Protein permeability in lung injury: now in real time again?

THE FORMATION AND THE RESOLUTION of pulmonary edema is determined by several mechanisms, including lung vascular pressure, lung endothelial and epithelial permeability to protein, and the capacity of the alveolar epithelium to effectively remove alveolar edema fluid. Impaired alveolar fluid clearance (AFC, i.e., the resolution of pulmonary edema) is a common characteristic among patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The level of AFC impairment has significant prognostic value in determining morbidity and mortality (8, 11). Increased alveolar epithelial and endothelial protein permeability, another significant characteristic of ALI and/or ARDS, can influence the resolution of pulmonary edema (7).

Most current techniques to measure the effects of increased protein permeability (i.e., extravascular lung water) in patients with ALI are invasive and static or rely on scintigraphy using $^{67}$Ga-labeled transferrin and $^{99m}$Tc-labeled red blood cells for vascular volume correction to measure vascular protein permeability or protein leak index (4, 6, 10). However, the response of the epithelial or endothelial layers may differ depending on the type and the route of injury (2, 12). In addition, in ALI and/or ARDS, the permeability of the epithelium to protein may be more significant in influencing AFC as reflected by the recent interest with cAMP agonists in ALI patients (9). Regardless, measuring both epithelial and endothelial protein permeability in ALI may shed light into the temporal and spatial contribution of each barrier to impaired AFC, which may make it possible to monitor interventional strategies.

In this issue of the *Journal of Applied Physiology*, de Prost et al. (3) used a simple double-isotope imaging technique to noninvasively measure the simultaneous changes in lung microvascular and alveolar permeability to proteins in ventilated rats induced by different levels of lung distension. The authors injected $^{99m}$Tc-albumin into the distal air spaces and $^{111}$In-transferrin into the circulation and measured the percent change in $^{99m}$Tc-albumin in the lung as well as the $^{111}$In-transferrin lung-to-heart ratio from different levels of end-inspiratory airway pressures ranging from 15 to 30 cmH$_2$O during positive-pressure ventilation. Increasing lung tissue stretch by ventilation at high airway pressure immediately increased both microvascular and alveolar epithelial permeability to protein. The same end-inspiratory pressure threshold (between 20 and 25 cmH$_2$O) was observed for both epithelial and endothelial changes, which corresponded to a tidal volume (Vt) between 13.7 ± 4.7 and 22.2 ± 2.1 ml/kg body weight. Interestingly, whereas protein flux from plasma to the alveolar space remained constant over the duration of the experiment (120 min), the percent change in $^{99m}$Tc-albumin from the air spaces decreased with time, possibly following a two-compartment model with the interstitium as an intermediate space.

The study by de Prost et al. (3) is novel for several reasons. The authors introduced a simple double-isotope imaging technique to noninvasively explore the simultaneous changes in lung microvascular and alveolar permeability to proteins in vivo. They discovered that both lung endothelial and epithelial barriers became permeable at the same threshold value, at plateau pressure or Vt levels that corresponded to the upper inflection point of the respiratory pressure-volume curve. However, to measure both barriers simultaneously, the authors assumed the absence of lung and blood volume changes. Previously, in rats with ventilator-induced lung injury, the authors demonstrated that $^{111}$In-transferrin lung distribution correlated significantly with extravascular lung water and a decrease in lung compliance (1). This assumption may be problematic in models of inflammatory syndromes such as ALI where the thoracic volume is in flux because of changes in permeability, capillary pressure, lymph flow, and interstitial compartmentalization. Nevertheless, the double-isotope imaging technique may be useful in understanding the temporal and spatial changes in alveolar and vascular permeability associated with other forms of lung injury such as sepsis and aspiration. More significantly, such techniques may aid in our understanding of the changes in AFC in relation to alveolar-capillary permeability and how alveolar fluid clearance is influenced by changes in lung protein permeability.

Historically, the major questions that arose with the clinical use of tracer protein equilibration methods have been: Are small changes in protein flux due to an increase in microvascular permeability or just a change in surface area, can this technique be used clinically in patients with ALI to assess the effect of interventions on lung protein permeability, and how relevant is this information relative to extravascular lung water or other historical measures used to assess the severity of ALI (6, 10)? A recent clinical study that tested the correlation between endothelial protein permeability (using a noninvasive double-radionuclide technique) and extravascular lung water blood volume ratios in response to volume loading in patients with ALI suggests that the correlation may be imperfect (5). The additional information provided by $^{99m}$Tc-albumin in the air space to measure epithelial permeability may help but must be confirmed in future clinical studies.

Regardless, the article by de Prost et al. (3) will aid in our understanding of the contribution of both epithelial and endothelial protein permeability to lung injury and may reinvigorate attempts using noninvasive techniques to monitor the course and severity of lung injury. Although much has been learned about the mechanisms that upregulate and downregulate alveolar fluid clearance (7–8), we still need to understand how lung edema formation and resolution is regulated and affected by small, moderate, and large changes in lung endothelial and epithelial permeability to protein and its significance to the course of the clinical syndrome of lung injury.

REFERENCES


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