Role of the Coagulation System in ARDS*

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The pathologic findings of the adult respiratory distress syndrome (ARDS) are well described and include lung edema, microthrombi, inflammatory cell infiltration, and late fibrosis.¹ ² The exact pathogenesis of this syndrome, however, is not well characterized. Considerable evidence from clinical and in vivo investigation implicates neutrophils as important tissue injury mediators in ARDS.³ ⁴ There is also compelling evidence that a variety of mediators, including cytokines, proteases, activated complement system fragments, and arachidonic acid metabolites are important amplifiers of the inflammatory response in ARDS.⁵ ⁶ Moreover, impaired host defenses and abnormalities

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![Coagulation System Diagram](https://example.com/coagulation-diagram.png)

**Intrinsic Pathway**
- XII
- HMWK
- XI
- Ca²⁺
- IX
- Ca²⁺
- IXa
- Prothrombin
- TF
- VII
- X
- Insoluble Fibrin Clot
  (Strong)
- Fibrinogen
- Fibrin Monomer
- Soluble Fibrin Clot
  (Weak)
- Thrombin

**Extrinsic Pathway**
- PK
- HMWK
- Xla
- Ca²⁺
- VIII/TF
- Xla
- Ca²⁺
- VIIa/TF
- Ca²⁺
- Fibrinogen
- Fibrin Monomer
- Soluble Fibrin Clot
  (Weak)
- Thrombin

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**Figure 1.** A schematic diagram of the coagulation system showing the intrinsic and the extrinsic pathways. The coagulation factors are designated with roman numbers, and their active forms are indicated as "a." HMWK = high molecular weight kininogen; PK = prekallikrein; PL = phospholipid; TF = tissue factor; Ca²⁺ = calcium.

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α1-PI = α1-plasmin inhibitor; AT III = antithrombin III; ARDS = adult respiratory distress syndrome; DIC = disseminated intravascular coagulation; FDP = fibrin degradation products; GMP-140 = granule membrane protein 140; PAF = platelet-activating factor; PAI = plasminogen activator inhibitor; TM = thrombomodulin; t-PA = tissue plasminogen activator

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The role of surfactant probably contribute to progressive lung damage.⁹ Central to these multiple cellular and inflammatory responses is the activation of coagulation. Autoamplification by activated complexes with reduction and/or inhibition of coagulation inhibitors produce fibrinolysis. Initiation within these complex cascades of events ends in an acute lung injury pattern designated as ARDS.¹⁰ This localized process is set in motion by sepsis, trauma, and other critical diseases.¹¹ Understanding the significance of the coagulation system in ARDS will be beneficial in planning successful treatment strategies.

Review of the current understanding of normal coagulation and fibrinolysis will be discussed. Pathophyslogic evidence pointing to involvement of the coagulation system in ARDS and acute lung injury will be presented. Therapeutic strategies to minimize lung injury by modulating the coagulation system will be proposed.

**Physiology of the Coagulation System**

The coagulation system is broken down into a series of reactions (Fig 1) that result in the production of thrombin.¹² ¹³ This cascade of enzymatic reactions is divided into two pathways of activation: an intrinsic and an extrinsic. In the presence of thrombin, fibrin-
Kininogen is converted into fibrin. Each reaction requires conversion of an inactive protein into an activated form. Contact activation of the intrinsic pathway and kinin pathway are evoked when the Hageman factor (factor XII) contacts exposed negatively charged vascular subendothelial connective tissue. The activation of factor XII (XIIa) is followed by a subsequent series of proteolytic reactions which yield thrombin. The extrinsic pathway is activated when factor VII forms a complex with tissue factor derived from damaged cells. Tissue factor is a type of lipoprotein expressed on the cellular membrane of endothelial cells, monocytes, neutrophils, and macrophages during inflammation. Factor X activation is an important link between the intrinsic and extrinsic pathways. Factor X is activated by activated factor IX (IXa) which is generated by the intrinsic pathway. Factor X can also be activated directly by activated factor VII (VIIa) which is produced by the extrinsic pathway. Activation through either pathway results in a sequence of enzymatic steps leading to the generation of thrombin and hemostasis. The main role of thrombin is to convert fibrinogen into fibrin which then polymerizes into a hemostatic insoluble gel. This reaction is accelerated through the action of activated factor XIIIa.

