Pulmonary edema fluid movement within the lung

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DESPITE MUCH RESEARCH and many medical advances, pulmonary edema remains one of the more common causes for admission to the hospital and intensive care units. Although many illnesses lead to pulmonary edema, the underlying pathophysiological mechanisms are one of two processes that may operate individually or in concert. Pulmonary edema occurs when the safety mechanisms of the lung (reviewed in Ref. 14) are overwhelmed by either high transvascular pressure gradients, as in cardiogenic edema, or increases in the microvascular permeability to solutes, as in the premature and adult acute respiratory distress syndromes. The excess fluid first accumulates in the interstitial spaces of the lungs (15), with few or no associated clinical symptoms. The interstitium can only accommodate a few hundred milliliters of excess fluid (14) so the fluid soon floods the airspaces, which in a 70-kg adult approximates 5,000 ml. This airspace flooding is associated with profound respiratory distress because the acini can no longer effectively exchange gases.

It is important to study the mechanisms involved in airspace fluid clearance because little is gained if one removes the cause of the edema and the lungs cannot clear the alveolar fluid. Increased work of breathing, hypoxemia, and pulmonary hypertension would lead to adverse clinical outcomes. This was best illustrated by studies (10, 18) of adult patients with cardiogenic and noncardiogenic edema where survival was associated with evidence of the active absorption of airspace fluid. Airspace fluid clearance is not only important in pulmonary edema but also during birth when the airspaces are filled with fetal lung liquid (reviewed in Ref. 11). All infants are born with “alveolar flooding,” yet the vast majority of newborn infants uneventfully survive their “salt water drowning” and do not develop respiratory distress syndrome.

How is airspace fluid cleared? Historically, it was assumed that Starling forces were responsible for fluid clearance. However, in vivo studies subsequently showed that the lung could clear fluid from its airspaces against unfavorable transcapillary hydrostatic and colloid osmotic pressure gradients (9), raising the possibility of active transport processes. In vitro experiments with primary cultures of adult type II cells (5, 8) and late-gestation fetal distal lungs (13) showed that the epithelium actively transported Na$^+$ via amiloride-sensitive pathways. In vivo pharmacological (12) and genetic (6) experiments documented the critical physiological importance of distal lung epithelial Na$^+$ transport in airspace fluid clearance at the time of birth. Studies in the adult lung (3, 10) have indicated that the fluid clearance rate in humans is ~18%/h, with variable rates in other mammals (dog, 4%/h; sheep, 8%/h; rabbit, 15%/h; mouse, 27%/h).

New observations reported in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology (17) suggest that liquid can very rapidly move out of a fluid-filled acinus. Wang et al. (17), using an optical “real-time” method, provide direct and indirect evidence that liquid very rapidly leaves a fluid-filled acinus when the remainder of the lung is filled with air. The half-life of fluid movement was only 5 s, and changes in lung volume or intracellular Ca$^{2+}$ concentration modulated the rate of fluid movement. The authors acknowledge that they are not studying active transport by the distal lung epithelium. As outlined above, the time frame of fluid movement is inconsistent with active

1 This speculation was also supported on a theoretical basis. Because the reflection coefficient of the alveolar epithelium for Na$^+$ is 1 (1), a phenomenon arising from the 4-Å effective molecular radius of the intercellular junction, electrolytes become osmotically relevant in transepithelial fluid and solute movement. Because each 1 mosmol/l generates 19 mmHg pressure, the approximate 1.5 mosmol/l protein-induced osmotic pressure becomes trivial relative to the 280 mosmol/l electrolyte-induced osmotic pressure. Electrolytes, and not colloids, are therefore the quantitatively most important osmotic particle when airspaces with normal epithelium are filled with fluid.
transport processes, and their experiments showed that inhibitors of epithelial active ion transport did not alter the rate of fluid movement. It should also be noted that the authors were measuring the removal of fluid from the injected acinus and were not measuring the movement of fluid out of the lung. As such, despite the novelty of their observations, the clinical relevance of their findings needs further study because if there is only a shift of fluid from one acinus to another acinus, there would not be any benefit to the patient.

Mechanical forces, including those involved in lung interdependence (reviewed in Ref. 7), and surface tension forces at the air-liquid interface may be responsible for movement of the injected fluid. One could argue that the movement of fluid from the injected acinus to an adjacent acinus is the fluid equivalent of “pendulluft,” a phenomenon where air moves from one acinus to another adjacent acinus (7). Although neither surfactant nor surface tension forces were assessed during the present study (17), the authors appropriately asked whether or not surface tension forces at the air-liquid interfaces are involved in the phenomenon they observed. Indeed, the work of Espinosa et al. (2) may be relevant; they indicate that bulk fluid movement can occur in response to gradients in surface tension, a phenomenon termed the “Marangoni effect.” Their work suggests the interesting possibility that the high surface tension at the airway surface (4) draws the fluid out of the airspaces and up into the airways (2) where it could then either enter an adjacent acinus or be absorbed by respiratory bronchiolar and bronchial epithelia. Indeed, the smallest airways are lined by Clara cells, which are known to transport Na+ at ~10 times the rate of alveolar type II epithelium (16).

The present observations (17) are relevant to previous work investigating the sequence of events during the formation of interstitial and alveolar edema. In a classic paper, Staub et al. (15) determined the sequence of events leading from interstitial to air-space edema. As edema formation occurs, the gas volume of the alveolus decreases in a nonlinear relationship with the distending pressure and the absolute size of the alveolus decreases as it becomes fluid filled (Fig. 1). A decrement in acinar size with fluid filling is consistent with the data provided by Wang et al. (Fig. 2 in Ref. 17). As such, the argument provided by Wang et al. (APPENDIX A in Ref. 17) may need revision as they speculate that the fluid-filled alveolus A has a greater diameter than the partially filled alveolus B.

The state-of-the-art optical imaging developed by Wang et al. (17) represents a major advance. Their ability to provide “real-time” measurements of fluid movement within the distal regions of the lung is an important new approach that will supplement the existing gravimetric and histopathological techniques in studying the resolution of pulmonary edema.

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REFERENCES


