Alveolar Epithelium
Role in Lung Fluid Balance and Acute Lung Injury

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The resolution of alveolar edema is regulated by active sodium and chloride transport across the pulmonary epithelium, including alveolar epithelial type I and II cells as well as distal airway epithelia. Catecholamine-dependent mechanisms can markedly upregulate alveolar fluid clearance even under pathological conditions, an effect that is mediated by both epithelial sodium channel (ENaC) and cystic fibrosis transmembrane conductance regulator (CFTR). Under pathological conditions, impaired alveolar fluid clearance is associated with worse survival in patients with acute lung injury. However, there is some experimental and clinical evidence that cAMP stimulation could accelerate the resolution of pulmonary edema in the presence of acute lung injury. Clinical trials are needed to test this potential therapeutic strategy in patients with acute lung injury.

Keywords: pulmonary edema; acute respiratory distress syndrome; alveolar fluid clearance; cystic fibrosis

The mechanisms that regulate active salt and water transport by the alveolar and distal airway epithelium of the lung have emerged as an area of research with important implications for understanding lung fluid balance under both normal and pathologic conditions. Studies of epithelial fluid transport by the distal pulmonary epithelium have provided important new concepts regarding the resolution of pulmonary edema, a common clinical problem that has direct relevance to the pathophysiology of acute lung injury. This article provides a summary of the major issues discussed by Dr. Matthay at the University of Pittsburgh Acute Lung Injury Conference in October 2004. It is not meant to be a comprehensive review article of the field of alveolar epithelial fluid clearance. There are several reviews of this field (1–4). The first section of this article reviews some of the mechanisms that regulate reabsorption of alveolar edema fluid in the lung with an emphasis on studies of cystic fibrosis transmembrane conductance regulator (CFTR) and fluid transport, an area of new interest in this field. The second section considers examples of alveolar fluid transport in the presence of acute lung injury, based on both experimental and clinical studies. The final section of the article briefly discusses the role of β_2 adrenergic agonists as a possible treatment for patients with acute lung injury. Some of the information in this article has been reviewed in another publication (1).

RESOLUTION OF ALVEOLAR EDEMA: BASIC MECHANISMS

Prior to 1982, there was no information on how lung fluid balance was regulated across the distal airway and alveolar epithelial barriers of the mature lung. Some work had been done on secretion and absorption of alveolar fluid in the fetal and newborn lung (5). In 1982, new research provided evidence that fluid balance in the lung was regulated by active ion transport mechanisms (6, 7). For many years, it had been generally believed that differences in hydrostatic and protein osmotic pressures (Starling forces) accounted for the removal of excess fluid from the airspaces of the lung. This misconception persisted in part because some experiments that measured solute flux across the epithelial and endothelial barriers of the lung were done at room temperature and the studies were done in dogs, a species that turned out to have a very low rate of active sodium and fluid transport (1). Also, until the early 1980s, there were no satisfactory animal models to study the resolution of alveolar edema, and the isolation and culture of alveolar epithelial type II cells was just becoming a useful experimental method. Although the removal of interstitial pulmonary edema by lung lymphatics and the lung microcirculation was discussed by Staub (8) in 1974 in his review of pulmonary edema, there was no information on how pulmonary edema was removed from the distal airspaces of the lung. On the basis of both *in vivo* and *in vitro* studies, there is convincing evidence that the vectorial transport of salt and water across the alveolar and distal airway epithelium is the primary determinant of fluid clearance, thus accounting for the ability of the lung to remove alveolar fluid at the time of birth as well as in the mature lung when pathologic conditions lead to the development of pulmonary edema.

Active Ion Transport Drives Alveolar Fluid Clearance

With few exceptions, the general model for transepithelial fluid movement is that active salt transport drives osmotic water transport. This paradigm is probably correct for removal of alveolar edema fluid across the distal lung epithelium (1). The results of several *in vivo* studies have demonstrated that changes in hydrostatic or protein osmotic pressures cannot account for the removal of excess fluid from the distal airspaces. Furthermore, pharmacologic inhibitors of sodium transport can reduce the rate of fluid clearance in the lungs of several different species, including the human lung. In addition, there is convincing evidence that isolated epithelial cells from the distal airspaces of the lung actively transport sodium and other ions.

