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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Acute Lung Injury and Acute Respiratory Distress Syndrome; Guest Editors, John A. Belperio, M.D., Michael A. Matthay, M.D., F.C.C.P.

Semin Respir Crit Care Med 2006;27:337–349. Copyright © 2006 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.
DOI 10.1055/s-2006-948288. ISSN 1069-3424.

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

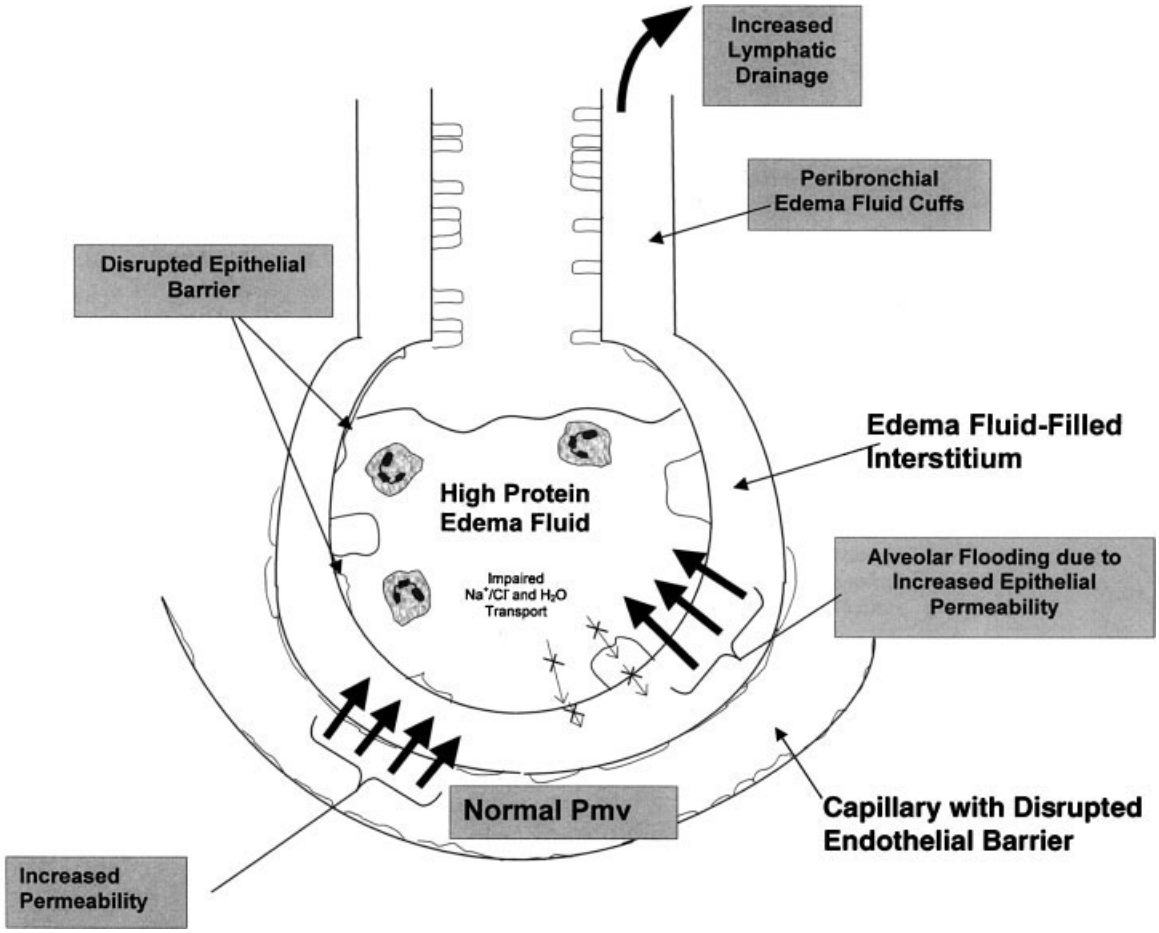

Figure 1 Physiological basis of pulmonary edema in acute lung injury and acute respiratory distress syndrome. Acute lung injury is characterized by an increase in the permeability of the microvascular membrane resulting in a marked increase in the amount of fluid and protein leaving the vascular space. 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

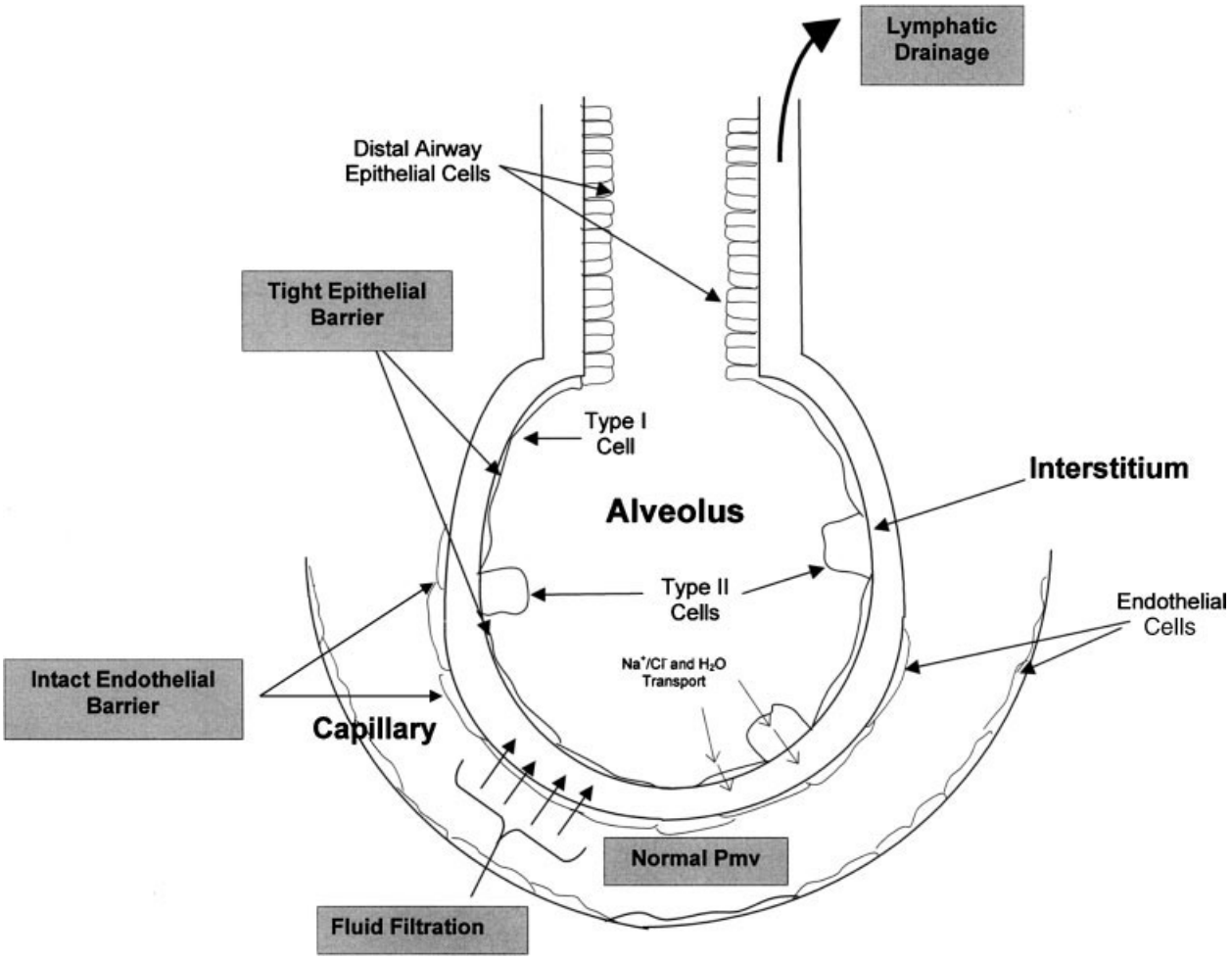

Figure 2 Lung fluid balance in the normal lung. There is normally a continuous outward movement of fluid from the vascular to the interstitial space in the lung. The net transvascular filtration of fluid (Q) into the lung interstitium is determined by the net difference between hydrostatic and protein 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.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. Lancet 1967;2:319–323
2. Ware LB, Matthay MA. Medical progress: the acute respiratory distress syndrome. N Engl J Med 2000;342: 1334–1349
3. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 1993;147:218–233
4. Gregory TJ, Longmore WJ, Moxley MA, et al. Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. J Clin Invest 1991;88: 1976–1981
5. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 2002;346: 1281–1286
6. Pelosi P, D'Onofrio D, Chiumello D, et al. Pulmonary and extrapulmonary acute respiratory distress syndrome are different. Eur Respir J Suppl 2003;42:48S–56S
7. Pratt PC, Vollmer RT, Shelburne JD, et al. Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. Am J Pathol 1979;95:191–214
8. Bachofen M, Weibel ER. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. Am Rev Respir Dis 1977;116:589–615
9. Bachofen M, Weibel ER. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med 1982;3:35–56
10. Matthay MA, Zimmerman GA, Esmon C, et al. Future research directions in acute lung injury: summary of a National Heart, Lung and Blood Institute working group. Am J Respir Crit Care Med 2003;167:1027–1035
11. Anderson WR, Thielen K. Correlative study of adult respiratory distress syndrome by light, scanning, and transmission electron microscopy. Ultrastruct Pathol 1992;16: 615–628
12. Matthay MA, Broaddus VC. Fluid and hemodynamic management in acute lung injury. Semin Respir Crit Care Med 1994;15:271–288
13. Ware LB, Matthay MA. Clinical practice: acute pulmonary edema. N Engl J Med 2005;353:2788–2796
14. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002;82:569–600
15. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:1376–1383
16. Prewitt RM, McCarthy J, Wood LDH. Treatment of acute low pressure pulmonary edema in dogs. J Clin Invest 1981;67:409–418
17. Zimmerman GA, Albertine KH, Carveth HJ, et al. Endothelial activation in ARDS. Chest 1999;116:18S–24S
