The Acute Respiratory Distress Syndrome

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Clinical Principles

Severe respiratory distress and 1 or more risk factors (including infection, aspiration, pancreatitis, and trauma)

Impaired arterial oxygenation (hypoxemia)

Bilateral pulmonary infiltrates on chest radiograph

No clinical evidence of elevated left atrial pressure (or pulmonary artery occlusion pressure of ≤ 18 mm Hg if measurements are available)

Physiologic Principles

The cardinal feature of ARDS, refractory hypoxemia, is caused by formation of protein-rich alveolar edema after damage to the integrity of the lung's alveolar-capillary barrier.

Alveolar-capillary damage in ARDS can be initiated by physical or chemical injury or by extensive activation of innate inflammatory responses. Such damage causes the lung's edema safety factor to decrease by about half, and edema develops at low capillary pressures.

Widespread alveolar flooding in ARDS impairs alveolar ventilation, excludes oxygen, and inactivates surfactant; this, in turn, decreases lung compliance, increases dispersion of ventilation and perfusion, and produces intrapulmonary shunt.

Intrapulmonary shunt is disclosed when hypoxemia does not improve despite oxygen administration; hypoxemia in ARDS does respond to positive end-expiratory pressure, which is applied carefully in accordance with strategies of lung-protective ventilation designed to avoid ventilator-associated lung injury and worsening ARDS.

The acute respiratory distress syndrome (ARDS) is defined by noncardiogenic pulmonary edema and respiratory failure in the seriously ill patient. The diagnosis is clinical, established by the development of new bilateral pulmonary infiltrates and severe hypoxemia without congestive heart failure (1). The risk for ARDS also depends on both host and etiologic factors. The most common causes are sepsis, pneumonia, aspiration, trauma, pancreatitis, several blood transfusions, smoke or toxic gas inhalation, and certain types of drug toxicity (2, 3). Several etiologic factors often are present, and this increases the probability of developing the syndrome. The acute respiratory distress syndrome is a major cause of morbidity, death, and cost in intensive care units.

Our review describes the clinical, etiologic, and physiologic basis of ARDS and summarizes our understanding of how its molecular pathogenesis leads to the physiologic alterations of respiratory failure, emphasizing factors known to be involved in the formation and resolution of permeability pulmonary edema. It also provides a physiologic basis for understanding and implementing modern strategies for the respiratory management of patients with ARDS.

In 1967, Ashbaugh and colleagues (4) defined ARDS as an acute lung injury syndrome associated with trauma, sepsis, or aspiration. The syndrome's similarities to shock lung and neonatal respiratory distress led to its original name, the adult respiratory distress syndrome, now the acute respiratory distress syndrome. Over the years, ARDS became associated with clinical risk factors that may cause lung injury either by direct involvement or by secondary processes that activate systemic inflammation and coincidentally damage the lung.

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The incidence of ARDS in at-risk populations is not certain, but prospective estimates range from 1.5 to 12.9 cases per 100 000 people per year depending on diagnostic criteria (5). The most common cause of ARDS, severe infection, accounts for approximately half of cases. These infections may involve localized disease (such as pneumonia) or systemic disease, including sepsis, sepsis syndrome, and septic shock. Sepsis-related conditions, particularly severe gram-negative infections, are also associated with multiple organ failure with or without progressive respiratory failure. The multiple organ failure syndrome is the major cause of death in ARDS, and the mortality rate of the syndrome with ARDS is about 40% (6–9).

The American–European Consensus Conference on ARDS formally defined ARDS (see Clinical Principles) to improve diagnostic consistency and interpretation of epidemiologic and therapeutic studies (1). The American–European Consensus Conference also recommended a working definition for milder acute lung injury also based on the presence of hypoxemia and pulmonary infiltrates without elevated left atrial pressure. Usually, the compliance of the lungs also decreases. The acute respiratory distress syndrome is distinguished solely by pulmonary gas exchange defined by the ratio of PaO_2 to the inspired fraction of oxygen (FiO_2). A PaO_2–FiO_2 ratio of 300 or less defines acute lung injury, and a ratio of 200 or less defines ARDS regardless of the amount of positive end-expiratory pressure (PEEP) needed to support oxygenation. Physiologic indexes of oxygenation are diagnostically useful, but the PaO_2–FiO_2 ratio and physiologic scoring systems do not correlate with prognosis (9, 10). The consensus definitions recognize the clinical syndromes without attention to specific molecular, immune, or physical events that cause respiratory failure. The acute respiratory distress syndrome is thus the clinical expression of a group of diverse processes that produce widespread alveolar damage. Regardless of cause, lung damage causes fluid to leak across the alveolar–capillary barrier (despite relatively normal pulmonary circulatory pressures) and to produce enough alveolar edema to cause the cardinal physiologic manifestation of the syndrome, refractory hypoxemia (**Figure 1**).