Pulmonary Surface Area for Alveolar Fluid Reabsorption

Although the large surface area of the alveoli seems to favor the hypothesis that most fluid reabsorption occurs at the alveolar level, active fluid reabsorption could occur across all of the different segments of the pulmonary epithelium of the distal airspaces of the lung. The precise contribution of each of the anatomic segments of the distal airspaces to fluid reabsorption is not firmly established. The distal airway epithelium is composed of terminal respiratory and bronchiolar units with polarized epithelial cells that have the capacity to transport sodium and chloride, including ciliated Clara cells and nonciliated cuboidal cells. The alveoli themselves are composed of a thin alveolar epithelium (0.1–0.2 μm) that covers 99% of the airspace surface area in the lung and contains thin, squamous, type I cells and cuboidal type II cells. The alveolar type I cell covers 95% of the alveolar surface.

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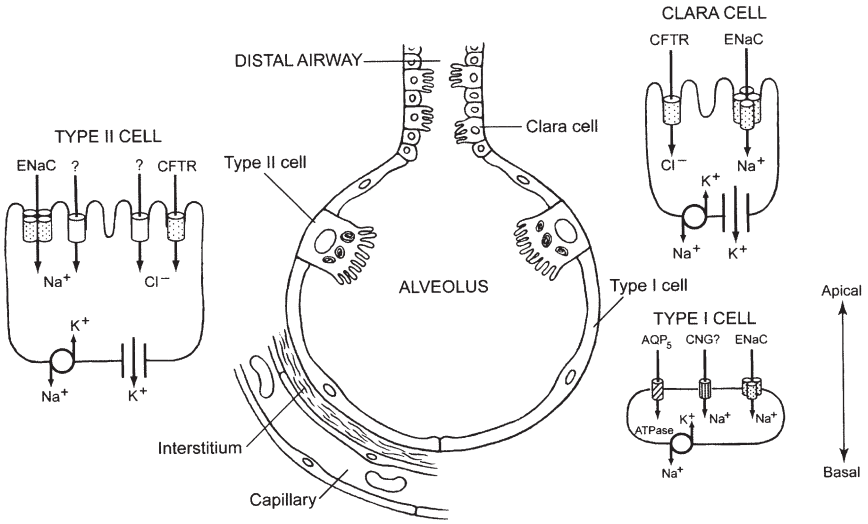

Figure 1. A schematic diagram of the distal pulmonary epithelium that is relevant for salt and water transport. AQP_5 = aquaporin 5; CNG = cyclic nucleotide-gated channel; ENaC = epithelial sodium channel. Reprinted by permission from Reference 1.

The close apposition between the alveolar epithelium and the vascular endothelium facilitates efficient exchange of gases, but also forms a tight barrier to movement of liquid and proteins from the interstitial and vascular spaces, thus assisting in maintaining relatively dry alveoli (1). All of the cells in the alveoli and the distal airway epithelia contain ion transporters and may contribute to vectorial salt and water clearance from the distal airspaces of the lung (Figure 1).

Alveolar Epithelial Type II Cells

The most extensively studied cell in the distal pulmonary epithelium is the alveolar type II cell, partly because type II cells can be readily isolated from the lung and studied *in vitro.* The alveolar type II cell is responsible for the secretion of surfactant (9) as well as vectorial transport of sodium from the apical to the basolateral surface (10–15). The active transport of sodium by type II cells provides a major driving force for removal of fluid from the alveolar space. Sodium uptake occurs on the apical surface, partly through amiloride-sensitive and -insensitive channels. Subsequently, sodium is pumped actively from the basolateral surface into the lung interstitium by Na,K-ATPase. An epithelial sodium channel (ENaC), which participates in sodium movement across the cell apical membrane, was cloned and characterized in 1994 (16), and work by other investigators has provided new insight into the molecular and biochemical basis for sodium uptake in alveolar epithelial cells (17, 18).

