Commentary

# Human endotoxemia and human sepsis: limits to the model

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## Abstract

Sepsis remains the most common cause of death in intensive care units of the developed world. Accurate models of this disease syndrome are crucial for to the understanding of the complex pathophysiology of this disorder. The administration of a small dose of lipopolysaccharide to healthy volunteers is one such model of spontaneous human sepsis. Although this human endotoxemia model appears to be reasonably effective in mimicking early biochemical, metabolic, hematologic and cardiovascular septic responses in septic shock, the ability to mimic other aspects of human sepsis is open to question. The current study demonstrates that human experimental endotoxemia fails to generate evidence of increased vascular permeability within the relatively short time frame of the study.

Sepsis continues to be the most common cause of death in nonsurgical intensive care units. The mortality rate has remained high and substantially unchanged over the past century [1]. Recently, there has been a flurry of investigative work demonstrating the clinical benefit of certain interventions for sepsis, severe sepsis and septic shock [2]. The studies documenting improved outcomes with these therapies were borne of earlier efforts to elucidate the pathophysiology of this complex disease.

Much of the initial research effort focused on the development of appropriate models of disease. Early models of sepsis involved the rapid administration of large doses of endotoxin or live bacteria to experimental animals [3,4]. Subsequently, models involving cecal ligation/perforation and peritoneal implantation of infected clots were shown to mimic some aspects of sepsis more accurately [3]. However, both are necessarily imperfect in that human responses cannot be examined. The development of a human model of endotoxemia utilizing rapid administration of 4 ng/kg of reference endotoxin solved this problem. This model of endotoxemia has been used to examine a wide range of inflammatory, hemostatic, cardiovascular and respiratory responses characteristic of spontaneous sepsis in humans [5–14]. However, the integration of human responses into an endotoxemia model also creates necessary limitations. No such human model can mimic all of the critical elements present in spontaneous human sepsis.

In this issue, van Eijk and colleagues [15] test the utility of this model of human endotoxemia in the examination of microvascular permeability alterations characteristic of sepsis and septic shock. Despite meticulous effort, they were unable to support the current widely used human endotoxemia model as a suitable proxy for study of the septic microvascular permeability responses.

Three separate methods were used by the authors to measure vascular permeability: transcapillary escape rate of $I^{125}$-albumin, venous occlusion strain-gauge plethysmography, and bioelectrical impedance analysis. No statistical difference in vascular permeability between those who received endotoxin and control individuals receiving placebo was noted, despite the significant divergence of the two groups in proinflammatory cytokine and cardiovascular responses. The authors concluded that the human endotoxemia model is inadequate for study of the pathophysiology of capillary leak in sepsis.

There are significant qualifiers in regard to the findings reported by van Eijk and coworkers. First, as the authors themselves note, the dose of endotoxin used may have been suboptimal to induce capillary leakage. Although the typical cardiovascular response was indeed seen, most of the previous studies utilized twice the dose (i.e. 4 ng/kg) that was used by van Eijk and colleagues [5,6,11–13]. Furthermore the cardiovascular changes seen by Suffredini [11] and Kumar [13] and their colleagues appear to have been much more profound that those observed by van Eijk and coworkers, suggesting that, despite the seemingly adequate

cytokine response, the cardiovascular (and perhaps permeability) effects may be dose dependent.

Second, although early vascular dysfunction with venodilatation is typical of experimental endotoxemia and septic shock, more prolonged inflammatory stimulation may be required for major vascular permeability increases (even though both responses may be mediated by nitric oxide generation [16–18]). If this is the case, then the duration of the inflammatory stimulus induced by transient endotoxemia might also have been insufficient to induce the increase in vascular permeability seen in clinical sepsis.

Third, insufficient exogenous fluids might have been provided. In their human endotoxemia studies, Suffredini [11] and Kumar [13] and coworkers, for example, infused anywhere from 3 to 5 l of crystalloid over a period of about 5 hours. In comparison, the volunteers included in the study by van Eijk and coworkers [15] only received 375 ml over 5 hours. Furthermore, Suffredini and colleagues [6] detected a difference in pulmonary gas exchange only after more than 2 l of saline was infused to individuals given endotoxin, suggesting that endotoxemia by itself may be inadequate to elicit a detectable increase in capillary permeability.

A final possibility, of course, is that the human endotoxemia model simply fails to replicate the conditions of sepsis, as seen in spontaneous human or animal disease. Noninfectious models of septic shock typically involve bacterial toxins or proximal endogenous mediators such as tumor necrosis factor-α. Even infusion of live organisms can represent toxin model equivalents if the infused organism is of low virulence. For example, many such models use laboratory strains of highly serum-sensitive organisms. In these cases, the replicative component of infection is missing. Although one difference between such models and those involving live infection at a focal site may be the degree to which the inflammatory stimulus is sustained, other important differences may also exist that could explain the failure to generate increased vascular permeability in the human endotoxemia model. These could potentially include specific bacterial structural antigens (e.g. bacterial DNA) or exotoxins that are not found in noninfectious models.

Regardless, although one can argue that the conclusions drawn by van Eijk and coworkers may be somewhat too sweeping, they do raise valid questions that ultimately need to be answered if we are to advance our understanding of the pathophysiology of microvascular leakage in sepsis. What roles do the endothelium and interstitium play in capillary permeability in the setting of sepsis? Which mediators are responsible for microvascular leak? Can the serum kinetics of these mediators have an impact on the permeability response? How does the endothelium interact and modulate responses to potential mediators?

Although the answers to these questions will invariably be found in the basic science laboratory, the final arbiter of clinical relevance is the application of the same in humans. To paraphrase from William E Paul, no experimental model can settle the empirical issue of clinical medicine.

## Competing interests

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

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