Norepinephrine in Septic Shock: A Mixed Blessing

Sepsis, defined as a dysregulated host response to an infection leading to life-threatening organ dysfunction, is the most frequent cause of hospital mortality and a major healthcare burden worldwide (1). Septic shock is the most severe presentation of sepsis, characterized by persistent hypotension and hyperlactatemia in spite of adequate fluid resuscitation (2). This hemodynamic failure occurs despite elevated endogenous catecholamine (epinephrine and norepinephrine) levels as part of the archetypal "fight or flight" response to stress and is for a large part related to decreased adrenoreceptor sensitivity and altered adrenergic signaling (3). To overcome these alterations and restore tissue perfusion, catecholamines are administered therapeutically in supraphysiologic doses to patients with septic shock. Today, norepinephrine remains the mainstay vasopressor treatment for septic shock (4). Whereas the lifesaving properties of norepinephrine are undisputed, growing experimental evidence suggests that excessive dosing or duration of norepinephrine infusion could adversely affect patient outcomes because of its multiple "collateral" effects on immunity, metabolism, and coagulation (5, 6). In particular, preclinical data indicate that norepinephrine treatment can exert immunosuppressive effects and may facilitate infection; i.e., norepinephrine has been shown to modify the phenotype of leukocytes exposed to bacterial agonists to a more antiinflammatory profile, with reduced production of proinflammatory cytokines such as TNF-α (tumor necrosis factor-α) and increased production of the antiinflammatory cytokine IL-10, as well as to enhance bacterial growth both *in vitro* and in animal studies (7–10). However, thus far, the immunologic effects of norepinephrine had never been investigated in humans in detail.

In this issue of the *Journal*, Stolk and colleagues (pp. 830–842) report a comprehensive set of bench-to-bedside studies that provide further support for the hypothesis that norepinephrine has antiinflammatory effects in sepsis (11). *In vitro*, the authors confirm that norepinephrine reduces the production of proinflammatory mediators and reactive oxygen species and increases the production of IL-10 by leukocytes and monocytes stimulated with microorganisms or components thereof (among which LPS, the main component of the outer membrane of Gram-negative bacteria). The effects of norepinephrine were dose dependent, mainly mediated through the β_2-adrenoreceptor, and associated with a global decrease in cell metabolism (glycolysis and oxidative phosphorylation). Continuous infusion of norepinephrine via microosmotic pumps reproduced these antiinflammatory and immune-suppressive effects in mice challenged with LPS *in vivo*, and in a murine model of polymicrobial sepsis induced by cecal ligation and puncture, norepinephrine modified the pro/antiinflammatory plasma cytokine ratios to more antiinflammatory, which was associated with increased bacterial dissemination. In healthy subjects infused intravenously with LPS, norepinephrine induced a modest decrease in proinflammatory CXCL10 (IFN-γ–induced protein-10) and an increase in IL-10 plasma levels, again indicating a net antiinflammatory effect. Finally, in an observational cohort of 192 patients with septic shock, the dose of norepinephrine administered correlated with decreased TNF-α/IL-10 ratios, consistent with a more antiinflammatory cytokine balance, and this effect was mitigated in patients who received chronic medication with β-blockers (11).

Though Stolk and colleagues deserve to be complemented for their extensive and careful analyses, their study does not provide insight into the association between norepinephrine treatment and clinically relevant adverse outcomes. For example, though a previous study reported an independent association between norepinephrine treatment and mortality in patients with septic shock (12), it remains to be determined whether the antiinflammatory effects of norepinephrine result in an enhanced susceptibility to secondary infections in patients with septic shock. In addition, Stolk and colleagues limited their analyses of norepinephrine effects on the host response in patients with sepsis to measurements of plasma TNF-α and IL-10; other responses implicated in immune suppression in sepsis, such as major histocompatibility class II expression on circulating monocytes and T-lymphocyte dysfunction, were not examined (11).

As evidence accumulates regarding its potentially deleterious effects, has the time come for norepinephrine to fall from grace? Probably not. After being challenged for more than 50 years, norepinephrine remains the first-line vasopressor with the best safety and tolerance profile in patients with septic shock. Nonetheless, the article by Stolk and colleagues add to the list of studies that call for a revision of our practices for the management of vascular dysfunction in patients with septic shock. In line with the trendy "less is more" paradigm, recent evidence has shown that reducing the dose of norepinephrine by targeting lower blood pressures in patients with septic shock is safe (13). In addition, various nonadrenergic vasopressors have been investigated as alternative or adjunctive therapies to catecholamines, of which vasopressin is among the most promising (14). Despite no benefit on overall mortality compared with norepinephrine alone, vasopressin can reduce catecholamine requirement, which may mitigate the negative impact of adrenergic vasopressors on the immune response. Importantly, Stolk and colleagues demonstrated that, in contrast to norepinephrine, vasopressin did not have any immunomodulatory effect, either *in vitro* or *in vivo* (11). Moreover, as also suggested in the study by Stolk (11), the use of β-blocking agents could be an appealing strategy to attenuate of the excessive response to adrenergic stress and modulate immune cell function. A single center study assessing the effect of titrated doses of esmolol in patients with severe septic shock and tachycardia showed that treatment with this short-acting β-blocker reduced requirement for vasopressor therapy and improved cardiac performance and patient survival (15).