18. Raijmakers PGHM, Groeneveld ABJ, Teule GJJ, et al. The diagnostic value of the ^{67}gallium pulmonary leak index in pulmonary edema. J Nucl Med 1996;37:1316–1322
19. Fein A, Grossman RF, Jones JG, et al. The value of edema protein measurements in patients with pulmonary edema. Am J Med 1979;67:32–39
20. Sprung C, Rackow E, Fein I, et al. The spectrum of pulmonary edema: differentiation of cardiogenic intermediate and noncardiogenic forms of pulmonary edema. Am Rev Respir Dis 1981;124:718–722
21. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 1990;142:1250–1257
22. Pittet JF, MacKersie RC, Martin TR, et al. Biological markers of acute lung injury: prognostic and pathogenetic significance. Am J Respir Crit Care Med 1997;155:1187–1205
23. Fagan KA, McMurtry IF, Rodman DM. Role of endothelin-1 in lung disease. Respir Res 2001;2:90–101
24. Pittet JF, Morel DR, Hemsen A, et al. Elevated plasma endothelin-1 concentrations are associated with the severity of illness in patients with sepsis. Ann Surg 1991;213: 261–264

25. Morel DR, Lacroix JS, Hemsen A, et al. Increased plasma and pulmonary lymph levels of endothelin during endotoxin shock. Eur J Pharmacol 1989;167:427–428
26. Miyauchi T, Yanagisawa M, Tomizawa T, et al. Increased concentrations of endothelin-1 and big endothelin-1 in acute myocardial infarction. Lancet 1989;2:53–54
27. Druml W, Steltzer H, Waldhausl W, et al. Endothelin-1 in adult respiratory distress syndrome. Am Rev Respir Dis 1993;148:1169–1173
28. Langleben D, Demarchie M, Laporta D, et al. Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. Am Rev Respir Dis 1993;148:1646–1650
29. Sanai L, Haynes WG, Mackenzie A, et al. Endothelin production is sepsis and the adult respiratory distress syndrome. Intensive Care Med 1996;22:52–56
30. Ware LB, Conner ER, Matthay MA. von Willebrand factor antigen is an independent marker of poor outcome in patients with early acute lung injury. Crit Care Med 2001; 29:2325–2331
31. Ware LB, Eisner MD, Thompson BT, et al. Significance of von Willebrand factor in septic and non-septic patients with acute lung injury. Am J Respir Crit Care Med 2004;170: 766–772
32. Hurley JV. Types of pulmonary microvascular injury. Ann NY Acad Sci 1982;384:269–286
33. Wiener-Kronish JP, Albertine KH, Matthay MA. Differential responses of the endothelial and epithelial barriers of the lung in sheep to *Escherichia coli* endotoxin. J Clin Invest 1991;88:864–875
34. Baker CS, Evans TW, Randle BJ, et al. Damage to surfactant-specific protein in acute respiratory distress syndrome. Lancet 1999;353:1232–1237
35. Bitterman PB. Pathogenesis of fibrosis in acute lung injury. Am J Med 1992;92:39S–43S
36. Matthay MA, Eschenbacher WC, Goetzl EJ. Elevated concentrations of leukotriene D4 in pulmonary edema fluid of patients with adult respiratory distress syndrome. J Clin Immunol 1984;4:479–483
37. Parsons PE, Fowler AA, Hyers T, et al. Chemotactic activity in bronchoalveolar lavage fluid from patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985;132:490–493
38. Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;150: 113–122
