

Commentary

Recombinant activated protein C in sepsis: endothelium protection or endothelium therapy?

Veronique Regnault¹ and Bruno Levy²

¹Inserm, U734; Coordination Circulation, Henri Poincare University, Nancy France

²Coordination Circulation UHP-INSERM, Contrat Avenir INSERM, Groupe CHOC, Faculté de Médecine. Université de Nancy-1, Nancy, France

Corresponding author: Bruno Levy, b.levy@chu-nancy.fr

Published: 11 January 2007

This article is online at <http://ccforum.com/content/11/1/103>

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Critical Care 2007, **11**:103 (doi:10.1186/cc5135)

See related review by Looney and Matthay, <http://ccforum.com/content/10/6/239>

Abstract

Endothelium dysfunction is one of the hallmarks of sepsis. Looney and Matthay, in the previous issue of *Critical Care*, highlight the role of activated protein C (APC) as a protective endothelial drug in septic situations. Nevertheless, the results of *in vivo* studies are less explicit and it remains uncertain whether these properties are relevant in human septic shock. Before considering recombinant APC (rAPC) as a therapeutic drug for the endothelium, we have to demonstrate its efficiency to protect or to reduce endothelium injury when infused a long time after the septic challenge. Nevertheless, if rAPC is efficient when infused in the early phase of septic challenge, we thus need to treat our patients earlier. At the least, genetically engineered variants have been designed with greater anti-apoptotic activity and reduced anticoagulant activity relative to wild-type APC. Further studies are needed to demonstrate the usefulness of these variants in septic shock therapy.

The use of recombinant activated protein C (rAPC) is one of the hottest topics in septic shock therapy. The pivotal phase 3 placebo-controlled Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) clinical trial demonstrated a 19.4% relative risk reduction in 28-day mortality (6.1% absolute risk reduction) with an increased risk (3.5% versus 2.0%) of serious bleeding events compared with placebo.

Two recent and important articles have highlighted the role of APC as a protective endothelial drug [1] and as a cytoprotective drug [2]. Beneficial effects of rAPC in the PROWESS study were thought to be related to a reduction in coagulation and, to a lesser extent, to a reduction in inflammatory response to sepsis [3]. Post-PROWESS investigations have been associated with a myriad of cellular or animal studies demonstrating that rAPC, through reactions mediated by endothelial protein C receptor and the effector receptor, protease activated receptor-1, acts directly on cells to exert multiple cytoprotective effects including: down regulation of

pro-inflammatory gene expression [4]; anti-inflammatory activities [5]; anti-apoptotic activity [6]; and protection of endothelial barrier function [1,2].

Endothelium dysfunction is one of the hallmarks of sepsis [7]. Sepsis, *per se*, may induce phenotypic modulations of the endothelium through direct or indirect interaction of the endothelial layer with components of the bacterial wall, inducing a myriad of host-derived factors from endothelial cells. Phenotypic modifications include changes in pro-coagulant and proadhesive properties, increased endothelial permeability, endothelial cell apoptosis and changes in vasomotor properties; the last of these is crucial since vasoplegia is directly related to septic shock mortality. Recent animal and human data have suggested that rAPC may improve both vascular and myocardial dysfunction and vascular reactivity to catecholamine during endotoxin and/or septic challenge [8,9].

From bench to bedside

Experimental evidence supports a role of APC in maintaining the integrity of the endothelium through both direct and indirect mechanisms. Nevertheless, the results of *in vivo* studies are less explicit. In a retrospective study of septic shock in humans, Monnet and colleagues [9] demonstrated that APC infusion was associated with a decrease in the amount of delivered norepinephrine. Wiel and colleagues [10] demonstrated in a rabbit model of endotoxin induced shock that APC decreased aorta endothelial injury. By contrast, in a lung model of endotoxin induced inflammation, Robriquet and colleagues [11] demonstrated a trend to an increased vascular permeability using high doses of human APC. This last result was in sharp contrast with the results obtained by Nick and colleagues [12] in a human model of pulmonary endotoxin administration. APC appears to improve

PROWESS = Protein C Worldwide Evaluation in Severe Sepsis; rAPC = recombinant activated protein C.

mortality in septic shock with a high APACHE 2 score and is potentially detrimental in severe sepsis. In rats, APC markedly decreased tumour necrosis factor concentrations whereas they remained unchanged in either human septic shock or endotoxemia. The question arises, therefore, as to whether it is truly possible to reconcile all these discrepancies? Moreover, can these stirring laboratory data be translated into clinical practice?

Limitations of experimental studies: endothelium protection versus endothelium therapy

Clearly, in cellular and animal models, rAPC has been given either as a pre-treatment or concurrent with septic challenge. This mode of administration favours the anti-inflammatory effects of rAPC, which are particularly efficient in murine models in protecting the endothelium from cytokine-mediated apoptosis or upregulation of endothelial adhesion molecules. Thus, studies using post-injury treatment are needed in models that mimic septic shock, such as experimental pneumonia or peritonitis treated by antibiotics and volume resuscitation, and where the effects of rAPC would be investigated 16 to 24 hours after septic challenge. If we can demonstrate the efficiency of rAPC to protect or to reduce endothelium injury in these conditions, we can ultimately postulate that rAPC is also a therapeutic drug for the endothelium.

The earlier the better

If rAPC is efficient when infused in the early phase of septic challenge, we thus need to treat our patients earlier. At least two studies suggest that treatment with rAPC within 24 hours may carry a larger survival advantage for patients with severe sepsis, compared with those treated more than 24 hours after organ dysfunction [13]. Interventions directed at specific endpoints, when initiated early in the 'golden hours' of a patient's condition, seem to be promising [14]. The beneficial effects of earlier administration of rAPC to appropriate patients may fit into this paradigm.

The future

Extensive *in vivo* and *in vitro* studies have focused on the cytoprotective effects of APC and most authors agree that its anticoagulant and cytoprotective effects are mediated by distinct APC structural features. Positively charged residues in surface loops in the APC protease domain have been identified as participating in the anticoagulant activity but not in cellular effects. Hence, variants have been designed with greater anti-apoptotic activity and reduced anticoagulant activity relative to wild-type APC [2]. Whether these genetically engineered variants actually provide superior pharmacological properties remains to be elucidated *in vivo*. Such investigations may allow the design of therapeutic APC variants with decreased anticoagulant activity to reduce the risk of bleeding on the one hand, but also with normal cytoprotective properties in order to retain full beneficial effects on sepsis outcome.

Competing interests

BL has received reimbursements and funding from Eli Lilly, France.

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