Commentary

The inflammation–coagulation axis as an important intermediate pathway in acute lung injury

Marcel Levi[1] and Marcus Schultz[2]

[1]Department of Vascular Medicine & Internal Medicine (F-4), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands
[2]Department of Intensive Care, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

Corresponding author: Marcel Levi, m.m.levi@amc.uva.nl

Published: 30 April 2008
This article is online at http://ccforum.com/content/12/2/144

Critical Care 2008, **12:**144 (doi:10.1186/cc6866)

See related research by McClintock *et al*., http://ccforum.com/content/12/2/R41

Abstract

Markers of inflammation, coagulation, and fibrinolysis predict an adverse outcome in patients with sepsis. These markers also seem predictive of an adverse outcome in patients with localized infection and inflammation, such as in acute lung injury. Whether this is entirely related to the disease or is also due to ventilation strategies that may be harmful for the lungs, however, is not clear. In the present issue of *Critical Care*, McClintock and colleagues demonstrate that these biomarkers retain their predictive effect even if lung-protective ventilation strategies are applied. Besides being biomarkers that predict outcome in patients with acute lung injury, their activation of inflammation and coagulation seems also to play a pivotal role in the pathogenesis of acute lung injury, and may thereby represent an interesting novel target for therapeutic intervention.

In this issue of *Critical Care*, McClintock and colleagues have studied markers of inflammation, coagulation and fibrinolysis in critically ill patients with acute lung injury [1]. Severe infection and the consequent systemic inflammation are associated with significant morbidity and mortality. Risk stratification of patients upon admission to the emergency room or the intensive care unit may be required for early identification of patients at high risk for organ dysfunction or a complex clinical course. Several biomarkers have been shown strong predictors of increased morbidity, and even mortality. Moreover, biomarker studies may be helpful to further elucidate molecular pathways that are important in the pathogenesis of disease – and this knowledge may lead to new therapeutic targets. Biomarkers can then subsequently serve as surrogate indicators of a potential beneficial effect, although eventually the ultimate proof of efficacy needs to be shown on clinically relevant endpoints.

In patients with sepsis, proinflammatory cytokines such as IL-1 or IL-6 are important biomarkers and independent predictors of an adverse outcome [2,3]. Inflammatory activation in patients with severe infection is almost invariably related to activation coagulation, which in turn may modulate the inflammatory response [4]. In fact, the presence of a severe derangement of coagulation (disseminated intravascular coagulation) in patients with sepsis was shown to be an independent and strong predictor of mortality, probably even stronger than other risk stratifiers [5,6]. It would be interesting to see whether this predictive property of biomarkers of inflammation and coagulation would also be present in more localized forms of infection and inflammation.

In the present issue of *Critical Care*, McClintock and colleagues demonstrate that abnormal markers of inflammation, coagulation and fibrinolysis are significant predictors of mortality in patients with acute lung injury (ALI) who required mechanical ventilation [1]. Previous studies also pointed to a predictive value of inflammatory markers (such as intercellular adhesion molecule 1 or IL-6) or coagulation parameters (such as markers for thrombin generation) in ventilated patients who developed ALI. Since it has been shown that mechanical ventilation itself may cause lung injury associated with enhanced inflammatory and coagulation activation, however, it was not clear how much of the effect was purely caused by the ALI.

In McClintock and colleagues' study all patients were treated with a lung-protective ventilatory strategy with low tidal volumes [1]. Indeed, this strategy was found to cause less bronchoalveolar activation of inflammation and coagulation. In their population, various biomarkers of inflammation, coagulation, and fibrinolysis remained different between survivors and nonsurvivors, indicating a mediatory role of these systems in the pathogenesis of ALI apart from the ventilatory insult *per*

ALI = acute lung injury; ARDS = adult respiratory distress syndrome; IL = interleukin.

se. Three biomarkers – IL-8, intercellular adhesion molecule 1 and protein C – were independent predictors of mortality after multivariate analysis.

The question that arises from the present observations, but also from other similar studies, is whether these biomarkers are a true reflection of ongoing localized inflammatory activity and activation of coagulation and fibrinolysis contributing to bronchoalveloar fibrin turnover, or whether this is an epiphenomenal reflection of a systemic disease state. There is ample evidence, however, that local activation of the inflammatory–coagulation axis is important in the pathogenesis of ALI. In fact, local fibrin generation can be considered host-protective in containing inflammation to the site of infection [7]. On the other hand, bronchoalveolar procoagulant activity can be disadvantageous if there is an excess of fibrin formation (one of the pathologic hallmarks of adult respiratory distress syndrome (ARDS)) [8].

The mechanisms that contribute to disturbed alveolar fibrin turnover are thought to be similar to those found in the intravascular spaces during severe systemic inflammation [9]. Similar to sepsis, alveolar thrombin generation in ARDS and pneumonia seems to be mediated by the tissue factor–activated factor VII pathway. Indeed, there is abundant tissue factor expressed on the surface of activated macrophages present in the bronchoalveolar space. Patients who develop ventilator-associated pneumonia indeed have increased bronchoalveolar levels of soluble tissue factor and factor VII.

