Pulmonary coagulopathy

Pulmonary coagulopathy: a potential therapeutic target in different forms of lung injury

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The role and source of tissue factor

A large body of evidence has shown that *systemic* coagulopathy is a key event in severe systemic inflammation, such as that which occurs in sepsis.[1] Systemic coagulopathy is the net result of activation of coagulation and defective systems of natural inhibition of coagulation, on the one hand, and attenuation of fibrinolysis on the other. Activation of coagulation is primarily driven by the extrinsic coagulation pathway which starts with expression of tissue factor (TF) on mononuclear cells and endothelial cells. TF then binds and activates factor VII which activates downstream coagulation cascades.[2 3] Mechanisms that regulate the coagulation pathway under normal conditions involve natural inhibitors of coagulation, including activated protein C (APC), antithrombin (AT) and tissue factor pathway inhibitor (TFPI). In general, they all interfere with the TF–factor VIIa-induced activation of coagulation, but on different levels. In patients with sepsis, increased coagulant activity is not sufficiently counterbalanced by these natural inhibitors. In addition, a rapid sustained increase in synthesis of plasminogen activator inhibitor (PAI)-1 is present during the septic response. PAI-1 is the main inhibitor of tissue-type and urokinase-type plasminogen activator (tPA and uPA) which activate the fibrinolytic system. The importance of systemic coagulopathy with sepsis has been established in experimental studies and in the randomised, prospective, double-blind, placebo-controlled PROWESS trial in which infusion of recombinant human (rh)-APC resulted in improved survival of patients with severe sepsis.[4]

LOCAL COAGULOPATHY WITH ACUTE LUNG INJURY

Coagulopathy with acute lung injury and/or pneumonia

Recent studies have clearly shown that prominent changes in *local* fibrin turnover are an important feature of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and pulmonary infection. The profile and extent of these changes vary with the severity of inflammation: in severe pneumonia demanding mechanical ventilation the changes are nearly identical to those in ARDS,[5 6] while less prominent alterations of alveolar fibrin turnover have been measured in spontaneously breathing patients with pneumonia.[5] The mechanisms that contribute to disturbed alveolar fibrin turnover are not clearly understood, but are thought to be similar to those found in the intravascular spaces during severe systemic inflammation.[7–9] Similar to sepsis, in ARDS and pneumonia alveolar thrombin generation seems to be mediated by the TF–factor VIIa pathway. Patients who develop ventilator-associated pneumonia have increased bronchoalveolar levels of soluble TF and factor VII.[9] In patients with ARDS an increase in soluble TF, factor VIIa and TF-dependent factor X activation in bronchoalveolar lavage (BAL) fluid has been demonstrated. In addition, inhibition of the TF–factor VIIa pathway completely abrogated intrapulmonary fibrin deposition in patients with ARDS.[10] Although the lung has only a limited capacity to produce protein C, APC is present in BAL fluid.[11] The protein C system has been shown to be suppressed in patients with ventilator-associated pneumonia[12 13] and pulmonary inflammation.[14] In association with enhanced fibrin production, fibrinolytic activity is depressed in BAL fluid of patients with ALI/ARDS or pneumonia,[5] related to high pulmonary concentrations of PAI-1. PAI-1 is increased in ALI/ARDS and is probably secreted by lung epithelial cells, fibroblasts and endothelial cells.[15 16] Patients at risk of ventilator-associated pneumonia show similar changes in pulmonary fibrin turnover.[9] The important role of the fibrinolytic system in the pathogenesis of pneumonia is underscored by the observation that the depression of bronchoalveolar fibrinolysis precedes the clinical occurrence of ventilator-associated pneumonia by several days.[9]

Ventilator-induced coagulopathy

Compelling evidence from preclinical and clinical studies shows that mechanical ventilation aggravates or may even initiate lung injury.[17 18] The similarities between the inflammatory responses in pneumonia and ALI/ARDS suggest that similar changes in coagulation and fibrinolysis may occur in ventilator-induced lung injury. The knowledge on ventilator-induced coagulopathy is rapidly growing. Several preclinical studies and one clinical study in healthy subjects suggest that pulmonary fibrin turnover is indeed influenced by mechanical ventilation.[19–21] Some suggestion on the existence of TF-mediated coagulation caused by mechanical ventilation comes from a preliminary report on short-term mechanical ventilation in patients undergoing a surgical procedure.[21] In addition, small but consistent changes in pulmonary coagulation in mice have been found with injurious forms of mechanical ventilation (Wolthuis, unpublished data). Only two preclinical studies have focused on the effect of mechanical ventilation on pulmonary fibrinolysis,[19 20] in which it was found that injurious mechanical ventilation attenuates fibrinolytic activity in rats, which appears to be caused by increased production and/or release of PAI-1.