CLINICAL–PATHOLOGIC CORRELATION IN ARDS

The lung's alveolar–capillary structure normally provides a large surface for gas exchange and a tight barrier between alveolar gas and pulmonary capillary blood. Diffuse damage to the alveolar region occurs in the acute or exudative phase of acute lung injury and ARDS (**Figure 2**). This damage involves both the endothelial and epithelial surfaces and disrupts the lung's barrier function, flooding alveolar spaces with fluid, inactivating surfactant, causing inflammation, and producing severe gas exchange abnormalities and loss of lung compliance. These events are reflected in the presence of bilateral infiltrates, which are indistinguishable by conventional radiology from cardio-

Figure 1. **Relationships between extravascular lung water and development of hypoxemia in the acute respiratory distress syndrome.**
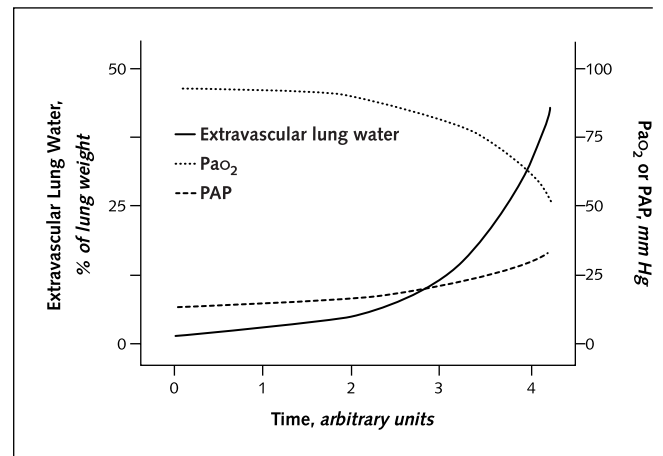

The graph illustrates the decrease in PaO_2 as a function of the increases in lung water and mean pulmonary artery pressure (*PAP*).

genic pulmonary edema (11). Computed tomography of the chest often demonstrates heterogeneous areas of consolidation and atelectasis, predominantly in the dependent lung (12, 13), although areas of apparent sparing may still show inflammation. Pathologic findings consist of diffuse alveolar damage, including capillary injury, and areas of exposed alveolar epithelial basement membrane (14–16). The alveolar spaces are lined with hyaline membranes and are filled with protein-rich edema fluid and inflammatory cells. The interstitial spaces, alveolar ducts, small vessels, and capillaries also contain macrophages, neutrophils, and erythrocytes.

The acute phase may resolve or progress to a fibrosis phase with persistent hypoxemia, increased dead space, pulmonary hypertension, and further loss of lung compliance. Chest radiographs may show new linear opacities consistent with evolving fibrosis. Computed tomography often shows diffuse interstitial thickening and blebs or honeycombing (13). Pathologic examination of the lung shows fibrosis with collagen deposition, acute and chronic inflammation, and incomplete resolution of edema (16). The recovery phase of ARDS is characterized by resolution of hypoxemia and improvement in dead space and lung compliance. Radiographic abnormalities usually resolve, but microscopic fibrosis remains.

Clinically, failure to improve in the first week of treatment and the presence of extensive alveolar epithelial injury are poor prognostic signs (3, 10, 17). Survivors of ARDS tend to be young, and pulmonary function generally recovers gradually over a year, but residual abnormalities often remain (18–24), including mild restriction or obstruction, low diffusing capacity, and impaired gas exchange with exercise (18–21). Persistent abnormalities of pulmonary function occur more commonly after severe

Figure 2. **Cellular and molecular events that interfere with gas exchange in the acute respiratory distress syndrome.**
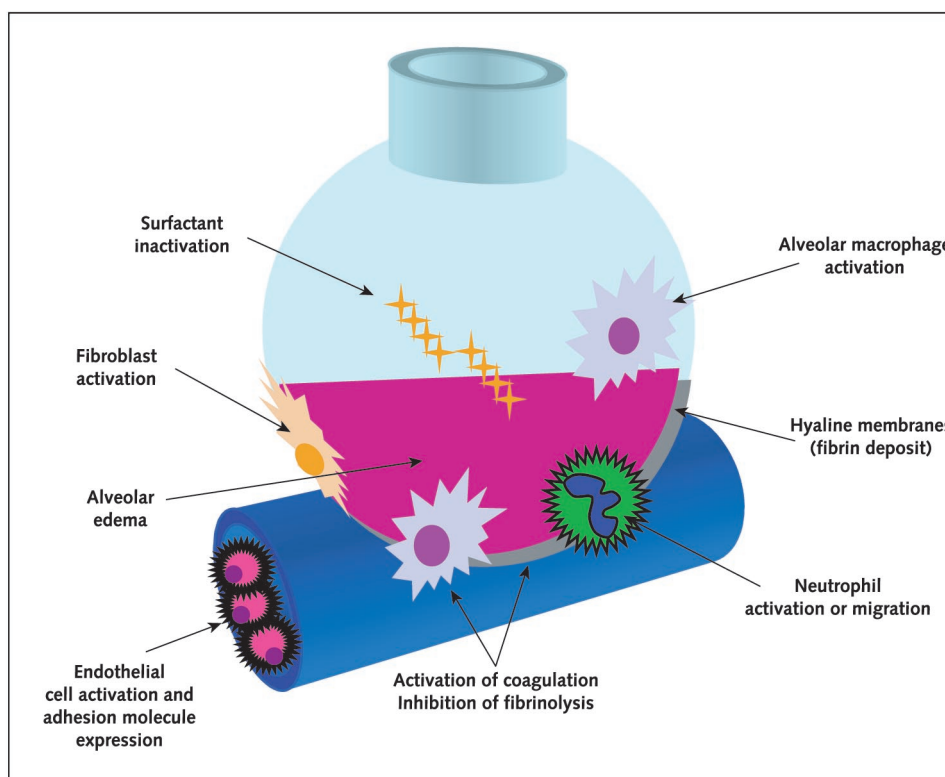
These events include endothelial activation, recruitment of inflammatory cells, activation of coagulation, and inhibition of fibrinolysis. See text for explanation.

ARDS and a need for prolonged mechanical ventilation (20, 21). Survivors of ARDS also have diminished health-related and pulmonary disease–specific quality of life, as well as systemic effects, such as muscle wasting, weakness, and fatigue (22–24).

