Given the multiplicity of anti-inflammatory actions of activated protein C (APC), it is perhaps not surprising that APC would be effective in reducing the severity of lung injury produced by the use of large tidal volumes during mechanical ventilation. In this issue of *Critical Care*, Maniatis and colleagues [1] provide data showing that pretreatment of mice with inhaled APC is protective against ventilator-induced lung injury (VILI). While the mechanisms responsible for this effect require additional elucidation, inhaled APC appears to be a potentially useful intervention in diminishing the severity of ventilator-induced lung injury and other forms of acute lung injury.

Inhaled activated protein C: a new therapy for the prevention of ventilator-induced lung injury?

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See related research by Maniatis *et al*., http://ccforum.com/content/14/2/R70

### Abstract

Systemic administration of activated protein C (APC) has been shown to reduce pulmonary inflammation in preclinical models of acute lung injury. However, there is only limited information concerning the effects of inhaled APC in modulating the severity of pulmonary inflammation. In a study reported in this issue of *Critical Care*, Maniatis and colleagues show that pretreatment of mice with inhaled APC is protective against ventilator-induced lung injury. While the mechanisms responsible for this effect require additional elucidation, inhaled APC appears to be a potentially useful intervention in diminishing the severity of ventilator-induced lung injury and other forms of acute lung injury.

In addition to its effects on coagulation cascades, APC has been shown to have a number of actions that may contribute to reducing inflammation in the setting of sepsis or acute lung injury. For example, APC has potent anti-apoptotic effects on endothelial cells that remain even when modified forms of APC that lack anti-coagulant properties are used [2]. Interaction between APC and the endothelial protein C receptor, which is actually a misnomer since this receptor is also found on other cell populations, including neutrophils and mononuclear cells, results in diminished migration toward inflammatory gradients [3]. In human studies in which lipopolysaccharide (LPS) was instilled into airways, there were decreased numbers of neutrophils in the airways among the volunteers randomly assigned to infusions of APC [3]. Recent data have shown that APC cleaves histones released by dying cells, diminishing the damage to endothelial cells and inflammatory responses initiated by exposure to histones [4]. Finally, interaction of APC with protease-activated receptor-1 can diminish the activation of macrophages and other cell populations [5-7].

While the authors of this article hypothesize that the beneficial actions of inhaled APC in VILI result from inhibition of activation of the extracellular-regulated kinase (ERK) pathway, this potential mechanism is not directly explored. Rather, diminished ERK activation is shown in lung homogenates and in cultured lung epithelial cells after treatment with APC. However, it remains unclear whether the decrease in ERK activation is the cause of the beneficial effects of APC or rather is simply a reflection of the decrease in inflammation produced by APC treatment. Additional experiments in which ERK was specifically inhibited would be necessary to determine the importance of this signaling pathway in modulating the effects of APC in VILI.

Several previous studies have shown that inhaled APC reduces lung injury and inflammation in models of LPS-induced lung injury [8-10]. In those studies, despite decreases in histologic indices of lung injury, neutrophil numbers and concentrations of proinflammatory...
cytokines did not appear to be reduced after APC treatment. In contrast, in at least one study, inhaled APC did reduce the severity of coagulation abnormalities in the lungs [10]. Such results suggest that the beneficial effects of inhaled APC may result from reversing alterations in coagulation and fibrinolysis, which are almost ubiquitous findings in acute lung injury, or possibly from diminishing the enhanced apoptosis of epithelial and other cell populations which accompanies acute lung injury.

In the present experiments, treatment with APC was started before the initiation of injurious ventilation. Therefore, it remains unknown at present whether inhaled APC would be beneficial if initiated after the lungs have been exposed to large tidal volumes, an important clinical issue. Additionally, low-tidal-volume ventilation has become the standard of care in critically ill patients because of studies showing that its use improves outcome, including diminishing mortality, in patients with acute lung injury and also is likely to prevent the development of lung injury when used as the initial mode of ventilation [11-14]. Therefore, the clinically relevant questions now become whether inhaled APC can diminish the severity of lung injury when used in conjunction with low-tidal-volume ventilation in the presence of acute lung injury due to sepsis or other etiologies and whether inhaled APC can prevent or minimize primary or secondary lung damage when low tidal volumes are used for mechanical ventilation.

Abbreviations
APC, activated protein C; ERK, extracellular-regulated kinase; LPS, lipopolysaccharide; VILI, ventilator-induced lung injury.

Competing interests
The author declares that he has no competing interests.

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