Tight regulation of the coagulation system exists which prevents propagation of the formed hemostatic plug beyond the site of injury. This regulation is dependent on dilution of procoagulants, antagonism of activated complexes, and promotion of fibrinolysis (Fig 2). Antithrombin III (ATIII) and proteins C and S are synthesized in the liver and play an important role in the down regulation of procoagulant activities and thereby inhibit coagulation. Circulating ATIII is transformed into its activated form by binding to a heparin cofactor (heparan sulfate proteoglycans) expressed on endothelial cells. An active site on ATIII then becomes readily accessible to serine protease procoagulants. Administered heparin activates ATIII in a similar manner. Activated ATIII complexes and subsequently inactivates thrombin and other serine protease procoagulants (activated factor XII, XI, IX, X). Circulating protein C is converted into an active protease by thrombin after it is bound to thrombomodulin (TM). This thrombin-binding receptor is expressed on the endothelial surface. Protein S is required in protein C activation. The resultant activated protein C controls procoagulant activities by irreversibly inhibiting activation of factors V and VIII.

Immediately with tissue damage and formation of a clot, the fibrinolytic systems through several pathways interrupt clot formation (Fig 2). The principal pathway is through the intraclot formation of plasmin from plasminogen by tissue plasminogen activator (t-PA), which is a serine protease; t-PA is released from
endothelial cells and is present in most tissues of the body. Plasmin degrades fibrin and fibrinogen into low molecular weight fragments measured clinically as fibrin and fibrinogen degradation products (FDP). Any free plasmin that escapes the clot microenvironment is rapidly neutralized by an α2-plasmin inhibitor (α2-PI) which effectively prevents systemic fibrinolysis. Plasminogen activator inhibitor 1 (PAI-1) is found in endothelial cells and plasminogen activator inhibitor 2 (PAI-2) is derived mainly from placental cells. Both assist in maintaining balance between the fibrinolytic pathways and clot formation.16

**Epidemiology**

In patients with ARDS, considerable clinical evidence exists for the presence of pulmonary vascular microemboli.17 Global disturbances of key hemostatic systems as in multiple organ system failure have also been associated with a higher incidence of coagulation disorders in ARDS nonsurvivors.18 The incidence of coagulopathies in patients with ARDS is approximately 26 percent.19 Common ARDS-associated coagulation disorders include diffuse intravascular coagulation and inhibition of fibrinolysis.20 In disseminated intravascular coagulation (DIC), an acute thrombocytopenia develops and there is evidence of intense coagulation cascade activation resulting in proteolysis of fibrinogen by thrombin. Support for this association between ARDS and DIC has been reported by Bone et al.20 In 23 percent of ARDS patients, DIC developed. Disseminated intravascular coagulation may not only be associated with ARDS, but in another report by Hardaway,21 DIC is a possible predisposing factor for developing ARDS. The clinical utility of laboratory evidence in predicting and diagnosing the early development of ARDS was studied.22 Conventional DIC laboratory values (platelet count, activated partial thromboplastin time, thrombin time, fibrinogen, and FDP) did not reliably discriminate between patients with and without ARDS. Elevated factor VIII-related antigen levels, low ATIII, and low plasminogen levels were found more often in patients developing ARDS. This discrimination seen with factor VIII-related antigen and PAI-1 is a nonspecific predictor of ARDS development, since many other critically ill patients without ARDS also have these laboratory findings.23 Elevated levels of FDP are often found in the blood of patients with ARDS. In contrast, those patients with sepsis and trauma without pulmonary dysfunction do not develop elevated FDP levels.24 Fragment D, a low molecular weight FDP, has been associated with extensive microvascular injury and is proposed as a marker and mediator of ARDS.24

Trauma is an important risk factor leading to ARDS.25 The incidence of ARDS in traumatized patients is estimated to be 12 percent.26 Specific lung tissue injury caused by trauma which results in pulmonary microemboli has been demonstrated at autopsy.27 Posttraumatic pulmonary microemboli appear to occur with coagulation system activation and with inhibition of the fibrinolytic system by PAI. The resultant impaired lysis of these microemboli can be associated with the development of ARDS.2829 Traumatic tissue and vascular disruption leading to ischemia and an early inflammatory response probably play a key role in activating the clotting cascade.29 Work by Hardaway et al30 and Feola et al31 demonstrates that activation occurs with localized trauma-induced mechanical disruption and vascular injury.