CAUSES OF ARDS

In North America and Europe, sepsis (including pneumonia) is the most common cause of ARDS, but multiple transfusions, severe trauma, and aspiration of gastric contents are also independent risk factors (1–3, 5). Patients with sepsis are at the highest risk, and many patients with severe sepsis develop respiratory failure (25). Many infectious organisms, as well as molecular components of gram-negative and gram-positive bacteria, can trigger intense pulmonary inflammation. The presence and duration of septic shock, particularly if circulating endotoxin (lipopolysaccharide) is present, are associated with a higher incidence of ARDS (1). However, many patients with sepsis never develop ARDS, and many patients with sepsis-induced ARDS survive. In all causes of ARDS, innate genetic differences regulate the lung's immune responses and are important in pathogenesis.

Innate immunity provides the first-line host defense against pathogens and may play a key role in the development of ARDS in both infections and other conditions. The innate immune system identifies certain patterns of cell activation; therefore, a few pattern recognition receptors recognize a wide range of microbes and endogenous ligands (such as fibronectin and hyaluronic acid) (26, 27). For instance, pattern recognition receptors recognize the highly conserved lipid A portion of lipopolysaccharide, which produces a pathogen-associated molecular pattern. Some pattern recognition receptors act directly, such as CD14-recognizing and -binding lipopolysaccharide, whereas others, such as toll-like receptor 4 (TLR4), recognize complexes generated by a pathogen-associated molecular pattern (for example, the complex of lipopolysaccharide with CD14 and lipopolysaccharide-binding protein). The toll receptor family contains at least 10 pattern recognition receptors that trigger coordinated immune responses to both microbial peptides and endogenous ligands. This family of transmembrane receptors activates proinflammatory transcription factors (nuclear transcription factor-κB and activator protein-1) in mammalian cells after stimulation with lipopolysaccharide, prokaryotic DNA, and other microbial products (26, 28).

Despite the importance of TLR4 in mediating the mammalian response to lipopolysaccharide, other genes are involved in this complex biological response. For example,

polymorphisms in the *TLR4* gene are associated with lipopolysaccharide hyporesponsiveness (29), but not all that are hyporesponsive to lipopolysaccharide have *TLR4* polymorphisms and not all *TLR4* polymorphisms are hyporesponsive. Similarly, *TLR4* polymorphisms identify only a few individuals with severe gram-negative sepsis (30). Some responses to lipopolysaccharide are modulated by MHC class II genes, such as those in macrophages (31), and by other TLR4-associated proteins (MyD88 and MD-2) (32, 33). Activation of such innate responses generates the inflammatory mediators of ARDS. Understanding the genetic risk for progression to ARDS in patients with exogenous risk factors can lead to improvements in treating and preventing this devastating condition.

PHYSIOLOGIC BASIS OF ARDS

To understand the physiologic nature of ARDS, it is useful to recall how healthy lungs exchange gas by matching ventilation with perfusion (34). Gas exchange occurs in the alveolar region, which in the adult lung covers roughly the area of a tennis court and contains more than 100 million capillaries. The alveolar–capillary unit consists of the capillary endothelium and its basement membrane, the interstitial space, and the alveolar epithelium (type I and type II cells) and its basement membrane. The alveolar–capillary barrier separating airspace from capillary averages only 0.5 micron thick, which allows it to efficiently exchange gas, provided that ventilation is adequate.

At rest, the alveolar ventilation (minute ventilation minus dead space ventilation) is approximately 5 L/min, which is also the approximate value of the cardiac output. Since the entire cardiac output passes through the lungs, the ventilation–perfusion ratio (VA/Q) of the cardiopulmonary system is approximately 1. At a local level, however, VA/Q ratios vary considerably because of hydrostatic and intraregional differences in the distribution of blood flow. This heterogeneity of the VA/Q ratio (dispersion) increases as people age and during lung disease because of dispersion of the ventilation or cardiac output or both. Areas of high VA/Q ratio cause inefficient ventilation (VA/Q = ∞ is dead space), and areas of low VA/Q ratio cause hypoxemia (VA/Q = 0 is shunt) because of perfusion of poorly or nonventilated alveoli.

In ARDS, gas exchange is affected by increases in the dispersion of both alveolar ventilation and cardiac output because bronchial and vascular functions are altered by disease-related factors, such as the effects of inflammatory mediators on airway and vascular smooth-muscle tone. Because CO_2 exchange is determined by alveolar ventilation, areas of high VA/Q ratio and dead space in ARDS increase the ventilation required to keep the arterial PCO_2 level constant. As lung compliance decreases, the work to expand the lungs to maintain the arterial PCO_2 level must also increase. Hypoxemia produced by alveolar edema is most important to gas exchange in the acute phase. Pulmonary

Figure 3. **Capillary fluid filtration described by the Starling equation.**
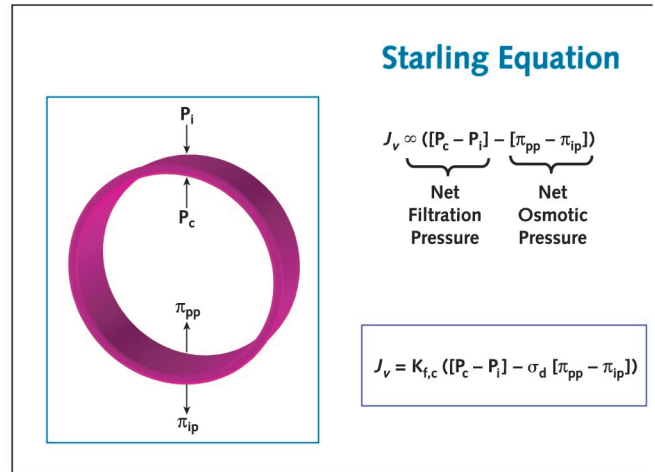
Pulmonary capillaries filter fluid (J_v) in proportion to the net capillary filtration pressure minus the net osmotic pressure across the vessel wall. The hydraulic conductance ($K_{f,c}$) is the capacity to filter fluid as filtration pressure increases relative to number and size of endothelial openings per unit surface area. The osmotic reflection coefficient (σ_d) determines osmotic permeability to specific proteins (0 is permeable and 1 is impermeable). Capillary damage in the acute respiratory distress syndrome may increase $K_{f,c}$ and decrease σ_d, increasing capillary fluid flux at constant hydrostatic pressure. P_c = mean capillary hydrostatic pressure; P_i = mean interstitial hydrostatic pressure; π_{ip} = interstitial protein osmotic pressure; π_{PP} = plasma protein osmotic pressure.

