Pathophysiology of Acute Lung Injury and the Acute Respiratory Distress Syndrome

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ABSTRACT

Since the adult respiratory distress syndrome was first described substantial progress has been made in understanding the pathogenesis of this complex syndrome. This review summarizes our current understanding of the pathophysiology of what is now termed the acute respiratory distress syndrome (ARDS) and its less severe form acute lung injury (ALI), with an emphasis on cellular and molecular mechanisms of injury that may represent potential therapeutic targets. Although it is difficult to synthesize all of these abnormalities into a single, unified, pathogenetic pathway, a theme that emerges repeatedly is that of imbalance, be it between pro- and anti-inflammatory cytokines, oxidants and antioxidants, procoagulants and anticoagulants, neutrophil recruitment and activation and mechanisms of neutrophil clearance, or proteases and protease inhibitors. Future therapies aimed at restoring the overall balance of cytokines, oxidants, coagulants, and proteases may ultimately be successful where therapies that target individual cytokines or other mediators have not.

KEYWORDS: Acute lung injury, acute respiratory distress syndrome, pathophysiology, noncardiogenic pulmonary edema

Since the adult respiratory distress syndrome was first described in 1967 by Ashbaugh and Petty,[1] substantial progress has been made in understanding the pathogenesis of this complex syndrome. This review summarizes our current understanding of the pathophysiology of what is now termed the acute respiratory distress syndrome (ARDS) and its less severe form acute lung injury (ALI), with an emphasis on cellular and molecular mechanisms of injury that may represent potential therapeutic targets.

OVERVIEW OF CLINICAL FEATURES

The initial acute or exudative phase of ALI/ARDS is characterized by the rapid onset of dyspnea, hypoxemia, respiratory failure, and bilateral infiltrates on chest radiograph that are consistent with pulmonary edema.[2] The rapid onset of respiratory failure usually requires mechanical ventilation. Respiratory failure is probably multifactorial in most patients, with contributions from arterial hypoxemia due to alveolar filling by high protein pulmonary edema (to be discussed further), decreased lung compliance due to interstitial and alveolar edema and surfactant dysfunction[3,4] with resultant alveolar collapse, and increased dead space fraction due to injury to or destruction of the pulmonary microvascular bed.[5] Increased intra-abdominal pressure with decreased chest wall compliance may also contribute to increased work of breathing in some patients with extrapulmonary causes of ALI/ARDS.[6] ALI/ARDS usually occurs in

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Table 1 Conditions Associated with Noncardiogenic Pulmonary Edema or Acute Lung Injury

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with multiple transfusions
Pulmonary contusion	Cardiopulmonary bypass
Fat or air emboli	Drug overdose or toxic ingestions
Near drowning	Acute pancreatitis
Inhalational injury	Transfusion of blood products
Reperfusion injury	

Adapted from Ware and Matthay.[2]

the setting of a clinical risk factor. The most common underlying etiologies of ALI/ARDS are listed in Table 1.

Although infrequently obtained, lung biopsies in the acute phase show diffuse alveolar damage with protein-rich pulmonary edema, neutrophils, macrophages, and erythrocytes in the alveolar spaces.[7] The alveolar epithelium is disrupted and the denuded basement membrane may be lined by fibrin-rich hyaline membranes.[8,9] Microthrombi may be visualized in the pulmonary capillaries. Injury to the capillary endothelium may be visualized by electron microscopy.[8,9] Although most histopathological studies have focused on the lung, ALI/ARDS is rarely a single-organ disease. Rather, these syndromes are almost allows systemic with multiorgan involvement.[10]

Although the acute phase of ALI/ARDS may resolve with no sequelae in some patients, others progress to a more protracted phase of persistent respiratory failure that is characterized clinically by persistent hypoxemia and decreased lung compliance and histologically by fibrosis along with acute and chronic inflammation and partial resolution of pulmonary edema.[7,11] This fibrosing alveolitis phase may be complicated by severe pulmonary hypertension sometimes accompanied by right ventricular failure.[12]

PATHOPHYSIOLOGY OF INCREASED PERMEABILITY PULMONARY EDEMA

Altered lung fluid balance leading to increased permeability pulmonary edema is a pathophysiological hallmark of ALI/ARDS. Increased permeability edema is caused by an increase in pulmonary capillary permeability resulting in an increase in transvascular flux of fluid and protein into the lung interstitium (Fig. 1).[13] Increased permeability pulmonary edema has a high protein content because the outward movement of plasma proteins is less restricted by the more permeable pulmonary capillary membrane. The degree of alveolar flooding in ALI/ARDS depends on several factors: the extent of interstitial edema, the presence or absence of concomitant injury to the alveolar epithelium, and the capacity of the alveolar epithelium to actively remove alveolar edema fluid from the airspaces.[14] In ALI/ARDS, alveolar epithelial injury leads to a decrease in the capacity for alveolar epithelial fluid transport that may contribute to the severity and duration of pulmonary edema.[8,15] Because of the increase in microvascular permeability in ALI, concomitant increases in lung microvascular hydrostatic pressure (as might occur with aggressive volume resuscitation) will lead to even greater formation of pulmonary edema.[16]