Alveolar Epithelial Type I Cells

Some investigators have assessed the potential contribution of the alveolar type I cell to vectorial fluid transport. On the basis of studies in freshly isolated type I cells, it is known that these cells have a high osmotic permeability to water with expression of aquaporin 5 on the apical surface (19). Recent studies have reported the presence of the α_1 and α_2 subunits of Na,K-ATPase in both type I–like cells *in vitro* (20). The presence of the Na,K-ATPase could be consistent with a role for this cell in vectorial fluid transport, although it is not conclusive because the Na,K-ATPase may be needed to maintain cell volume. Also, recent studies of freshly isolated alveolar type I cells from rats demonstrated that these cells express the Na,K-ATPase α_1 and β_1 subunit isoforms (21). In the same study, there was evidence for α_1 Na,K-ATPase expression on the basolateral surface of the alveolar epithelial type I cells *in situ* in the rat lung. In addition, there is evidence for expression of all the subunits of ENaC in freshly isolated alveolar type I cells from two laboratories (21, 22) as well as *in situ* in the rat lung (22). Finally, there is some evidence that ^{22}Na uptake can be partially inhibited by amiloride in the freshly isolated rat alveolar type I cells (22), although definitive studies of cultured, polarized, type I cells have not yet been achieved. Additional data demonstrate that the α_2 subunit is located on alveolar type I cells and plays an important role in alveolar fluid reabsorption (23). There is also evidence that β-receptors are expressed on type I cells and there is also evidence they are present on type II cells (24). There is also new preliminary evidence that highly selective cation channels are present by patch clamp on alveolar type I cells (25). Although the inability to study alveolar type I cells in culture has slowed progress in assessing their capacity for ion transport and the role they may play in vectorial fluid transport across the alveolar epithelium, the new data provide suggestive evidence that alveolar type I cells may participate in vectorial salt transport in the lung.

In Vivo Evidence for Active Ion Transport

The first *in vivo* evidence that active ion transport could account for the removal of alveolar edema fluid across the distal pulmonary epithelium of the mature lung was obtained in studies of anesthetized, ventilated sheep (6). In those studies, the critical discovery was that isosmolar fluid clearance of salt and water occurred in the face of a rising concentration of protein in the airspaces of the lung, whether the instilled solution was autologous serum or an isosmolar protein solution. The initial protein concentration of the instilled protein solution was the same as the circulating plasma. After 4 h, the concentration of the protein had risen from approximately 6.5 g/100 ml to 8.4 g/100 ml, whereas the plasma protein concentration was unchanged. In longer term studies in unanesthetized, spontaneously breathing sheep, alveolar protein concentrations increased to very high levels. After 12 and 24 h, the alveolar protein concentration increased to 10.2 and 12.9 g/100 ml, respectively (26). The overall rise in protein concentration was equivalent to an increase in distal airspace protein osmotic pressure from 25 to 65 cm H_2O (Figure 2). The concentration of protein in the lung lymph draining the lung interstitium declined, providing further evidence that protein-free fluid was being reabsorbed from the distal airspaces into the lung interstitium (6). Also, morphologic studies showed that the interstitial fluid did not contain the Evans blue dye–labeled alveolar protein (27). These data provided convinc-

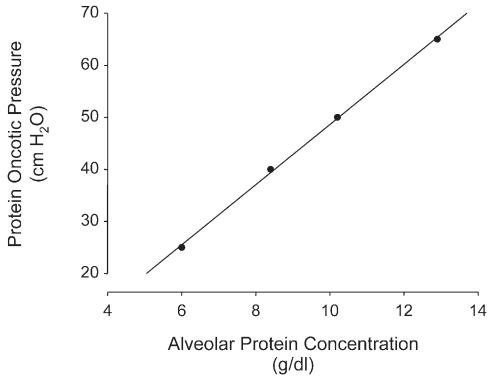

Figure 2. In spontaneously breathing, unanesthetized sheep, alveolar fluid protein concentration increased from 6.0 g/dl to a maximum of 13.8 g/dl (*x axis*) after 24 h. This increase in protein concentration was paralleled by a marked increase in protein oncotic pressure (*y axis*). Reprinted by permission from Reference 1.

ing evidence that active ion transport must be responsible for the fluid clearance, especially in the face of a rising alveolar protein osmotic pressure that was approximately 40 cm H_2O greater than the protein osmotic pressure in the vascular or interstitial spaces of the lung (6, 26).

