Resolution of Pulmonary Edema

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Patients with pulmonary edema from acute lung injury or ARDS who have impaired epithelial fluid clearance show poorer outcomes than patients with intact fluid clearance. From in vivo studies in sheep done 20 years ago, it was suggested that clearance of alveolar edema fluid requires active ion transport. Subsequent studies confirmed that active sodium transporters expressed in the alveolar epithelium are primarily responsible for fluid removal from the lung during disease or injury. Upregulating alveolar Na+ transporters and Na+,K+-ATPases increases fluid resorption and may be achieved with β-adrenergics or by catecholamine-independent methods, offering potentially clinically relevant therapeutic possibilities.

In the normal lung, the relative amounts of fluid in the interstitium and alveolar airspaces remain nearly constant, although there is considerable movement of water between these tissue compartments. An ultrafiltrate of plasma moves from microvessels into interstitial tissue and then into lymphatic channels. The volume of water and protein movement depends on the balance of pressures across the pulmonary microvasculature and on the permeability of the capillary endothelium.

A moderate increase in pulmonary venous pressure caused by left ventricular decompensation increases lung lymphatic flow so that pulmonary extravascular fluid volume remains nearly constant. If the pressure is high enough and the elevation is maintained, fluid accumulation in the lung occurs despite the increased lymphatic flow.

Pulmonary edema develops when these homeostatic mechanisms are overwhelmed by either high transvascular pressure gradients, as in cardiogenic edema, or by increases in the microvascular permeability to protein and solutes, as in acute lung injury or the acute respiratory distress syndrome.

The excess fluid first accumulates in the interstitial spaces of the lung, usually producing few or no clinical symptoms. The capacity of the lung interstitium for excess fluid is only a few hundred milliliters, and so interstitial edema fluid floods the airspaces once the capacity of the lung interstitium is exceeded. The result is severe respiratory distress, because the alveoli can no longer effectively exchange gases.

When the disease process is treated and the cause of edema is rectified, little is gained if the lungs cannot clear the alveolar fluid. Fluid removal may be impaired during lung injury, causing increased work of breathing, hypoxemia, pulmonary hypertension, and respiratory failure. This effect was demonstrated in adults with noncardiogenic edema, in whom survival was associated with evidence of rapid, active absorption of alveolar fluid. Clearance of airspace fluid also is important after birth, when the fetal lungs are filled with liquid that must be removed.

Historically, it was believed that alveolar fluid clearance was due to Starling forces. Differences in hydrostatic and osmotic pressures were thought to produce a net eflux of fluid from the alveoli to the interstitium, where it was cleared by the lymphatics. However, in studies done 20 years ago, the basic mechanisms responsible for edema fluid removal from the adult lung were redefined.

Clearance of alveolar fluid was shown to depend on active sodium transport across the alveolar epithelium, via Na+ channels and Na+,K+-ATPases. Subsequent studies found that active vectorial transport of Na+ produces a transepithelial osmotic gradient that causes water to move passively from...
the airspaces to the interstitium and pulmonary circulation.

This flux accounts for the ability of the lung to remove alveolar fluid at the time of birth as well as in the mature lung afflicted with disease. Recently, evidence also indicates a role for chloride transport, especially in the presence of cAMP stimulation.

This article reviews the advances in understanding the regulation of lung fluid balance, which has important implications for the resolution of clinical pulmonary edema.

**Polarized Cells Provide Directional Ion Transport**

For years, it was believed that the same forces that caused fluid filtration into the lung worked in reverse to remove fluid. Because the pulmonary capillaries and lymphatics normally maintain a negative hydrostatic pressure in the interstitial spaces, it was assumed that fluid would flow passively from the alveoli and interstitium into the capillaries and lymphatics. Yet, in vivo studies showed that the lung could still clear fluid from airspaces despite unfavorable transepithelial hydrostatic and colloid osmotic pressure gradients.

Since the initial studies in 1982, the general model for transepithelial fluid movement has posited that active vectorial salt transport drives osmotic water transport. In this model, clearance of fluid from the normally dry airspaces depends

**In acute lung injury or ARDS**, increased microvascular permeability allows influx of protein-rich edema fluid and inflammatory cells into the interstitium and alveolar airspaces. Macrophages and neutrophils secrete proinflammatory cytokines, such as IL-1 and TNF-α, which stimulate production of extracellular matrix by fibroblasts in the interstitium and recruit other inflammatory cells.