CELLULAR AND MOLECULAR MECHANISMS OF INJURY

Endothelial Injury

Widespread injury to and activation of both the lung and systemic endothelium with a resultant increase in permeability and expression of adhesion molecules is characteristic of ALI/ARDS.[17] Injury to the microvascular endothelium of the lung in clinical ARDS was first recognized by ultrastructural studies almost 30 years ago.[8,9] Increases in lung microvascular permeability have since been confirmed using radiolabeled tracer proteins in patients with ALI/ARDS[18] and by comparing simultaneous concentrations of protein in the pulmonary edema fluid and the plasma from patients with ALI/ARDS.[15,19–21] A variety of circulating markers of endothelial cell injury and activation have been studied in patients with ALI/ARDS.[22] Endothelin-1, a vasoconstrictor and proinflammatory peptide that is released by endothelial cells as a result of injury,[23–26] is increased in the plasma of patients with ALI/ARDS[27–29] as is von Willebrand factor (VWF) antigen, another marker of endothelial cell activation and injury.[30] Higher levels of plasma VWF were independently associated with mortality by multivariate analysis in two independent studies of patients with ALI/ARDS, indicating that the degree of pulmonary and systemic endothelial activation and injury at the onset of ALI/ARDS may be an important determinant of outcome.[30,31]

Although injury to the lung microvascular endothelium is the underlying cause of increased permeability pulmonary edema in ALI/ARDS, endothelial injury and activation may also lead to obstruction or destruction of the pulmonary vascular bed, another pathophysiological hallmark of ALI/ARDS. The degree of obstruction and destruction of the lung microvascular bed in ALI/ARDS is an important determinant of outcome and can be estimated by the pulmonary dead-space fraction. In a recent study the dead space fraction was elevated and was an independent predictor of mortality in 179 mechanically ventilated patients with ALI/ARDS.[5] The exact