Abnormalities in the coagulation system are also identified in patients with sepsis.32 Sepsis is the most common precipitating event for ARDS and it is reported that 25 to 40 percent of patients with the sepsis syndrome will develop ARDS.3334 The endotoxemia that produces sepsis is capable of activating the coagulation cascade leading to a hypercoagulable state with formation of pulmonary microemboli.35 Examining the coagulation system in 60 patients with severe septic shock, Fourrier et al36 noted that activation of the coagulation system was marked by persistently low levels of ATIII in plasma and correlated with a poor prognosis. Hesselvik et al36 investigated the relationship among coagulation, fibrinolysis, and outcome in patients with sepsis. Both survivors and nonsurvivors had evidence for coagulation activation. Nonsurvivors who had sepsis, however, demonstrated a procoagulant state with high circulating levels of a potent fibrinolysis inhibitor. Van Deventer et al37 provided evidence that a similar effect is seen in healthy human volunteers who receive an endotoxin infusion. Endotoxin infusion results in a release of PAI with rapid counteraction of the initial fibrinolytic response. This is followed by sustained thrombin activation and hyperthrombinaemia.

Additional studies of sepsis and trauma indicate differences in the degree of activation of the coagulation system. Coagulation variables such as the prothrombin time and ATIII level are significantly lower in patients with sepsis as compared with patients who have sustained trauma.38 This could indicate that patients with sepsis have greater activation of the coagulation system. These differences have been ascribed to greater activation of the contact phase of blood coagulation by endotoxin.11 Sepsis and trauma appear to initiate a common pathway (namely coagulation activation) by different mechanisms leading to a shared end point classified as ARDS. Shock with decreased organ perfusion, especially of the liver, contributes to this massive hemostatic activation.

**The Alveolar Clotting and Fibrinolytic Systems**

Bronchoalveolar lavage (BAL) fluid obtained from normal lungs contains the necessary tissue factor.
complexes and enzymes capable of activating factor V through the extrinsic pathway of coagulation.\textsuperscript{39,40} Indeed, unlike the vascular compartment, the alveolar compartment is functionally saturated with active complexes of tissue factor and factor VII. Alveolar macrophage-derived complexes account for these potential localized procoagulant activities.\textsuperscript{39,40} The alveolar procoagulant pathway is regulated by the availability of distal clotting factors needed for thrombus formation and by the presence of fibrinolytic activity.\textsuperscript{41,42} In normal humans, this fibrinolytic activity is due to urokinase-like plasminogen activators isolated in BAL fluid.\textsuperscript{43} The alveolar macrophage is the main cellular source of alveolar urokinase.\textsuperscript{44} This alveolar urokinase system is constantly working to lyse fibrin in the normal alveolus. Chapman et al\textsuperscript{45} showed that most of the detectable plasminogen antigen in normal lavage samples is already activated to plasmin. These findings suggest the lack of available distal coagulation factors and an inherent alveolar fibrinolytic activity normally prevent alveolar fibrin deposition.

**Alveolar Clotting and Fibrinolysis Alterations in ARDS**

In contrast to the normal situation, patients with ARDS demonstrate prominent alveolar fibrin deposition. Disruption of the alveolocapillary membrane integrity results in leakage of distal coagulation factors into the alveolus. A procoagulant state ensues with alveolar fibrin deposition.\textsuperscript{46} Idell et al\textsuperscript{46-47} reported finding elevated procoagulant activities and decreased fibrinolytic activities in BAL fluid obtained from patients with ARDS. Decreased alveolar fibrinolytic activity is a result of the production of PAI-2. Both a reduction in fibrinolytic activities by alveolar urokinase-like plasminogen activators and an increased release of PAI-2 is found in BAL fluid from patients with ARDS.\textsuperscript{48} In alveolar macrophage cultures exposed to endotoxin, measurable quantities of PAI-2 are released. Inactivation of urokinase produced by these alveolar macrophages correlates with the increase in PAI-2.\textsuperscript{49} These findings raise the possibility that it is the combination of high levels of alveolar-activated procoagulant factors and inhibited alveolar urokinase that leads to alveolar fibrin deposition and hyaline membrane formation in ARDS.

Inflammatory cell chemotaxis and modulation of the immune system results in a progression of alveolar inflammation initiated by local coagulation derangements.\textsuperscript{50,51} Clinically this manifests as decreased lung compliance, atelectasis, and abnormal gas exchange in patients with ARDS.