SOURCE OF TF IN ALVEOLAR SPACES

One limitation with all studies on pulmonary coagulopathy so far is that they do not give sufficient insight into the potential sources of TF in the alveolar spaces. It has been suggested that changes in coagulation and fibrinolysis found in the pulmonary compartment are the result of leakage of coagulation factors into the lungs from the systemic circulation. Indeed, concordant increased activation of coagulation in the systemic compartment was found with infectious pulmonary coagulopathy in one study.[9] However, TF is not present in the systemic circulation. In addition, pulmonary infection was characterised by local (but not systemic) attenuation of fibrinolysis, suggesting that pulmonary coagulopathy is a localised process.

In this issue of *Thorax*, Bastarache *et al*[22] report their findings on the ability of the alveolar epithelium to initiate intra-alveolar coagulation by expressing active TF (***see page 608***). Using an in vitro cell surface TF assay and TF ELISA, they measured the production and activity of TF in cultured alveolar epithelial cells following exposure to different stimuli. TF activity, mRNA and protein levels increased in A549 cells after stimulation with a pro-inflammatory stimulus (cytomix). Importantly, increased TF activity was also measured following incubation with pulmonary oedema fluid from

patients with ALI/ARDS. Furthermore, immunohistochemistry for TF in human lung tissue from patients with ALI/ARDS showed prominent TF staining in alveolar epithelial cells as well as intra-alveolar macrophages and hyaline membranes. Given the markedly increased levels in pulmonary oedema fluid compared with plasma, it strongly suggests that there is an intra-alveolar source of TF. The reported findings further provide convincing evidence that the alveolar epithelium can initiate TF-dependent intra-alveolar coagulation in this disease setting. The major strengths of the study include the use of a well-characterised and large cohort of patients with ALI/ARDS with an appropriate control group, the use of co-staining with a type II epithelial cell marker in the immunohistochemical studies and the fact that TF measurements were performed on undiluted pulmonary oedema fluid rather than using BAL fluid, thus avoiding potential complications due to dilution effects. One weakness of the study is that the investigators did not study alveolar macrophages, as it has been shown that alveolar macrophages from humans contain procoagulant activity.[23] Also, they did not consider the pulmonary vascular endothelium as a potential source of TF during pulmonary inflammation.

CLINICAL CONSIDERATIONS

Infusion of rh-APC has been found to reduce mortality of patients with severe sepsis.[4] Many patients included in this trial had concomitant ARDS, and many had pneumonia as the primary source of sepsis.[24] One can hypothesise that the beneficial effect of APC was the result, at least in part, of APC on intra-alveolar coagulopathy. Indeed, rh-APC exerts anticoagulant effects in the human lung challenged with endotoxin:[25] activation of coagulation after pulmonary challenge with endotoxin is inhibited and increased PAI-1 activity is diminished by infusion of rh-APC. Thus, systemic administration of APC influences pulmonary fibrin turnover.

Clinical trials in ALI/ARDS have primarily targeted inflammation and not coagulation, although nebulisation of heparin has been found to be beneficial in preclinical and clinical studies in patients with inhalation trauma.[26–30] The results from new studies on interventions on (alveolar) fibrin turnover with TFPI and rh-APC are presently awaited. In view of the results from the study by Bastarache *et al*,[22] epithelial-directed treatment that could be delivered by inhalation of nebulised anticoagulant or profibrinolytic agents seems an attractive approach in treating patients with or at risk of pulmonary coagulopathy.

CONCLUSION

Alveolar fibrin deposition is an important feature of pulmonary infection or inflammation. Some studies also suggest that pulmonary coagulopathy is a feature of ventilator-induced lung injury. Mechanisms that contribute to this fibrin deposition are localised thrombin generation and depression of bronchoalveolar fibrinolysis. Remarkably, changes in alveolar coagulation and fibrinolysis closely resemble those found systemically in patients with sepsis. Recent studies have demonstrated the beneficial effect of anticoagulant therapy in sepsis. Theoretical considerations suggest novel therapeutic strategies or preventive measures in critically ill patients, but clinical studies are needed to examine this hypothesis.

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