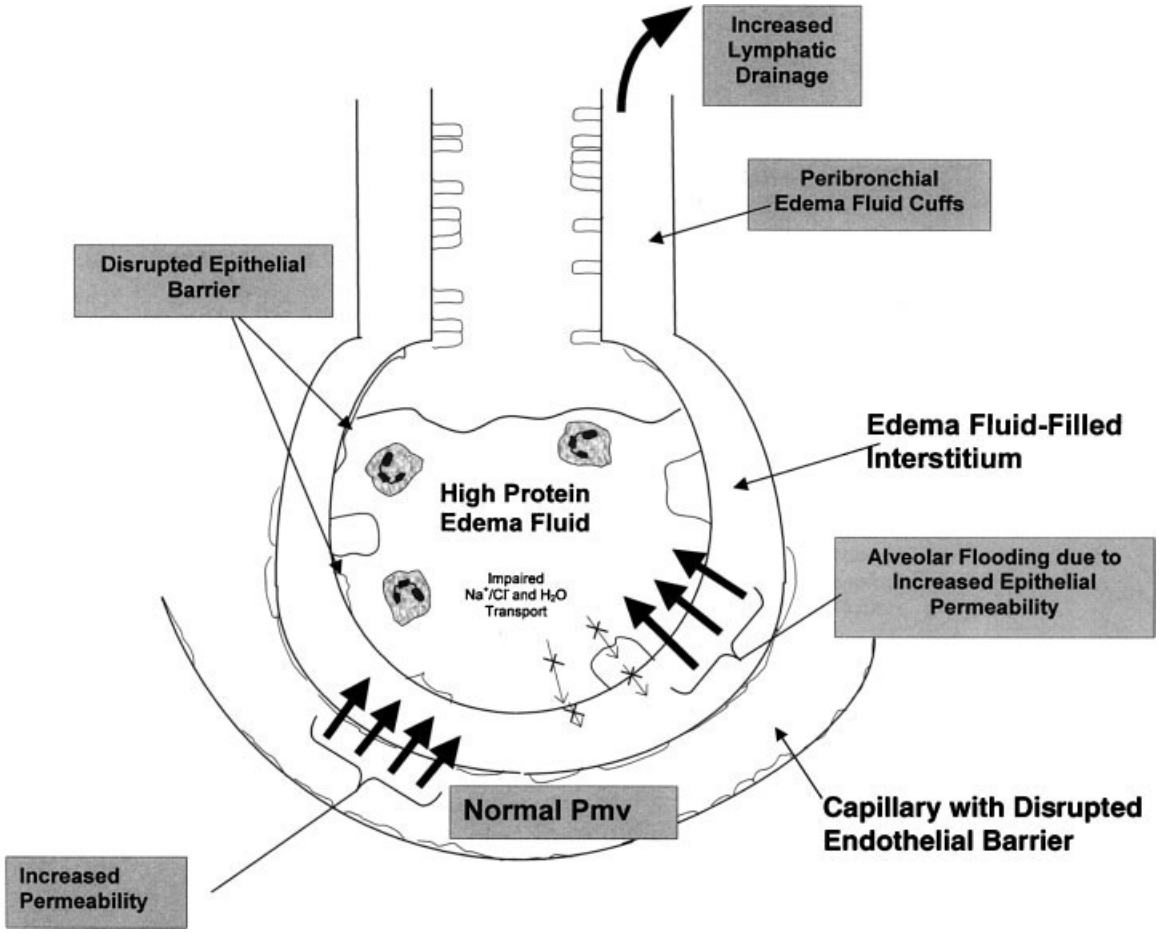

Figure 1 Physiological basis of pulmonary edema in acute lung injury and acute respiratory distress syndrome. Acute lung injury is characterized by an increase in the permeability of the microvascular membrane resulting in a marked increase in the amount of fluid and protein leaving the vascular space. Pulmonary edema in acute lung injury has a high protein content because the more permeable microvascular membrane has a reduced capacity to restrict the outward movement of larger molecules such as plasma proteins. The degree of alveolar flooding depends on the extent of interstitial edema, the presence or absence of injury to the alveolar epithelium, and the capacity of the alveolar epithelium to actively remove alveolar edema fluid. In acute lung injury edema, alveolar epithelial injury commonly causes a decrease in the capacity for alveolar fluid removal, delaying the resolution of pulmonary edema. Pmv, microvascular pressure.

etiology of the increase in dead-space fraction was not determined in this study and could be due to either capillary destruction or reversible or irreversible capillary obstruction. Nevertheless, this study highlights the importance of injury to the capillary bed in the pathogenesis of ALI/ARDS.

Further insight into the role of endothelial injury has been gained from animal models of ALI/ARDS. After an experimental insult, endothelial injury is prominent within minutes to hours and is characterized by the formation of intercellular gaps between endothelial cells along with variable degrees of necrosis, fragmentation, and sloughing of the endothelium. It is this focal and reversible gap formation that is accepted as the ultrastructural basis for increased microvascular permeability in the lung.[32] However, endothelial injury alone appears to be insufficient to cause ALI.[33]

Epithelial Injury

The importance of epithelial injury to both the development of and recovery from ALI/ARDS has become increasingly apparent. The normal alveolar epithelium is composed predominantly of flat type I cells that cover 90% of the alveolar surface area for gas exchange and are easily injured. Cuboidal type II cells cover the remaining 10% of the alveolar surface area and are more resistant to injury. Alveolar epithelial type II cells have several critical functions, including surfactant production and ion transport. They also function as progenitor cells for regeneration of type I cells after injury. Epithelial lesions in the earliest ultrastructural studies of patients dying with ALI/ARDS include a spectrum from cytoplasmic swelling, vacuolization, and bleb formation to necrosis and complete denuding of epithelial cells.[8,9] This loss of epithelial integrity has several ramifications. The

epithelial barrier is normally a much tighter barrier than the endothelial barrier. Thus loss of epithelial integrity contributes to the formation of alveolar edema (Fig. 1). Pulmonary edema is further exacerbated by the impairment of the normal fluid transport function of the epithelium due to the loss of epithelial barrier integrity along with injury to type II cells. Injury to type II cells also impairs surfactant production and turnover, contributing to the abnormalities of both the lipid and protein components of surfactant that are characteristic of ALI/ARDS.[3,4] Increased permeability pulmonary edema further exacerbates surfactant dysfunction due to the presence of serum proteins[3] and proteolytic enzymes[34] in the alveolar space. Finally, as will be discussed later, repair of epithelial injury is an important step in the resolution of ALI/ARDS. If injury to the epithelium is severe or repeated, disorganized or inadequate epithelial repair may culminate in fibrosis.[35] In clinical studies, the degree of injury to the alveolar epithelium has been shown to be an important predictor of outcome in ALI/ARDS.[15,21]

Neutrophil-Mediated Injury

Several lines of evidence suggest a critical role for the neutrophil in the pathogenesis of most cases of ALI/ARDS. Histologic studies of early ALI/ARDS consistently show a marked accumulation of neutrophils in the lung.[8,9] Pulmonary edema fluid and bronchoalveolar lavage fluid from ALI/ARDS patients also have a predominance of neutrophils.[36–38] Labeled autologous neutrophils when reinfused into patients with ALI/ARDS localize to the lung.[39] Finally, many animal models of ALI are neutrophil dependent.[40,41] Although ALI/ARDS has been reported to occur in the absence of neutrophils,[42] this is rare. For these reasons, the role of the neutrophil in ALI/ARDS has been extensively investigated.

To cause lung injury, neutrophils must be retained in the lung, come in close contact with the endothelium, and be activated to release injurious products.[43] Several theories have been proposed to explain the mechanism by which neutrophils are retained in the lung in ALI/ARDS. One theory proposes that neutrophil retention is due to the interaction between cell surface adhesion molecules on neutrophils and endothelial cells. However, only a limited role for adhesion molecules such as P-selectin, ICAM-1 (intercellular adhesion molecule-1) and CD11/CD18 has been found in experimental lung injury.[44–47] The second theory is that neutrophils are retained in the pulmonary circulation due to the induction of stiffness.[48] In the normal lung, the neutrophil must deform to pass through the pulmonary microvasculature.[49] Neutrophil deformability is adversely affected by several cytokines and chemoattractants and this reduction in deformability may hinder passage through the pulmonary capillary bed. Several chemoattractants commonly implicated in ALI/ARDS, including C5a, leukotriene B_4, interleukin (IL)-8, and endotoxin, can activate neutrophils and render them stiffer and less able to deform, hindering passage through the capillary bed.[49–52] IL-8 and other chemoattractants also recruit neutrophils to leave the vasculature and accumulate in the airspace.[53]