A surfactant deficiency and/or dysfunction may underlie many of these clinical findings.\textsuperscript{52} Fibrinogen and FDP are known to be potent inhibitors of surfactant.\textsuperscript{53} Alveolar fibrin formation may act as a nidus for further fibrosis throughout the lungs. Pathologic studies have revealed that a site of persistent fibrin deposition corresponds to the areas of pulmonary fibrotic change.\textsuperscript{54} Animal studies suggest alveolar fibrin deposition after an acute lung injury results in chronic fibrotic changes and portends a higher animal mortality.\textsuperscript{55} In vitro data demonstrate fibrin forms a matrix on which fibroblasts may aggregate and secrete collagen.\textsuperscript{56} In addition, thrombin binds to thrombin receptors on fibroblasts promoting their proliferation.\textsuperscript{57} These findings support the hypothesis that fibrin formed by activation of the coagulation system and inhibition of fibrinolysis contribute to the pathogenesis of acute lung injury.

**Experimental Evidence for the Role of the Coagulation System in Acute Lung Injury**

Two types of experimental evidence demonstrate activation of the coagulation system can result in acute lung injury. In vitro studies involving infusion of thrombin and FDP demonstrate a dose-dependent activation of the coagulation system and correlate with an acute lung injury. In vitro studies using neutrophils and pulmonary endothelial cells illustrate that these direct effects produced by thrombin, fibrin, FDP, and plasmin occur at a cellular level.

**In Vivo Models of Acute Lung Injury**

Holcroft et al\textsuperscript{58} reported on coagulation abnormalities that resulted in pulmonary microemboli in dogs with sepsis. Hardaway et al\textsuperscript{59} also demonstrated that traumatic acute lung injury in pigs was associated with a hyperthrombinemic state. This may be similar to the intense activation and lung injury seen in ARDS.

Intravenously infused thrombin initiates a sequence of events through activation of the coagulation cascade. Increases in extravascular lung water, pulmonary vascular permeability, and microemboli formation in lung tissue occur with thrombin infusion.\textsuperscript{60,61} There are several reasons why fibrin production and resultant clot formation have importance in thrombin-induced lung injury: (1) \(\gamma\)-thrombin, which lacks clotting activity as well as fibrinogen recognition sites,\textsuperscript{62} did not produce lung injury;\textsuperscript{62} (2) administration of anecrod, a purified fraction of Malayan pit viper venom, causes defibrinogenation and attenuates thrombin-induced lung injury;\textsuperscript{63,64} and (3) the duration of fibrin entrapment in the pulmonary vasculature directly correlates with the duration of neutrophil sequestration and lung injury.\textsuperscript{65} Neutrophils have been identified as important mediators in thrombin-induced lung injury.\textsuperscript{66-67} (1) Thrombin infusion causes a decrease in the number of peripherally circulating neutrophils;\textsuperscript{68,69} (2) sequestration of the neutrophils into a variety of organs, including the lungs, is observed after thrombin injection;\textsuperscript{61,69} (3) neutrophil depletion prior to thrombin infusion attenuates thrombin-induced lung injury;\textsuperscript{68} and (4) neutrophil depletion reverses the
protective effect of neutropenia on thrombin-induced increases in lung vascular permeability.\textsuperscript{70} Thrombin-induced neutrophil kinetics are principally mediated by complement and arachidonic acid metabolites.\textsuperscript{66,67} Complement system activation appears to work hand in hand with plasmin generation.\textsuperscript{71} With complement system activation, a number of complement-derived factors (C3a and C5a) appear to promote chemotaxis and aggregation of neutrophils.\textsuperscript{72} If complement is depleted prior to thrombin infusion, attenuation of both sequestration of neutrophils and lung injury occurs.\textsuperscript{73} This system of neutrophil activation by C3a and C5a appears to provide a link between inflammation and thrombin-induced acute lung injury. Platelet-activating factor (PAF), an arachidonic acid metabolite, is also reported to play a role in thrombin-induced neutrophil recruitment into the lung.\textsuperscript{74} Other arachidonic acid metabolites induced by thrombin infusion cause chemotaxis of neutrophils and subsequent alveolar injury.\textsuperscript{75} Lipoxigenase metabolites, including leukotriene B4 and 5-hydroxy-eicosatetraenoic acid, are detected in BAL fluid and pulmonary lymph after thrombin administration.\textsuperscript{75,76} Neutrophil chemotactic activity in BAL fluid and pulmonary lymph obtained from thrombin-injected animals may result from the effects of leukotriene B4 and 5-hydroxy-eicosatetraenoic acid. Pulmonary macrophages have been demonstrated to produce these mediators.\textsuperscript{75,76} Once sequestrated, neutrophils produce lung injury, in part, by release of oxygen radicals. Exogenously administered superoxide dismutase (a scavenger of $O_2^-$) attenuates thrombin-induced lung injury.\textsuperscript{77} The oxidative burst generated by neutrophils and macrophages after thrombin infusion probably produces direct lung injury. Multiple undefined links between these mediators of inflammation exist. Neutrophil activation by such mediators can disrupt the normal balance between hemostasis and fibrinolysis.

