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

Marcus J Schultz, Marcel Levi

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. 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. 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.

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, while less prominent alterations of alveolar fibrin turnover have been measured in spontaneously breathing patients with pneumonia. 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. 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. In patients with ARDS an increase in soluble TF, factor VII 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. Although the lung has only a limited capacity to produce protein C, APC is present in BAL fluid. The protein C system has been shown to be suppressed in patients with ventilator-associated pneumonia and pulmonary inflammation. In association with enhanced fibrin production, fibrinolytic activity is depressed in BAL fluid of patients with ALI/ARDS or pneumonia, 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. Patients at risk of ventilator-associated pneumonia show similar changes in pulmonary fibrin turnover. 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.

Vентилатор-индуцированная коагулопатия

Совершенно ясно, что значительные изменения в локальной коагуляции являются важным признаком острых легочных заболеваний (АЛП)/острой дыхательной недостаточности (ARDS) и пневмонии. Профиль и распространенность этих изменений зависят от тяжести воспаления: при тяжелой пневмонии, требующей искусственной вентиляции, эти изменения почти идентичны тем, что встречаются в ARDS, тогда как менее значительные изменения в альвеолярной коагуляции были измерены в дыхательных пациентах с ARDS. Механизмы, приводящие к нарушению альвеолярной коагуляции, не ясны, но полагают, что они аналогичны тем, что встречаются в внутрикапиллярных пространствах при тяжелом системном воспалении. Аналогично сепсису, в ARDS и пневмонии альвеолярная генерация тромбина кажется быть медиацией путем TF-фактор VIIa пути. Пациенты, у которых развился вентилятор-ассоциированная пневмония, имеют увеличенные бронхоальвеолярные уровни солuble TF и фактор VII. У пациентов с ARDS увеличение солuble TF, фактор VII и TF-зависимого фактор X активации в бронхоальвеолярной лаваже (BAL) жидкость было продемонстрировано. В дополнение к этому, ингибирование TF-фактор VIIa пути полностью отменяло внутрилегочное накопление фибрина в пациентах с ARDS. Хотя легкие имеют ограниченную способность производить протеин С, APC присутствует в BAL жидкость. Системный протеин С система была показана быть подавленной в пациентах с вентилятор-ассоциированной пневмонией и пневмонией. В ассоциации с увеличением продукции фибрина, фибринолитическая активность была подавлена в BAL жидкость пациентов с ALI/ARDS или пневмонией, связанной с высоким уровнем системной концентрации PAI-1. PAI-1 увеличивается в ALI/ARDS и вероятно секретируется лекгочными эпителиальными клетками, фибробластами и эндотелиальными клетками. Пациенты с риском вентилятор-ассоциированной пневмонии показывают сходные изменения в альвеолярной коагуляции. Основная роль фибринолитической системы в патогенезе пневмонии подчеркнута наблюдением, что депрессия бронхоальвеолярной фибринолиза предшествует клиническому появлению вентилятор-ассоциированной пневмонии на несколько дней.
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.21 Also, they did not consider the pulmonary vascular endothelium as a potential source of TF during pulmonary inflammation.

**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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