edema causes hypoxemia by creating areas of low VA/Q ratio and shunt; the latter cannot be overcome by oxygen administration because of the absence of alveolar ventilation.

PHYSIOLOGIC BASIS OF PULMONARY EDEMA

The lung's small vessels and capillaries, collectively its microcirculation, drive the pathogenesis of ARDS because the lung's water content depends on the integrity of the endothelial barrier. The alveolar–capillary barrier is not symmetrical; the airspace side is very thin, with minimal interstitial space, while the capillary side contains a substantial interstitial space that allows fluid influx from the capillary. The capillary forces that transport fluid and solute across the endothelium into the interstitial space determine how the alveolar spaces fill with edema fluid when left atrial pressure is elevated or the lung's endothelium is damaged (35). These forces are described later for a simplified distal pulmonary system.

The main force that regulates the lung's fluid balance is the microvascular pressure, primarily in the capillaries. The main pathways for fluid to exchange between blood and lung are located in the walls of capillaries at junctions between endothelial cells (35). Capillary fluid filtration is determined by the hydrostatic and osmotic pressure gradients across the capillary wall, as described by the Starling equation (**Figure 3**). Fluid leaves the capillary and enters the interstitial space in proportion to the net capillary hy-

Figure 4. **The lung's edema safety factor in the acute respiratory distress syndrome.**
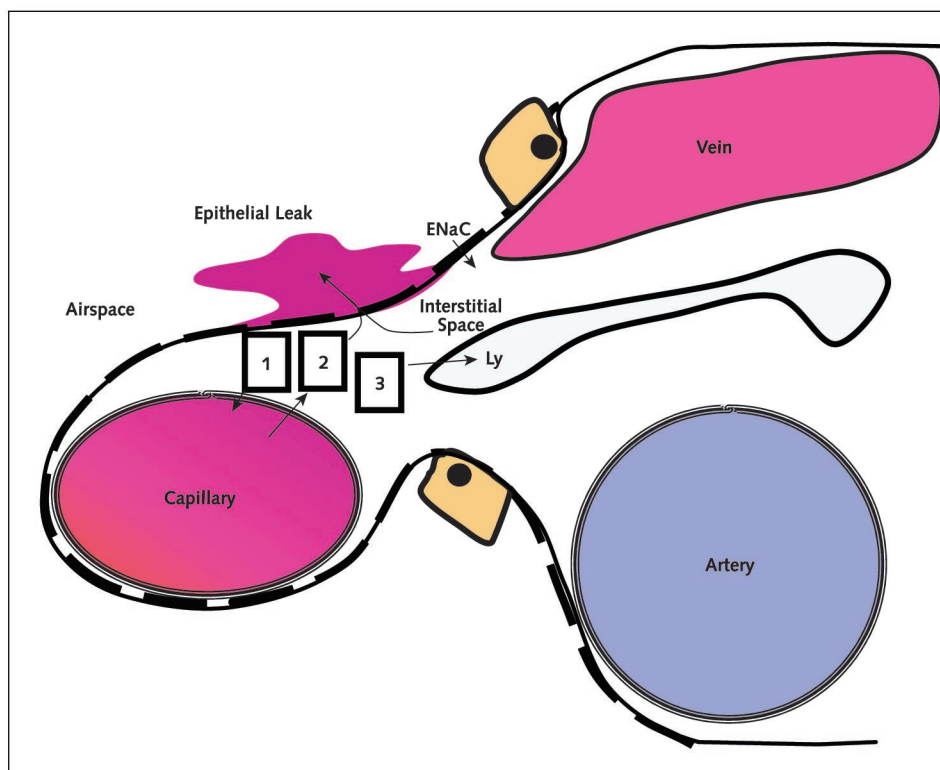
The safety factor prevents airspace flooding during increases in filtration (hydrostatic) pressure (*arrow*). The safety factor has 3 components arranged in a series (*squares 1, 2, and 3*). As filtration pressure increases, dilute fluid is forced into the interstitial space, which increases the absorption force (*arrowhead*) opposing it (*square 1*). The increase in interstitial fluid volume causes perivascular swelling (*square 2*), and interstitial fluid is removed at a greater rate (*square 3*) by lung lymphatics (*Ly*). A breech of the alveolar epithelium allows plasma and interstitial fluid to leak into the airspaces faster than salt and water can be pumped back into the interstitial space. ENaC = epithelial sodium channel.

drostatic (filtration) pressure minus the net osmotic (oncotic) pressure across the vessel wall. Interstitial fluid influx is enhanced by increases in the filtration pressure or decreases in the osmotic pressure gradients.