Infusion of FDP causes similar acute lung injury patterns. However, FDP by itself does not appear to be capable of inducing acute lung injury without thrombin in some animal models. Rabbit studies using FDP caused extravascular accumulation of albumin tracer and pulmonary edema.\textsuperscript{78} By depleting neutrophils before FDP administration, FDP-induced lung injury is attenuated.\textsuperscript{79} These findings are most likely species-specific since FDP infusion in a sheep model did not alter pulmonary transvascular fluid and protein leakage. If a combination of insults were used with FDP and thrombin infusion, an enhanced transvascular fluid filtration could be produced.\textsuperscript{80}

![Figure 3. Intravascular interaction of the coagulation system on neutrophil and endothelial cell function.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21688/ on 06/21/2017)

PMN = polymorphonuclear neutrophil; FDP = fibrin and fibrinogen degradation products; PAF = platelet-activating factor; GMP-140 = granule membrane protein 140.
In Vitro Studies of Neutrophils and Endothelial Cells

As mentioned in the preceding discussion, neutrophils play an important role in thrombin- and FDP-induced pulmonary injury. This role involves the interaction of the coagulation system with neutrophil and endothelial cell function (Fig 3).

Modulation of Neutrophil Function by the Coagulation and Fibrinolytic Systems: Thrombin induces chemotaxis and aggregation of human neutrophils. This chemotactic migration and aggregation are due to neutrophil receptor site induction by thrombin. This response is specific and is required for an aggregation response. The active site and the fibrinogen recognition domains of thrombin are nonessential to the induction of chemotaxis, whereas an active catalytic site is required for the aggregation response. Thrombin is a chemotactic factor and also functions as a neutrophil chemotactic modulator. Drake et al reported coincubation of neutrophils with thrombin-enhanced interleukin 1 and tumor necrosis factor-induced neutrophil-endothelial cell adhesion and transendothelial migration of neutrophils. Generation of toxic oxygen-derived metabolites, superoxide anion \((O_2^-)\), hydrogen peroxide \((H_2O_2)\), and hydroxyl radicals \((OH\cdot)\) occurs with neutrophil activation. Chan et al studied the effect of thrombin on oxygen radical production of neutrophils by measuring chemiluminescence. Thrombin alone is not able to induce chemiluminescence in neutrophils. Thrombin, however, enhances opsonized zymosan-induced chemiluminescence of neutrophils. Thrombin may act as an amplifier of neutrophil-induced reactive oxygen radical generation resulting in tissue injury.

Other determinants of neutrophil sequestration in the lung following thrombin infusion include fibrin. The microthrombi formed from fibrin become ideal sites for neutrophil adherence. Neutrophils are able to adhere to fibrin through the CD11/CD18 adhesion glycoprotein complex which usually functions to bind to a counter ligand on endothelial cells.

Fibrin degradation products, including fibrinopeptide B and BB1-42, also induce neutrophil chemotaxis. Neutrophil aggregation, release of lysosomal enzymes, or production of superoxide anions are not induced by FDP. Plasmin induces neutrophil adherence to the endothelium. This is mediated by an up-regulation in the activity and function of neutrophil adhesion glycoprotein complexes such as CD11/CD18. This interaction takes place at specific lysine-binding sites on plasmin and is independent of the proteolytic actions of plasmin.