39. Warshawski FJ, Sibbald W, Driedger A, et al. Abnormal neutrophil-pulmonary interaction in the adult respiratory distress syndrome: qualitative and quantitative assessment of pulmonary-neutrophil kinetics in humans with in vivo indium-111 neutrophil scintigraphy. Am Rev Respir Dis 1986;133:792–804
40. Matthay MA. Conference summary: acute lung injury. Chest 1999;116:119S–126S
41. Prescott SM, McIntyre TM, Zimmerman G. Two of the usual suspects, platelet-activating factor and its receptor, implicated in acute lung injury. J Clin Invest 1999;104: 1019–1020
42. Laufe MD, Simon RH, Flint A, et al. Adult respiratory distress syndrome in neutropenic patients. Am J Med 1986;80:1022–1026
43. Worthen GS, Downey GP. Mechanisms of neutrophil mediated injury. In: Evans TW, Haslett C, eds. ARDS Acute Respiratory Distress in Adults. London, UK: Chapman & Hall; 1996:99–114
44. Doerschuk CM, Quinlan WM, Doyle NA, et al. The role of P-selectin and ICAM-1 in acute lung injury as determined using blocking antibodies and mutant mice. J Immunol 1996;157:4609–4614
45. Folkesson HG, Matthay MA. Inhibition of CD18 or CD11b attenuates acute lung injury after acid instillation in rabbits. J Appl Physiol 1997;82:1743–1750
46. Mulligan MS, Polley MJ, Bayer RJ. Neutrophil-dependent acute lung injury: requirement for P-selectin (GMP-140). J Clin Invest 1992;90:1600–1607
47. Nagase T, Ohga E, Sudo E, et al. Intercellular adhesion molecule-1 mediates acid aspiration-induced lung injury. Am J Respir Crit Care Med 1996;154:504–510
48. Doerschuk CM. Mechanisms of leukocyte sequestration in inflamed lungs. Microcirculation 2001;8:71–88
49. Worthen GS, Schwab B, Elson EL, et al. Mechanics of stimulated neutrophils: cell stiffening induces retention in capillaries. Science 1989;245:183–185
50. Lavkan AH, Astiz ME, Rackow EC. Effects of proinflammatory cytokines and bacterial toxins on neutrophil rheologic properties. Crit Care Med 1998;26:1677–1682
51. Erzurum S, Downey G, Doherty D, et al. Mechanisms of lipopolysaccharide induced neutrophil retention. J Immunol 1992;149:154–162
52. Inano H, English D, Doerschuk C. Effect of zymosan activated plasma on deformability of rabbit polymorphonuclear leukocytes. J Appl Physiol 1992;73:1370–1376
53. Puneet P, Moochhala S, Bhatia M. Chemokines in acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 2005;288:L3–15
54. Moraes TJ, Zurawska JH, Downey GP. Neutrophil granule contents in the pathogenesis of lung injury. Curr Opin Hematol 2006;13:21–27
55. Suzuki T, Moraes TJ, Vachon E, et al. Proteinase-activated receptor-1 mediates elastase-induced apoptosis of human lung epithelial cells. Am J Respir Cell Mol Biol 2005; 33:231–247
56. Donnelly SC, MacGregor I, Zamani A, et al. Plasma elastase levels and the development of the adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151: 1428–1433
57. Gando S, Kameue T, Nanzaki S, et al. Increased neutrophil elastase, persistent intravascular coagulation, and decreased fibrinolytic activity in patients with posttraumatic acute respiratory distress syndrome. J Trauma 1997;42:1068–1072
58. Christner P, Fein AM, Goldberg S, et al. Collagenase in the lower respiratory tract of patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985;131:690–695
