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Emerging Role of Anticoagulants and Fibrinolytics in the Treatment of Acute Respiratory Distress Syndrome

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Abstract

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are associated with high mortality rates despite therapeutic advances. The pathogenesis of ALI and ARDS is similar to that of sepsis, as these disease states involve uncontrolled host defense responses that lead to inflammation, endothelial damage, enhanced coagulation, diminished fibrinolysis, and fibroproliferation. Recent studies of anticoagulants have shown positive outcomes in patients with severe sepsis. In addition, emerging evidence suggests that the use of anticoagulants, such as tissue factor pathway inhibitor, antithrombin, thrombomodulin, heparin, activated protein C, and fibrinolytics (plasminogen activators and particularly tissue plasminogen activator), may be useful in the treatment of ALI and ARDS. Data from experimental models of sepsis, ALI, and ARDS indicate that some of these agents improve lung function and oxygenation. Although clinical data are less convincing than these findings, results from clinical trials may influence the design of future studies.

Keywords

acute respiratory distress syndrome; ARDS; acute lung injury; ALI; inflammation; coagulation; fibrinolysis; tissue factor pathway inhibitor; activated protein C; thrombomodulin; antithrombin; heparin; plasminogen activators; t-PA; u-PA

Substantial progress has been made in the understanding of the pathophysiology of acute respiratory distress syndrome (ARDS) since it was initially described in 1967.[1] Enhanced coagulant activity was first recognized 31 years ago, when autopsy findings in patients with ARDS showed fibrin microthrombi in the alveoli and pulmonary vasculature that formed independent of clotting activity in the systemic circulation.[2] Amplified coagulation and inhibition of the fibrinolytic systems are intrinsic to the pathophysiology of sepsis, the most common underlying etiology of ARDS.[3] Emerging evidence demonstrates the substantial contribution of these systems in the pathogenesis of acute lung injury (ALI) and ARDS and their potential as therapeutic targets.[4-9]

Definitions and Epidemiology

Similar to sepsis syndrome, which ranges from infection to shock, ALI and ARDS are a continuum of a single pathologic process differing only in the severity of acute respiratory failure. Both ALI and ARDS are characterized by the acute development of bilateral infiltrates

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on chest radiographs and a pulmonary capillary wedge pressure of 18 mm Hg or lower or the absence of clinically evident left atrial hypertension.[10, 11] A difference between ARDS and ALI is the extent of impaired oxygenation, which is defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2). This ratio is 300 or less for ALI and 200 or less for ARDS.

The combined incidence of ALI and ARDS is estimated to be 20–75 cases/100,000 persons/year, with mortality rates of 30–75%. Only 10–25% of affected individuals die from ALI or ARDS as the primary cause; most deaths are attributable to pneumonia, sepsis, or multiorgan dysfunction. Approximately 2–3% of patients admitted to intensive care units develop ALI or ARDS.[12-15]

Pathophysiology

Diffuse alveolar damage is the hallmark of ARDS. This injury affects all parts of the alveolus —the epithelium, the endothelium, and the interstitial space. Initiating events that lead to diffuse alveolar damage and subsequently to ALI or ARDS include pneumonia, aspiration, pulmonary emboli, near-drowning, inhalation injury, reperfusion pulmonary edema, trauma, surgery, burn injury, drug overdose, acute pancreatitis, cardiopulmonary bypass, and massive blood transfusions (Figure 1).[3, 11, 16]

Overall, sepsis is associated with the highest risk of developing ALI or ARDS; 18–40% of patients with sepsis develop ALI or ARDS.[11-15] An uncontrolled host defense response that leads to inflammation, endothelial damage, enhanced coagulation, diminished fibrinolysis, and fibroproliferation in the lungs results in diffuse alveolar damage.[3-9, 13] It is not surprising that sepsis has the greatest propensity to cause ALI or ARDS because the early pathologic mechanisms of sepsis and those of ALI and ARDS are similar.[13] The primary difference is that ALI and ARDS are confined to the alveolocapillary units of the lungs, whereas sepsis is a systemic process that involves several organs. In addition, ALI and ARDS develop over several days to weeks (Figure 1), although their progression may be rapid, as is typical of sepsis.

Three overlapping phases—exudation, proliferation, and fibrosis—characterize ARDS. This article focuses on the involvement of the coagulation and fibrinolytic systems in the pathogenesis of ALI and ARDS during the exudative phase.[3-9] The exudative phase of ARDS is characterized by an influx of hyaline membranes and neutrophils (Figure 1). Hyaline membranes are homogenous eosinophilic structures that contain fibrin and cytoplasmic and nuclear debris from sloughed cells.[16] This cellular infiltration contributes to inflammation perpetuated by enhanced production of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-6, as well as by the loss of fibrinolytic and coagulation homeostasis.[3-9, 13]

The host defense to noxious stimuli involves an interactive network of pathways that act in synergy to increase the probability of survival. Responses are similar regardless of the tissue involved and consist of a complex cascade.[13] These adaptive responses are intended to be protective as they work in combination to confine or eliminate the noxious stimulus and to repair tissue damage. The formation of microthrombi and the deposition of fibrin in alveoli during ALI and ARDS are intended to limit the systemic invasion of the noxious stimulus when the primary insult occurs in the lungs and to minimize further pulmonary toxicity when the primary insult occurs systemically. Fibrin deposition may initially exert beneficial effects on gas exchange by sealing leakage sites in injured endothelium and epithelium.[3] However, if unregulated, the host response produces organ dysfunction rather than protection and tissue repair. In patients with ALI or ARDS, microthrombi and fibrin deposition leads to the activation of neutrophils and fibroblasts, to additional endothelial injury, to diminished surfactant production that favors alveolar collapse, to decreased alveolar fluid clearance, and to increased

pulmonary dead space (which itself is an independent predictor of mortality).[3, 13] These processes collectively lead to the activation and propagation of coagulation and the suppression of fibrinolysis.

Activation of Coagulation

The result of an unregulated host defense response is diffuse alveolar damage involving the epithelium, endothelium, and interstitial space.[3-9, 13] A key concept of the host response that has emerged over the past decade is the importance of the association between inflammation and coagulation. During the initial phase of injury, the host defense response produces inflammatory cytokines from lymphocytes, activated macrophages, and endothelium. These cytokines include but are not limited to interleukin-1, interleukin-6, and TNF-α. These inflammatory cytokines further contribute to endothelial damage that results in exposure of the cell surface and the production of tissue factor. Tissue factor is a 47-kD membrane-bound protein and the most potent initiator of the extrinsic coagulation cascade. When bound to factor VIIa, tissue factor catalyzes the activation of factor X, ultimately leading to thrombin generation and fibrin formation (Figure 2).[4-8] To be functionally active, tissue factor must be exposed on cell surfaces in an appropriate membrane microenvironment (e.g., pH, temperature).[6]

Regulation of tissue factor is complex. Circulating blood is normally exposed to only small amounts of tissue factor. However, when the endothelium is injured or when other pathophysiologic states occur, the expression of tissue factor by endothelial cells and monocytes is enhanced. A primary mechanism of enhanced expression involves activation of the transcription factor nuclear factor–κ B. Inflammatory cytokines activate nuclear factor–κ B, as do bacteria, bacterial products, reperfusion injury, and reactive oxygen species generated by neutrophils and macrophages.[4-8] Therefore, this mechanism of enhanced expression of tissue factor may be particularly important in ARDS and illustrates a likely link between inflammation and coagulation that is common to sepsis, ALI, and ARDS.