Other studies in the intact lung have supported the hypothesis that removal of alveolar fluid requires active transport processes. For example, elimination of ventilation to one lung did not change the rate of fluid clearance in sheep, thus ruling out changes in transpulmonary airway pressure as a major determinant of fluid clearance, at least in the uninjured lung (28). Furthermore, if active ion transport were responsible for fluid clearance, then fluid clearance should be temperature dependent. In an *in situ* perfused goat lung preparation, the rate of fluid clearance progressively declined as temperature was lowered from 37 to 18°C (29). Similar results were obtained in perfused rat lungs (30) and *ex vivo* human lung studies (31) in which hypothermia inhibited sodium and fluid transport.

Additional evidence for active ion transport was obtained in intact animals with the use of amiloride, an inhibitor of sodium uptake by the apical membrane of alveolar epithelium and distal airway epithelium. Amiloride inhibited 40 to 70% of basal fluid clearance in sheep, rabbits, rats, guinea pigs, mice, and in the human lung (1). Amiloride also inhibited sodium uptake in distal airway epithelium from sheep and pigs (32, 33). To further explore the role of active sodium transport, experiments were designed to inhibit Na,K-ATPase. It has been difficult to study the effect of ouabain in intact animals because of cardiac toxicity. However, in the isolated rat lung, ouabain inhibited more than 90% of fluid clearance (34, 35). Subsequently, after the development of an *in situ* sheep preparation for measuring fluid clearance in the absence of blood flow, it was reported that ouabain inhibited 90% of fluid clearance over a 4-h period (28).

Catecholamine-dependent Regulation of Alveolar Fluid Clearance

Studies in newborn animals indicate that endogenous release of catecholamines, particularly epinephrine, stimulates reabsorption of fetal lung fluid from the airspaces of the lung (5, 36–38). In most adult mammal species, including the human lung, stimulation of β_2-adrenergic receptors either by salmeterol, terbutaline, or epinephrine increases fluid clearance (39–45). This stimulatory effect occurs rapidly after intravenous administration of epinephrine or instillation of terbutaline in alveolar space and is prevented by either a nonspecific β_2-receptor antagonist, propranolol, or in rats by a β_2-antagonist. The increased fluid clearance by β_2-agonists can be prevented by amiloride, indicating that the stimulation was related to an increased transepithelial sodium transport (39, 44). On the basis of studies of the resolution of alveolar edema in humans, it has been difficult to quantify the effect of catecholamines on the rate of fluid clearance (46). However, studies of fluid clearance in the isolated human lung have demonstrated that β-adrenergic agonist therapy increases fluid clearance, and the increased fluid clearance can be inhibited with propranolol or amiloride (31, 45). These data are particularly important because aerosolized β-agonist treatment in some patients with pulmonary edema might accelerate the resolution of alveolar edema.

Potential Role of CFTR in cAMP-mediated Upregulated Fluid Transport

Although most experimental studies have attributed a primary role for active sodium transport in the vectorial transport of salt and water from the apical to the basal surface of the alveolar epithelium of the lung, the potential role of chloride, especially in mediating the cAMP-mediated upregulation of fluid clearance across distal lung epithelium, has been the subject of recent studies. One older study of cultured alveolar epithelial cells concluded that vectorial transport of chloride across alveolar epithelium occurs by a paracellular route under basal conditions and perhaps by a transcellular route in the presence of cAMP stimulation (47). Another study of cultured alveolar epithelial type II cells suggested that cAMP-mediated apical uptake of sodium might depend on an initial uptake of chloride (48). A subsequent study of cultured alveolar type II cells under apical air–liquid interface conditions reported that β-adrenergic agonists produced acute activation of apical chloride channels with enhanced sodium absorption (49).