An increase in soluble tissue factor, activated factor VII and tissue factor-dependent factor X activation in bronchoalveolar lavage fluid has also been demonstrated in patients with ARDS. In addition, inhibition of the tissue factor–activated factor VII pathway completely abrogated intrapulmonary fibrin deposition in patients with ARDS [10]. In association with enhanced fibrin production, fibrinolytic activity is depressed in bronchoalveolar lavage fluid of patients with ALI/ARDS or pneumonia – related to high pulmonary concentrations of plasminogen activator inhibitor 1, which is increased in ALI/ARDS and is probably secreted by lung epithelial cells, fibroblasts, and endothelial cells [11]. Interestingly, all these changes concur with the observations of McClintock and colleagues in their patients with ALI.

The enhanced activation of bronchoalveolar coagulation seems to be amplified by impaired function of natural anticoagulant mechanisms. Along with a reduction in activated protein C levels, soluble levels of thrombomodulin in pulmonary edema fluid from patients with ALI/ARDS are significantly higher than those in plasma [12]. This is thought to be due to oxidation of thrombomodulin and shedding of thrombomodulin from the cell surface, and is associated with worse clinical outcomes. The important role of activated protein S is further illustrated by the observation that administration of recombinant human activated protein C was able to block activated bronchoalveolar coagulation in subjects challenged with intrabronchial endotoxin [13]. In the observations of McClintock and colleagues, protein C levels were also one of the strongest predictors of an adverse outcome. Taken together, these observations point to a potential therapeutic role of activated protein C, either systemically or locally, in patients with severe pneumonia. Interestingly, this notion is supported by studies in which inhaled activated protein C significantly diminished pulmonary inflammation in a murine model of intranasal lipopolysaccharide-induced ALI/ARDS [14,15].

In conclusion, bronchoalveolar inflammation and coagulation activation are independent predictors of the outcome in ventilated patients with ALI, even when the patients are treated with lung-protective ventilation strategies. Besides being a marker of increased morbidity and mortality in these patients, biomarkers of inflammation and coagulation are likely to be pivotal mediators in the pathogenesis of ALI and may be considered targets for novel therapeutic interventions.

Competing interests

The authors declare that they have no competing interests.

References

1. McClintock D, Zhuo H, Wickersham N, Matthay MA, Ware LB: **Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury.** *Crit Care* 2008, **12:**R41.
2. Dinarello CA, Gelfand JA, Wolff SM: **Anticytokine strategies in the treatment of the systemic inflammatory response syndrome.** *JAMA* 1993, **269:**1829-1835.
3. Wakefield CH, Barclay GR, Fearon KC, Goldie AS, Ross JA, Grant IS, Ramsay G, Howie JC: **Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intra-abdominal sepsis. Scottish Sepsis Intervention Group.** *Br J Surg* 1998, **85:**818-825.
4. Levi M, van der Poll T, Buller HR: **Bidirectional relation between inflammation and coagulation.** *Circulation* 2004, **109:**2698-2704.
5. Bakhtiari K, Meijers JC, de Jonge E, Levi M: **Prospective validation of the international society of thrombosis and maemostasis scoring system for disseminated intravascular coagulation.** *Crit Care Med* 2004, **32:**2416-2421.
6. Dhainaut JF, Yan SB, Joyce DE, Pettila V, Basson BR, Brandt JT, Sundin D, Levi M: **Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation.** *J Thromb Haemost* 2004, **2:**1924-1933.
7. Opal SM: **Phylogenetic and functional relationships between coagulation and the innate immune response.** *Crit Care Med* 2000, **28:**S77-S80.
8. Levi M, Schultz MJ, Rijneveld AW, van der Poll T: **Bronchoalveolar coagulation and fibrinolysis in endotoxemia and pneumonia.** *Crit Care Med* 2003, **31:**S238-S242.
9. 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-L248.
10. Welty-Wolf KE, Carraway MS, Miller DL, Ortel TL, Ezban M, Ghio AJ, Idell S, Piantadosi CA: **Coagulation blockade prevents sepsis-induced respiratory and renal failure in baboons.** *Am J Respir Crit Care Med* 2001, **164:**1988-1996.
11. Schultz MJ, Millo J, Levi M, Hack CE, Weverling GJ, Garrard CS, van der Poll T: **Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia.** *Thorax* 2004, **59:**130-135.
12. 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-L521.

13. 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:** 1125-1128.
14. Choi G, Vlaar AP, Schouten M, van 't Veer C, van der Poll T, Levi M, Schultz MJ: **Natural anticoagulants limit LPS-induced pulmonary coagulation but not inflammation.** *Eur Respir J* 2007, **30:**423-428.
15. Slofstra SH, Groot AP, Maris NA, Reitsma PH, Cate HT, Spek CA: **Inhalation of activated protein C inhibits endotoxin-induced pulmonary inflammation in mice independent of neutrophil recruitment.** *Br J Pharmacol* 2006, **149:**740-746.