Once activated, neutrophils can release several potentially injurious metabolites, including proteolytic enzymes, reactive oxygen and nitrogen species, cytokines, and growth factors.[54] Proteases damage the extracellular matrix of the lung to facilitate migration of neutrophils from the capillary into the airspace.[22] The predominant protease released by neutrophils in ALI/ARDS is neutrophil elastase. In addition to its proteolytic activity, elastase may induce epithelial apoptosis that is mediated through proteinase-activated receptors.[55] Plasma and bronchoalveolar lavage levels of elastase are increased in patients at risk for[56] or with established[57] ARDS. Collagenase[58] and gelatinases A and B[59,60] have also been identified in the bronchoalveolar lavage fluid of patients with ALI/ARDS.[61]

The destructive products released by neutrophils can be counteracted by a complex array of endogenous antiproteases and antioxidants, synthesis of which can be upregulated by proinflammatory cytokines. For example, much of the neutrophil elastase recovered from the injured lung is complexed to endogenous inhibitors such as α1-antitrypsin or α2-macroglobulin and is not functional.[62–67] The balance between these destructive and protective compounds seems to be important in limiting tissue damage in ALI/ARDS.[68] Other potentially injurious products released by neutrophils include platelet activating factor (PAF) and arachidonic acid metabolites such as the leukotrienes.[22] Neutrophil-mediated injury in ALI/ARDS may also be modulated by natural inhibitors of neutrophil function. CC16 is a neutrophil chemotaxis inhibitor that has been identified in ARDS bronchoalveolar lavage fluid.[69]

Neutrophil turnover may also be dysregulated in ALI/ARDS and may function as a proinflammatory stimulus. Neutrophil-mediated inflammation is normally terminated by apoptosis of neutrophils, with subsequent removal of apoptotic neutrophils from the airspace. The primary pathway for removal of apoptotic neutrophils is through phagocytosis by alveolar macrophages, a mechanism that clears neutrophils without further release of potentially harmful proteolytic enzymes. In patients with ALI/ARDS there is evidence for disruption of normal neutrophil clearance mechanisms. Neutrophils isolated from bronchoalveolar lavage of ARDS patients[70,71] had decreased levels of apoptosis, and bronchoalveolar lavage from ARDS patients inhibited apoptosis in normal human neutrophils,[70] an effect that was due primarily to G-CSF (granulocyte-colony stimulating factor) and GM-CSF (granulocyte monocyte-colony stimulating factor). In animal models,

induction of neutrophil apoptosis ameliorates ALI,[72] and the onset of neutrophil apoptosis coincides with the resolution phase of lung injury.[73]

Cytokine-Mediated Inflammation and Injury

The inflammatory response in ALI/ARDS is initiated, amplified, and modulated by a complex network of cytokines and other proinflammatory molecules that are produced by a variety of cell types in the lungs, including fibroblasts, epithelial cells, and inflammatory cells.[74] For example, tumor necrosis factor (TNF)-α and IL-1 are early response cytokines that are produced predominantly by monocytes and macrophages in response to a direct or indirect insult to the lung such as endotoxin or other microbial products.[75] TNF-α and IL-1 act locally on other cells, including macrophages, endothelial cells, fibroblasts, and epithelial cells to stimulate production of other cytokines, such as the neutrophil chemotactic factor IL-8. High concentrations of IL-8 are present in the alveolar space of patients with ALI/ARDS.[76] In animal models, antibodies to IL-8 can prevent several types of experimental lung injury.[77,78] Thus the local release of cytokines can initiate a cascade of amplifying and modulating effects that culminate in neutrophil influx and release of toxic mediators.

The balance between proinflammatory and anti-inflammatory mediators may be a more important determinant of the overall inflammatory response, the extent of lung injury, and the outcome than levels of a single proinflammatory cytokine in ALI/ARDS.[79] Several endogenous inhibitors of the proinflammatory activity of cytokines have been identified. For example, a receptor antagonist for IL-1 has been identified that competitively inhibits IL-1 activity and is produced by monocytes after exposure to endotoxin. Similarly, two soluble forms of TNF receptor have been described that bind TNF-α and prevent it from binding membrane TNF receptors. Both soluble TNF receptors and the IL-1 receptor antagonist are present in the bronchoalveolar lavage fluid of patients with ALI/ARDS, often in higher concentrations than the cytokines themselves. Anti-inflammatory cytokines such as IL-10 and IL-11 may also protect against lung injury, and autoantibodies against IL-8 have been isolated in patients with ALI/ARDS.[80,81] In one study, outcome from ARDS was better predicted by levels of IL-8:anti-IL-8 autoantibody complexes than levels of IL-8 alone,[81] even though complexing of anti-IL-8 antibody with IL-8 neutralizes its neutrophil chemotactic activity.[82]