The capillary filtration and osmotic pressure gradients are also regulated by properties of the vessel wall: The filtration gradient is a function of the vessel's capacity to filter fluid (hydraulic conductance), and the osmotic gradient is related to its selective permeability to proteins (osmotic reflection coefficient) (**Figure 3**). Thus, even when vascular and plasma osmotic pressures are constant, interstitial fluid flux can be enhanced by increasing hydraulic conductance or by decreasing the vessel's reflection coefficient from damage to the microcirculation (35).

The importance of microvascular capillary pressure to interstitial fluid flux is also shown by its regulation by local pre- and postmicrocirculatory resistances and left atrial and pulmonary artery pressures. Increases in left atrial pressure most commonly cause elevations in pulmonary capillary pressure, but increases in pulmonary artery pressure and outflow resistance may also elevate capillary pressure. Finally, capillary pressure is directly related to the pulmonary blood flow (that is, cardiac output), by the relationship:

$$P_c = P_{LA} + (R_v \times Q),$$

where P_c indicates microvascular capillary pressure, P_{LA} indicates left atrial pressure, R_v indicates outflow resistance, and Q indicates cardiac output.

If left atrial pressure and outflow resistance are constant, then microvascular capillary pressure varies directly with cardiac output. In many patients with ARDS, particularly those with sepsis, cardiac output is elevated, which in conjunction with endothelial barrier dysfunction contributes to the formation of pulmonary edema.

The lungs are protected from pulmonary edema by an intrinsic safety factor that protects against water accumulation over a physiologically important range of capillary pressures (36). The safety factor is determined primarily by 3 components: change in absorption forces caused by increased filtration pressure, capacity of the interstitial space to absorb fluid, and capacity of the lung's lymphatic system to transport fluid out of the lung (**Figure 4**). These mechanisms maintain dry alveoli even when microvascular capillary pressure is moderately elevated, such as during exercise or hypoxia, or with compensated mitral stenosis. The

Figure 5. **Pulmonary edema formation in congestive heart failure (*CHF*) and the acute respiratory distress syndrome (*ARDS*).**
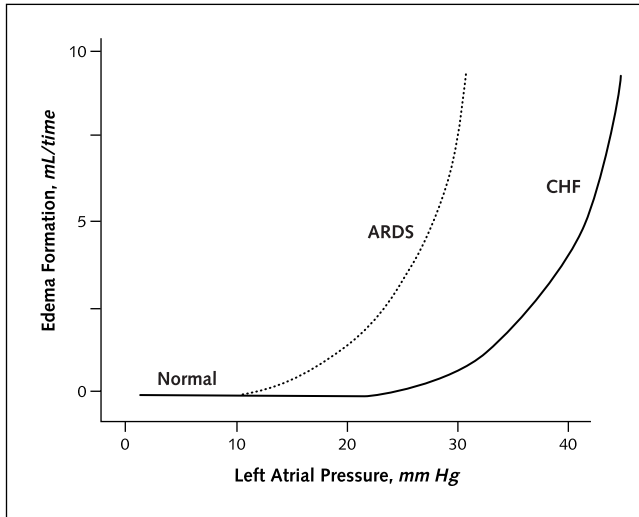
In CHF, the edema safety factor prevents pulmonary edema fluid accumulation until pulmonary capillary pressure is elevated to approximately 22 mm Hg. In ARDS, an increase in capillary permeability produces edema at normal capillary pressures and greatly increases the rate of edema formation at elevated capillary pressures.

safety factor is the sum of the 3 components and amounts to approximately 21 mm Hg for the healthy lung. Therefore, the lung's capillary hydrostatic pressure must increase to more than 21 mm Hg to flood alveoli.

As capillary pressure increases, the edema safety factor is introduced. First, filtration pressure increases and diluted fluid from the capillaries enters the interstitial space. The dilution decreases interstitial osmotic pressure, which increases the absorption force opposing the hydrostatic pressure. Second, as the interstitial pressure increases, interstitial fluid enters the perivascular space where lymphatic channels arise. The perivascular space swells, causing perivascular cuffing and interstitial edema without affecting gas exchange. The third component of the safety factor is the actual removal of interstitial fluid by the lymphatic system, which has at least an order of magnitude of reserve flow capacity.

The interstitial fluid pressure exceeds the safety factor when interstitial volume increases by about 40%, and alveolar flooding will begin (11). The mechanisms of alveolar edema are still not understood completely, but the barrier tends to collapse suddenly. Although the exact site of the initial alveolar leak is debated, 2 main sites are considered: the level of the small alveolar ducts where they join the epithelium (37) or between epithelial cell tight junctions. In either site, the leak is nonselective and passes plasma proteins of all sizes (38). Protein-rich edema impairs gas exchange by excluding oxygen and inactivating surfactant, which is vital at the air–liquid interface to prevent alveolar collapse at low distending pressures.

WHY DOES EDEMA ACCUMULATE IN ARDS?

In ARDS, permeability edema occurs because capillary conductance increases and the reflection coefficient decreases (35, 39). An increase in capillary conductance negates much of the lymphatic capacity because lymph flow must handle the larger fluid conductance as capillary filtration pressure increases. On the other hand, as the reflection coefficient decreases, the interstitial osmotic pressure becomes higher around leaky capillaries. This shifts the pressure–fluid curve of the lung to the left because the net absorption force in the Starling equation is minimized by capillary leakiness (**Figure 5**). In ARDS, the edema safety factor decreases by about half, and flooding develops at lower capillary pressures. Pulmonary edema may actually contribute to the pathogenesis of ARDS (35), and the syndrome has been observed after episodes of pulmonary edema—for instance, with ischemia–reperfusion after lung transplantation. Reperfusion injury may damage the capillary endothelium and thereby lead to the development of permeability edema, particularly if lymph flow is impaired.

