Commentary

Renal blood flow in sepsis: a complex issue

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Abstract

The clinical complexity of sepsis and the regional variability in renal blood flow present a difficult challenge for the clinician or investigator in understanding the role and clinical importance of reduced blood flow in the pathophysiology of sepsis-induced acute renal failure. Understanding the role of regional microvasculature flow and interactions between endothelium and white blood cells in the local delivery of oxygen and substrates is of critical importance. Therefore, measuring total renal blood flow may not permit an adequate understanding of the role of altered hemodynamics in septic patients who develop acute renal failure.

Langenberg and colleagues [1] have completed an exhaustive literature review documenting the effect of sepsis on total renal blood flow (RBF) in humans and in animal models of human sepsis. This is an extremely important area of study because sepsis is the major cause of acute renal failure (ARF) in hospitalized patients, the incidence of sepsis is increasing at a rate of 1.5% per year [2], and the 28-day mortality rate in cases of severe sepsis is as high as 50% [2,3]. In a prospective study [4] the incidence of ARF in sepsis was 19%, in severe sepsis it was 23% and in septic shock it was 51%. Understanding the role, and the determinants, of RBF alterations in the pathophysiology of sepsis-induced ARF is therefore of critical clinical importance.

The finding of heterogeneity in RBF during sepsis should be of little surprise. First, sepsis is a heterogeneous disease process for several reasons, including the bacteria (Gram-negative or Gram-positive) or toxin (lipopolysaccharide; LPS) involved, the route of delivery (intraperitoneal, intravenous, or cecal ligation and puncture (CLP)), the rate of delivery, the genetic make-up of the patient or animal (high versus low cytokine responders), clinical stage of sepsis (early versus late), and the associated co-morbid conditions (congestive heart failure), to name just a few. For example, many previous studies have used the administration of LPS in high dose to initiate a 'sepsis-like syndrome' [5].

Although the LPS model can have a role in helping to understand the sepsis phenotype, many investigators now favor the use of the CLP model for several reasons. First, sepsis is a complex phenomenon and although it is in part due to the generation, release and biologic reactions of LPS, additional factors are present in clinical sepsis that are more completely modeled by bacterial-generated models such as CLP [6]. Second, although both LPS and CLP models had similar mortality rates, there were significant differences in the kinetics and magnitude of cytokine production. The very rapid production and extremely high levels of tumor necrosis factor-α and cytokines in response to LPS resulted in a vasoconstrictive phenotype with reduced cardiac output. However, the CLP model resulted in an early hyperdynamic phase characterized by low vascular resistance, low blood pressure and increased cardiac output. These differences were borne out in the review of the literature by Langenberg and colleagues [1]. Perhaps the therapeutic approaches for sepsis based on cytokine production after an LPS challenge might therefore be misdirected because the LPS model does not accurately reproduce the cytokine profile in sepsis.

The above-mentioned variables, plus additional variables including the volume status of the animal, will then influence the effect of sepsis on RBF in any clinical or experimental setting. That cardiac output was the one determinant variable of RBF, in a multi-variant analysis, is an important observation on the essential role of cardiac output in patients with sepsis and ARF. However, as pointed out by Langenberg and colleagues [1], glomerular filtration rate can decrease even with normal or increased cardiac output or RBF if there is a disproportionate degree of vasodilatation between the afferent and efferent arterioles. Probably even more important

ARF = acute renal failure; CLP = cecal ligation and puncture; LPS = lipopolysaccharide; RBF = renal blood flow.

than this possibility is the effect of sepsis on the intra-renal distribution of blood flow. The fact that total RBF is normal or increased does not mean that reduced perfusion to microvascular beds, and worsening hypoxia in these zones of the kidney, is not leading to a cycle of continued inflammatory response and the associated endothelial and epithelial cell injury [7,8].

The heterogeneity and complexity of sepsis-induced alterations in both total and regional RBF are therefore clinically important but poorly understood. It will be crucial to enhance our knowledge in this area as the search for effective therapies to prevent and treat the devastating disease of ARF associated with sepsis continues. New data indicate that this understanding must extend to the level of the regional microvasculature. Additionally, the role of potential therapies to minimize inflammation, endothelial dysfunction and the resulting interactions between endothelium and white blood cells must be thoroughly investigated.

Competing interests

The author(s) declare that they have no competing interests.

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