], which would tie in with von Willebrand factor. A study included 861 patients enrolled in the National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Network trial of lower tidal volumes compared with traditional tidal volumes for acute lung injury [12]. The important findings were that Interleukin-6 and interleukin-8 levels were associated with a significant decrease in ventilator free and organ failure free days, while sepsis patients had the highest cytokine levels and the greatest risk of death per cytokine elevation. By day 3, the 6 mL/kg strategy was associated with a greater decrease in interleukin-6 and interleukin-8 levels. In another study of ARDS, ARDS was accompanied by a hyperdynamic circulatory pattern with both pulmonary hypertension and increased cardiac output with depressed total vascular resistance [13]. Venous ET-1 concentration was massively increased in ARDS (9.8 +/- 1.2 versus 2.1 +/- 0.2 pmol/L, p < 0.001).

A study was designed to test the hypothesis that a biomarker panel would be useful for biologic confirmation of the clinical diagnosis of ARDS in patients at risk of developing ARDS due to severe sepsis [14]. Using the five best-performing biomarkers (surfactant protein-D (SP-D), receptor for advanced glycation end-products (RAGE), interleukin-8 (IL-8), club cell secretory protein (CC-16), and interleukin-6 (IL-6)) the area under the receiver operator characteristic curve (AUC) was 0.75 (95% CI: 0.7 to 0.84) for the diagnosis of ARDS. The AUC improved to 0.82 (95% CI: 0.77 to 0.90) for diagnosis of severe ARDS, defined as ARDS present on all four of the first four ICU days.

Clearly, with several biomarkers identified, greater clarity was needed. This might be enlightened by a quantitative overview of plasma-derived biomarkers associated with acute respiratory distress syndrome diagnosis or mortality [15]. In this meta-analysis clinical outcomes included 1) diagnosis of acute respiratory distress syndrome and 2) mortality in ARDS patients. Pooled odds ratios for clinical outcome by each biomarker were calculated and they were ranked according to pooled odds ratio. Fifty-four studies appeared eligible for meta-analysis, together including 3,753 patients.

The biomarkers most strongly associated with ARDS diagnosis in the at-risk population, when increased, were Krebs von den Lungen-6, lactate dehydrogenase, soluble receptor for advanced glycation end products, and von Willebrand Factor, and those most strongly associated with ARDS mortality, when increased, were interleukin-4, interleukin-2, angiopoietin-2, and Krebs von den Lungen-6. But decreased levels of Protein C were associated with increased odds for ARDS diagnosis and mortality.

Trauma evokes a non-specific, systemic immune response (SIRS)that results in reduced resistance to infection. This results in damage to multiple organs caused by a cascade of inflammation aggravated by subsequent sepsis to which the body has become susceptible. Mediators of tissue damage gain access to the intercellular space as a result of endothelial exposure to inflammatory cytokines. Damage-associated molecular patterns (DAMPs) or 'alarmins' are secreted by activated immune cells after tissue injury [16]. DAMPs directly activate several immune cells via cell-surface DAMP receptors and are potent activators of complement, which leads to rapid generation of C3a and C5a. Statins promote the bactericidal function of neutrophils having a role in therapy.

Pneumonia is the most common infection that complicates ARDS with a mortality rate that approaches 90%, and ICU admission leads to ARDS in approximately 10% of patients. The existence of ALI, its predisposing conditions, coexisting illnesses, and the therapeutic interventions used for patients with lung injury all can interfere with lung host defenses and set the stage for bacterial infection of the already-injured lung [17]. ARDS may follow when a hemodynamic and end-organ response develops in as many as 40% of patients. The key to improving survival requires understanding and modifying (or eliminating) factors that may initiate (or modulate) the developing syndromes - ARDS and multi-organ failure (MOF) [18]. ARDS and MOF-complicating sepsis have in common bacterially derived (e.g. endotoxin or lipopolysaccharides [LPS]) and host-derived humoral and cellular mediators. A variety of inflammatory cells (neutrophils, mono-

nuclear phagocytes, platelets), activated complement and coagulation components, vasoactive mediators (kinins, arachidonic acid metabolites, lipids, peptides), reactive oxygen radicals, and diverse cytokines have a role as mediators in SIRS, ARDS, and ALI [18]. Cytokine networking and nonimmune cells have a complex, putative role in the in the orchestration of the inflammatory response associated with ARDS and MOF. Damage associated molecular patterns (DAMPs) are thought to initiate the SIRS response by activating circulating immune cells through surface expressed pathogen recognition receptors. Neutrophils react and have a robust functional response to DAMP stimulation. It has been shown that mitochondrial DAMPs (mtDAMPs) are potent activators of human neutrophils and signaling through the mitogen-activated-protein-kinases p38 and extracellular-signal-related-kinase 1/2 (ERK1/2) is essential for this response [19].

Perhaps there is much more to be said that would enlighten our understanding of this matter. What we can discern in all of this is that the neutrophil, platelet activation, are essential components of the immune response that are activated in sepsis, moderate and severe sepsis, ARDS, ALI, and MODS with different sensitivities and in relationship to specific interleukins and DAMP signaling. The effect of moderate use of ICU tidal-volume ventilatory support is stressed.

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