59. Delclaux C, d'Ortho MP, Delacourt C, et al. Gelatinases in epithelial lining fluid of patients with adult respiratory distress syndrome. Am J Physiol 1997;272:L442–L51
60. Pugin J, Verghese G, Widmer M-C, et al. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of ARDS. Crit Care Med 1999; 27:304–312
61. Ricou B, Nicod L, Lacaraz S, et al. Matrix metalloproteinases and TIMP in acute respiratory distress syndrome. Am J Respir Crit Care Med 1996;154:346–352
62. Weiland JE, Davis B, Holter JF, et al. Lung neutrophils in the adult respiratory distress syndrome: clinical and

pathophysiologic significance. Am Rev Respir Dis 1986; 133:218–225
63. Lee CT, Fein AM, Lipmann M, et al. Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory distress syndrome. N Engl J Med 1981;304:192–196
64. McGuire WW, Spragg RC, Cohen AB, et al. Studies on the pathogenesis of the adult respiratory distress syndrome. J Clin Invest 1982;69:543–553
65. Suter PM, Suter S, Girardin E, et al. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. Am Rev Respir Dis 1992;145:1016–1022
66. Fowler AA, Walchak S, Giclas PC, et al. Characterization of antiprotease activity in the adult respiratory distress syndrome. Chest 1982;81:50S–51S
67. Idell S, Kucich U, Fein A, et al. Neutrophil elastase releasing factors in bronchoalveolar lavage from patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985;132:1098–1105
68. Gadek JE, Pacht ER. The interdependence of lung antioxidants and antiprotease defense in ARDS. Chest 1996; 110:273S–277S
69. Geerts L, Jorens PG, Willems J, et al. Natural inhibitors of neutrophil function in acute respiratory distress syndrome. Crit Care Med 2001;29:1920–1924
70. Matute-Bello G, Liles WC, Radella F II, et al. Neutrophil apoptosis in the acute respiratory distress syndrome. Am J Respir Crit Care Med 1997;156:1969–1977
71. Lesur O, Kokis A, Hermans C, et al. Interleukin-2 involvement in early acute respiratory distress syndrome: relationship with polymorphonuclear neutrophil apoptosis and patient survival. Crit Care Med 2000;28:3814–3822
72. Sookhai S, Wang JJ, McCourt M, et al. A novel therapeutic strategy for attenuating neutrophil-mediated lung injury in vivo. Ann Surg 2002;235:285–291
73. Hussain N, Wu F, Zhu L, et al. Neutrophil apoptosis during the development and resolution of oleic acid-induced acute lung injury in the rat. Am J Respir Cell Mol Biol 1998;19:867–874
74. Goodman R, Pugin J, Lee JS, et al. Cytokine mediated inflammation in acute lung injury. Cytokine Growth Factor Rev 2003;14:523–535
75. Nathan CF. Secretory products of macrophages. J Clin Invest 1987;79:319–326
76. Miller EJ, Cohen AB, Matthay MA. Increased interleukin-8 concentrations in the pulmonary edema fluid of patients with acute respiratory distress syndrome from sepsis. Crit Care Med 1996;24:1448–1454
77. Folkesson HG, Matthay MA, Hebert CA, et al. Acid aspiration induced lung injury in rabbits is mediated by interleukin-8 dependent mechanisms. J Clin Invest 1995; 96:107–116
78. Yokoi K, Mukaida N, Harada A, et al. Prevention of endotoxemia-induced acute respiratory distress syndrome-like lung injury in rabbits by a monoclonal antibody to IL-8. Lab Invest 1997;76:375–384
