CRITICAL CARE

COMMENTARY

A plethora of angiopoietin-2 effects during clinical sepsis

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See related research by Davis *et al.*, http://ccforum.com/content/14/3/R89

Abstract

The interesting study by Davis and colleagues in the current issue of *Critical Care* expands on the increasingly recognized role of angiopoietins in human sepsis but raises a number of questions, which are discussed in this commentary. The authors describe an association between elevated angiopoietin (ang)-2 levels and impaired vascular reactivity, measured by the partly nitric oxide-dependent finger hyperemic response to forearm vascular occlusion, in patients with sepsis. This suggests that the ang-1/2-Tie2 system is involved in a number of pathophysiologic, phenotypic and perhaps prognostic alterations in human sepsis, on top of the effect on pulmonary endothelial barrier function. The novel inflammatory route may be a target for future therapeutic studies in human sepsis and acute lung injury, including those with activated protein C.

In the past decade, the angiopoietin (ang)-1/2-Tie2 system has increasingly been suggested to play a major role in the various features of human sepsis and acute lung injury and has thereby been considered as a novel therapeutic target [1-3]. High circulating ang-2 levels promote inflammation and vascular permeability (in the lungs), while ang-1 has a protective effect, and these associations are confirmed by clinical studies [4,5]. The putative role of the ang-2/1 balance is gradually being expanded by studies showing that ang-2 levels may predict acute kidney injury and ICU outcome, even independently of disease severity [4,6].

In the current issue of *Critical Care*, Davis and colleagues [1] provide additional evidence that ang-2 release is associated with impaired vasoreactivity in patients with early sepsis, probably via interference with nitric oxide (NO), which can be considered as a pivotal pathophysiologic alteration in human sepsis. They measured vascular reactivity by the non-invasive reactive hyperemia-peripheral artery tonometry (RH-PAT) technique, reviewed elsewhere [7]. Based on these observations, the authors conclude that ang-2 is a more meaningful biomarker of endothelial function in sepsis than 'currently used surrogate measures', but formal evaluation of predictive values are lacking and the correlations are moderate at best. Also, the authors did not measure ang-1 levels, although the balance between ang-2 and ang-1 may determine the net biological effect. Finally, an intervention targeted at these molecules would be needed to reveal a direct role in microvascular responses in sepsis. Indeed, the angiopoietin-1/2-Tie2 system controls the responsiveness of the endothelium via multiple signal transduction pathways, including activation of Rho-like small GTPases, protein kinase C-zeta and Src [2,5], while the protein C system, a therapeutic target of alleged benefit in human septic shock, may also be involved, as recently suggested [8]. Ang-1 may be associated with enhanced and ang-2 with decreased endothelial NO synthase and release, even clinically [9,10]. Conversely, changes in RH-PAT are but partly dependent on changes in NO levels [7]; we do not know this relationship in sepsis nor whether changes in the former are of prognostic significance for organ failure and mortality, so cannot be certain of their clinical significance.

Cytokine-induced exocytosis by Weibel-Palade bodies of procoagulant factors as well as ang-2 is associated with downregulation of endothelial NO synthase and release [11,12]. The NO and ang-2/1 balance may thus be inversely interrelated, both in control of synthesis in the endothelium as well as in pro-inflammatory effects [10]. Hence, this may further explain the inverse relation (in time) between endothelial NO-dependent vascular reactivity and circulating ang-2 in the study by Davis and colleagues [1]. Finally, vasopressin (V)2 receptors may contribute to exocytosis - a well known effect of selective V2 receptor-stimulating desmopressin and aselective

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V1/2 receptor-stimulating vasopressin, for instance - but selective V1 receptor stimulation may antagonise it, as suggested by recent experimental work showing that the latter may reduce lung leakage and injury in a Gram-positive ovine model of septic shock [13]. If that is the case, the excess mortality suggested by the trial on vasopressin in the treatment of septic shock, at least when corticosteroids were not co-administered, can be explained, but ang-2 levels were not measured [14]. However, anti-inflammatory effects of low dose vasopressin have also been observed but the role of the V1 receptor remains unclear [9,15]. Taken together, the control of Weibel-Palade bodies in sepsis deserves further study.

In conclusion, the study by Davis and colleagues [1] suggests that ang-2 plays a role in the pathogenesis of sepsis beyond its well-appreciated role in inflammation and vascular permeability, by interfering with microvascular control of blood flow. The novel inflammatory route may be a target for future therapeutic studies in human sepsis and acute lung injury, including those with activated protein C, V receptor agonists, statins and agents that improve endothelial NO.

Abbreviations

ang = angiopoietin; NO = nitric oxide; RH-PAT = reactive hyperemia-peripheral artery tonometry; V = vasopressin.

Competing interests

The authors declare that they have no competing interests.

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