Thrombin-Induced Neutrophil Adhesion to Endothelium: Adhesion of neutrophils to vascular endothelium is a fundamental and initial step in the development and enhancement of neutrophil-induced injury. Neutrophil adherence to and migration across the endothelium involves interactions between adhesion molecules expressed on the surface of neutrophils and endothelial cells. Thrombin can increase adhesion between neutrophils and endothelial cells. Adhesion between these two cell types results from thrombin-induced increases in adhesion molecules produced by endothelial cells. Endothelial cells stimulated with thrombin express a proadhesive molecule. This granule membrane protein 140 (GMP-140) appears on the plasma membrane of endothelial cells within minutes. The counter ligands on neutrophils against GMP-140 are most likely glycoprotein receptors. Platelet-activating factor is rapidly synthesized and is coexpressed with GMP-140 on endothelial cells. Neutrophils binding to PAF through receptors are activated resulting in activation-dependent alterations of CD11/CD18 membrane glycoproteins. This promotes neutrophil adhesion to counter receptors on endothelial cells.

Direct Effects of the Coagulation and Fibrinolytic System on Endothelial Cells: Endothelial cells are major target sites in acute lung injury. Thrombin produces direct effects on pulmonary endothelial cell cultures. Increased permeability, altered cell shape, and disassembly of actin microfilaments are detected within 2 min of exposure to increasing concentrations of thrombin. Electron microscopic examination confirms the presence of endothelial "gap" formations in endothelial cells treated with thrombin. Increased permeability is related to the enzymatic activity of thrombin. Intracellular calcium and protein kinase C regulate this cell membrane process.

Fibrin deposition has been histologically associated with direct endothelial cell injury. In thrombin-injected dogs, electron microscopy demonstrates these cellular disruptions. Pulmonary endothelium is swollen, highly vacuolated, and blistered with proximal or direct fibrin contact. Contact of the confluent endothelial cell monolayer with fibrin induces disappearance of the normal cobblestone morphology, disorganization, and aggregation of cells. On the contrary, Lo et al recently demonstrated that a 3-h incubation of fibrin with endothelium resulted in endothelial increases of albumin permeability partly due to transcytosis. No morphologic abnormalities were seen by electron microscopic examination. Direct endothelial injury by fibrin may be one of the mechanisms by which increased vascular permeability occurs.

The effect of FDP on the pulmonary endothelium is controversial. Ge et al documented that highly purified 1-mM fragment D caused an increase in endothelial monolayer permeability in 2 h without cell detachment and lysis. This concentration is similar to plasma fragment D levels detected in patients with ARDS. Changes in the contractile and anchoring properties of endothelial cells are central to this response. This effect is associated with redistribution...
of endothelial cell F-actin microfilaments. More recently Ge et al.\(^ {106} \) showed prolonged fragment D challenge causes endothelial cell detachment from the substratum and resultant denudation of the endothelial barrier. Rowland et al.\(^ {103} \) reported low-molecular-weight cleavage of fibrin and fibrinogen produces nontoxic and reversible endothelial cell retraction.

Thrombin that is incorporated within fibrin clots can escape from degradation by proteases. This results in increased local concentrations.\(^ {107} \) Therefore, at the fibrin-deposited site, the concentration of thrombin, fibrin, and FDP may exceed the endothelial cell's toxicity tolerance limit. Impairment of the pulmonary microcirculation in conjunction with macrocirculation changes (ie, decreased procoagulant clearance) can contribute to this local concentration effect.

**Therapeutic Strategies to Minimize Lung Injury by Modulating the Coagulation System**

Modulating the coagulation system can be directed at (1) preventing fibrin formation or (2) stimulating fibrinolysis. Several studies have been performed to examine the therapeutic efficacy of coagulation system modulators in sepsis and trauma.\(^ {108,109} \)

**Modulators of Coagulation**

The outcome of different strategies using both native and derived anticoagulants varies according to the animal models studied. Few prospective clinical trials are available in humans.

Emerson et al.\(^ {110} \) investigated the effect of ATIII on endotoxin-induced lung injury in sheep. Lung injury was quantified by measuring lung lymph flow rates and lymphatic protein concentrations. In animals pretreated with both ATIII and α-proteinase inhibitor prior to endotoxin injection, lung injury was attenuated. Pretreatment with either agent alone did not produce attenuation. No therapeutic benefit was noted when endotoxin infusion was followed by these coagulation inhibitors. These studies suggest ATIII and proteinase inhibitors might have some use infused early in endotoxin-induced lung injury. Infused ATIII is rapidly inactivated by neutrophil elastase as well as other proteases. Coadministration of a proteinase inhibitor may be necessary to produce optimal ATIII activity. These findings are contrasted by conflicting results seen in other animal models. Spannagl et al.\(^ {111} \) examined the possible protective value of a purified complex of human ATIII and heparin in pig endotoxin-induced lung injury. Laboratory evidence of DIC was inhibited; however, endotoxin-induced lung injury and animal mortality remained unchanged. Prophylactic low-dose heparin treatment alone was successful in preventing thrombin-induced DIC and lung edema in baboons.\(^ {112} \)

