CRITICAL CARE

COMMENTARY

Sepsis and the broken endothelium

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See related research by Yang *et al.*, http://ccforum.com/content/15/1/R11

Abstract

The study by Yang and colleagues examined 81 patients with septic shock due to pneumonia, along with 20 patients with pneumonia without organ dysfunction. Their major findings were that circulating levels of soluble vascular endothelial cell growth factor receptor-1 (sVEGFR-1) and urokinase-type plasminogen activator (uPA) were associated with organ dysfunction and mortality, whereas vascular endothelial cell growth factor (VEGF) levels had no such predictive power. Yang and colleagues are to be complimented for a well-conducted study of a reasonably (and helpfully!) homogeneous population of patients with sepsis that carefully and comprehensively analyzed the relationship between sVEGFR-1, uPA, VEGF and clinical outcome. The study serves not only to provide evidence in support of new diagnostic biomarker targets in sepsis, but also to augment the growing evidence of an important role of the endothelium in sepsis in general, and the VEGF signaling axis in particular.

While the exact mechanisms behind the relationship between elevated soluble vascular endothelial cell growth factor receptor-1 (sVEGFR-1) levels and clinical outcome remain controversial, the finding in the current study by Yang and colleagues [1] that sVEGFR-1 is a promising sepsis biomarker is quite consistent with previous studies [2,3]. In fact, in a recent investigation, we demonstrated that sVEGFR-1 performed with a diagnostic accuracy equal to, or exceeding, that of the commonly used sepsis biomarkers interleukin-6 and serum lactate [3]. Interestingly, preclinical studies have demonstrated that sepsis induces elevated levels of vascular endothelial cell growth factor (VEGF), as well as elevated levels of sVEGFR-1 [4,5]. These studies have shown that VEGF exacerbates sepsis and mediates morbidity and mortality, while it is thought that circulating sVEGFR-1 binds and neutralizes the adverse/pro-inflammatory effects of VEGF. This hypothesis is supported by the observation that supratherapeutic levels of sVEGFR-1 in murine models of sepsis deplete the blood of free VEGF and protect against morbidity and mortality.

If sVEGFR-1 is protective, then why are elevated circulating levels of sVEGFR-1 associated with worse clinical outcome in sepsis? The apparent dichotomy may be explained by one or more of the following hypotheses: 1, sVEGFR-1 levels simply reflect the vigor of the anti-inflammatory response in sepsis (akin to policeman at the scene of a crime - likely the more policeman, the worse the crime); 2, elevated sVEGFR-1 may cause profound immune depression by interfering with sVEGFR-1-mediated signaling in monocytes; and 3, sVEGFR-1 may interfere with endothelial repair by inhibiting VEGF signaling in endothelial cells.

As Yang and colleagues point out, the existing literature concerning circulating VEGF levels in sepsis is controversial. Previous studies have shown that adverse outcomes in sepsis are associated with either high [2,6,7] or low [8] VEGF levels. In the current study, VEGF levels did not predict adverse clinical outcomes. However, it should be noted that the investigation used total VEGF levels, which is different than measuring physiologically active free or unbound VEGF. Additionally, obtaining reproducible VEGF measurements is notoriously difficult. In any event, the diagnostic value of VEGF remains circumspect. However, given the biological plausibility of a pathogenic role for VEGF in sepsis pathophysiology (by virtue of its pro-inflammatory, permeability-promoting and procoagulant effects at the level of the endothelium) we believe that the VEGF signaling axis remains a viable therapeutic target. To test this hypothesis, we are currently investigating the use of an anti-VEGF antibody in patients with septic shock (clinicaltrials.gov identifier NCT01063010).

Finally, we submit that while the exact mechanisms governing the observed association between urokinase-type plasminogen activator (uPA) and outcomes in this study is unknown, the presence of this association

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underscores the importance and dynamic role of the endothelium in sepsis. The conversion of plasminogen to plasmin, which is primarily governed by uPA, occurs at the level of the endothelium and is a primary regulator of the hemostatic balance in sepsis. As the evidence for a central role of the endothelium in sepsis builds, it is likely that a number of other endothelial-related biomarkers will emerge that reflect a 'broken endothelium'. Perhaps one or more of these markers can be leveraged in future trials to guide therapy with novel yet-to-be-determined endothelium-sparing agents.

Abbreviations

sVEGFR-1, soluble vascular endothelial cell growth factor receptor-1; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial cell growth factor.

Competing interests

The authors declare that they have no competing interests.

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