The influx of protein-rich edema fluid results in inactivation of surfactant and is associated with sloughing of both bronchial and alveolar epithelial cells, although type II cells may be relatively spared.
Alveolar epithelium consists of type I and type II cells. The cuboidal type II cells are responsible for secretion of surfactant as well as the active, vectorial transport of sodium. Na uptake occurs on the apical surface, partly through amiloride-sensitive and insensitive epithelial Na channels (ENaC). Na is pumped out basolaterally via Na$^+$.K$^+$.ATPase into the lung interstitium. The cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride transporter that may help drive Na and fluid transport.

Thin, squamous type I cells cover 95% of the alveolar surface, but their role in vectorial fluid transport is unclear. They have a high osmotic permeability to water due to the expression of aquaporin-5 (AQP-5) channels on apical surfaces. ENaC also is present on apical surfaces, and Na$^+$.K$^+$.ATPase is present on basal surfaces. (CNG, cyclic nucleotide-gated cation channel.)

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**on the net transport of sodium and water in only one direction.**

In the human lung, the distal airway epithelium is composed of terminal respiratory and bronchiolar units with polarized epithelial cells, including ciliated Clara cells and nonciliated cuboidal cells. The distal airways are capable of directional ion transport, and their cells possess the necessary components of the transport system: sodium and chloride transporters and associated water channels. Therefore, distal airway epithelia may also contribute to the resolution of airspace edema fluid.

The alveoli contain a thin epithelium that constitutes 99% of the surface area of the lung and consists of squamous type I cells and cuboidal type II cells. The close apposition of alveolar epithelium and vascular endothelium facilitates efficient exchange of gases but also forms a tight barrier to prevent movement of fluid and proteins from interstitial and vascular spaces, thus maintaining the relatively dry alveoli.

Tight junctions connect adjacent epithelial cells near their apical surfaces, helping to maintain apical and basolateral cell polarity. Ion transporters and other membrane proteins are asymmetrically distributed on opposing cell surfaces, conferring vectorial transport properties to the epithelium.

Within the distal pulmonary epithelium, the most extensively studied cell is the alveolar type II cell, partly because these cells can be readily isolated from the lung and studied in vitro. The alveolar type II cell is responsible for the secretion of surfactant as well as for active, directional transport of sodium.

Active transport of sodium by type II cells appears to provide the major driving force for the removal of fluid from the alveolar space. Sodium is taken up at the apical surface, partly through amiloride-sensitive and insensitive epithelial Na channels (ENaC). Na is pumped out basolaterally via Na$^+$.K$^+$.ATPase into the lung interstitium. The cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride transporter that may help drive Na and fluid transport.

The role of alveolar type I cells in fluid clearance is uncertain because cultures of polarized type I cells have not been achieved. From studies in freshly isolated cells, it is known that type I cells have a high osmotic permeability to water and that they express an aquaporin-
in water channel on the apical surface. These cells also express epithelial sodium channels (ENaC) and Na⁺,K⁺-ATPase.

**Alveolar Type II Cells Express Multiple Types of Sodium Channels**

Experimental studies of fluid transport are conducted by using substances that block one component or another of the transport process. In intact animals, the reagent amiloride, a diuretic, inhibits apical membrane sodium uptake and reduces basal fluid clearance by 40 to 70%.

While experiments showed that amiloride blockade could reduce fluid clearance by 40 to 50% in human lung, a substantial fraction, about 50%, remained insensitive to amiloride blockade, suggesting the presence of other pathways which enable fluid clearance.

Amiloride-sensitive sodium channels have been demonstrated in the apical membranes of alveolar type II cells. Of the three types described, the most frequently observed is a nonselective cation (NSC) channel, which is equally permeable to sodium and potassium. It is voltage-independent, calcium-activated, and completely blocked by 1 μM amiloride.

The second type has a high permeability to sodium relative to potassium (7 to 1) and is also completely blocked by 1 μM amiloride.

Finally, there is a highly selective cation (HSC) channel that has a lower conductance and is blocked by lower concentrations of amiloride (<0.1 μM). Various other channels also have been described in alveolar type II cells, including some regulated by G proteins.