Data derived from serial samples of bronchoalveolar lavage fluid from patients with ARDS exemplify the relevance of tissue factor. Procoagulant activity increased at 3 days and subsided by 7 days.[17] An antibody to tissue factor blocked almost all of the procoagulant activity; this result suggested that tissue factor is the primary driver of coagulation in ALI and ARDS. Of note, the level of protein expression for tissue factor was correlated with intraalveolar concentrations of inflammatory cytokines, a finding that further supported the association between inflammation and coagulation.[8]

Increased concentrations of tissue factor in bronchoalveolar lavage fluid have been observed in various etiologies of ALI and ARDS, demonstrating a common pathologic mechanism.[18, 19] Although elevated plasma concentrations of tissue factor in patients with ALI and ARDS are associated with poor clinical outcomes and although they suggest that activated systemic coagulation may contribute to the pathogenesis of ALI and ARDS, recent in vitro data demonstrated that alveolar epithelium and macrophages can activate intraalveolar coagulation by increasing the activity of tissue factor.[6]

Another participant in activating the coagulation system during lung injury is tissue factor pathway inhibitor. Under normal conditions, approximately 85% of tissue factor pathway inhibitor is bound to endothelial cell surfaces, 5% is stored in platelets, and 10% circulates. Of the circulating portion, 90% is bound to lipoproteins (e.g., low-density lipoprotein cholesterol, high-density lipoprotein cholesterol).[20] Tissue factor pathway inhibitor is produced in the vascular endothelium and on the surface of platelets and requires binding to factor Xa to become active. This requirement indicates that coagulation must begin for tissue factor pathway inhibitor to function. The primary physiologic function of this protein is the inhibition of tissue

factor, which occurs when tissue factor pathway inhibitor binds to the tissue factor–factor VIIa–factor X complex and when it prevents the formation of factor Xa (Figure 2).[4-8]

During sepsis, increased levels of cytokines (e.g., TNF-α) prompt the release of tissue factor pathway inhibitor from the surfaces of endothelial cells. This process ultimately depletes tissue factor pathway inhibitor from the endothelium. Therefore, the rationale for administering this inhibitor to patients with severe sepsis is to restore pools of tissue factor pathway inhibitor and to protect the endothelium from tissue factor–mediated injury.[21] This therapeutic effect of tissue factor pathway inhibitor was demonstrated in various animal models of sepsis in which its administration offered protection against organ dysfunction and mortality.[22-24] The same models demonstrated that the inhibitor attenuated the influx of neutrophils into the lung; however, it had a limited effect on alveolar-capillary permeability.[25, 26] Specific blockade of tissue factor with inactivated factor VIIa decreased intraalveolar inflammation, fibrin production, and protein leakage.[27-29]

Propagation of Coagulation

The protein C pathway is an important regulator of blood coagulation. Protein C is a hepatically synthesized vitamin K–dependent glycoprotein that circulates as an inactive zymogen. Activated protein C is also a normal circulating component of plasma. It is produced when protein C interacts with the thrombin-thrombomodulin complex (Figure 2). Activated protein C subsequently suppresses thrombin generation by inhibiting the expression of tissue factor and by proteolytically inactivating factors Va and VIIIa. In addition, activated protein C diminishes the activity of plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor, enhancing fibrinolysis. Finally, activated protein C inhibits thrombin-mediated inflammation, attachment of leukocytes to the endothelium, and neutrophil activation.[4-8]

Activated protein C also plays an important physiologic role in maintaining vascular patency. As the concentration of thrombin increases (e.g., during thrombus formation), most of it binds to thrombomodulin on the endothelial cell surface, activating protein C. This function of activated protein C is exaggerated in the capillary beds. Because thrombomodulin is uniformly expressed on the endothelium throughout the circulation, the ratio of thrombomodulin:blood volume is higher in capillaries than in large vessels. Capillary patency is maintained because, as thrombin moves through the capillaries, it binds to thrombomodulin, resulting in the rapid activation of protein C.[30]

In patients with sepsis, ventilator-associated pneumonia, ALI, or ARDS, coagulation is propagated because the protein C system is suppressed.[4-8] This suppression is partly due to a reduction in thrombomodulin on endothelial cell surfaces secondary to oxidation and shedding.[31, 32] In addition, interleukin-1 and TNF-α down-regulate the endothelial production of thrombomodulin.[4-8]

Oxygenation measured by using the PaO_2:FiO_2 ratio is lowest in patients with sepsis and disseminated intravascular coagulopathy.[33] Animal models of ALI have demonstrated that activated protein C downregulates nuclear factor–κ B, reducing TNF-α and interleukin-1β concentrations in pulmonary edema fluid.[34-37] These finding illustrate the antiinflammatory activity of activated protein C, which further substantiates the association between inflammation and coagulation.

Although the lung has a limited capacity to produce protein C, activated protein C is present in bronchoalveolar lavage fluid. In animal models of ALI, the administration of thrombomodulin reduced the accumulation of leukocytes, vascular permeability, inflammation, and interstitial pulmonary edema in a manner correlated with its ability to

generate activated protein C.[38-41] In several experimental models of endotoxemia, ALI, or ARDS, activated protein C prevented lung injury and improved oxygenation.[34-37, 42, 43] Therefore, decreased activation of protein C on the pulmonary endothelium contributes to microvascular thrombosis and inflammation, which may contribute to detrimental outcomes.

An evaluation of 779 patients from the Acute Respiratory Distress Syndrome Network clinical trial of low versus high tidal volume showed that low plasma concentrations of protein C and elevated concentrations of PAI-1 were independent predictors of mortality.[44] When patients with sepsis were excluded from the analysis, the predictive values of these markers were unchanged. This result suggests that altered regulation of coagulation and fibrinolysis are associated with ALI and ARDS regardless of the etiology. Of interest, low tidal volume reduced mortality but did not alter plasma concentrations of protein C or PAI-1.

Antithrombin, a serine protease inhibitor, limits thrombin activity by forming a thrombinantithrombin complex that the reticuloendothelial system removes from the circulation.[4-8] The inhibitory actions of antithrombin on coagulation pathways, together with heparin or tissue factor pathway inhibitor, inactivate the tissue factor–factor VIIa complex. In patients with severe sepsis, low plasma concentrations of antithrombin are correlated with the development of ALI or ARDS and promulgate coagulation.[33, 45]

Antithrombin binds to proteoglycans and glycosaminoglycans (e.g., heparin) on endothelial surfaces. Antithrombin must bind to heparin to inactivate thrombin and reduce fibrin formation. In the absence of heparin, antithrombin binds to the other moieties of endothelial surfaces to act as an anticoagulant and stimulate prostacyclin production. Prostacyclin inhibits platelet aggregation, diminishes synthesis of proinflammatory cytokines, attenuates neutrophilic activation, and reduces the release of reactive oxygen species.[4-8]

In animal models of lung injury, intravenous antithrombin reduced vascular injury, accumulation of leukocytes, and vascular permeability.[46-49] However, concurrent administration of unfractionated heparin and antithrombin did not prevent lung injury.[50] The administration of antithrombin in the presence of indomethacin, an inhibitor of prostacyclin production, likewise did not prevent lung injury.[50, 51] These data suggest that prostacyclin mediates the antiinflammatory properties of antithrombin, which represent the primary mechanism of the protective activity of antithrombin in lung injury. The dose of antithrombin needed to prevent endothelial cell injury and reduce inflammation exceeded the dose required to inhibit coagulation.[46]

Impaired Fibrinolysis

Fibrin degradation by the plasminogen system normally balances fibrin formation involving the tissue factor and protein C pathways. Just as a shift toward procoagulant activity occurs in sepsis, ALI, and ARDS by upregulating tissue factor and downregulating activated protein C, inhibition of fibrinolysis occurs by increasing levels of PAI-1 and thrombin-activatable fibrinolysis inhibitor.[4-8]

The two types of plasminogen activators are urokinase plasminogen activator (u-PA) and tissue plasminogen activator (t-PA). Although both can activate plasminogen, u-PA is a cell-surface protein resulting in fibrinolysis at the tissue level, whereas t-PA is found in the vascular compartment and causes intravascular thrombolysis. For u-PA to produce fibrinolysis, it must bind to a plasminogen activator receptor at the tissue level for activation. In contrast, t-PA does not; it is a weak protease until it binds to fibrin, when its activity is enhanced.