Recently the upstream regulation of transcription of proinflammatory cytokines and mediators has become a focus of pathogenetic research in ALI/ARDS. Nuclear factor kappa-B (NFκB), a transcription factor that regulates the expression of ICAM-1, IL-1β, IL-6, IL-8, and TNF-α, among others,[83,84] has been the most widely studied. Activation of NFκB, allows it to localize to the nucleus and alter transcription. This nuclear localization of NFκB may be a key proximal activation signal in the initiation, amplification and maintenance of the proinflammatory cytokine cascade in ALI/ARDS.[84]

Oxidant-Mediated Injury

Reactive oxygen and nitrogen species can be generated by activated alveolar macrophages and lung endothelial and lung epithelial cells in response to inflammatory stimuli. Reactive oxygen species may be responsible for much of the cellular damage that occurs in ALI/ARDS.[22] Oxidation of membrane fatty acids can increase cell membrane permeability, oxidation of proteins can render them inactive, and oxidation of DNA can arrest protein synthesis. In the endothelium, oxidant stress increases endothelial permeability through a variety of mechanisms.[85] Lung epithelial permeability is also increased by oxidant stress,[86] and alveolar epithelial fluid transport is impaired.[87] Recent evidence indicates that reactive oxygen and nitrogen species may also act through nonoxidant pathways termed redox signaling.[88]

There is emerging evidence that the oxidant/antioxidant balance is an important determinant of the level of oxidant stress in the lung in ALI/ARDS. There is marked imbalance between oxidants and antioxidants in the lung in patients with ALI/ARDS.[89] Increased levels of reactive oxygen and nitrogen species are accompanied by decreases in normal antioxidant defense systems, with drops in levels of antioxidant enzymes such as superoxide dismutase and catalase, low molecular weight scavengers such as vitamins E, C, and glutathione, and impairment of repair mechanisms to restore oxidatively damaged proteins and DNA.[89]

Ventilator-Induced Lung Injury

Experimental evidence has been accumulating since the 1970s that mechanical ventilation at high volumes and high pressures can injure the lung.[90] The consequences of high-volume ventilation include increased permeability pulmonary edema in the uninjured lung[91,92] and enhanced edema formation in the injured lung.[93,94] Initial theories to explain these deleterious effects focused on alveolar overdistension, with injury attributed predominantly to capillary stress failure with resultant endothelial and epithelial injury. New evidence suggests that high tidal volume ventilation can also cause lung injury by initiating a proinflammatory cascade. These proinflammatory effects bear a marked resemblance to the primary mechanisms underlying lung injury in ALI/ARDS, as already discussed. For example, in a rat model, high-volume ventilation caused the release of several proinflammatory mediators, including TNF-α and IL-1.[95] High-volume ventilation has also been shown

to release metalloproteinases[96] and to cause oxidative stress in the lung as measured by lipid peroxidation and H_2O_2 production.[97] In addition to the injurious effects of high lung volumes, the repeated collapse and reopening of alveoli can also initiate a cascade of proinflammatory cytokines.[98]

The tidal volumes and pressures used in many of the animal studies already described here far exceed those commonly used in clinical practice. Nevertheless, these experimental findings likely still have applicability in humans, particularly in the setting of ALI/ARDS. The pattern of lung injury in patients with ALI/ARDS is heterogeneous, such that ventilation with a standard tidal volume of 10 to 15 mL/kg may overdistend those alveoli that are relatively uninjured. Alveolar overdistension may promote further injury and inhibit resolution of lung injury, contributing to multiorgan failure.[98] Repetitive alveolar collapse and reopening likely also occur in clinical ALI/ARDS, particularly in areas where function of surfactant is impaired. Several clinical trials of protective ventilatory strategies to reduce alveolar overdistension and increase the recruitment of atelectatic alveoli have recently been undertaken. In a landmark trial, the ARDS Network reported that ventilation with a tidal volume of 6 mL/kg predicted body weight compared with 12 mL/kg predicted body weight reduced mortality in patients with ALI/ARDS.[99] Confirming that these strategies may target an important source of continued inflammation in the injured lung, both the pulmonary and systemic cytokine responses were reduced in a recent study of a protective ventilatory strategy.[100]

Coagulation Pathway

Dysregulation of the coagulation and fibrinolytic cascades has been well described in ALI/ARDS.[101–103] A variety of markers of activation of coagulation have been measured in the plasma, bronchoalveolar lavage fluid, or pulmonary edema fluid of patients at risk for[104] or with established ARDS[105,106] including tissue factor, a highly thrombogenic mediator in the extrinsic coagulation pathway.[107,108] Simultaneously, levels of endogenous anticoagulants are decreased. For example, circulating levels of protein C are decreased in patients with ALI/ARDS, and lower levels are associated with poor outcomes.[109] High levels of plasminogen activator inhibitor-1 in the bronchoalveolar lavage fluid[106,110] and pulmonary edema fluid[111] of patients with ALI/ARDS suggest impaired fibrinolysis. Thus intra-alveolar fibrin deposition, a histologic hallmark of ALI/ARDS, is promoted by an overall imbalance between procoagulant, anticoagulant, and fibrinolytic forces.[9,112,113] Intravascular coagulation with the formation of microthrombi also occurs and likely contributes to the frequent occurrence of multiorgan system failure in patients with ALI/ARDS.[114,115] Initiation of coagulation is also a potent proinflammatory stimulus. Generation of thrombin induces adhesion of neutrophils to the endothelium,[116] expression of selectin,[117] and activation of platelet receptors.[118] Generation of fibrin is also proinflammatory, increasing vascular permeability, activating endothelial cells, and inducing neutrophil adhesion and margination.[103] The recent observation that treatment of patients with severe sepsis with recombinant activated protein C significantly reduced mortality[119] suggests that therapies that target alterations in coagulation and fibrinolysis may have a role in the treatment of ALI/ARDS.