To define the role of chloride transport in the active transport of salt and water across the distal pulmonary epithelium of the lung, our research group used *in vivo* lung studies to define the mechanisms and pathways that regulate chloride transport during the absorption of fluid from the distal airspaces of the lung. This approach may be important because studies in several species have indicated that distal airway epithelia are capable of ion transport (32, 33) and both ENaC and CFTR are expressed in alveolar and distal airway epithelia (50–54).

The potential role of CFTR under basal and cAMP-stimulated conditions was tested using intact lung studies in which CFTR was not functional because of failure in trafficking of CFTR to the cell membrane, the most common human mutation in cystic fibrosis (ΔF508 mice). The results supported the hypothesis that CFTR was essential for cAMP-mediated upregulation of isosmolar fluid clearance from the distal airspaces of the lung because fluid clearance could not be increased in the ΔF508 mice with either β-agonists or with forskolin, unlike the wild-type control mice (55). Additional studies using pharmacologic inhibition of CFTR in both the mouse and human lung with glibenclamide supported the same conclusion, namely that chloride uptake and CFTR-like transport seemed to be required for cAMP-stimulated fluid clearance from the distal airspaces of the lung (55). Glibenclamide can also inhibit potassium channels, so the inhibitory effects are not specific for CFTR, but the ΔF508 mouse studies have provided more direct evidence. Although the absence of CFTR in the upper airways results in enhanced sodium absorption (56), the data in these studies provided evidence that the absence of CFTR prevents cAMP-upregulated fluid clearance from the distal airspaces of the lung, a finding that is similar to work on the importance of CFTR in mediating cAMP-stimulated sodium absorption in human sweat ducts (57).

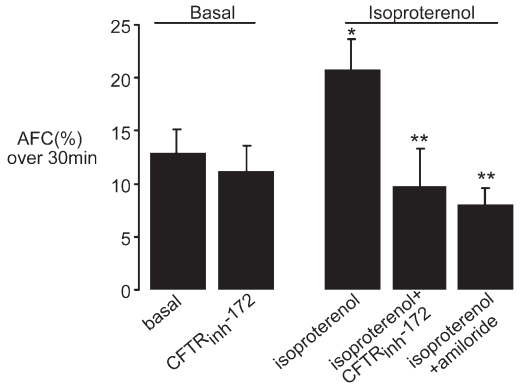

Figure 3. Effect of $CFTR_{inh}$-172 on basal and isoproterenol (cAMP-stimulated) alveolar fluid clearance (AFC) in *in situ* mouse lungs. Where indicated, the tracheal instillation contains $CFTR_{inh}$-172 (10^{-4} M, n = 6), isoproterenol (10^{-4} M, n = 6), isoproterenol + $CFTR_{inh}$-172 (n = 8), and isoproterenol + amiloride (amiloride 10^{-4} M, n = 4). *$p < 0.05$ compared with control; **$p < 0.05$ compared with isoproterenol. Data are mean ± SD.

Because CFTR is distributed throughout the distal pulmonary epithelium in distal airway epithelium as well at the alveolar level in the human lung (53), the data also suggest that the cAMP-mediated upregulated reabsorption of pulmonary edema fluid may occur across distal airway epithelium as well as at the level of the alveolar epithelium. Additional studies indicated that the lack of CFTR results in a greater accumulation of pulmonary edema in the presence of a hydrostatic stress, thus demonstrating the potential physiologic importance of CFTR in upregulating fluid transport from the distal airspaces of the lung (55). Another group of investigators has also demonstrated that rat alveolar type II cells express CFTR protein and also indicates they possess CFTR-like channels on the basis of patch-clamp studies (54). Recent work from our own laboratory indicates that human alveolar type II cells express CFTR at the gene level and also have CFTR inhibitable current by short-circuit studies as well as *in vitro* studies of vectorial fluid transport in human and rat alveolar epithelial type II cells (58).

Also, we have recently administered a CFTR inhibitor (59) to mice and found that their CFTR inhibitor completely blocked cAMP-stimulated fluid clearance and had no effect on basal fluid clearance (Figure 3). These data provide additional *in vivo* evidence that CFTR plays an important role in cAMP-simulated fluid clearance across the intact lung.