During acute illness, upregulation of the fibrinolytic system leads to acute fibrinolysis.[4-8] In particular, sepsis is associated with enhanced production of t-PA, which is important in host

defense responses and which is independent of the proteolytic function of the protein.[52] However, this initial response is quickly followed by rapid and sustained generation of PAI-1 and thrombin-activatable fibrinolysis inhibitor, with subsequent inhibition of plasminogen activator resulting in microvascular thrombosis and ischemia.[4-8] As in the tissue factor and protein C pathways, PAI-1 activity is closely linked to inflammation. The inflammatory cytokines interleukin-1β and TNF-α promote the production of PAI-1, and their blockade in animal models of sepsis reduced, but did not entirely attenuate, this response.[53, 54] This result may partly be due to sepsis-induced suppression of activated protein C activity, which may permit enhancement of PAI-1 activity (Figure 2). In similar fashion, thrombin-activatable fibrinolysis inhibitor production is upregulated. However, unlike PAI-1 production, synthesis of thrombin-activatable fibrinolysis inhibitor is due to the limited activity of thrombomodulin, which allows thrombin to promote clot formation (Figure 2).[4-8]

Under normal conditions, human macrophages express plasminogen activator and can degrade an insoluble fibrin matrix in the presence of plasminogen. However, in ARDS, the exposure of macrophages to inflammatory stimuli enhances their expression of PAI-1.[55-57] Coupled with a reduction in t-PA production by endothelial cells, the t-PA:PAI-1 ratio, which is normally 1, is reduced in ARDS.[4, 58, 59] Further exemplifying this disruption in fibrinolytic homeostasis is the disproportionately high concentrations of PAI-1 versus u-PA in bronchoalveolar lavage fluid and plasma among patients with ALI as opposed to control patients with hydrostatic pulmonary edema.[18, 59, 60] Of interest, the substantially higher PAI-1 concentrations in bronchoalveolar lavage fluid than in plasma suggest an intraalveolar source of PAI-1 during ALI.[60] In small studies, concentrations of PAI-1 in bronchoalveolar lavage fluid were correlated with negative clinical outcomes.[61, 62] Only the evaluation of low tidal volume in 779 patients with ALI or ARDS showed an association between plasma PAI-1 concentrations and mortality.[44]

Fibroproliferation

Although some patients with ARDS die or recover during the first week of the disease, most progress to the late, or subacute, phase (Figure 1). During the proliferative phase of ARDS, the alveolar spaces fill with mesenchymal cells, and new blood vessels form. The lungs develop interstitial and alveolar fibrosis, and type II collagen cells proliferate. These changes can lead to extensive pulmonary fibrosis (fibrotic phase) and the development of emphysematous regions in the lungs.[4-8, 10] Nevertheless, in most patients who survive, pulmonary function returns to near-normal in the first year. Patients who have persistent lung dysfunction are those whose disease was severe and prolonged ≥ 14 days). All survivors of ARDS report having a reduced quality of life.[14, 15, 63]

At present, no definitive pharmacotherapy for ALI or ARDS is available. Failed therapies include antioxidants (*N*-acetylcysteine or procysteine), ketoconazole, pentoxifylline or lisofylline, and systemic vasodilators. Inhaled vasodilators, such as nitric oxide, prostacyclin, or liposomal prostaglandin E_1, target delivery to pulmonary vasculature receiving the best ventilation and rapidly improve oxygenation for 24–72 hours. However, the lack of a sustained clinical benefit precludes the routine use of inhaled vasodilators. Treatment with aerosolized β_2-adrenergic agonists enhances the clearance of alveolar epithelial fluid and may reduce endothelial permeability. These agents also possess weak antiinflammatory activity.[11, 12, 64] For example, albuterol significantly reduced extravascular lung water in 40 patients with ARDS.[65]

Systemic administration of corticosteroids reduces pulmonary inflammation, as evidenced by decreased concentrations of inflammatory cytokines in bronchoalveolar lavage fluid.[13] Markers of fibrin deposition and collagen formation are also reduced, further demonstrating the interaction between inflammation and coagulation.[13] Methylprednisolone administered

within 14 days of the onset of ARDS and continued for several weeks improved oxygenation and lung injury, shortened mechanical ventilation, and arguably reduced the mortality risk.[66-68] Administration of corticosteroids after 14 days was associated with morbidity and mortality.[68] After the disorder progresses from inflammation to fibrosis, the adverse effects of antiinflammatory therapies likely outweigh any potential benefit. The only nonpharmacologic therapy with a proven mortality benefit is ventilation with low tidal volume (6 ml/kg ideal body weight).[44]

A conservative fluid management strategy (i.e., maintaining euvolemia) improves oxygenation and lung injury scores and shortens the duration of mechanical ventilation.[69] Use of nutritional products enriched with omega-3 fatty acids (eicosapentaenoic acid and γ-linoleic acid) and antioxidants reduced mortality and shortened ventilation requirements in populations with ARDS and sepsis, but studies were limited by their small numbers, by the lack of intent-to-treat analyses, and by the fact that control groups used products with high amounts of omega-6 fatty acids.[70, 71] The Acute Respiratory Distress Syndrome Network is conducting a study of supplementation with omega-3 fatty acid that should provide necessary information before these nutritional products are clinically applied.

Other nonpharmacologic therapies that improve oxygenation are prone positioning of patients, partial liquid ventilation, and high-frequency oscillatory ventilation.[11, 12, 64] None of these are standard therapies. Therefore, definitive treatment of patients with ARDS includes ventilation with low tidal volume and euvolemic fluid management. Corticosteroids may be administered during the first 14 days of ARDS, but this practice remains controversial. Despite the lack of data supporting efficacy, aerosolized β_2-adrenergic agonists are frequently administered. Given the evidence supporting the loss of coagulation and fibrinolysis homeostasis during ARDS, recent therapies are directed at reestablishing balance between these pathways.

Pharmacotherapy

Tissue Factor Pathway Inhibitor

Experimental data from baboon and rat studies showed that the administration of tissue factor pathway inhibitor or factor VIIa inhibitor reduced lung injury and systemic levels of inflammatory cytokines.[22-29] These studies were extended to humans by using the recombinant tissue factor pathway inhibitor tifacogin. This product is produced by using recombinant DNA technology in which tissue factor pathway inhibitor is expressed in *Escherichia coli*. Recombinant tissue factor pathway inhibitor differs from the human native protein by a single additional alanine at the amino terminus, and it is not glycosylated.

A phase II, randomized, placebo-controlled, dose-escalation trial of recombinant tissue factor pathway inhibitor 0.025–0.05 mg/kg/hour for 96 hours was conducted in 210 patients with severe sepsis.[21] Administration of the drug produced a 20% relative reduction in the 28-day all-cause mortality rate. Logistic regression modeling indicated the beneficial effect was most pronounced in patients with an elevated pretreatment international normalized ratio (INR). Among 116 patients with ARDS at the start of treatment, the mortality rate was significantly lower in the group receiving recombinant tissue factor pathway inhibitor than in others (37% vs 57%, p=0.045). In addition, the degree of improvement in pulmonary function was greater in the group given the pathway inhibitor than in other patients (response rate 32% vs 14%, p=0.056).

A phase III trial of recombinant tissue factor pathway inhibitor dosed at 0.025 mg/kg/hour for 96 hours included 1754 patients with severe sepsis and coagulopathy (INR ≥ 1.2).[72] About 86% of patients had ALI (PaO_2:$FiO_2 \leq 300$), although chest radiographic abnormalities may

not have been simultaneously present, and 201 patients had sepsis without coagulopathy (INR < 1.2). During the first planned interim evaluation of the initial 722 patients, treatment was associated with a large 28-day mortality benefit compared with placebo (mortality rate 29.1% vs 38.9%, p=0.006). However, this benefit was lost among the 1955 patients who completed the study (treatment 34.2% vs placebo 33.9%, p=0.88).

In contrast to the phase II study, the phase III study showed a low mortality rate in the group given tissue factor pathway inhibitor only when patients with low INRs were evaluated (12% vs 22.9%, p=0.03), although the pathway inhibitor attenuated the production of thrombin-antithrombin complex over a range of INRs. In the phase III study, mortality rates in the treatment and placebo groups were similar when the subgroup of patients with baseline PaO_2:FiO_2 of 300 or less was analyzed (treatment 35% vs placebo 34.4%). The investigators did not report the occurrence of new organ dysfunction. Therefore, whether recombinant tissue factor pathway inhibitor affected the onset of ALI or ARDS was not determined. Occurrence rates of adverse events with or without bleeding were similar between the placebo and treatment groups in both studies. However, the frequency of bleeding was higher in patients treated with recombinant tissue factor pathway inhibitor (INR ≥ 1.2) than placebo (INR ≥ 1.2) in the phase III study (24% vs 19%, p=0.008).