79. Martin TR. Cytokines and the acute respiratory distress syndrome (ARDS): a question of balance. Nat Med 1997; 3:272–273
80. Parsons PE. Interleukin-10: the ambiguity in sepsis continues. Crit Care Med 1998;26:818–819
81. Kurdowska A, Noble JM, Steinberg KP, et al. Anti-interleukin 8 autoantibody: interleukin 8 complexes in the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:463–468
82. Kurdowska A, Miller EJ, Noble JM, et al. Anti-IL-8 autoantibodies in alveolar fluid from patients with the adult respiratory distress syndrome. J Immunol 1996;157:2699–2706
83. Fan J, Ye RD, Malik AB. Transcriptional mechanisms in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2001;281:L1037–L50
84. Christman JW, Sadikot RT, Blackwell T. The role of nuclear factor-κ B in pulmonary diseases. Chest 2000;117: 1482–1487
85. Lum H, Roebuck KA. Oxidant stress and endothelial cell dysfunction. Am J Physiol Cell Physiol 2001;280:C719–C741
86. Waters CM, Savla U, Panos RJ. KGF prevents hydrogen peroxide-induced increases in airway epithelial cell permeability. Am J Physiol 1997;272:L681–L9
87. Hu P, Ischiropoulos H, Beckman JS, et al. Peroxynitrite inhibition of oxygen consumption and sodium transport in alveolar type II cells. Am J Physiol 1994;266:L628–L34
88. Haddad JJ. Oxygen homeostasis, thiol equilibrium and redox regulation of signalling transcription factors in the alveolar epithelium. Cell Signal 2002;14:799–810
89. Chabot F, Mitchell JA, Gutteridge JMC, et al. Reactive oxygen species in acute lung injury. Eur Respir J 1998;11: 745–757
90. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end expiratory pressure. Am Rev Respir Dis 1974;110:556–565
91. Dreyfuss D, Basset G, Soler P, et al. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985;132:880–884
92. Dreyfuss D, Soler P, Basset G, et al. High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137:1159–1164
93. Bowton DL, Kong DL. High tidal volume ventilation produces increased lung water in oleic acid-injured rabbit lungs. Crit Care Med 1989;17:908–911
94. Corbridge TC, Wood LDH, Crawford GP, et al. Adverse effects of large tidal volumes and low PEEP in canine acid aspiration. Am Rev Respir Dis 1990;142:311–315
95. Tremblay L, Valenza F, Ribeiro SP, et al. Injurious ventilatory strategies increase cytokines and *c-fos* mRNA expression in an isolated rat lung model. J Clin Invest 1997; 99:944–952
96. Pardo A, Ridge K, Segura L, et al. Gelatinase A and interstitial collagenase are upregulated during high tidal volume mechanical ventilation [abstract]. Am J Respir Crit Care Med 1996;153:A531
97. Howard AB, Alexander R, Nerem R, et al. Cyclic strain induces an oxidative stress in endothelial cells. Am J Physiol 1997;272:C421–C427
98. Slutsky AS, Tremblay LN. Multiple system organ failure: is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 1998;157:1721–1725
99. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with

traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342: 1301–1308
100. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. JAMA 1999;282:54–61
101. Ware LB, Bastarache JA, Wang L. Coagulation and fibrinolysis in human acute lung injury: new therapeutic targets? Keio J Med 2005;54:142–149