INFLAMMATION ACTIVATES CAPILLARY ENDOTHELIUM IN ARDS

Overt damage to pulmonary capillary endothelium with destruction of endothelial cells has long been recognized as a key feature of ARDS (40). Endothelial cell function in ARDS, however, may be altered independently of cellular injury. This concept, known as endothelial activation, emerged years after the description of ARDS but is now part of our understanding of the disease (41, 42). Pathologic studies of patients with sepsis first suggested that pulmonary endothelial cells are activated in ARDS because pulmonary vascular endothelial integrity is often preserved microscopically even at sites of leukocyte accumulation (14, 43). Endothelial activation, however, is not precisely definable because different stresses, such as sepsis and trauma, activate endothelial cells in unique ways.

Endothelial activation was first defined as whether a new protein was synthesized in response to endothelial cell stimulation. However, protein synthesis is not a prerequisite for activation. For instance, the cell may be altered by mediators that interact with surface receptors to modify its response to new challenges. These changes in phenotype can be initiated by many factors implicated in ARDS pathogenesis, such as microbial products, chemokines, cytokines, α-thrombin, histamine, oxidants, and microcirculatory stress (42, 44, 45). Endothelial activation can be homeostatic or deregulated. Deregulation of activation seems to distinguish ARDS from disorders in which regulation is retained, such as pneumonia that soon resolves.

Endothelial activation in ARDS has several physiologic implications, but most decisively, the activated endothelium participates and partly drives the neutrophil inflammatory response that contributes to edema formation and fibrosis (46). Beyond this generality, the consequences of

activation are difficult to establish because the responses vary with the type of injury and its timing and intensity. Consequently, researchers have not found molecular markers that reflect endothelial cell activation consistently enough to provide reliable diagnostic or prognostic use. The acute respiratory distress syndrome often involves more than 1 injury, such as simultaneous stimuli, or stimulation after previous limited activation ("priming"), which makes finding simple biomarkers problematic.

Processes that activate endothelial cells result in the expression of adhesion and signaling molecules, which facilitate leukocyte adherence (44–47). In addition, local coagulation is activated, tissue factor is produced, and fibrinolysis is inhibited; the resulting procoagulant environment is proinflammatory because of excessive fibrin deposition and cross-talk between coagulation and inflammation (48). Several inducible molecules regulate endothelial interactions with leukocytes, and human endothelial cells express different adhesion and signaling molecules recognized by different leukocytes under different conditions (42, 44–47). Furthermore, activated human endothelial cells show different adhesion and signaling patterns for specific leukocytes, such as neutrophils, which may initiate or amplify lung injury (43, 45, 46).

The expression of molecules for leukocyte recruitment, adhesion, and signaling is a virtual sine qua non of endothelial activation. Leukocyte studies also suggest endothelial activation in ARDS because neutrophils accumulate in the lung with no evidence of in vitro hyperadhesiveness (47). This leukocyte sequestration is attributable to mechanical and adhesive interactions between cognate receptors on endothelial cells and leukocytes (45). Adhesion receptor-binding activates leukocytes together with soluble or membrane-bound chemokines, such as interleukin-8. Neutrophil activation increases expression of β_2-integrins that allows firm adhesion, which is necessary for them to migrate into the lung. Once neutrophils are adhered firmly to endothelium or epithelium or to interstitial matrix proteins, lung injury may occur; however, migrating neutrophils ordinarily do not damage alveolar epithelium to the extent that pulmonary edema develops—this remains a paradox of neutrophil-mediated lung injury in ARDS (49).

Certain soluble adhesion molecules, such as selectins, have been proposed as endothelial activation markers because they increase in the plasma of patients with ARDS and other forms of noncardiogenic edema (50, 51). However, the clinical significance of circulating cell adhesion molecules is questionable because plasma adhesion molecule concentrations are difficult to interpret in critically ill patients (for example, decreased clearance vs. increased release) (52). Furthermore, except for E-selectin, shed markers of cell adhesion are also produced in cells other than endothelial cells.

Endothelial activation affects capillary fluid flux in the lung in at least 3 ways. First, activated (or damaged) endothelium releases inflammatory mediators that amplify endothelial injury directly or by recruiting inflammatory cells into the vascular, interstitial, and alveolar spaces. Second, certain mediators, such as tumor necrosis factor-α and α-thrombin, activate protein kinase-C–dependent signaling pathways (39). Activation of specific protein kinase-C isoforms causes endothelial cytoskeletal elements to contract, which promotes barrier dysfunction. Finally, some mediators (for example, angiotensins, bradykinin, α-thrombin, thromboxane, prostacyclin, and endothelin) have important vasomotor effects, and their metabolism may be impaired by endothelial cell damage. This can lead to untoward effects on interstitial fluid flux through physiologic mechanisms that are usually regulated closely. Altered levels of endothelium-derived vasoactive mediators in addition to those already mentioned also contribute to microcirculatory dysfunction in ARDS, including reactive nitrogen and oxygen species. If these reactive species enhance local blood flow or increase postcapillary resistance, they may increase capillary pressure and worsen pulmonary edema.

ALVEOLAR EPITHELIUM IN ARDS

Endothelial activation, inflammation, and increased endothelial permeability drive the pathogenesis of ARDS, but the severity of injury and its resolution also depend heavily on the alveolar epithelium (17, 53). In ARDS, diffuse alveolar damage involves the epithelium and pulmonary edema formation requires alveolar epithelial dysfunction. The epithelium is also the site of alveolar fluid reabsorption and is involved in the pathogenesis of fibrosis (54).