Fibrosing Alveolitis

Following the acute or exudative phase of ALI/ARDS, some patients have an uncomplicated course with rapid resolution . Others progress to fibrotic lung injury, which can be observed on biopsies as early as 5 to 7 days after the onset of ALI/ARDS.[7,22] This fibrosing alveolitis is thought to be a maladaptive fibroproliferative repair response to injury to the alveolar components and seems to result from interactions among myofibroblasts, fibroblasts, acute inflammatory cells, and epithelial cells along with cytokines, growth factors, colony stimulating factors, and fibrin.[22,35] Mesenchymal cells and proliferating fibroblasts fill the alveolar space along with new blood vessels.[120] Patients dying with ALI/ARDS have a marked increase in the lung content of collagen types I and III and fibronectin.[121] The finding of fibrosing alveolitis on lung biopsy correlates with an increased mortality from ALI/ARDS.[122]

Although fibrosing alveolitis typically develops many days into the course of ALI/ARDS, the molecular mechanisms that determine whether a patient will develop[123] fibrosing alveolitis may be set in motion remarkably early in the course of ALI/ARDS and may be a function of the severity of the initial lung injury. Levels of procollagen III peptide in the alveolar compartment may be elevated very early in the course of ALI/ARDS, even at the time of diagnosis; higher levels are associated with increased mortality.[123–125] Early proinflammatory mediators such as IL-1 may promote induction of fibrogenesis.[126,127] Bronchoalveolar lavage fluid and pulmonary edema fluid from patients with early ALI/ARDS are mitogenic for human lung fibroblasts,[128,129] an effect that is dependent on bioactive interleukin-1. Taken together, these findings suggest that early proinflammatory mechanisms are closely associated with the initiation of fibroproliferation.[129]

SPECIAL PATIENT POPULATIONS

ALI and ARDS are heterogeneous syndromes. The pathophysiology of ALI/ARDS may be different depending on a variety of host factors, including the underlying insult leading to development of ALI/ARDS.

Although it is beyond the scope of this review to discuss the pathophysiology of ALI/ARDS as it relates to each individual underlying etiology, it is useful to consider a few areas, including chronic alcohol abuse and transfusion-related ALI, where substantial recent progress has been made in understanding the underlying pathophysiology of lung injury in these settings.

Alcohol Abuse

Chronic alcohol abuse has been associated with development of respiratory failure in trauma patients,[130] and development of ARDS in patients at risk for ARDS due to a variety of diagnoses.[131–133] For example, in a prospective study of patients with septic shock, the incidence of ARDS was 70% in patients with a history of chronic alcohol abuse compared with 31% in those without chronic alcohol abuse.[133] In addition to predisposing to the development of ALI/ARDS, chronic alcohol abuse is also associated with increased mortality[132] and with the development of multiple organ system failure[133] in patients with established ALI/ARDS.

The mechanisms for increased susceptibility to ALI/ARDS in patients who abuse alcohol have been investigated in both animal and human studies. A growing body of evidence suggests that depletion of the endogenous antioxidant glutathione plays an important role in the pathogenesis of alcohol-associated ALI/ARDS.[134,135] In rats, chronic feeding with ethanol reduces levels of glutathione in lung tissue, lung lavage fluid, and alveolar epithelial type II cells.[136] Chronic ethanol feeding also increased the severity of both endotoxin-induced and cecal ligation and puncture-induced lung injury.[136,137] In humans, individuals who chronically abuse alcohol but are otherwise healthy have lower levels of glutathione and a higher percentage of oxidized glutathione in bronchoalveolar lavage fluid compared with controls.[138] Patients with ARDS who abuse alcohol also have decreased levels of glutathione in bronchoalveolar lavage fluid compared with normal controls.[139,140] In addition to alterations in glutathione homeostasis, chronic alcohol abuse may alter surfactant synthesis and secretion,[136] alveolar epithelial cell apoptosis,[141,142] alveolar capillary barrier permeability,[143,144] alveolar epithelial fluid transport function,[143] and alveolar macrophage function.[145–147]

Transfusion-Related Acute Lung Injury

Transfusion-related ALI (TRALI) is defined as the development of noncardiogenic pulmonary edema that is temporally related to the transfusion of blood products.[148] TRALI most commonly occurs with transfusion of packed red blood cells, fresh-frozen plasma, platelets, and whole blood. Onset is usually within 6 hours of the start of transfusion.[149,150] Although the presentation of TRALI is similar to ALI/ARDS with acute onset of dyspnea, bilateral infiltrates, and respiratory failure, resolution of TRALI is usually rapid (within 96 hours) and mortality is low ($< 10\%$).[151]