102. Idell S. Anticoagulants for acute respiratory distress syndrome: can they work? Am J Respir Crit Care Med 2001; 164:517–520
103. Abraham E. Coagulation abnormalities in acute lung injury and sepsis. Am J Respir Cell Mol Biol 2000;22:401–404
104. Seeger W, Hubel J, Klapettek K, et al. Procoagulant activity in bronchoalveolar lavage of severely traumatized patients-relation to development of acute respiratory distress. Thromb Res 1991;61:53–64
105. Fuchs-Buder T, deMoerloose P, Ricou B, et al. Time course of procoagulant activity and D dimer in bronchoalveolar fluid of patients at risk for or with acute respiratory distress syndrome. Am J Respir Crit Care Med 1996;153:163–167
106. Idell S, Koenig K, Fair D, et al. Serial abnormalities of fibrin turnover in evolving adult respiratory distress syndrome. Am J Physiol 1991;261:L240–L8
107. Idell S, Gonzalez K, Bradford H, et al. Procoagulant activity in bronchoalveolar lavage in the adult respiratory distress syndrome. Am Rev Respir Dis 1987;136:1466–1474
108. Idell S, James K, Levin E, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. J Clin Invest 1989;84:695–705
109. Ware LB, Matthay MA. Lower plasma protein C is associated with worse clinical outcomes in patients with acute lung injury [abstract]. Am J Respir Crit Care Med 2002;165:A476
110. Bertozzi P, Astedt B, Zenzius L, et al. Depressed bronchoalveolar urokinase activity in patients with adult respiratory distress syndrome. N Engl J Med 1990;322:890–897
111. Prabhakaran P, Ware LB, White KE, Cross MT, Matthay MA, Olman MA. Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid predict the outcome of clinical acute lung injury. Am J Physiol: Lung Cell Mol Physiol 2003;285(1):L20–L28
112. McDonald J. The yin and yang of fibrin in the airways. N Engl J Med 1990;322:929–931
113. Idell S. Extravascular coagulation and fibrin deposition in acute lung injury. New Horiz 1994;2:566–574
114. Matthay M. Severe sepsis—a new treatment with both anticoagulant and anti-inflammatory properties. N Engl J Med 2001;344:759–762
115. Vincent J-L. New therapeutic implications of anticoagulation mediator replacement in sepsis and acute respiratory distress syndrome. Crit Care Med 2000;28:S83–S5
116. Lo S, Lai L, Ja C, et al. Thrombin-induced generation of neutrophil activating factors in the blood. Am J Pathol 1988;130:22–32
117. Kaplanski G, Fabrigoule M, Boulay V, et al. Thrombin induces endothelial type II activation in vitro: IL-1 and TNF-alpha-independent IL-8 secretion and E-selectin expression. J Immunol 1997;158:5435–5441
118. Coughlin S. Thrombin signaling and protease-activated receptors. Nature 2000;407:258–264
119. Bernard G, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709
120. Fukuda Y, Ishizaki M, Masuda Y, et al. The role of intra-alveolar fibrosis in the process of pulmonary structural remodeling in patients with diffuse alveolar damage. Am J Pathol 1987;126:171–182
121. Martin C, Papazian L, Payan MJ, et al. Pulmonary fibrosis correlates with outcome in the adult respiratory distress syndrome. Chest 1995;107:196–200
122. Zapol WM, Trelstad RL, Coffey JW, et al. Pulmonary fibrosis in severe acute respiratory failure. Am Rev Respir Dis 1979;119:547–554