Given the apparent importance of tissue factor in the pathogenesis of ARDS, results of the phase III study are disappointing and somewhat unexpected. One possible explanation for the outcomes is that sufficient inhibition of tissue factor was not achieved with the lowest dosage assessed in the phase II study. This is relevant because organ protection is correlated with the amount of tissue factor inhibition.[4-8] Therefore, if pulmonary anticoagulation and antiinflammation were not achieved, production of thrombin, fibrin, and blockage of inflammatory mediators might have been insufficient to demonstrate a benefit. In addition, the selection of patients with coagulopathy might have prevented the observation of a beneficial effect, although the phase II study showed enhanced benefits as INR increased. Moreover, coagulopathy has many etiologies that may not respond equally to exogenous tissue factor pathway inhibitor. Baseline presence of coagulopathy may indicate a disease state that has progressed and that is unlikely to respond to anticoagulation-antiinflammation therapy. Finally, an elevated baseline INR likely increases the risk of hemorrhage when anticoagulation therapy is started.

Before randomized controlled trials are conducted in patients with ALI and ARDS, the mechanisms of tissue factor–mediated coagulation and inflammation specific to ALI and ARDS must be fully elucidated, and the utility of surrogate markers, such as the magnitude of tissue factor inhibition, must be assessed.[4-8] An international placebo-controlled trial is being conducted to assess the use of tissue factor pathway inhibitor in 2100 patients with severe community-acquired pneumonia.[73]

Activated Protein C

In patients with ARDS, concentrations of activated protein C are low, and these low levels in the bronchoalveolar lavage fluid appear to be correlated with poor outcomes.[4, 32, 33, 44] In patients with sepsis, protein C deficiency (defined as a plasma level < 80% of normal) is common and also correlated with poor outcomes.[8, 74-78]

A double-blind, placebo-controlled study of recombinant activated protein C (drotrecogin alfa [activated]) was performed in a human model of endotoxin-induced lung injury.[79] Recombinant activated protein C significantly reduced leukocyte accumulation and neutrophil chemotaxis in the airspaces. In addition, intravenous administration of recombinant activated protein C resulted in detectable levels of activated protein C in the lung, a result supporting the utility of this route of delivery to treat ARDS.[80]

Drotrecogin alfa (activated) is the first United States Food and Drug Administration–approved treatment for severe sepsis in patients who are at high risk for death. It is produced by means of recombinant DNA technology in which a human cell line that possesses the complementary DNA for the inactive human protein C is used. Purified protein C is then activated by exposing it to thrombin. The resulting recombinant activated protein C has the same amino acid sequence and glycosylation pattern as those of the native human protein.

In a phase III trial, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), 1690 patients with severe sepsis received activated protein C 24 μg/kg/hour for 96 hours within 48 hours of the onset of organ dysfunction.[78] Treatment reduced the mortality rate versus placebo (24.7% vs 30.8%, p=0.005), resulting in a 19.4% reduction in the relative risk of death. In addition, patients receiving activated protein C had more ventilator-free days than did other patients (14.3 vs 13.2 days, p=0.049). However, the benefits of treatment were associated with a heightened frequency of serious bleeding (3.5% vs 2.0%, p=0.06). Therefore, this risk must be weighed against the benefit of activated protein C.

Patients with and those without protein C deficiency benefited from treatment with activated protein C. This outcome suggests that this therapy could have broad utility in patients with ARDS. In addition, these results provide evidence that activated protein C does not elicit its therapeutic effect by correcting protein C deficiency. Plasma concentrations of both D-dimer and interleukin-6 substantially decreased with activated protein C, a change demonstrating that activated protein C reduced fibrin formation and inflammation.

Among patients with baseline respiratory dysfunction, post hoc analysis showed that the time to resolution was considerably shorter in patients receiving activated protein C than those given placebo.[80] Rates of new-onset respiratory dysfunction were not lowered with activated protein C.

Economic evaluations of activated protein C for severe sepsis showed that the use of activated protein C was cost-effective only in patients with severe sepsis (Acute Physiology and Chronic Health Evaluation [APACHE] II score $\geq$ 25) who had a reasonable life expectancy.[81, 82] Given the results of PROWESS, activated protein C treatment is anticipated to benefit patients with ARDS. A phase II, randomized, double-blind study sponsored by the National Institutes of Health is under way to assess activated protein C for the treatment of ALI.[83]

Thrombomodulin and Antithrombin

To our knowledge, no clinical trials of thrombomodulin have been completed. However, in rat models of lipopolysaccharide-induced sepsis, the administration of recombinant soluble or recombinant human thrombomodulin reduced fibrin deposition in alveolar arterioles, microthrombi, leukocyte accumulation, vascular permeability, and edema.[38-41] In addition, the safety of recombinant human thrombomodulin has been demonstrated in healthy volunteers.[84] These data support the rationale for clinical trials of recombinant human thrombomodulin in patients with severe sepsis, ALI, or ARDS. Studies of recombinant human thrombomodulin to manage sepsis-induced disseminated intravascular coagulopathy are under way.

Several animal models of lipopolysaccharide-induced sepsis have shown that antithrombin reduced vascular injury, permeability, leukocyte infiltration, hypoxemia, and pulmonary inflammation.[46-49] Many of these effects are likely secondary to an antithrombin-induced production of prostacyclin.[50, 51] Several phase II studies of antithrombin for severe sepsis showed nonsignificant improvements in survival, but changes in lung function were not reported.[85-88] A study of 40 patients with trauma did not demonstrate any influence of

antithrombin on respiratory failure or on the duration of mechanical ventilation, although the duration of ARDS was shortened.[89] Of note, levels of thrombin-antithrombin complex decreased, but PAI-1, neutrophil elastase, and inflammatory cytokines were unaffected.

A meta-analysis of these small studies demonstrated a 22.9% reduction in 30-day mortality with antithrombin therapy.[6] This finding led to a phase III trial of antithrombin, with a total of 30,000 IU given over 96 hours.[90] Researchers enrolled 2314 patients within 6 hours of the onset of severe sepsis. Overall, 28-day mortality rates were similar between groups (treatment 38.9% vs placebo 38.7%, p=0.94). Among 698 patients not using heparin, the 28-day mortality rate was not significantly lower in those given antithrombin therapy compared with those given placebo (37.8% vs 43.6%, p=0.08), but a beneficial trend was significant after 90 days in 686 patients (44.9% vs 52.5%, p=0.03). Patients who received both antithrombin and heparin had more instances of bleeding than did patients receiving placebo (23.8% vs 13.5%, p<0.001). Changes in lung function were not reported, but rates of pulmonary dysfunction were similar between the groups (treatment 22.5% vs placebo 26.6%).

Although the results of this study do not support further clinical investigation of antithrombin, the different outcomes depending on the use of concomitant heparin provide further evidence of the importance of coagulation and impaired fibrinolysis in the pathogenesis of sepsis and ARDS. They also highlight the complex nature of the intertwined cascades.

Unfractionated and Low-Molecular-Weight Heparins

To our knowledge, no randomized controlled trials of unfractionated heparin or low-molecular-weight heparin have been conducted in the setting of ALI or ARDS. The effectiveness of heparin in blocking fibrin deposition in the lung, with subsequent improvement in pulmonary function, is controversial. In dogs, a large dose of unfractionated heparin 500 U/kg effectively blocked pulmonary deposition of fibrin after microembolization.[91] By contrast, fibrin deposition was unaltered with heparin 3000 U/kg in a similar microembolization model in sheep.[92]

Both experimental and clinical evidence suggest that heparins have antiinflammatory activity in addition to anticoagulant activity.[93] Heparin and low-molecular-weight heparin inhibit lipopolysaccharide-induced genetic expression of proinflammatory cytokine in monocytes by suppressing the activation of nuclear factor–κ B independent of their anticoagulant activity.[93, 94] In an ovine smoke-inhalation model, heparin 400 U/kg followed by an infusion to maintain an activated clotting time of 250–300 seconds reduced pulmonary edema and improved oxygenation at 12–72 hours.[95] However, lung infiltration by leukocytes and production of reactive oxygen species were similar to what was observed in controls. Other experimental models involving heparin showed variable improvement in oxygenation, but all results confirmed that heparin did not affect the accumulation of leukocytes.[8, 12, 96, 97] To our knowledge, low-molecular-weight heparins have not been assessed in animal models or humans in this setting. Based on the results from experimental models, the clinical utility of heparins for the treatment of ARDS has not been pursued.