Originally Published in Press as DOI: 10.1164/rccm.202006-2301ED on August 19, 2020

Stolk and colleagues provide the first *in vivo* human evidence that norepinephrine exerts antiinflammatory effects (11). Given that septic shock is associated with profound suppression of a variety of innate and adaptive immune responses, norepinephrine administration may further tip the balance toward impaired immunity in an already vulnerable host. Though norepinephrine remains the best option for the management of vascular dysfunction in septic shock, efforts should be pursued to get the best from its wanted hemodynamic properties while limiting its unwanted immunological side effects. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Fabrice Uhel, M.D., Ph.D.
Tom van der Poll, M.D., Ph.D.
Amsterdam University Medical Centers
University of Amsterdam
Amsterdam, the Netherlands

ORCID ID: 0000-0002-9199-5079 (T.v.d.P.).

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, *et al*. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200–211.
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, *et al*.; Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:775–787.
3. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, *et al*. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. *Intensive Care Med* 2010;36: 2019–2029.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43: 304–377.
5. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med* 2016;42: 1387–1397.
6. Stolk RF, van der Poll T, Angus DC, van der Hoeven JG, Pickkers P, Kox M. Potentially inadvertent immunomodulation: norepinephrine use in sepsis. *Am J Respir Crit Care Med* 2016;194:550–558.
7. van der Poll T, Jansen J, Endert E, Sauerwein HP, van Deventer SJ. Noradrenaline inhibits lipopolysaccharide-induced tumor necrosis factor and interleukin 6 production in human whole blood. *Infect Immun* 1994;62:2046–2050.
8. Elenkov IJ, Haskó G, Kovács KJ, Vizi ES. Modulation of lipopolysaccharide-induced tumor necrosis factor-alpha production by selective alpha- and beta-adrenergic drugs in mice. *J Neuroimmunol* 1995;61:123–131.
9. Lyte M, Bailey MT. Neuroendocrine-bacterial interactions in a neurotoxin-induced model of trauma. *J Surg Res* 1997;70:195–201.
10. Lyte M, Freestone PP, Neal CP, Olson BA, Haigh RD, Bayston R, *et al*. Stimulation of Staphylococcus epidermidis growth and biofilm formation by catecholamine inotropes. *Lancet* 2003;361: 130–135.
11. Stolk RF, van der Pasch E, Naumann F, Schouwstra J, Bressers S, van Herwaarden AE, *et al*. Norepinephrine dysregulates the immune response and compromises host defense during sepsis. *Am J Respir Crit Care Med* 2020;202:830–842.
12. Póvoa PR, Carneiro AH, Ribeiro OS, Pereira AC; Portuguese Community-Acquired Sepsis Study Group. Influence of vasopressor agent in septic shock mortality: results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Crit Care Med* 2009;37:410–416.
13. Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, *et al*. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med* 2018;44:12–21.
14. Russell JA. Vasopressor therapy in critically ill patients with shock. *Intensive Care Med* 2019;45:1503–1517.
15. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, *et al*. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013;310:1683–1691.

The Elephant Man Meets Pulmonary Hypertension
A Cautionary Tale

Neurofibromatosis (NF) has achieved notoriety because of Joseph Merrick, a medical and sideshow phenomenon in the late 1800s in London who was diagnosed with NF in 1909 (1). His life has been chronicled in several books and films, including the critically acclaimed film *The Elephant Man* in 1980, as well as theatrical productions in both London and New York City. From these, NF became more accepted and investigated (found to be three subtypes: NF1, NF2, and schwannomatosis), and the genetic mutations have been identified (2). Over the years, complications and issues associated with the neurofibromatoses have become apparent. In this issue of the *Journal*, Jutant and colleagues (pp. 843–852) describe a little-appreciated aspect of NF1, pulmonary hypertension (PH) (3).

PH is a rare and incompletely characterized complication of NF1. First described in 1986, the largest previously reported series included just eight patients and was notable for a poor response to PH-specific therapy and poor outcomes (4, 5). Since that report in 2011, individual cases of PH-NF1 have appeared in the literature. In this issue of the *Journal*, Jutant and colleagues, using data from the French Pulmonary Hypertension Network, describe clinical, functional, hemodynamic, and radiographic characteristics as well as responses to pulmonary arterial hypertension (PAH)-specific therapy in 49 cases of PH-NF1, thereby comprising the largest and

Originally Published in Press as DOI: 10.1164/rccm.202006-2142ED on July 15, 2020