

Commentary

Human endotoxemia and human sepsis: limits to the model

Ramon Anel¹ and Anand Kumar²

¹Assistant Professor, Section of Critical Care Medicine, Section of Nephrology, University of North Dakota, Grand Forks, North Dakota, USA

²Associate Professor, Section of Critical Care Medicine, Section of Infectious Diseases, University of Manitoba, Winnipeg, Canada, and University of Medicine and Dentistry, UMDNJ, Camden, New Jersey, USA

Corresponding author: Anand Kumar, akumar61@yahoo.com

Published online: 4 March 2005

This article is online at <http://ccforum.com/content/9/2/151>

© 2005 BioMed Central Ltd

Critical Care 2005, **9**:151-152 (DOI 10.1186/cc3501)

See related research by van Eijk *et al.* in this issue [<http://ccforum.com/content/9/2/R157>]

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 I¹²⁵-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 than 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.

References

1. Chaudry IH: **Sepsis: lessons learned in the last century and future directions.** *Arch Surg* 1999, **134**:922-929.
2. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, *et al.*: **Surviving sepsis campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.
3. Deitch EA: **Animal models of sepsis and shock: a review and lessons learned.** *Shock* 1998, **9**:1-11.
4. Lagoa CE, de Figueiredo LF, Cruz RJ Jr, Silva E, Rocha e Silva M: **Effects of volume resuscitation on splanchnic perfusion in canine model of severe sepsis induced by live *Escherichia coli* infusion.** *Crit Care Med* 2004, **8**:R221-R228.
5. Hesse DG, Tracey KJ, Fong Y, Manogue KR, Palladino MA Jr, Cerami A, Shires GT, Lowry SF: **Cytokine appearance in human endotoxemia and primate bacteremia.** *Surg Gynecol Obstet* 1988, **166**:147-153.
6. Suffredini AF, Shelhamer JH, Neumann RD, Brenner M, Baltaro RJ, Parrillo JE: **Pulmonary and oxygen transport effects of intravenously administered endotoxin in normal humans.** *Am Rev Resp Dis* 1992, **145**:1398-1403.
7. Catania A, Suffredini AF, Lipton JM: **Endotoxin causes release of alpha-melanocyte-stimulating hormone in normal human subjects.** *Neuroimmunomodulation* 1995, **2**:258-262.
8. von der Mohlen MA, Kimmings AN, Wedel NI, Mevissen ML, Jansen J, Friedmann N, Lorenz TJ, Nelson BJ, White ML, Bauer R, *et al.*: **Inhibition of endotoxin-induced cytokine release and neutrophil activation in humans by use of recombinant bactericidal/permeability-increasing protein.** *J Infect Dis* 1995, **172**: 144-151.
9. Pajkrt D, Doran JE, Koster F, Lerch PG, Arnet B, van der Poll T, ten Cate JW, van Deventer SJ: **Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia.** *J Exp Med* 1996, **184**:1601-1608.
10. Suffredini AF, Harpel PC, Parrillo JE: **Promotion and subsequent inhibition of plasminogen activation after administration of intravenous endotoxin to normal subjects.** *N Engl J Med* 1989, **320**:1165-1172.
11. Suffredini AF, Fromm RE, Parker MM, Brenner M, Kovacs JA, Wesley RA, Parrillo JE: **The cardiovascular response of normal humans to the administration of endotoxin.** *N Engl J Med* 1989, **321**:280-287.
12. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Cerami A, Wolff SM, Wilmore DW: **Detection of circulating tumor necrosis factor after endotoxin administration.** *N Engl J Med* 1988, **318**:1481-1486.
13. Kumar A, Bunnell E, Lynn M, Anel R, Habet K, Neumann A, Parrillo JE: **Experimental human endotoxemia is associated with depression of load-independent contractility indices: prevention by the lipid a analogue E5531.** *Chest* 2004, **126**:860-867.
14. Preas HL II, Jubran A, Vandivier RW, Reda D, Godin PJ, Banks SM, Tobin MJ, Suffredini AF: **Effect of endotoxin on ventilation and breath variability: role of cyclooxygenase pathway.** *Am J Respir Crit Care Med.* 2001, **164**:620-626.
15. van Eijk LTGJ, Pickkers P, Smits P, van den Broek W, Bouw MPWJM, van der Hoeven JG: **Microvascular permeability during experimental human endotoxemia: an open intervention study.** *Crit Care* 2005, **9**:R157-R164.
16. Kubes P: **Nitric oxide modulates microvascular permeability.** *Am J Physiol.* 1992, **262**:H611-H615.
17. Wang le F, Patel M, Razavi HM, Weicker S, Joseph MG, McCormack DG, Mehta S: **Role of inducible nitric oxide synthase in pulmonary microvascular protein leak in murine sepsis.** *Am J Respir Crit Care Med* 2002, **165**:1634-1639.
18. Vane JR, Anggard EE, Botting RM: **Regulatory functions of the vascular endothelium.** *N Engl J Med* 1990, **323**:27-36.