Plasminogen Activators

The disease ARDS is associated with the formation of microclots in the lung vasculature with subsequent pulmonary hypertension. Exogenous plasminogen activators have different physiologic effects.[43] Both u-PA and streptokinase enhance inflammation, whereas t-PA possesses antiinflammatory activity and reduces apoptosis independent of its proteolytic action.[98, 99] In ARDS, a paucity of t-PA in the lungs is coupled with an increase in PAI-1.[4, 6-8, 17, 58] Experimental evidence supports the potential use of plasminogen activators for ARDS, but clinical data are lacking.[100] A porcine model of lethal trauma–induced ALI showed

that the administration of u-PA 250,000 U given over 44 hours or t-PA 50 mg given over 9 hours prevented hypoxemia and improved survival.[101] Pulmonary hemorrhage and neutrophil accumulation were not apparent on autopsy.

In two uncontrolled studies, patients with trauma or sepsis were given u-PA, t-PA, or streptokinase.[102, 103] Streptokinase was systemically administered as a 60,000-U/kg bolus followed by 15,000 U/kg/hour for a mean of 60 hours; u-PA 455 U/kg was given over 10 minutes, then 455 U/kg/hour for 24 hours; and t-PA 50 mg was administered over 9 hours. Both u-PA and tPA improved oxygenation in the absence of bleeding and changed clotting times. However, the studies were small, they involved a broad dosage range, and they were not placebo controlled. As a result, conclusions about efficacy and safety could not be made. In addition, the choice of plasminogen activator was arbitrary; therefore, it was not possible to determine differences in efficacy among the agents. It is reasonable to expect that efficacies differ because data from experimental models varied with the type and dosage of the plasminogen activator. It is important to note that the dose of t-PA required for antiinflammatory activity was higher than that needed for fibrinolysis.[99, 104]

Because a high dose of t-PA can substantially increase the risk of bleeding, systemic administration of t-PA is not reasonable. Therefore, to circumvent this problem, we considered the possibility of targeted pulmonary delivery of t-PA and, in doing so, developed a pulmonary formulation of the drug (BioTherapeutics, LLC, Denver, CO, and HTD Biosystems, Inc., Hercules, CA). We subsequently demonstrated the feasibility of this formulation by showing that it could be nebulized without a loss of protein integrity or function.[105] In addition, nebulization of the pulmonary formulation of t-PA into a human cadaver model resulted in a respirable dose of 65%, establishing that the protein distributed to the lower airways of the lungs. Work is being conducted to characterize the safety and efficacy of the pulmonary formulation of t-PA in an experimental model of ARDS with the intention of moving to clinical trials.

Conclusion

Sepsis is the leading cause of death in critically ill patients in the Western world and the most common underlying etiology of ARDS. The pathophysiology of ALI and ARDS is similar to that of severe sepsis, as they all involve an uncontrolled host defense response. Under normal conditions, coagulation and fibrin deposition are controlled in the systemic circulation and lungs. In severe sepsis, ALI, and ARDS, these systems shift toward states of procoagulation and antifibrinolysis in the setting of uncontrolled inflammation. Inflammatory mediators perpetuate this response by impairing anticoagulation and fibrinolysis. In turn, the formation of thrombin augments the inflammatory response and worsens injury. In ALI and ARDS, fibrin deposition and subsequent degradation stimulate fibroblast aggregation and collagen secretion, leading to pulmonary fibrosis.

Animal studies have consistently demonstrated a reduction in lung injury and/or improved oxygenation with the administration of anticoagulants, such as recombinant tissue factor pathway inhibitor, antithrombin, recombinant human thrombomodulin, heparin, and recombinant activated protein C. These agents also possess antiinflammatory and fibrinolytic activities of various capacities. However, data from clinical studies are less convincing than results from animal studies. In a phase II study of severe sepsis, recombinant tissue factor pathway inhibitor improved lung function and survival in patients with ARDS at baseline. A phase III study, however, did not show improvement in overall survival and did not report changes in organ function. Antithrombin similarly demonstrated benefits in most small studies but did not alter 30-day mortality in the phase III study of severe sepsis. The concomitant use of heparin may have influenced the results, as a trend toward survival benefit was observed in the absence of heparin. Again, lung function was not reported.

To our knowledge, thrombomodulin and heparin have not been evaluated in clinical trials with a rigorous scientific approach. Only the administration of recombinant activated protein C in patients with severe sepsis has reduced mortality rates, hastened recovery of respiratory function, and shortened the duration of mechanical ventilation. However, given the high cost and risk of hemorrhage, use of recombinant activated protein C cannot be recommended to treat ALI or ARDS until studies demonstrate a definitive benefit in patients with this disease. Ongoing studies of anticoagulants are anticipated to provide additional information regarding the clinical application of these agents.

The degradation of fibrin may be as important as limiting inflammation and coagulation. Plasminogen activators improved oxygenation in animals and in critically ill patients in small, uncontrolled studies. However, large-scale studies have not been conducted. The choice of plasminogen activator likely matters, as only t-PA possesses antiinflammatory properties; however, these properties are apparent at doses higher than those required for fibrinolysis. As a consequence, the concern about hemorrhage may prevent the study of these agents in systemic administration. Targeted pulmonary administration may prove to be the best route of administration for the clinical evaluation of plasminogen activators.

In the past, clinical evaluations of pharmacotherapy for ARDS were conducted in sequence instead of in parallel or in combination, and little consideration has been given to multipronged approaches. Given the complexity of the disease, a single agent is unlikely to serve as a sole therapeutic option. The pathogenesis of ARDS is still not fully understood, and this limitation, too, may impede progress in identifying feasible therapeutic agents. The intricacies of ARDS has certainly made the identification of effective pharmacotherapy difficult. The fact that promising experimental data have not translated to efficacy in clinical studies further confounds this problem. A contributing factor may be the lack of novel experimental models that accurately mimic the clinical situation of ARDS. Therefore, advances in the treatment of ARDS may be stifled unless innovative preclinical models of ARDS are developed in parallel with clinical work.

A considerable body of evidence now proposes that disrupted coagulation and fibrinolytic homeostasis participates in the pathogenesis of ARDS. Emerging animal and clinical data suggest that pharmacotherapy targeted at these systems may be advantageous. However, much remains to be learned about the efficacy, safety, mechanism of action, and optimal delivery route of these agents in the management of ALI or ARDS.

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References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2:319–23. [PubMed: 4143721]
2. Bone RC, Francis PB, Pierce AK. Intravascular coagulation associated with the adult respiratory distress syndrome. Am J Med 1976;61:585–9. [PubMed: 984062]
3. Ware LB. Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Semin Respir Crit Care Med 2006;27:337–49. [PubMed: 16909368]
4. Ware LB, Bastarache JA, Wang L. Coagulation and fibrinolysis in human acute lung injury: new therapeutic targets? Keio J Med 2005;54:142–9. [PubMed: 16237276]
5. Ware LB, Camerer E, Welty-Wolf KE, Schultz MJ, Matthay MA. Bench to bedside: targeting coagulation and fibrinolysis in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2006;291 (3):L307–11. [PubMed: 16648240]