The localization of sodium and chloride transporters that probably participate in vectorial ion and fluid transport in alveolar epithelial type I and II cells as well as distal airway epithelia is summarized in Figure 1.

Catecholamine-independent Regulation of Alveolar Fluid Clearance

In the last few years, several interesting catecholamine-independent mechanisms have been identified that can upregulate fluid transport across the distal airspaces of the lung as well as in cultured alveolar type II cells. Hormonal factors, such as glucocorticoids, can upregulate transport by transcriptional mechanisms, whereas thyroid hormone may work by a post-translational mechanism (1, 60). Some growth factors can work by either a transcriptional or direct membrane effect, or by enhancing the number of alveolar type II cells. There is also evidence that proinflammatory molecules, such as tumor necrosis factor α and leukotriene D4, can upregulate sodium uptake and fluid transport (61, 62). Finally, serine proteases can regulate the activity of ENaC and potentially increase fluid clearance across the distal airway epithelium (63).

EPITHELIAL FLUID TRANSPORT UNDER PATHOLOGIC CONDITIONS

Fluid clearance from the distal airspaces of the lung has been measured in mechanically ventilated patients with acute respiratory failure from pulmonary edema as well as in several animal models designed to simulate clinically relevant pathologic conditions. Figure 4 shows a histologic section from a patient who died of pulmonary edema and illustrates how sodium transporters may function to drive the resolution of alveolar edema.

Clinical Studies

Studies of fluid clearance have been done in intubated, ventilated patients by measuring the concentration of total protein in sequential samples of undiluted pulmonary edema fluid aspirated from the distal airspaces of the lung with a standard suction catheter passed through the endotracheal tube into a wedged position in the distal airways of the lung. This method for measuring fluid clearance in patients was adapted from the method for aspirating fluid from the distal airspaces of the lung in experimental studies in small and large animals (15, 39). The clinical procedure has been validated in patients by demonstrating that there is a relationship between fluid clearance and the improvement in oxygenation and the chest radiograph (46, 64).

Resolution of Increased Permeability Edema from Clinical Acute Lung Injury

The majority of patients with increased permeability edema and acute lung injury have impaired alveolar epithelial fluid transport, a finding that is associated with more prolonged acute respiratory failure and a higher mortality (Figure 5). In contrast, a minority of patients can remove alveolar edema fluid rapidly and these patients have a higher survival rate (46, 65, 66). These results indicate that a functional, intact distal lung epithelium is associated with a better prognosis in patients with acute lung injury, thus supporting the hypothesis that the degree of injury to the distal lung epithelium is one important determinant of outcome in patients with increased permeability pulmonary edema from acute lung injury.

Mechanisms That Impair Fluid Clearance in Acute Lung Injury

What are the mechanisms that can impair fluid clearance from the airspaces of the lung? Some patients have pathologic (67, 68) and biochemical (69) evidence of injury to the alveolar epithelium. There are also some clinical data that a decrease in fluid clearance may be associated with higher levels of nitrate and nitrite in pulmonary edema fluid, a finding that supports the hypothesis that nitration and oxidation of proteins essential to the epithelial fluid transport may occur in some patients with lung injury, depressing their ability to remove alveolar edema fluid (70). Several experimental studies support this mechanism as well (1, 2). Also, in animal studies, neutrophil depletion prevented the shock-induced decrease in alveolar fluid clearance (1).