TRALI is thought to be mediated primarily by neutrophils. Because TRALI usually occurs in patients undergoing surgery or admitted to the intensive care unit, "a two-hit" hypothesis has been proposed for the pathogenesis.[148] The first hit is related to the underlying condition of the patient and is thought to lead to neutrophil priming and adherence to the pulmonary endothelium. Clinical risk factors for TRALI that may lead to the first insult include recent surgery, sepsis, trauma, massive transfusions, hematologic malignancies, and cardiac disease.[150–152] The second insult is thought to be directly related to the blood product transfusion and leads to activation of the primed neutrophils with resultant pulmonary capillary leakage and noncardiogenic pulmonary edema. There are two primary theories as to the pathophysiology of the neutrophil activation. Both are supported by human and animal evidence.[148] The first theory is that neutrophil activation is mediated by donor antibodies to neutrophil-specific epitopes and class I and II human leukocyte antigens (HLAs). In support of this hypothesis there are many reports in the literature of identification of granulocyte and HLA antibodies in blood products that were associated with the development of TRALI. The second theory is that neutrophils are activated by biologically active lipids such as lysophosphatidylcholines that are released from cell membranes as stored blood products break down over time.[150,153] In support of this hypothesis, several studies have suggested that blood products that are stored longer may be more likely to produce TRALI in at-risk groups such as trauma[154] and severe sepsis patients.[155]

RESOLUTION OF ALI/ARDS

Recently, the importance of the resolution phase of ALI/ARDS has been better recognized. Complete resolution of ALI/ARDS involves several steps. Alveolar edema and protein must be removed from the distal airspaces. Injury to the alveolar endothelium and epithelium must be repaired and inflammatory cells must be cleared. Finally, fibrosis must be remodeled to restore normal alveolar architecture. Understanding these mechanisms of resolution is particularly important in the design of treatment strategies because pharmacological strategies to enhance resolution may be more successful than those designed to attenuate early inflammatory lung injury.

To restore adequate gas exchange, alveolar edema must be removed, a process that is driven by the active transport of sodium and chloride from the distal

