The challenge of modeling human acute respiratory distress syndrome: a new model of lung injury due to sepsis with impaired alveolar edema fluid removal

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ACUTE LUNG INJURY (ALI)/acute respiratory distress syndrome (ARDS) is usually a complication of sepsis, pneumonia, aspiration of gastric content, pancreatitis, and severe trauma (19). Overall, sepsis is associated with the highest risk of progression to ALI/ARDS, ~40%. Although mortality of ALI/ARDS has declined over the past 20 years with improved supportive care, the improvement in survival was not observed in patients with sepsis, which remains the most common cause of death (19).

The pathophysiology of ALI affects multiple components of the alveolocapillary membrane. Alterations of the microvascular endothelium and the alveolar epithelium result in 1) alveolar edema due to enhanced endothelial and epithelial permeability to protein and 2) decreased removal of edema fluid from the alveolar spaces by the alveolar epithelium. Impaired alveolar fluid clearance (AFC) in patients with ALI is associated with more prolonged acute respiratory failure and a higher mortality and morbidity (20). In the alveolar environment, AFC is defined as the vectorial transport of edema fluid from the alveoli to the interstitium, and this process results from the electroosmotic gradient created across the alveolar epithelium by active sodium (Na+) transport. AFC is determined predominantly by amiloride-sensitive and -insensitive epithelial Na+ channels (ENaC) located at the apical membrane and the activity of the Na-K-ATPase located at the basolateral membrane (7). In ALI, multiple pathways have been implicated in an attempt to uncover the mechanisms that reduce AFC. In cultured human alveolar epithelial type II cells, human edema fluid obtained from patients with ALI reduced gene and protein expression of the key Na transport proteins (4). More specifically, AFC is reduced by downregulation of Na transport activity by two of the most important proinflammatory cytokines in ALI edema fluid, IL-1β (13) and TNF-α (22), as well as by alveolar hypoxia (10).

Enhanced AFC is critical to recovery from ALI/ARDS. Several stimuli can upregulate AFC, including cAMP-dependent and -independent pathways. In the mouse, rat, and human lung, cAMP-dependent increase in alveolar fluid transport depends on the activity of ENaC and Na-K-ATPase. Catecholamine-independent pathways can also upregulate fluid clearance, including growth factors, glucocorticoids, and thyroid hormone (6).

Sepsis is one of the main risk factors for ALI/ARDS. Animal models and more recently an ex vivo perfused human model of lung injury from sepsis have been developed to study the details of the early phase of ALI/ARDS with a particular focus on the mechanisms of alveolar edema formation and removal. Different strategies have been developed to investigate the mechanisms of alveolar edema in sepsis (8). One model mimicked bacterial sepsis with septic shock in response to systemic administration of bacteria or bacterial products (endotoxin). This model targets primarily the capillary endothelium with various degrees of increased alveolocapillary permeability. The second model mimics pneumonia by delivering live bacteria into the lungs. This model targets primarily the alveolar epithelium and is associated with neutrophilic alveolitis. Although these animal models did not fully reproduce the pathophysiological changes observed in ALI/ARDS in humans, they have been widely used to evaluate the effects of sepsis on the capacity of alveolar epithelium to reabsorb edema fluid. In the rat, systemic administration of gram-negative bacteria (Pseudomonas aeruginosa) induced severe bacteremia with acute shock, increased endothelial and epithelial permeability, and markedly upregulated alveolar fluid reabsorption over 4 h following septic shock. The elevated levels of epinephrine and norepinephrine as well as the inhibition of sepsis-induced increase in AFC by propranolol strongly supported a catecholamine-dependent mechanism (9). In the sheep, intravenous or intratracheal endotoxin also markedly increased lung vascular permeability with a rise in protein-rich lung lymph flow after 24 h, whereas no change lung epithelial permeability or alveolar fluid removal was noted at 4 or 24 h (21). In contrast to these results, Tsubouchi et al. (15) reported a biphasic changes in AFC following intravenous, endotoxin in the rat: AFC decreased at 6 h and increased at 24 h. Interestingly, similar results were reported in a human model of sepsis induced by intratracheal endotoxin by Lee et al. (5). They found that intratracheal instillation of Escherichia coli endotoxin in the isolated perfused human lung rapidly induced mild pulmonary edema with a loss of alveolar fluid transport due to decrease in transepithelial Na transport. Taken together, these studies indicate considerable variability in the change of alveolar fluid reabsorption following endotoxin administration, likely due to a difference in the susceptibility between species (8). AFC has been also evaluated after local administration of live bacteria into the lungs, which results in localized pneumonia without ARDS (8). In sheep, administration of large dose of bacteria P. aeruginosa into the lungs increased both endothelial and epithelial permeability, produced alveolar flooding, and modestly impaired the ability of alveolar epithelium to remove alveolar fluid (21). In rats, instillation of P. aeruginosa increased alveolar barrier permeability and decreased fluid transport in isolated perfused lung preparation (17). Conversely, Rezaiguia et al. (12) reported an upregulation...
of amiloride-sensitive AFC following instillation of P. aeruginosa. The mechanism involved the tumor necrosis factor-α and was catecholamine independent. As previously mentioned for endotoxin/bacteremia models, the results concerning AFC in bacterial pneumonia are not univocal due to biological variability depending on the size of inoculum, the bacterial species, and the systemic manifestations.

In this issue, Berger et al. (1) studied edema formation and removal in a new model of sepsis-induced lung injury. The sepsis was induced in the rat by cecal ligation and puncture (CLP) and lung injury developed within 24 to 72 h. As previously described (18), CLP was associated with a high mortality rate (20%), mild lung injury, and a small increase in lung water with neither alveolar edema nor change in epithelium and endothelium permeability. The total as well as the amiloride-sensitive part of AFC measured in isolated perfused lung was dramatically decreased, indicating that sepsis affects transepithelial Na transport. Interestingly, norepinephrine and epinephrine levels were increased in septic rats and likely prevented a more pronounced decrease in AFC. The cellular mechanisms of sepsis-induced decrease of Na transport were examined in freshly isolated type II cells isolated from septic rats by evaluating the expression of two major Na transport proteins, ENaC and Na-K-ATPase. Although $\alpha_1$ or $\beta_1$-Na-K-ATPase or $\alpha$-ENaC protein levels were unchanged in whole cell extracts, the authors found a decrease of the number of $\alpha_1$ Na-K-ATPase subunits in the basolateral plasma membrane, suggesting that sepsis reduces the trafficking of Na-K-ATPase from the cytoplasm to the membranes. Consistent with this hypothesis, isoproterenol, which promotes insertion of new Na-K-ATPase into the membrane (14), increased AFC in control and septic rats.

This is the first study that evaluates the ability of alveolar epithelium to remove fluid in a new model of sepsis with lung injury following peritonitis. This study is important for two reasons: many cases of human sepsis follow intraperitoneal injury following peritonitis. This study is important for two reasons: many cases of human sepsis follow intraperitoneal injury following peritonitis. It provides important information concerning alveolar fluid removal. Further studies are needed to explore the cellular mechanisms of sepsis-induced changes in Na protein trafficking during ALI/ARDS.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