The effect of endotoxemia and bacteremia on lung vascular permeability was well described in studies in sheep several years ago (71, 72). However, the impact on the function of the alveolar epithelial barrier was not addressed in those studies. Subsequent work indicated that the acute shock produced by severe bacteremia in rats markedly increases plasma epinephrine levels, as in hemorrhagic shock, and the elevated epinephrine levels can markedly upregulate the fluid transport capacity of the distal lung epithelium (44). Thus, it is possible that in the short term,

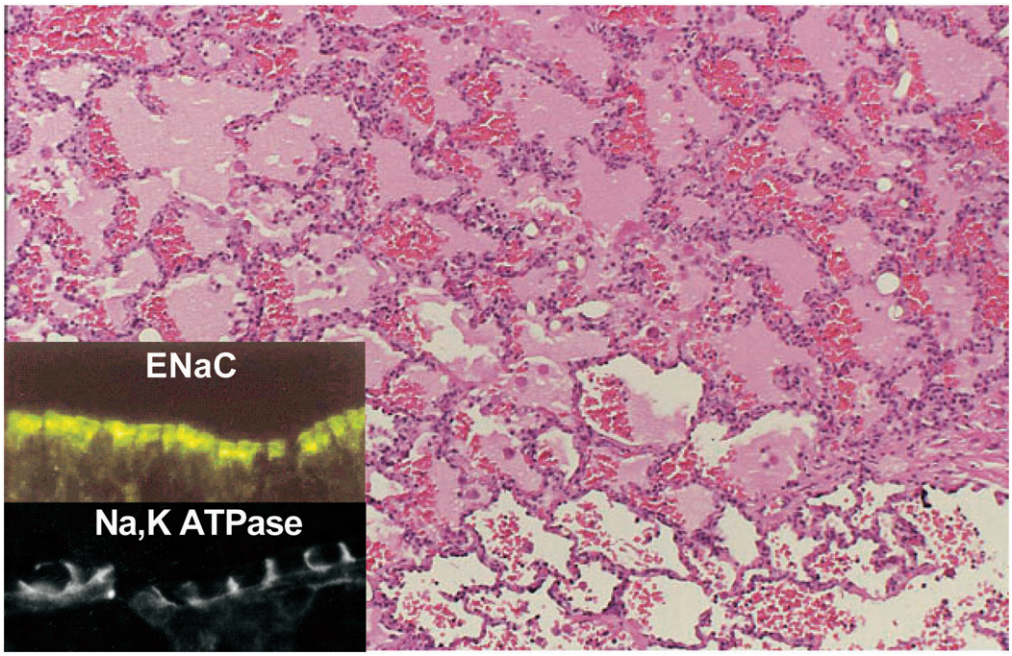

Figure 4. The histologic section stained with hematoxylin and eosin is taken from a patient who died from pulmonary edema. The edema fluid is stained *pink* in the alveoli with a few red blood cells. Note that the *insert* below identifies the two most important sodium transporters, ENaC, which labels the apical surface, and sodium pump (Na,K-ATPase), which labels the basolateral surface. Reprinted by permission from Reference 1.

upregulation of fluid clearance may protect the airspaces against alveolar flooding when there is an increase in lung vascular permeability and accumulation of interstitial edema. In fact, one study in sheep demonstrated that lung vascular permeability can be augmented markedly with intravenous endotoxin with a rise in protein-rich lung lymph flow, but this effect was not associated with a change in lung epithelial permeability to protein and there was no change in the capacity of the alveolar epithelium to remove alveolar fluid (73). These studies were done over 4 and 24 h in sheep, and in some of the studies, both intraalveolar and intravenous endotoxin were administered, but in all cases the epithelial barrier remained intact and capable of transporting alveolar fluid normally.

However, when large doses of live bacteria (*Pseudomonas aeruginosa*) were given to sheep, there was an increase in both lung endothelial and epithelial permeability to protein in the sheep that had developed the most severe shock (73). These sheep had alveolar flooding, and their capacity to remove alveolar fluid was impaired, similar to the findings in humans who develop severe permeability pulmonary edema with septic shock. The mechanisms for injury to the epithelial barrier probably depend on both neutrophil-dependent release of injurious proteases and reactive oxygen species and the bacterial exoproducts.