6. Bastarache JA, Ware LB, Bernard GR. The role of the coagulation cascade in the continuum of sepsis and acute lung injury and acute respiratory distress syndrome. Semin Respir Crit Care Med 2006;27:365–76. [PubMed: 16909370]
7. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia: a review. Crit Care Med 2006;34:871–7. [PubMed: 16521285]
8. Laterre PF, Wittebole X, Dhainaut JF. Anticoagulant therapy in acute lung injury. Crit Care Med 2003;31:S329–36. [PubMed: 12682461]
9. Sapru A, Wiemels JL, Witte JS, Ware LB, Matthay MA. Acute lung injury and the coagulation pathway: potential role of gene polymorphisms in the protein C and fibrinolytic pathways. Intensive Care Med 2006;32(9):1293–303. [PubMed: 16770611]
10. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol 2005;33:319–27. [PubMed: 16172252]
11. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334–49. [PubMed: 10793167]
12. Cepkova M, Matthay MA. Pharmacotherapy of acute lung injury and the acute respiratory distress syndrome. J Intensive Care Med 2006;21:119–43. [PubMed: 16672636]
13. MacLaren R, Jung R. Stress-dose corticosteroid therapy for sepsis and acute lung injury or acute respiratory distress syndrome in critically ill adults. Pharmacotherapy 2002;22:1140–56. [PubMed: 12222550]
14. Frutos-Vivar F, Ferguson ND, Esteban A. Epidemiology of acute lung injury and acute respiratory distress syndrome. Semin Respir Crit Care Med 2006;27:327–36. [PubMed: 16909367]
15. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685–93. [PubMed: 16236739]
16. Mendez JL, Hubmayr RD. New insights into the pathology of acute respiratory failure. Curr Opin Crit Care 2005;11:29–36. [PubMed: 15659942]
17. Idell S, Koenig KB, Fair DS, Martin TR, McLarty J, Maunder RJ. Serial abnormalities of fibrin turnover in evolving adult respiratory distress syndrome. Am J Physiol 1991;261:L240–8. [PubMed: 1928357]
18. Gunther A, Mosavi P, Heinemann S, et al. Alveolar fibrin formation caused by enhanced procoagulant and depressed fibrinolytic capacities in severe pneumonia: comparison with the acute respiratory distress syndrome. Am J Respir Crit Care Med 2000;161:454–62. [PubMed: 10673185]
19. Gando S, Nanzaki S, Morimoto Y, Kobayashi S, Kemmotsu O. Systemic activation of tissue-factor dependent coagulation pathway in evolving acute respiratory distress syndrome in patients with trauma and sepsis. J Trauma 1999;47:719–23. [PubMed: 10528607]
20. Lindahl AK, Sandset PM, Abildgaard U. The present status of tissue factor pathway inhibitor. Blood Coagul Fibrinolysis 1992;3:439–49. [PubMed: 1420819]
21. Abraham E, Reinhart K, Svoboda P, et al. Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: a multicenter, randomized, placebo-controlled, single-blind, dose escalation study. Crit Care Med 2001;29:2081–9. [PubMed: 11700399]
22. Creasey AA, Chang AC, Feigen L, Wun TC, Taylor FB Jr, Hinshaw LB. Tissue factor pathway inhibitor reduces mortality from *Escherichia coli* septic shock. J Clin Invest 1993;91:2850–60. [PubMed: 8514893]
23. Camerota AJ, Creasey AA, Patla V, Larkin VA, Fink MP. Delayed treatment with recombinant human tissue factor pathway inhibitor improves survival in rabbits with gramnegative peritonitis. J Infect Dis 1998;177:668–76. [PubMed: 9498446]
24. Opal SM, Palardy JE, Parejo NA, Creasey AA. The activity of tissue factor pathway inhibitor in experimental models of superantigen-induced shock and polymicrobial intra abdominal sepsis. Crit Care Med 2001;29:13–17. [PubMed: 11176151]
25. Enkhbaatar P, Okajima K, Murakami K, et al. Recombinant tissue factor pathway inhibitor reduces lipopolysaccharide induced pulmonary vascular injury by inhibiting leukocyte activation. Am J Respir Crit Care Med 2000;162:1752–9. [PubMed: 11069808]

26. Miller DL, Welty-Wolf K, Carraway MS, et al. Extrinsic coagulation blockade attenuates lung injury and proinflammatory cytokine release after intratracheal lipopolysaccharide. Am J Respir Cell Mol Biol 2002;26:650–8. [PubMed: 12034563]
27. Welty-Wolf KE, Carraway MS, Miller DL, et al. Coagulation blockade prevents sepsis-induced respiratory and renal failure in baboons. Am J Respir Crit Care Med 2001;164:1988–96. [PubMed: 11734456]
28. Carraway MS, Welty-Wolf KE, Miller DL, et al. Blockade of tissue factor: treatment for organ injury in established sepsis. Am J Respir Crit Care Med 2003;167:1200–9. [PubMed: 12714343]
29. Welty-Wolf KE, Carraway MS, Ortel TL, et al. Blockade of tissue factor-factor X binding attenuates sepsis-induced respiratory and renal failure. Am J Physiol Lung Cell Mol Physiol 2006;290:L21–31. [PubMed: 16100288]
30. Esmon CT. The protein C pathway. Chest 2003;124:26S–32. [PubMed: 12970121]
31. Redl H, Schlag G, Schiesser A, Davies J. Thrombomodulin release in baboon sepsis: its dependence on the dose of *Escherichia coli* and the presence of tumor necrosis factor. J Infect Dis 1995;171:1522–7. [PubMed: 7769287]
32. Ware LB, Fang X, Matthay MA. Protein C and thrombomodulin in human acute lung injury. Am J Physiol Lung Cell Mol Physiol 2003;285:L514–21. [PubMed: 12754194]
33. Fourrier F, Chopin C, Goudemand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest 1992;101:816–23. [PubMed: 1531791]
34. Murakami K, Okajima K, Uchiba M, et al. Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production. Am J Physiol 1997;272:L197–202. [PubMed: 9124369]
35. Yamamoto K, Loskutoff DJ. Extrahepatic expression and regulation of protein C in the mouse. Am J Pathol 1998;153:547–55. [PubMed: 9708814]
36. Taylor FB Jr. Studies on the inflammatory-coagulant axis in the baboon response to *E. coli*: regulatory roles of proteins C, S, C4bBP and of inhibitors of tissue factor. Prog Clin Biol Res 1994;388:175–94. [PubMed: 7831358]
37. Yasui H, Gabazza EC, Tamaki S, et al. Intratracheal administration of activated protein C inhibits bleomycin-induced lung fibrosis in the mouse. Am J Respir Crit Care Med 2001;163:1660–8. [PubMed: 11401891]
38. Hasegawa N, Kandra TG, Husari AW, et al. The effects of recombinant human thrombomodulin on endotoxin-induced multiple-system organ failure in rats. Am J Respir Crit Care Med 1996;153:1831–7. [PubMed: 8665042]
39. Uchiba M, Okajima K, Murakami K, Johno M, Okabe H, Takatsuki K. Recombinant thrombomodulin prevents endotoxin-induced lung injury in rats by inhibiting leukocyte activation. Am J Physiol 1996;271:L470–5. [PubMed: 8843797]
40. Uchiba M, Okajima K, Murakami K, et al. rhs-TM prevents ET-induced increase in pulmonary vascular permeability through protein C activation. Am J Physiol 1997;273:L889–94. [PubMed: 9357866]
41. Gomi K, Zushi M, Honda G, et al. Antithrombotic effect of recombinant human thrombomodulin on thrombin-induced thromboembolism in mice. Blood 1990;75:1396–9. [PubMed: 2156578]
42. Yoshikawa A, Kaido T, Seto S, Katsuura Y, Imamura M. Activated protein C prevents multiple organ injury following extensive hepatectomy in cirrhotic rats. J Hepatol 2000;33:953–60. [PubMed: 11131458]
43. Maybauer MO, Maybauer DM, Fraser JF, et al. Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis. Crit Care Med 2006;34(9):2432–8. [PubMed: 16810106]
44. Anonymous. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. N Engl J Med 2000;342:1301–8. [PubMed: 10793162]
45. Owings JT, Bagley M, Gosselin R, Romac D, Disbrow E. Effect of critical injury on plasma antithrombin activity: low antithrombin levels are associated with thromboembolic complications. J Trauma 1996;41:396–405. [PubMed: 8810955]discussion 405–6