Fluid balance in healthy alveoli is regulated to maintain a meniscus of epithelial fluid or lining layer. Liquid moves across the alveolar epithelium at the junctions between cells (paracellular) because of the osmotic gradient generated by active inward transepithelial sodium transport through apical epithelial sodium channels present in both type I and type II cells (55). Other transport proteins move water through transcellular pathways (56). The main water transport protein in the lung, aquaporin-5, is highly expressed in alveolar type I cells (57), which are rather permeable to water. Hence, water moves across the alveolar epithelium through type I cell water channels (58). Although these channels are involved in alveolar fluid homeostasis, little is known about their physiologic regulation.

After an acute lung injury, the alveolar epithelium seems to resist more injury than the adjacent endothelium (59). Unless type I cells are stripped away, the capacity to transport salt and water usually remains intact. In addition, pathologic events may upregulate epithelial fluid transport capacity. On the other hand, certain epithelial injuries may downregulate sodium transport (60), and type I cell destruction seriously impairs barrier function and pulmonary edema clearance.

For ARDS to resolve, functional alveolar epithelium must clear the edema. The process of edema resolution is

not fully understood, but the airspaces are normally kept relatively dry as noted by the alveolar epithelium's inward solute transport. Sodium transport is accompanied by osmotic water removal, followed by cellular protein clearance. These mechanisms are important in hydrostatic edema resolution after capillary pressure is brought under control. Because the epithelial leak that causes permeability edema in ARDS is nonselective, epithelial active transport mechanisms are not very effective for edema resolution because of back leakage of fluid. Thus, edema resolution in ARDS requires sealing the leak, perhaps by changes in epithelial cell shape, so that active salt and water transport processes can clear alveolar edema and the cells can remove alveolar protein.

The alveolar epithelium is fundamentally involved in repairing damaged alveolar structures. Repair requires type II alveolar epithelial cells, which are progenitors of the type I cell but account for less than 5% of the lung's epithelial surface area. Type II cells are more robust than type I cells, and although the rate of type II cell turnover in the lung is low (roughly 4% per day), it accelerates after acute lung injury (53, 54, 61).

Epithelial repair involves close coordination of several complex molecular processes. Optimal repair requires an intact basement membrane and provisional fibrin matrix to provide a platform for cell adhesion, spreading, and migration. Most modulators known to promote alveolar epithelial cell migration are heparin-binding proteins, such as epithelial growth factor, transforming growth factor-α, keratinocyte growth factor, hepatocyte growth factor, and fibroblast growth factor (62). Heparin-binding cytokines are associated with remodeling alveolar epithelium in lung development (63) and after lung injury (64–66). Keratinocyte growth factor promotes proliferation and migration of alveolar epithelial cells (67, 68) and can ameliorate lung injury when present locally beforehand (69, 70).

Clinical data suggest that the ability of the alveolar epithelial barrier to reabsorb edema fluid is intact 12 hours after onset of acute lung injury in one third of patients (14). Patients who do not reabsorb edema in this initial period have prolonged respiratory failure and increased mortality. These observations suggest that therapy for the alveolar epithelium may be useful to hasten edema resolution. If large areas of epithelium are stripped away, repair is necessary before edema can be reabsorbed. Markers of alveolar epithelial injury eventually might enable earlier detection of this injury (71).

Fluid clearance by the alveolar epithelium can be stimulated by using β-adrenergic agonists (72). Thus, β-agonists administered by either an aerosol or intravenous route could be beneficial to patients with ARDS. Furthermore, vasoactive agents commonly used in the intensive care unit, such as dopamine and dobutamine, have similar effects in animals (53). Clinical trials are evaluating the efficacy of β-agonists in ARDS, but their effects could differ greatly among patients with different levels of epithelial damage, bronchial tone, or endogenous adrenergic hormone release.

LUNG PROTECTIVE VENTILATION STRATEGIES IN ARDS

We mentioned earlier that death is caused in ARDS most often by multiple organ failure, not by respiratory failure. However, lung injury may be exacerbated by mechanical ventilation, and ventilator-induced lung injury may develop to a degree that decreases survival in ARDS (73, 74). Ventilator-induced lung injury occurs by several mechanisms, all of which exacerbate inflammation, including oxygen toxicity, lung overdistention, and destructive cycles of alveolar opening and closure. Thus, achieving adequate gas exchange at oxygen concentrations of 60% or less and tidal volumes and airway pressures as low as reasonably possible has been a "holy grail" of mechanical ventilation in ARDS. The approach is termed *lung-protective ventilation* (75). We review the physiologic concepts of lung-protective ventilation in ARDS but do not examine the ever-changing nuances of ventilator practice.

The main life-threatening problem of ARDS is hypoxemia, which must be alleviated by recruiting and stabilizing nonventilated alveoli because it is due to intrapulmonary shunt. The shunt problem is heterogeneous on a small-dimensional scale. Areas of consolidation and atelectasis are distributed around or between areas of a healthier lung; thus, regions with very different volume–pressure curves (compliance) are exposed to the same alveolar pressures by mechanical ventilation and PEEP.

Positive end-expiratory pressure improves oxygenation in ARDS by stabilizing damaged alveoli and improving areas of low VA/Q ratio and shunt (**Figure 6**). Positive end-expiratory pressure may also prevent further injury from repeatedly opening and closing alveoli. However, because of the heterogeneity mentioned earlier, a certain amount of PEEP may be appropriate in one region, too low in another, and too much in normal regions. In other words, local compliance differences reflect differences in the propensity of other units to inflate and remain open with positive-pressure ventilation and PEEP. Use of PEEP thus requires consideration of regional differences, and in general, 5 to 20 cm of H_2O provides a reasonable balance among the potential effects. Higher levels of PEEP may open more collapsed alveoli at the expense of cardiac output and overdistending already recruited alveoli. Therefore, PEEP of more than 20 cm of H_2O or PEEP associated with plateau pressures greater than 35 cm of H_2O is avoided. Other adverse effects of PEEP include increases in lung water; dead space; resistance in the bronchial circulation; and lung stretch during inspiration, which may exacerbate lung injury.