The importance of these epithelial sodium channels (ENaC) in the absorption of salt and fluid by lung epithelia has been established in knockout mice bearing inactivated subunits of ENaC. After inactivation of the α subunit, neonates de-
Pore-forming subunits of the highly selective epithelial sodium channel (ENaC) are composed of three homologous proteins named α, β, and γ. They share a structure that contains two hydrophobic membrane-spanning regions, intracellular amino and carboxy termini, and a large extracellular loop with highly conserved cysteine residues.

Some investigators propose that the epithelial sodium channel is a tetramer made of two α, one β, and one γ subunit, whereas others contend that the channel is a much larger complex of nine subunits, three of each kind.

Developmental respiratory distress syndrome and died within 40 hours of birth. Mice with deficient β or γ subunits were able to clear fluid at a slower-than-normal rate but died of hyperkalemia, suggesting that channels formed by the α subunit together with either the β or γ subunit can adequately remove alveolar fluid.

Mutations in the α, β, and γ subunits in humans have been described. In systemic pseudohypoaldosteronism, a salt-wasting nephropathy, patients develop respiratory illness caused by excessive fluid accumulation within months after birth. Liddle’s syndrome, caused by loss of β or γ subunits, is a hereditary form of arterial hypertension caused by excessive ENaC activity.

In mice, rats, and humans, studies have found mRNA for all three subunits of ENaC in alveolar type II cells, usually with greater expression of α than β or γ subunits. These different subunit combinations may determine the sodium channel characteristics and their sensitivity to amiloride.

In intact rat, sheep, mouse, or human lung, a high concentration of amiloride (about 1 mM) is required to reduce fluid clearance by 50 to 60%. The discrepancy between the in vivo and in vitro studies suggests that amiloride has poor affinity for the sodium channels that are actually present in alveolar epithelium. Hence, active sodium transport in vivo is thought to involve, in part, nonselective sodium channels (NSC), which are less sensitive to amiloride inhibition.

In addition to the well-described amiloride-sensitive mechanism of ion and fluid transport, up to 50% of fluid clearance is achieved by amiloride-insensitive mechanisms. There is some limited evidence that in rat tracheal epithelium, the amiloride-insensitive fraction of fluid clearance can be inhibited by agents that block cyclic nucleotide-gated (CNG) cation channels.

Such channels were originally identified and cloned from vertebrate rod photoreceptors and the olfactory neuroepithelium. Of three known isoforms, the CNG-1 channel has a wide tissue distribution, including expression in the lung.
Na⁺,K⁺-ATPase Pumps Sodium Out

Na⁺,K⁺-ATPase is a ubiquitous plasma membrane ion-transporting ATPase that maintains electrochemical sodium and potassium gradients across the membrane. It accomplishes this by pumping sodium out of the cell and potassium into the cell against their respective concentration gradients. The electrochemical gradient generated by the extrusion of sodium and uptake of potassium is essential for the secondary active movement of sodium ions into the cell through sodium channels.

In most epithelia, including the alveolar epithelia, Na⁺,K⁺-ATPase is confined to the basolateral domain of cells. Its polarized distribution is what produces the directional transport of sodium, followed isosmotically by water, while the ATPase in its housekeeping mode also controls cell volume and composition. In the alveolar epithelium, Na⁺,K⁺-ATPase is detected primarily in type II cells, with weaker expression in type I cells.

Na⁺,K⁺-ATPase is a heterodimeric transmembrane protein composed of one α and one β subunit, although many isoforms of both subunits may be expressed in a tissue-specific pattern. The α₁ isoform catalyzes the movement of sodium and potassium, is phosphorylated by ATP, and binds the inhibitor ouabain. The α₁ isoform is the predominant form in alveolar type II cells. The β subunit has three isoforms and targets the assembled molecule to the plasma membrane.

It is believed that a heterodimeric form composed of the α₁ and β₁ subunits is the principal Na⁺, K⁺-ATPase isoform in alveolar epithelial cells. It has been established that both α and β subunits are required for functional insertion of the molecule into the membrane.

Removing edema fluid from airspaces is accomplished by the polar distribution of Na⁺,K⁺-ATPases and sodium channels on the basolateral and apical surfaces of epithelial cells, respectively. In a two-step process, sodium enters the apical membrane of the alveolar cell and is then pumped out at the basolateral membrane by Na⁺,K⁺-ATPase.