123. Pugin J, Ricou B, Stenberg KP, et al. Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. Am J Respir Crit Care Med 1996;153:1850–1856
124. Chesnutt AN, Matthay MA, Tibayan FA, et al. Early detection of type III procollagen peptide in acute lung injury. Am J Respir Crit Care Med 1997;156:840–845
125. Clark JG, Milberg JA, Steinberg KP, et al. Type III procollagen peptide in the adult respiratory distress syndrome. Ann Intern Med 1995;122:17–23
126. Lindroos PM, Coin PG, Osornio-Vargas AR, et al. Interleukin-1β (IL-1β) and the IL-1β alpha 2-macroglobulin complex upregulate the platelet-derived growth factor alpha on rat pulmonary fibroblasts. Am J Respir Cell Mol Biol 1995;13:455–465
127. Martinet Y, Menard O, Vaillant P, et al. Cytokines in human lung fibrosis. Arch Toxicol Suppl 1996;18:127–139
128. Marshall R, Bellingan G, Webb S, et al. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. Am J Respir Crit Care Med 2000; 162:1783–1788
129. Olman MA, White KE, Ware L, et al. Microarray analysis indicates that pulmonary edema fluid from patients with acute lung injury mediates inflammation, mitogen gene expression, and fibroblast proliferation through bioactive interleukin-1. Chest 2002;121:69S–70S
130. Jurkovich GJ, Rivara FP, Gurney JG, et al. The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. JAMA 1993;270:51–56
131. Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 1995;151:293–301
132. Moss M, Bucher B, Moore FA, et al. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 1996;275:50–54
133. Moss M, Parsons PE, Steinberg KP, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med 2003;31:869–877
134. Moss M, Burnham EL. Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. Crit Care Med 2003;31:S207–S12
135. Guidot DM, Roman J. Chronic ethanol ingestion increases susceptibility to acute lung injury: role of oxidative stress and tissue remodeling. Chest 2002;122(Suppl 6):309S–314S
136. Holguin F, Moss I, Brown LA, et al. Chronic ethanol ingestion impairs alveolar type II cell glutathione homeostasis and

function and predisposes to endotoxin-mediated acute edematous lung injury in rats. J Clin Invest 1998;101:761–768
137. Velasquez A, Bechara RI, Lewis JF, et al. Glutathione replacement preserves the functional surfactant phospholipid pool size and decreases sepsis-mediated lung dysfunction in ethanol-fed rats. Alcohol Clin Exp Res 2002;26:1245–1251
138. Moss M, Guidot DM, Wong-Lambertina M, et al. The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. Am J Respir Crit Care Med 2000;161:414–419
139. Bunnell E, Pacht ER. Oxidized glutathione is increased in the alveolar fluid of patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1993;148:1174–1178
140. Pacht ER, Timerman AP, Lykens MG, et al. Deficiency of alveolar fluid glutathione in patients with sepsis and the adult respiratory distress syndrome. Chest 1991;100:1397–1404
141. Brown LA, Harris FL, Bechara R, et al. Effect of chronic ethanol ingestion on alveolar type II cell: glutathione and inflammatory mediator-induced apoptosis. Alcohol Clin Exp Res 2001;25:1078–1085