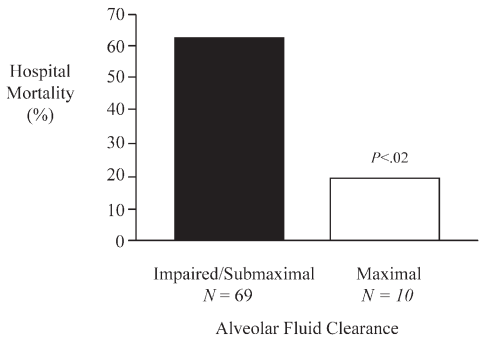

Figure 5. Hospital mortality (*y axis*) plotted against two groups of patients with acute lung injury or the acute respiratory distress syndrome: those with maximal fluid clearance (> 14%/h) and those with impaired or submaximal fluid clearance (< 14%/h). The columns represent percentage of hospital mortality in each group. Hospital mortality of patients with maximal fluid clearance was significantly less ($p < 0.02$). Reprinted by permission from Reference 61.

In sharp contrast to intraalveolar endotoxin, live bacteria in the distal airspaces of the lung increased alveolar epithelial barrier permeability and decreased fluid transport in sheep (73). Further studies indicated that the products of *P. aeruginosa* were important in determining the extent of injury. For example, exoenzyme S and phospholipase C mediated injury to the epithelial barrier in rabbits with a decrease in vectorial fluid transport (74). Subsequent studies indicated that bacterial pneumonia may progress to septic shock when the infecting gram-negative organism generates proinflammatory cytokines in the airspaces of the lung that are released into the circulation when bacterially mediated injury results in sufficient injury to the distal lung epithelial barrier (75). Several experimental studies have indicated that active and passive immunization against *P. aeruginosa* antigens can prevent epithelial injury in sheep (76) and in mice (77). A recent study of influenza infection demonstrated that acute infection can decrease the transport capacity of alveolar epithelial cells and reduce overall lung liquid clearance (78).

There is also evidence that unfavorable ventilatory strategies with a high tidal volume can impair alveolar epithelial fluid clearance (79). Lower tidal volume and reduced airway pressure preserve nearly normal alveolar fluid transport in the presence of acid-induced lung injury in rats, suggesting that protection of the alveolar epithelium may be one important mechanism to explain the mortality benefit of lung-protective ventilatory strategies.

It is important to appreciate that, in studying the function of the alveolar epithelial barrier, two separate mechanisms may impair net alveolar fluid clearance. First, there may be an increase in the permeability of the alveolar epithelial barrier that presents vectorial fluid transport because of the loss of the normally tight barrier properties of the alveolar epithelium (1). Second, there may be a decrease in net alveolar fluid transport

because of specific defects in the ion transport capacity of alveolar epithelial cells (1–4).

β-ADRENERGIC AGONIST THERAPY FOR THE TREATMENT OF ACUTE LUNG INJURY

Studies in rats demonstrated that a β_2-adrenergic agonist can enhance the resolution of lung edema and improve oxygenation in the resolution phase of hydrostatic pulmonary edema (80). Also, in isolated perfused rat lungs (81), there was a significant increase in fluid clearance with administration of isoproterenol or dopamine. In a recent study of the potential therapeutic value of β_2-adrenergic agonist therapy for the treatment of acid-induced lung injury in rats, we found that salmeterol, a β_2-adrenergic agonist given via the airspaces, reduced lung edema by both attenuating lung vascular injury and upregulating the clearance of alveolar edema fluid (82). One potential concern is that the use of β-adrenergic agonists might be associated with downregulation of the response. One rat study suggested that this might occur, whereas another mouse study did not (83, 84). From a practical perspective, it seems that the potential benefit of β_2-adrenergic therapy would be achieved with 3 to 4 d, a time period during which a significant downregulation to the aerosolized agonist seems unlikely.

From a clinical perspective, aerosolized β_2-agonist therapy has been shown to reduce the incidence of high-altitude pulmonary edema in subjects at risk for developing this condition (85). A small clinical trial in the United Kingdom has found that intravenous salbutamol, a β_2-agonist, reduces extravascular lung water in patients with acute lung injury (86). It may be reasonable to test the therapeutic value of aerosolized β_2-adrenergic agonist therapy for patients with acute lung injury, particularly because one study demonstrated that therapeutic levels of a commonly used β_2-agonist can be achieved in the pulmonary edema fluid in ventilated patients with standard aerosolization procedures (87).

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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