46. Uchiba M, Okajima K, Murakami K. Effects of various doses of antithrombin III on endotoxin-induced endothelial cell injury and coagulation abnormalities in rats. Thromb Res 1998;89:233–41. [PubMed: 9645917]
47. Dschietzig T, Alexiou K, Laule M, et al. Stimulation of pulmonary big endothelin-1 and endothelin-1 by antithrombin III: a rationale for combined application of antithrombin III and endothelin antagonists in sepsis-related acute respiratory distress syndrome? Crit Care Med 2000;28:2445–9. [PubMed: 10921577]
48. Giebler R, Schmidt U, Koch S, Peters J, Scherer R. Combined antithrombin III and C1-esterase inhibitor treatment decreases intravascular fibrin deposition and attenuates cardiorespiratory impairment in rabbits exposed to *Escherichia coli* endotoxin. Crit Care Med 1999;27:597–604. [PubMed: 10199542]
49. Okajima K. Antithrombin prevents endotoxin-induced pulmonary vascular injury by inhibiting leukocyte activation. Blood Coagul Fibrinolysis 1998;9(suppl 2):S25–37. [PubMed: 9662467]
50. Salvatierra A, Guerrero R, Rodriguez M, et al. Antithrombin III prevents early pulmonary dysfunction after lung transplantation in the dog. Circulation 2001;104:2975–80. [PubMed: 11739315]
51. Harada N, Okajima K, Uchiba M, Kushimoto S, Isobe H. Antithrombin reduces ischemia/reperfusion-induced liver injury in rats by activation of cyclooxygenase-1. Thromb Haemost 2004;92:550–8. [PubMed: 15351851]
52. Renckens R, Roelofs JJ, Florquin S, et al. Endogenous tissue-type plasminogen activator is protective during *Escherichia coli*-induced abdominal sepsis in mice. J Immunol 2006;177:1189–96. [PubMed: 16818777]
53. Montes R, Rodriguez-Whilhelmi P, Hurtado V, et al. The endotoxin-induced plasminogen activator inhibitor-1 increase in rabbits is not tumor necrosis factor-alpha dependent and can occur in the absence of interleukin-1beta. Thromb Haemost 2002;88:639–43. [PubMed: 12362236]
54. Saetre T, Lindgaard AK, Lyberg T. Systemic activation of coagulation and fibrinolysis in a porcine model of serogroup A streptococcal shock. Blood Coagul Fibrinolysis 2000;11:433–8. [PubMed: 10937804]
55. Chapman HA Jr, Stone OL. A fibrinolytic inhibitor of human alveolar macrophages. Induction with endotoxin. Am Rev Respir Dis 1985;132:569–75. [PubMed: 3898943]
56. Chapman HA, Yang XL, Sailor LZ, Sugarbaker DJ. Developmental expression of plasminogen activator inhibitor type 1 by human alveolar macrophages. Possible role in lung injury. J Immunol 1990;145:3398–405. [PubMed: 2230126]
57. Wygrecka M, Markart P, Ruppert C, et al. Compartment-and cell-specific expression of coagulation and fibrinolysis factors in the murine lung undergoing inhalational versus intravenous endotoxin application. Thromb Haemost 2004;92:529–40. [PubMed: 15351849]
58. Idell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. Crit Care Med 2003;31:S213–20. [PubMed: 12682443]
59. Grau GE, de Moerloose P, Bulla O, et al. Haemostatic properties of human pulmonary and cerebral microvascular endothelial cells. Thromb Haemost 1997;77:585–90. [PubMed: 9066014]
60. Prabhakaran P, Ware LB, White KE, Cross MT, Matthay MA, Olman MA. Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. Am J Physiol Lung Cell Mol Physiol 2003;285:L20–8. [PubMed: 12730079]
61. Moalli R, Doyle JM, Tahhan HR, Hasan FM, Braman SS, Saldeen T. Fibrinolysis in critically ill patients. Am Rev Respir Dis 1989;140:287–93. [PubMed: 2504087]
62. Groeneveld AB, Kindt I, Raijmakers PG, Hack CE, Thijs LG. Systemic coagulation and fibrinolysis in patients with or at risk for the adult respiratory distress syndrome. Thromb Haemost 1997;78:1444–9. [PubMed: 9423792]
63. Dowdy DW, Eid MP, Dennison CR, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. Intensive Care Med 2006;32:1115–24. [PubMed: 16783553]
64. Levitt JE, Matthay MA. Treatment of acute lung injury: historical perspective and potential future therapies. Semin Respir Crit Care Med 2006;27:426–37. [PubMed: 16909376]
65. Perkins GD, McAuley DF, Thickett DR, Gao F. The betaagonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006;173:281–7. [PubMed: 16254268]

66. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280:159–65. [PubMed: 9669790]

67. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in patients with early acute respiratory distress syndrome (ARDS) significantly improves lung function: results of a randomized controlled trial (RCT) [abstract]. Chest 2005;128(suppl):129S. [PubMed: 16261702]

68. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671–84. [PubMed: 16625008]

69. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–75. [PubMed: 16714767]

70. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med 2006;34:2325–33. [PubMed: 16850002]

71. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med 2006;34:1033–8. [PubMed: 16484911]

72. Abraham E, Reinhart K, Opal S, et al. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. JAMA 2003;290:238–47. [PubMed: 12851279]

73. LifeSciencesWorld. Chiron begins phase III trial for tifacogin. May 18. 2004 Available from www.lifesciencesworld.com/rss/tifacogin/news. Accessed October 12, 2006

74. Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR. Low levels of protein C are associated with poor outcome in severe sepsis. Chest 2001;120:915–22. [PubMed: 11555529]

75. Liaw PC, Esmon CT, Kahnamoui K, et al. Patients with severe sepsis vary markedly in their ability to generate activated protein C. Blood 2004;104:3958–64. [PubMed: 15319291]

76. Lorente JA, Garcia-Frade LJ, Landin L, et al. Time course of hemostatic abnormalities in sepsis and its relation to outcome. Chest 1993;103:1536–42. [PubMed: 8486040]

77. Mesters RM, Helterbrand J, Utterback BG, et al. Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications. Crit Care Med 2000;28:2209–16. [PubMed: 10921542]

78. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709. [PubMed: 11236773]

79. Nick JA, Coldren CD, Geraci MW, et al. Recombinant human activated protein C reduces human endotoxin-induced pulmonary inflammation via inhibition of neutrophil chemotaxis. Blood 2004;104:3878–85. [PubMed: 15339848]

80. van der Poll T, Levi M, Nick JA, Abraham E. Activated protein C inhibits local coagulation after intrapulmonary delivery of endotoxin in humans. Am J Respir Crit Care Med 2005;171:1125–8. [PubMed: 15750041]

81. Manns BJ, Lee H, Doig C, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. N Engl J Med 2002;347:993–1000. [PubMed: 12324556]

82. Angus DC, Linde-Zwirble WT, Clermont G, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. Crit Care Med 2003;31:1–11. [PubMed: 12544986]

83. United States National Library of Medicine. National Institutes of Health. Activated protein C to treat acute lung injuries. Oct 12. 2006 UpdatedAvailable from http://www.clinicaltrials.gov/ct/show/NCT00112164?order=1

84. Maruyama I. Recombinant thrombomodulin and activated protein C in the treatment of disseminated intravascular coagulation. Thromb Haemost 1999;82:718–21. [PubMed: 10605773]

85. Fourrier F, Chopin C, Huart JJ, Runge I, Caron C, Goudemand J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. Chest 1993;104:882–8. [PubMed: 8365305]

86. Baudo F, Caimi TM, de Cataldo F, et al. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: a controlled double-blind, randomized, multicenter study. Intensive Care Med 1998;24:336–42. [PubMed: 9609411]

87. Eisele B, Lamy M, Thijs LG, et al. Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intensive Care Med 1998;24:663–72. [PubMed: 9722035]

88. Inthorn D, Hoffmann JN, Hartl WH, Muhlbayer D, Jochum M. Antithrombin III supplementation in severe sepsis: beneficial effects on organ dysfunction. Shock 1997;8:328–34. [PubMed: 9361342]

89. Waydhas C, Nast-Kolb D, Gippner-Steppert C, et al. High-dose antithrombin III treatment of severely injured patients: results of a prospective study. J Trauma 1998;45:931–40. [PubMed: 9820705]

90. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869–78. [PubMed: 11597289]

91. Malik AB, van der Zee H. Time course of pulmonary vascular response to microembolization. J Appl Physiol 1977;43:51–8. [PubMed: 893266]

92. Binder AS, Nakahara K, Ohkuda K, Kageler W, Staub NC. Effect of heparin or fibrinogen depletion on lung fluid balance in sheep after emboli. J Appl Physiol 1979;47:213–19. [PubMed: 468663]