142. Brown LA, Harris FL, Guidot DM. Chronic ethanol ingestion potentiates TNF-alpha-mediated oxidative stress and apoptosis in rat type II cells. Am J Physiol Lung Cell Mol Physiol 2001;281:L377–L386
143. Guidot DM, Modelska K, Lois M, et al. Ethanol ingestion via glutathione depletion impairs alveolar epithelial barrier function in rats. Am J Physiol Lung Cell Mol Physiol 2000;279:L127–L135
144. Burnham E, Brown LAS, Eaton S, et al. Prolonged glutathione deficiency and increased total protein concentrations in the epithelial lining fluid of chronic alcoholics [abstract]. Am J Respir Crit Care Med 2001;163:A816
145. Baughman RP, Roselle GA. Surfactant deficiency with decreased opsonic activity in a guinea pig model of alcoholism. Alcohol Clin Exp Res 1987;11:261–264
146. Greenberg SS, Zhao X, Hua L, et al. Ethanol inhibits lung clearance of *Pseudomonas aeruginosa* by a neutrophil and nitric oxide-dependent mechanism, in vivo. Alcohol Clin Exp Res 1999;23:735–744
147. Omidvari K, Casey R, Nelson S, et al. Alveolar macrophage release of tumor necrosis factor-alpha in chronic alcoholics without liver disease. Alcohol Clin Exp Res 1998;22:567–572
148. Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. Chest 2004;126:249–258
149. Kopko PM, Marshall CS, MacKenzie MR, et al. Transfusion-related acute lung injury: report of a clinical look-back investigation. JAMA 2002;287:1968–1971
150. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood 2003;101:454–462
151. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985;25:573–577
152. Kopko PM, Holland PV. Transfusion-related acute lung injury. Br J Haematol 1999;105:322–329
153. Silliman CC, Paterson AJ, Dickey WO, et al. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. Transfusion 1997;37:719–726
154. Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg 1999;178:570–572
155. Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. Can J Anaesth 1997;44:1256–1261
156. Dobbs LG, Gonzalez R, Matthay MA, et al. Highly water-permeable type I alveolar epithelial cells confer high water permeability between the airspace and vasculature in rat lung. Proc Natl Acad Sci USA 1998;95:2991–2996
157. Perkins GD, McAuley DF, Thickett DR, et al. The beta-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006;173:281–287
158. Folkesson HG, Matthay MA, Westrom BR, et al. Alveolar epithelial clearance of protein. J Appl Physiol 1996;80:1431–1445
159. Kim CF, Jackson EL, Woolfenden AE, et al. Identification of bronchioalveolar stem cells in normal lung and lung cancer. Cell 2005;121:823–835
160. Ware LB, Matthay MA. Keratinocyte and hepatocyte growth factors in the lung: roles in lung development, inflammation and repair. Am J Physiol Lung Cell Mol Physiol 2002;282:L924–L40
161. Atabai K, Ishigaki M, Geiser T, Ueki I, Matthay MA, Ware LB. Keratinocyte growth factor can enhance alveolar epithelial repair by nonmitogenic mechanisms. Am J Physiol: Lung Cell Mol Physiol 2002;283:L163–L169
162. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. Nat Med 2003;9:702–712
163. Burnham EL, Taylor WR, Quyyumi AA, et al. Increased circulating endothelial progenitor cells are associated with survival in acute lung injury. Am J Respir Crit Care Med 2005;172:854–860