Aquaporins Are Present but Probably Unnecessary for Lung Fluid Transport

Since the first transcellular water channel was cloned in 1993, ten mammalian aquaporins have been identified, with four localized to the lung.

Contributions of aquaporins to fluid clearance have been studied in several lung preparations. Osmotic water permeabilities of endothelial and epithelial barriers in the lung have been found to be high, which suggests a facilitated water pathway. However, because there are no reliable, nontoxic inhibitors of water transport, knockout mice were needed to test the importance of aquaporins under physiologic conditions.

Loss of aquaporins in mice caused a modest decrease in hydrostatic fluid accumulation in the interstitium, but there was no effect on osmolar fluid clearance across the distal pulmonary epithelium. Aquaporin expression is strongly upregulated near the time of birth, but knockout mice have the same ability to clear lung fluid in the postnatal period as do wild-type controls. Knockout of aquaporins also had no effect on the formation or resolution of experimental pulmonary edema.

The insensitivity of fluid clearance to aquaporin deletion is probably the consequence of the substantially lower rate of active fluid transport presumably do not require very high cell membrane water permeabilities.

Aquaporins may have effects on other cell functions in the lung, especially volume regulation, particularly in the specialized alveolar type I cell, in alveolar fluid homeostasis, or in regulation of fluid secretion from mucus-secreting cells.

Fluid Clearance Is Stimulated by β-Adrenergic Agonists

Vectorial transport of fluid across the distal pulmonary epithelium can be upregulated by both catecholamine-dependent and independent mechanisms, which may have relevance to the treatment of various pathologic conditions.

Studies in newborn animals indicate that endogenous release of catecholamines, particularly epinephrine, stimulates reabsorption of fetal lung fluid from airspaces. The presence of β1 and β2-adrenergic receptors on alveolar type II cells has been demonstrated in vivo by autoradiographic and immunohistochemical techniques.

In most adult mammal species, stimulation of β2-adrenergic receptors increases fluid clearance. The stimulatory effect occurs rapidly after intravenous administration of epinephrine or instillation of terbutaline into the alveolar space, and it is completely prevented by either a nonspecific β receptor antagonist (propranolol) or, in rats, by a specific β2-antagonist. The increase in fluid clearance induced by β2-agonists can be prevented by amiloride, indicating that the stimulation is related to increased trans-epithelial sodium transport.

Experiments in isolated lungs and in vitro studies suggest that cAMP may be a second messenger for the β-adrenergic effects. It has been proposed that an increase in intracellular cAMP causes increased sodium transport across alveolar type II cells by independently upregulating the apical sodium pathways and basolateral Na+,K+-ATPase. An increase in intracellular calcium, due to cAMP-mediated activation of protein kinase A, also may influence NSC sodium channel opening.

Studies of the resolution of alveolar edema in humans have not been able to quantify the effect of catecholamines on the rate of fluid clearance. In the isolated human lung, β-adrenergic agonist therapy increases fluid clearance, and long-acting lipid-soluble β-agonists may be more potent than hydrophilic β-agonists. These data are important because aerosolized β-agonist treatment in some patients with pulmonary edema might accelerate clearance of alveolar edema.

Catecholamine-Independent Upregulation Also Occurs

In addition to catecholamines, it is also possible for hormones, growth factors, and proinflammatory cytokines to upregulate alveolar fluid clearance.

Glucocorticoid hormones regulate sodium uptake and fluid transport in both adult and fetal lungs, helping to maintain normal fluid balance and distal airspace fluid

**Alveolar fluid clearance** is inhibited by amiloride (which inhibits ENaC) and ouabain (which inhibits Na+,K+-ATPase) but stimulated by β-agonists. Clearance was measured in resected human lung following instillation of 40 mL of isosmolar albumin solution. Terbutaline doubled fluid clearance, but this effect was blocked by the β-antagonist propranolol and by amiloride.
In addition to its possible effects on apical sodium channels and Na⁺,K⁺-ATPase, cAMP also may stimulate chloride influx, upregulating sodium transport indirectly.

The pathways and mechanisms for chloride secretion and absorption in the lung are not well understood, and the role of chloride transport in basal fluid clearance also remains unclear. However, some evidence suggests that chloride transport may be accomplished via the cAMP-activated cystic fibrosis transmembrane conductance regulator (CFTR), a known chloride channel.

