Commentary

Recombinant human activated protein C in acute lung injury: what is the role of bronchial circulation?

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Abstract

Impairment of the protein C pathway plays a central role in the pathogenesis of sepsis. Treatment with recombinant human activated protein C (rhAPC) has been reported to increase survival from severe sepsis. Protein C levels also decrease markedly in acute lung injury, of both septic and nonseptic origin. Low levels of protein C in acute lung injury are associated with poor clinical outcome. The present article discusses the beneficial effects of rhAPC in oleic acid-induced lung injury as well as the controversies between different animal models and the timing of drug administration. The unique bronchial circulation in ovine models seems to be responsible for the beneficial effects of rhAPC when given simultaneously to the injury.

In the previous issue of *Critical Care* we read with great interest a report of the first experimental study of recombinant human activated protein C (rhAPC) in oleic acid-induced nonseptic acute lung injury (ALI) in sheep [1].

Impairment of the protein C pathway plays a central role in the pathogenesis of sepsis. Treatment with rhAPC has been reported to increase survival from severe sepsis [2]. The administration of rhAPC may correct the dysregulated anti-coagulant mechanism and prevent propagation of thrombin generation and the formation of microvascular thrombosis. Furthermore, rhAPC may simultaneously modulate the inflammatory response. It is likely that the beneficial effects of rhAPC observed in experimental and clinical studies of severe sepsis result from a combination of mechanisms that modulate the interdependent processes of coagulation and inflammation [3]. Protein C levels also decrease markedly in ALI, of both septic and nonseptic origin. Low levels of protein C in ALI are associated with poor clinical outcome [4,5].

In the present study, the authors of the well known group of Lars Bjertnaes (Tromsø, Norway) showed that simultaneous administration of rhAPC ameliorates oleic acid-induced (non-septic) lung injury. The rise in pulmonary artery pressure, the development of pulmonary edema and the derangement of arterial oxygenation subsequent to intravenous bolus infusion of oleic acid all improved significantly during coadministration of rhAPC [1]. These results are surprising, given the timing of rhAPC administration.

We recently reviewed studies of rhAPC treatment in sepsis-related ALI and found the timing of drug administration to be critical in these experiments [6]. When given prior to the injury in a porcine model [7] or given simultaneously in *Pseudomonas aeruginosa*-induced lung injury in rats [8], the oxygenation further deteriorated – beneficial effects could only be shown when rhAPC was given post injury in various ovine models [9-11]. We hypothesized that rhAPC in the early stage of ALI may disturb the complex coagulation balance at the alveolar level, and may impede an initially positive effect of coagulation activation, because in the early phase of ALI the epithelial side as well as the endothelial side of the capillary barrier are involved with fibrin deposition, reflecting a shift in the alveolar/fibrinolysis balance [6].

The beneficial effects of the simultaneous treatment in the present study [1], however, are in contrast to our hypothesis and lead away from the coagulation cascade to the activity of neutrophils in ALI. During inflammation, activated neutrophils accumulate in the lungs and other organs, thus contributing to organ system dysfunction. Neutrophils express receptors for rhAPC and neutrophil chemotaxis is inhibited by exposure to rhAPC, explaining its beneficial effects [12].

Our group uses an ovine model of smoke inhalation and sepsis to induce ALI [13], since smoke inhalation and sepsis are major contributors to mortality in burn patients [14]. The

ALI = acute lung injury; rhAPC = recombinant human activated protein C.

lungs of sheep have a special feature, a single bronchial artery, and a single lymphatic draining of the lung. A 10-fold increase in bronchial blood flow could be shown within 20 minutes of smoke inhalation. These same animals demonstrate a six-fold increase in pulmonary transvascular fluid flux [13]. The venous outflow of the bronchial circulation drains into the pulmonary microcirculation at the precapillary level. Considering the fact that initial damage to the airway appeared to drive the pathophysiology of the parenchyma, investigators hypothesized that the bronchial blood might deliver cytotoxic materials or cells into the pulmonary microcirculation. To test this hypothesis, several investigators have tied off the bronchial artery of sheep and then exposed the animals to smoke. In these studies the hypothesis was affirmed, and the lung parenchymal changes were reduced [15].

What could be the linkage between the airway, the bronchial venous drainage and parenchymal injury to the lung? Neutrophils activated in the bronchial circulation flow out into the bronchial venous drainage. Normally, the large neutrophil can traverse the pulmonary capillary by changing shape. Many of the neutrophils, however, have been activated in the bronchial areas – their F-actin is activated and the cells are stiff and cannot deform. These stiff cells are carried to the pulmonary microvasculature, where they are impaled by the narrow pulmonary capillaries. The activated neutrophils release reactive oxygen species and proteases that damage the parenchyma [15]. The final proof of this hypothesis was to deplete the animals of their neutrophils and determine how this affected the response to inhalation injury. In these studies of sheep depleted of their leukocytes, a high percentage of the response to smoke inhalation was blocked [16].

Neutrophils express receptors for rhAPC and neutrophil chemotaxis is inhibited by exposure to rhAPC [12]. When rhAPC binds to these receptors, before the cells are drained via the bronchial venous system into the pulmonary microvasculature, a reduction of ALI may be anticipated. Taking these facts together, the results of Waerhaug and colleagues appear in a different light [1]; of course oleic acid-induced ALI is different from smoke inhalation, but, given the direct injury to the lung and the fact that sheep have the single bronchial artery [13], the beneficial effects of a simultaneous treatment with rhAPC might be more advantageous than in other models – especially since only sheep subjected to peritoneal sepsis or endotoxin infusion presented with reduced extravascular lung water [10,11]. Future studies are warranted to determine the effects of rhAPC in an ovine model when the bronchial artery is tied off to clear its mechanism in ALI.

Competing interests

The authors declare that they have no competing interests.

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