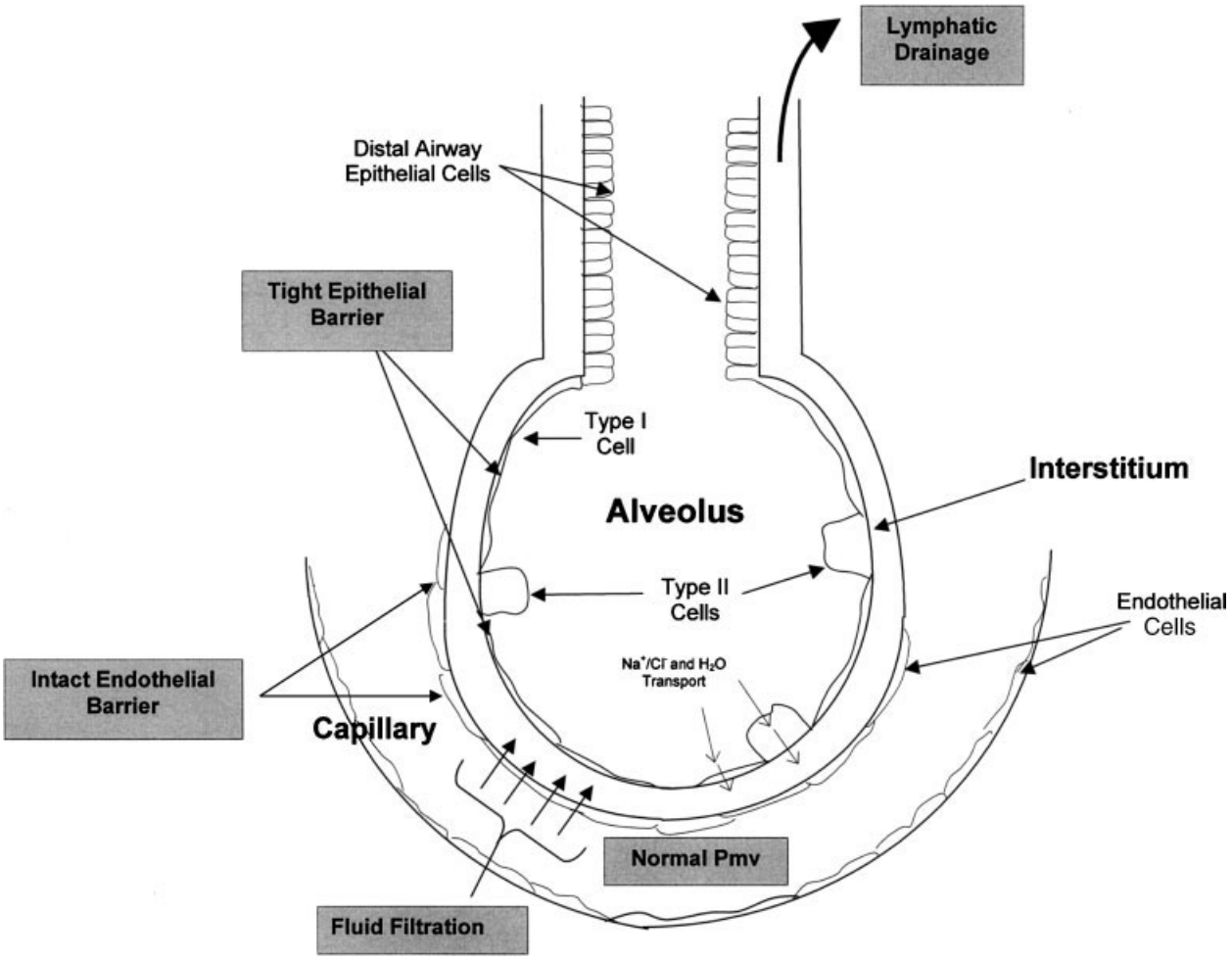

Figure 2 Lung fluid balance in the normal lung. There is normally a continuous outward movement of fluid from the vascular to the interstitial space in the lung. The net transvascular filtration of fluid (Q) into the lung interstitium is determined by the net difference between hydrostatic and protein osmotic pressures, as well as by the permeability of the capillary membrane as described by a simplified version of the Starling equation for filtration of fluid across a semipermeable membrane: $Q = K[(Pmv - Ppmv) - (\pi mv - \pi pmv)]$ where Q is the net transvascular flow of fluid, K is the membrane permeability, Pmv is the hydrostatic pressure in the microvessels, Ppmv is the hydrostatic pressure in the perimicrovascular interstitium, mv is the plasma protein osmotic pressure in the circulation, and pmv is the protein osmotic pressure in the perimicrovascular interstitium. In the normal lung, fluid leakage occurs primarily through small gaps between capillary endothelial cells. Fluid that is filtered into the alveolar interstitial space does not enter the alveoli because the alveolar epithelium is composed of very tight junctions. Filtered fluid that enters the alveolar interstitial space moves proximally into the peribronchovascular space and is removed by lymphatics and returned to the systemic circulation.

airspaces into the lung interstitium (Fig. 2).[14] Water follows passively to maintain isosmolar conditions, predominantly through transcellular water channels, the aquaporins, primarily located on alveolar type I cells.[156] In clinical studies of ALI/ARDS, alveolar fluid clearance occurs surprisingly early, often measurable within the first few hours after intubation and mechanical ventilation.[15] Patients with intact alveolar fluid clearance have a better outcome as measured by oxygenation, duration of mechanical ventilation, and survival.[15] In a small phase II study, acceleration of alveolar fluid clearance with an intravenous β-2 adrenergic agonist improved measurements of extravascular lung water in patients with ALI/ARDS.[157]

In addition to fluid and solute, both soluble and insoluble protein must be removed from the airspaces. Insoluble protein is particularly important because hyaline membranes may provide a framework for the growth of fibrous tissue.[158] Insoluble protein is probably removed by endocytosis and transcytosis by alveolar epithelial cells or phagocytosis by macrophages. Soluble protein appears to be removed primarily by diffusion between alveolar epithelial cells.[158]

The injured alveolar epithelium is restored primarily by alveolar epithelial type II cells that proliferate to line the denuded basement membrane then differentiate into type I cells, restoring the normal architecture of the alveolus. Recent evidence suggests that there may

also be a pool of bronchoalveolar stem cells that reside at the bronchoalveolar duct junction[159] although their role in alveolar epithelial repair in ALI is unknown. Proliferation of type II cells is controlled by several epithelial growth factors produced by mesothelial cells, including keratinocyte growth factor and hepatocyte growth factor.[160] Proliferation of type II cells also increases the fluid transport capacity of the alveolar epithelium.[161] Endothelial healing is less well understood and likely involves a combination of endothelial cell migration and proliferation. Circulating endothelial cell progenitor cells are known to participate in repair of damaged endothelium in animal models.[162] In a recent clinical study, increased circulating levels of endothelial progenitor cells were associated with improved survival in ALI.[163]

CONCLUSIONS

The pathophysiology of ALI/ARDS is complex and involves a complicated array of molecular, cellular, and physiological mechanisms. Although it is difficult to synthesize all of these abnormalities into a single unified pathogenetic pathway, a theme that emerges repeatedly is that of imbalance, be it between pro- and anti-inflammatory cytokines, oxidants and antioxidants, procoagulants and anticoagulants, neutrophil recruitment and activation and mechanisms of neutrophil clearance, or proteases and protease inhibitors. Although substantial progress has been made in the past 3 decades in understanding the mechanisms that underlie this devastating clinical syndrome, this progress has yet to translate into successful treatment strategies with the exception of a lung protective ventilator strategy and the use of activated protein C for patients with ALI/ARDS associated with severe sepsis. Future therapies aimed at restoring the overall balance of cytokines, oxidants, coagulants, and proteases may ultimately be successful where therapies that target individual cytokines or other mediators have not.

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