The role of CFTR was tested under basal and cAMP-stimulated conditions using intact mouse lung with a nonfunctional CFTR (ΔF508 mice). The results suggested that CFTR and chloride were essential for cAMP-mediated upregulation of isosmolar fluid clearance from distal airspaces, because fluid clearance could not be increased with β-agonists in the CFTR-deficient mice.

This model proposes that in situations of excess alveolar fluid, CFTR, stimulated by cAMP, may act to increase fluid transport across the alveolar epithelium, though it does not operate in this manner under basal conditions. Supporting this hypothesis, studies have shown that in the presence of hydrostatic stress, the lack of CFTR results in a greater accumulation of alveolar edema, indicating the potential importance of CFTR in clearing excess fluid. Because CFTR is distributed throughout the distal pulmonary epithelium, it is possible for cAMP-mediated upregulation of edema fluid resorption to occur across distal airways as well as alveolar epithelia, permitting a larger surface area for resorption.

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These data raise questions about how CFTR and epithelial sodium channels interact. Relative conductances for chloride and sodium are difficult to measure in vivo, but neither ion appears to have a limiting role. Under open-circuit conditions, the net transfer of sodium and chloride across the distal lung epithelium must be equal, because there cannot be a significant net charge accumulation. It is possible that with cAMP stimulation, conductances for chloride and sodium increase in parallel. This finding suggests that cAMP-mediated influx of Cl⁻ may stimulate Na⁺ uptake, and hence water, although further work is needed to establish the mechanisms.

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late lung fluid clearance rapidly, apparently by direct membrane effects which may be mediated by tyrosine kinase activity.

Keratinocyte growth factor (KGF) is a potent mitogen for alveolar type II cells. Its administration into the distal airspaces of rats increased fluid clearance by 66% over baseline levels, an effect possibly related to type II cell hyperplasia. Studies in cultured cells indicated that KGF also might work by enhancing expression of Na⁺,K⁺-ATPase subunits.

The sustained upregulation of fluid clearance by KGF suggests a potential therapeutic use for such an epithelial-specific mitogen. Addition of a β₂-adrenergic agonist further upregulated fluid clearance in rats, suggesting a possibility for combination therapy.

**Fluid Transport Is Impaired in Human Diseases**

The principal causes of pulmonary edema are cardiogenic, resulting from prolonged elevations in pulmonary venous pressure due to cardiac disease, and noncardiogenic, related to increases in lung endothelial and epithelial permeability due to infection, aspiration, or shock. Noncardiogenic pulmonary edema is also termed acute respiratory distress syndrome or acute lung injury.

Survival in these patients is associated with the rapid absorption of excess alveolar fluid. However, in some patients, there is an impairment of normal alveolar clearance, a finding that is associated with higher mortality.

Fluid clearance from the distal airspaces has been measured in mechanically ventilated patients with acute respiratory failure from pulmonary edema as well as in several animal models. In these studies, the total protein concentration is measured in sequential samples of edema fluid aspirated from distal airspaces by a standard suction catheter passed through an endotracheal tube. The procedure has been validated by showing a relationship between fluid clearance and improved oxygenation.

In a study of 65 patients with severe hydrostatic pulmonary edema, predominantly from acute or chronic left ventricular dysfunction, there was net fluid clearance in most patients during the first 4 hours after intubation and the start of positive pressure ventilation. Overall, 75% of these patients had intact fluid clearance. There was no significant correlation between the rate of fluid clearance and plasma epinephrine levels, although more patients with intact fluid clearance received aerosolized β-adrenergic therapy compared with those patients with impaired fluid clearance.

In the 25% of patients with poor fluid clearance, the inability to clear edema fluid was due to more than simply elevated pulmonary vascular pressures. Instead, several mechanisms may have downregulated fluid transport, including elevated levels of atrial natriuretic peptide (which can inhibit alveolar epithelial sodium uptake) or the presence of a ouabain-like substance in the circulation.

Despite these factors, hydrostatic pulmonary edema is typically associated with an uninjured epithelial barrier, in contrast to pulmonary edema resulting from acute lung injury, which is associated with increased vascular and epithelial permeability.

