

## Commentary

# Levels of protein C and activated protein C: what do they mean?

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## Abstract

Acute pancreatitis is a local inflammatory process that leads to a systemic inflammatory response in the majority of cases, and sometimes leads to multiple organ failure. It is obvious that coagulation and especially the protein C system are involved in this disease. The present commentary is related to a study in patients with pancreatitis with and without multiple organ failure in which protein C and activated protein C levels were studied. The protein C system and other studies analyzing (activated) protein C levels are discussed.

## Introduction

In the present issue of *Critical Care*, the Finnish group of Lindstrom and colleagues [1] describes a study in 31 patients with acute pancreatitis in which they assess the organ function and analyze the levels of protein C (PC) and activated protein C (APC), as well as the monocyte activation state, in order to evaluate the turnover of PC to APC. They categorized the patients into a group ( $n=13$ ) with severe acute pancreatitis with multiple organ failure and a control group ( $n=18$ ) with severe acute pancreatitis without multiple organ failure. In the group with multiple organ failure, the number of patients with decreased (<70% of the adult mean) levels of PC was significantly higher than in the group without multiple organ failure (92% versus 44%,  $P<0.008$ ). Although within normal limits, in all but one patient the minimum APC level was lower in cases with multiple organ failure than in controls (median 84.9% versus 96.5%,  $P=0.009$ ). Strikingly, samples in five patients were taken preceding multiple organ failure and showed low PC levels and high APC/PC ratios. The percentage of HLA-DR-positive monocytes correlated weakly with the PC and APC levels ( $r=0.38$  and  $r=0.27$ , respectively).

## Protein C pathway

The PC system has been extensively studied, not only because the decreased function of this natural anticoagulant pathway may be particularly problematic leading to thrombo-

sis, but also because of the other properties of the PC system. APC, and probably also PC, has specific immunomodulating properties: *in vitro*, APC inhibits tumor necrosis factor alpha elaboration from monocytes and blocks leukocyte adhesion to selectins, as well as influences apoptosis [2].

The PC pathway is initiated when thrombin binds to thrombomodulin on the surface of the endothelium. An endothelial cell PC receptor augments PC activation by the thrombin-thrombomodulin complex more than 10-fold *in vivo*. The endothelial cell PC receptor is shed from the endothelium by inflammatory mediators and thrombin. The exact function and properties of this soluble endothelial cell PC receptor are not known. The endothelial cell PC receptor can undergo translocation from the plasma membrane to the nucleus, where it redirects gene expression. During translocation it can carry APC to the nucleus, possibly accounting for the ability of APC to modulate inflammatory mediator responses in the endothelium [2].

The third important property of APC is the influence on fibrinolysis. APC is capable of neutralizing the fibrinolysis inhibitors plasminogen activator inhibitor 1 and thrombin activatable fibrinolysis inhibitor [3,4]. During acute inflammation and sepsis there is activation of coagulation, leading to the formation of thrombin being the trigger for the activation of PC to APC. High levels of thrombin lead to high levels of APC, which will complex to plasminogen activator inhibitor 1 or will be neutralized. Finally the level of PC will decrease, or there may even be a depletion of PC as can be seen in meningococcal sepsis.

## Levels of protein C and activated protein C in acute disease

Levels of PC have been studied extensively in several clinical situations, especially during meningococcal sepsis, but also during other forms of sepsis [5]. Of interest is the study in

APC = activated protein C; PC = protein C.

neutropenic patients with fever in which serial blood samples were taken. In those patients who developed sepsis, the clinical symptoms were preceded with a decline of their PC levels [6]. The same feature was found in the pancreatitis study of Lindstrom and colleagues [1].

APC levels have been studied less extensively, for several reasons. Measuring APC has only recently been feasible using an enzyme capture assay [7] requiring benzamidine as a special inhibitor during sampling, and the assay is time consuming (2 weeks) – although there is a new assay described using much less time [8]. Besides these technical specialties, the half-life of APC is about 15 min so just the level of APC is useless without other markers of coagulation and inflammation at the same time for analysis. The first studies were in healthy individuals [9], individuals with brain infarction, and smokers versus nonsmokers [10].