93. Hochart H, Jenkins PV, Smith OP, White B. Low-molecular weight and unfractionated heparins induce a downregulation of inflammation: decreased levels of proinflammatory cytokines and nuclear factor-κB in LPS-stimulated human monocytes. Br J Haematol 2006;133:62–7. [PubMed: 16512830]

94. Lever R, Page CP. Novel drug development opportunities for heparin. Nat Rev Drug Discov 2002;1:140–8. [PubMed: 12120095]

95. Cox CS Jr, Zwischenberger JB, Traber DL, Traber LD, Haque AK, Herndon DN. Heparin improves oxygenation and minimizes barotrauma after severe smoke inhalation in an ovine model. Surg Gynecol Obstet 1993;176:339–49. [PubMed: 8460409]

96. Abubakar K, Schmidt B, Monkman S, Webber C, deSA D, Roberts R. Heparin improves gas exchange during experimental acute lung injury in newborn piglets. Am J Respir Crit Care Med 1998;158:1620–5. [PubMed: 9817717]

97. Uchiba M, Okajima K, Murakami K, Okabe H, Takatsuki K. Attenuation of endotoxin-induced pulmonary vascular injury by antithrombin III. Am J Physiol 1996;270:L921–30. [PubMed: 8764216]

98. Stringer KA, Lindenfeld J, Repine AJ, Cohen Z, Repine JE. Tissue plasminogen activator (tPA) inhibits human neutrophil superoxide anion production in vitro. Inflammation 1997;21:27–34. [PubMed: 9179619]

99. Abraham E, Gyetko MR, Kuhn K, et al. Urokinase-type plasminogen activator potentiates lipopolysaccharide-induced neutrophil activation. J Immunol 2003;170:5644–51. [PubMed: 12759445]

100. Stringer KA, Hybertson BM, Cho OJ, Cohen Z, Repine JE. Tissue plasminogen activator (tPA) inhibits interleukin-1 induced acute lung leak. Free Radic Biol Med 1998;25:184–8. [PubMed: 9667494]

101. Hardaway RM, Williams CH, Marvasti M, et al. Prevention of adult respiratory distress syndrome with plasminogen activator in pigs. Crit Care Med 1990;18:1413–18. [PubMed: 2123144]

102. Hardaway RM, Harke H, Tyroch AH, Williams CH, Vazquez Y, Krause GF. Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. Am Surg 2001;67:377–82. [PubMed: 11308009]

103. Hardaway RM, Harke H, Williams CH. Fibrinolytic agents: a new approach to the treatment of adult respiratory distress syndrome. Adv Ther 1994;11:43–51. [PubMed: 10147145]

104. Stringer KA, Bose SK, McCord JM. Antiinflammatory activity of tissue plasminogen activator in the carrageenan rat footpad model. Free Radic Biol Med 1997;22:985–8. [PubMed: 9034237]

105. Dunn JS, Nayar R, Campos J, et al. Feasibility of tissue plasminogen activator formulated for pulmonary delivery. Pharm Res 2005;22:1700–7. [PubMed: 16180128]

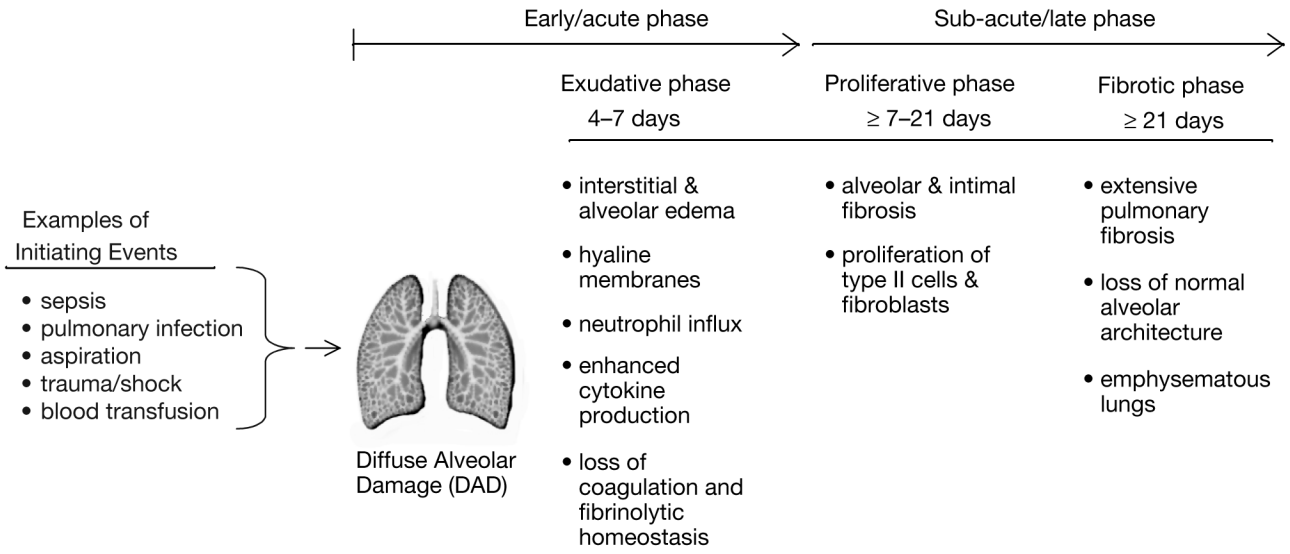

Figure 1.

Time course of pathophysiologic events in acute respiratory distress syndrome. Some patients recover during the exudative (acute) phase, but most progress to the subacute phase. Patients who do not recover during the proliferative phase may develop emphysematous regions in the lungs, but most patients regain normal lung function. (Adapted from references [3, 11], and [16].)

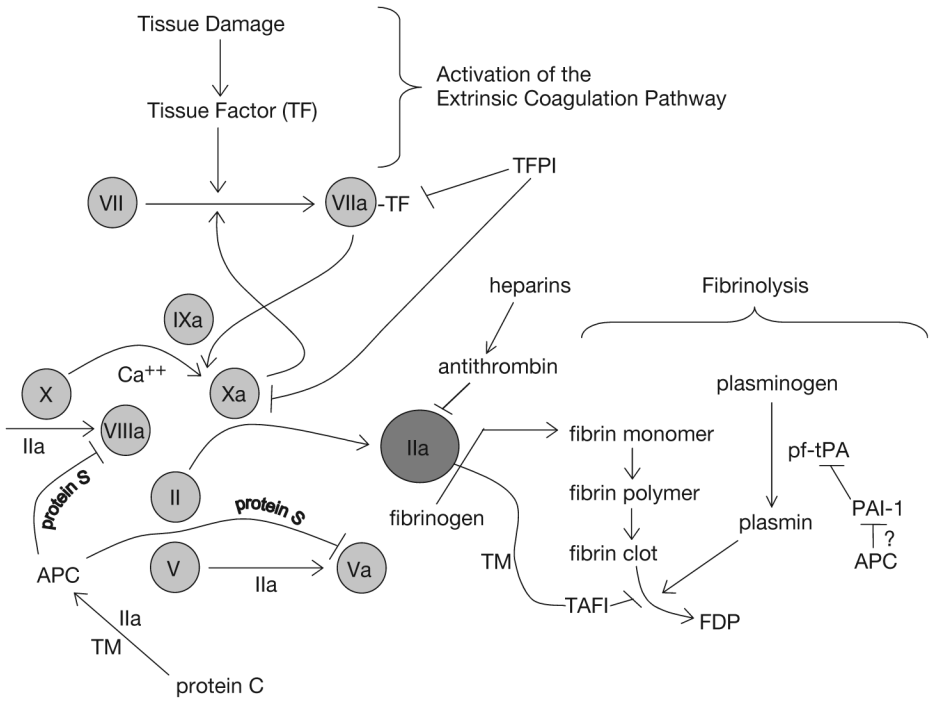

Figure 2.

Schematic shows the activation and propagation of the extrinsic coagulation pathway and fibrinolysis, as well as the sites of action for tissue factor pathway inhibitor (TFPI), activated protein C (APC), thrombomodulin (TM), antithrombin, heparins, and the pulmonary formulation of tissue plasminogen activator (pf-tPA). PAI-1 = plasminogen activator inhibitor-1; TAFI = thrombin-activated fibrinolysis inhibitor; FDP = fibrin degradation products. (Adapted from references [4-8].)