In animal models, the first major study to evaluate the effect of acute hydrostatic pulmonary edema on fluid clearance was done in anesthetized, ventilated sheep. An acute rise in left atrial pressure produced lung interstitial edema and an increase in protein-poor lung lymph flow. Large volumes of isosmolar 5% albumin solution were instilled into both lungs to simulate alveolar flooding. Remarkably, fluid clearance remained at a normal level over 4 hours.

Because there was a mild increase in plasma epinephrine lev-
els in these sheep, bilateral adrenalectomies were done to exclude the effects of endogenous β-adrenergic stimulation. Fluid clearance still functioned at 70% of normal rates, providing evidence that an intact distal lung epithelium could actively remove fluid despite the presence of interstitial edema and a moderately elevated left atrial pressure.

To test whether alveolar fluid resorption could be accelerated, sheep were given aerosolized salmeterol, a lipid-soluble β2-agonist. Although fluid clearance was not increased by salbuterol in the presence of elevated left atrial pressures, it was markedly increased by salbuterol under normalized vascular pressures.

Most patients with pulmonary edema with increased vascular permeability related to acute lung injury or ARDS have impaired alveolar epithelial fluid transport, a finding that is associated with prolonged respiratory failure and higher mortality. A minority of these patients can clear alveolar fluid rapidly, and these patients have a better survival rate.

These results indicate that a functional, intact distal lung epithelium is associated with a better prognosis and indicate that the degree of lung epithelial injury is an important determinant of outcome in patients with pulmonary edema related to increased vascular permeability.

A variety of factors may further impair alveolar fluid clearance in these patients, including necrotic injury to the epithelium. In addition, higher levels of nitrate and nitrite in the edema fluid may be associated with reduced fluid clearance, suggesting that nitration and oxidation of proteins essential to fluid transport may occur in some patients with lung injury.

Studies of sheep several years ago established the effect of endotoxemia and bacteremia on lung vascular permeability, but the impact on alveolar epithelial barrier function was not addressed. More recent work in rats has indicated that the acute shock produced by severe bacteremia markedly increases plasma epinephrine levels, as in hemorrhagic shock, so that the fluid transport capacity of the distal lung epithelium is up-regulated.

Thus, in the short term, up-regulation of fluid clearance may protect the airspaces against alveolar flooding when there is an increase in lung vascular permeability and accumulation of lung interstitial edema. However, in all of these studies, the epithelial barrier remained intact.
In contrast, when large doses of live bacteria were given to sheep, there was an increase in both endothelial and epithelial permeability to protein in the animals that developed the most severe shock. These sheep had alveolar flooding and impaired fluid transport, like that seen in humans who develop severe permeability pulmonary edema with septic shock.

Injury to the epithelial barrier probably arises in part from neutrophil-dependent release of proteases and reactive oxygen species as well as from bacterial exoproteins. In bacterial pneumonia, infection may progress to septic shock when the infecting gram-negative organisms generate proinflammatory cytokines in the airspaces that gain access to the circulation via the injured distal airway epithelium.

In the process of studying pneumonia in rats, one group of investigators found that the rate of fluid clearance was increased in rats that survived. The effect was found to be secondary to release of TNF-α, which was surprising because TNF-α is involved in mediating the host inflammatory response to infection and potentially contributes to the pathogenesis of septic shock. The process appears to be receptor-mediated, but the signaling pathways that are involved are unclear, because cAMP levels are not elevated by TNF-α.

Influenza virus infection can specifically alter epithelial ion transport by inhibiting amiloride-sensitive sodium currents across mouse tracheal epithelium. The effect is caused by binding of the viral hemagglutinin to a cell surface receptor that activates phospholipase C and protein kinase C. Protein kinase C can reduce epithelial sodium channel activity, providing a means for influenza infection to reduce sodium transport. This impaired sodium transport offers a possible explanation for the accumulation of alveolar edema fluid in patients with viral pneumonia and acute lung injury.

The past 20 years have witnessed a revision of traditional views about the regulation of lung fluid balance across the lung epithelial barrier. It is also now feasible to measure edema reabsorption from the distal airspaces in ventilated, critically ill patients. The next steps should be to test therapies suggested by these experimental studies. Such studies will show whether these therapies that enhance resolution of clinical pulmonary edema can improve clinical outcomes.

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