The results of the studies of APC levels in human sepsis are not all that obvious and may even seem contradictory. In the study of de Kleijn and colleagues in children with meningococcal sepsis, the APC levels paralleled thrombin markers and were positively related to severity with the highest levels in nonsurvivors [11]. In the study of Liaw and colleagues [8], from the 32 patients with severe sepsis studied, 20 patients had APC levels that paralleled thrombin markers and 12 patients did not, indicating an impaired PC activation. Severe sepsis is an extremely heterogeneous condition, and the factors involved in downregulation of the endothelium-based PC activation in patients remain to be identified, but severity of disease, age, cigarette smoking and pre-existing conditions are known to be among these factors.

### Limits of this study

Acute pancreatitis is a local inflammatory process that leads to a systemic inflammatory response in the majority of cases, and sometimes to multiple organ failure. In the present study of Lindstrom and colleagues [1] a small number of patients were analyzed. The relevance of studying PC and APC in this disease is certainly valid and supported by animal experiments [12]. The units in which APC was expressed are not very common, and make it difficult to compare the results with other studies. The differences between cases and controls are not dramatically clinically significant. The results on HLA-DR are not very well elaborated.

Nowadays the level of 30% HLA-DR-positive cells is considered a cutoff level for categorizing immune depression or not. It would have been interesting to categorize on the basis of that level and to analyze the APC and PC levels and ratios. On the other hand, we need these kinds of studies to determine the exact role of APC and PC in severe sepsis and the possible therapeutic role of PC and APC supplementation.

### Competing interests

The author declares that they have no competing interests.

### References

1. Lindstrom O, Kylanpaa L, Mentula P, Puolakkainen P, Kemppainen E, Haapiainen R, Fernandez JA, Griffin JH, Repo H, Petaja J: **Up-regulated but insufficient generation of activated protein C is associated with development of multiorgan failure in severe pancreatitis.** *Crit Care* 2006, **10**:R16.
2. Esmon CT: **Crosstalk between inflammation and thrombosis.** *Maturitas* 2004, **47**:305-314.
3. Hermans PW, Hazelzet JA: **Plasminogen activator inhibitor type 1 gene polymorphism and sepsis.** *Clin Infect Dis* 2005, **41** (Suppl 7):S453-S458.
4. Zeerleder S, Schroeder V, Hack CE, Kohler HP, Willemin WA: **TAFI and PAI-1 levels in human sepsis.** *Thromb Res* 2005 [epub ahead of print].
5. Iba T, Kidokoro A, Fukunaga M, Sugiyama K, Sawada T, Kato H: **Association between the severity of sepsis and the changes in hemostatic molecular markers and vascular endothelial damage markers.** *Shock* 2005, **23**:25-29.
6. Mesters RM, Helterbrand J, Utterback BG, Yan B, Chao YB, Fernandez JA, Griffin JH, Hartman DL: **Prognostic value of protein C concentrations in neutropenic patients at high risk of severe septic complications.** *Crit Care Med* 2000, **28**:2209-2216.
7. Gruber A, Griffin JH: **Direct detection of activated protein C in blood from human subjects.** *Blood* 1992, **79**:2340-2348.
8. Liaw PC, Esmon CT, Kahnamouy K, Schmidt S, Kahnamouy S, Ferrell G, Beaudin S, Julian JA, Weitz JI, Crowther M, et al.: **Patients with severe sepsis vary markedly in their ability to generate activated protein C.** *Blood* 2004, **104**:3958-3964.
9. Fernandez JA, Petaja J, Gruber A, Griffin JH: **Activated protein C correlates inversely with thrombin levels in resting healthy individuals.** *Am J Hematol* 1997, **56**:29-31.
10. Fernandez JA, Gruber A, Heeb MJ, Griffin JH: **Protein C pathway impairment in nonsymptomatic cigarette smokers.** *Blood Cells Mol Dis* 2002, **29**:73-82.
11. de Kleijn ED, de Groot R, Hack CE, Mulder PG, Engl W, Moritz B, Joosten KF, Hazelzet JA: **Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: a randomized, double-blinded, placebo-controlled, dose-finding study.** *Crit Care Med* 2003, **31**:1839-1847.
12. Yamenel L, Mas MR, Comert B, Isik AT, Aydin S, Mas N, Deveci S, Ozyurt M, Tasci I, Unal T: **The effect of activated protein C on experimental acute necrotizing pancreatitis.** *Crit Care* 2005, **9**:R184-R190.