Inhomogeneous lung injury also has important physiologic implications for selecting optimal tidal volume. Use of large tidal volumes in ARDS can overdistend areas of a healthy lung, which has normal compliance but occupies a

Figure 6. **The effects of alveolar–capillary leak and positive end-expiratory pressure (*PEEP*) on pulmonary gas exchange.**
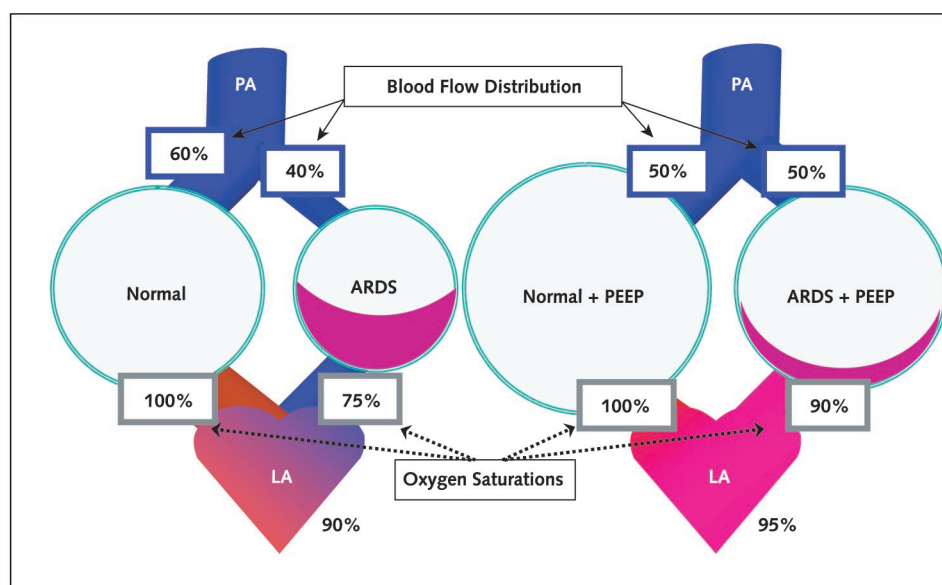
The left half of the diagram shows how alveolar flooding occurs when the capillary leak rate exceeds the safety factor. Flooded alveoli are noncompliant and become hypoxic because of poor or absent ventilation. Pulmonary arterial (*PA*) blood entering such units cannot be oxygenated and decreases the oxygen saturation of blood returning to the left atrium (*LA*). Local hypoxic pulmonary vasoconstriction diverts PA blood flow to better ventilated alveoli, which improves ventilation–perfusion matching. If hypoxic pulmonary vasoconstriction is absent or large areas of lung are flooded, pulmonary venous oxygen saturation decreases and hypoxemia occurs. The right half of the diagram illustrates the effect of PEEP, which stabilizes alveoli that are then better able to exchange gas because they have more surface area. When pulmonary venous oxygen saturation increases, hypoxic pulmonary vasoconstriction is relieved, allowing more uniform distribution of blood flow. However, PEEP may overdistend healthy alveoli, thereby damaging functional gas exchange units and redirecting blood flow toward damaged alveoli, worsening the capillary leak rate. ARDS = acute respiratory distress syndrome.

smaller volume than usual in the thorax. Lung overdistention causes barotrauma, which compromises alveolar integrity and produces additional capillary leak. If local alveolar pressure exceeds capillary pressure, blood flow also redistributes to less compliant areas that may already have microcirculatory damage and poor gas exchange. Such redistribution of blood flow cannot improve gas exchange but can increase capillary fluid flux and worsen pulmonary edema. Historically, tidal volumes of 12 to 15 mL/kg of body weight were used for mechanical ventilation in patients with ARDS, which often caused high airway pressures to overdistend less injured lung regions. More recently, ventilation with lower tidal volumes and lower peak airway pressures (<35 cm of H_2O) has been recommended to reduce ventilator-induced lung injury.

This problem was studied in a multicenter randomized, controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute and published in 2000 by the ARDS Network (76). The trial found that a low tidal volume (6 mL/kg) with a plateau pressure limit of 30 cm of H_2O decreased ARDS mortality from 40% to 31%, relative to a "traditional" tidal volume (12 mL/kg) with a plateau pressure limit of 50 cm of H_2O. The trial generated controversy because the "traditional" strategy had been replaced in many centers by use of intermediate tidal volumes and the 35-cm plateau pressure limit (77, 78). However, an expert panel for the Office for Human Re-

search Protections found that the trial did not cause undue harm to patients because no preexisting standard of care with respect to tidal volume was available (79). This is not the same, however, as recommending the low tidal volume as the standard of care. Some patients with ARDS do not tolerate low tidal volume ventilation, and the best choice for tidal volume is an open question. Methods to obtain additional information about lung distention and alveolar recruitment are also being investigated, such as assessing individual pressure–volume curves (80); however, no strategy yet improves on shunt calculations to assess the presence of mechanically silent zones of alveolar collapse.

In summary, the goals of mechanical ventilation in ARDS in principle are straightforward: Maintain adequate gas exchange until the inflammation and edema subside without causing ventilator-induced lung injury. These goals can theoretically be achieved by using lung-protective ventilation, but optimal strategies have been difficult to define because of technological problems in assessing the disease's regional heterogeneity.

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