Hirudin, a leech-derived anticoagulant, is a potent thrombin inhibitor differing from heparin and ATIII by its ability to react with clot-bound thrombin.\(^ {113,114} \) Besides its activity as an anticoagulant, hirudin attenuates thrombin-induced pulmonary endothelial permeability and neutrophil adhesion. When recombinant human hirudin was administered to pigs, endotoxin-induced increase in pulmonary vascular resistance and lung edema were reduced.\(^ {115} \)

Recombinant human TM has been shown to diminish the deposition of fibrin in large-sized pulmonary arteries after thrombin infusion.\(^ {116} \) Thrombomodulin modulates the coagulation system through (1) promotion of protein C activation and (2) inactivation of thrombin by binding to thrombin.\(^ {117} \)

**Modulator of Fibrinolysis**

Systemic infusion of fibrinolytic agents can prevent sepsis- and trauma-induced lung injury with improved animal survival rates. Hardaway et al.\(^ {118,119} \) treated traumatized pigs or dogs with t-PA or with urokinase 4 h after trauma. Arterial blood gas analysis and postmortem pathologic examination revealed that t-PA and urokinase prevented the development of trauma-induced acute lung injury.

In 1978, Hardaway\(^ {118} \) reported that administration of 45,000 units of activated plasminogen to patients with ARDS improved their condition dramatically. In a clinical trial using streptokinase in 30 patients with sepsis- and trauma-induced ARDS, improved oxygenation and survival rates were produced.\(^ {119} \)

**Conclusion**

Clinical and animal studies demonstrate abnormalities in the coagulation system in sepsis, trauma, and ARDS. Sepsis and trauma are important risk factors for the development of ARDS and intensely activate the coagulation cascade at different steps. However, once this autoamplifying cascade is started, a lung injury pattern consistent with ARDS is created. The coagulation system probably plays a pivotal role in the pathogenesis of these conditions from a number of fronts. Endothelial cell damage is directly or indirectly mediated through the activation of neutrophils and by thrombin, fibrin, and FDP. Neutrophils are important effector cells that are activated both directly and indirectly by the coagulation cascade. Animal experiments have demonstrated an improvement in survival rates and an attenuation of lung injury through modulation of the coagulation system. By interrupting the intense cascade activation early in sepsis and trauma, attenuation of lung injury may occur and increased survival may be achieved. Other aspects of this complicated and interdependent system of coagulation activation remain to be elucidated. How can inflammatory mediators, including cytokines and arachidonic acid metabolites, interact in this normally highly ordered set of reactions? Controlled clinical trials
based on effective animal models to study these complex interactions are needed.

References

5 Coris BJ. Mediators of multiple organ failure. Intensive Care Med 1990; 16(suppl):192-96
11 Carvalho AC, DeMarinis S, Scott CF, Silver LD, Schmaier AH, Colman RW. Activation of the contact system of plasma proteolysis in the adult respiratory distress syndrome. J Lab Clin Med 1988; 112:270-77
18 Bell RC, Coalson JJ, Smith JD, Johnson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 1983; 99:283-98

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Cooper JA, Lo SK, Malik AB. Fibrin is a determinant of neutrophil sequestration in the lung. Circ Res 1986; 63:735-41


Tahamont MV, Malik AB. Granulocytes mediate the increase in pulmonary vascular permeability after thrombin embolism. J Appl Physiol 1983; 54:1489-95


Johnson A, Perlman MB, Blumenstock FA, Malik AB. Superoxide dismutase prevents the thrombin-induced increase in lung vascular permeability: role of superoxide in mediating the alterations in lung balance. Circ Res 1986; 59:405-15

Manwaring D, Thornburg D, Curreri PW. Mechanisms of acute pulmonary dysfunction induced by fibrinogen degradation product D. Surgery 1978; 84:45-54

Manwaring D, Curreri PW. Cellular mediation of respiratory distress syndrome induced by fragment D. Ann Chir Gynaecol 1981; 70:304-07


Chan KL, Bizios R, Malik AB. Thrombin enhances opsonized