Norepinephrine in Septic Shock: A Mixed Blessing

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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). In order 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 life-saving properties of norepinephrine are undisputed, growing experimental evidence suggests that excessive dosing or duration of norepinephrine infusion could adversely affect patient outcomes due to 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 anti-inflammatory profile with reduced production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and increased production of the anti- inflammatory 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.

Here, Stolk and colleagues report a comprehensive set of bench-to- bedside studies that provide further support for the hypothesis that norepinephrine has anti- inflammatory effects in sepsis (11). *In vitro*, the authors confirm that norepinephrine reduces the production of pro-inflammatory mediators and reactive oxygen species, and increase the production of IL-10 by leukocytes and monocytes stimulated with microorganisms or

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components thereof (among which lipopolysaccharide [LPS], the main component of the outer membrane of Gram-negative bacteria). The effects of norepinephrine were dose-dependent, mainly mediated through the β2-adrenoreceptor, and associated with a global decrease in cell metabolism (glycolysis and oxidative phosphorylation). Continuous infusion of norepinephrine via micro-osmotic pumps reproduced these anti-inflammatory 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/anti-inflammatory plasma cytokine ratios to more anti-inflammatory, which was associated with increased bacterial dissemination. In healthy subjects infused intravenously with LPS, norepinephrine induced a modest decrease in pro-inflammatory interferon gamma- induced protein-10 (CXCL10) and an increase in IL-10 plasma levels, again indicating a net anti-inflammatory 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 anti-inflammatory cytokine balance, and this effect was mitigated in patients who received chronic medication with ß-blockers (11).

While 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, while 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 anti-inflammatory effects of norepinephrine result in an enhanced susceptibility to secondary infections in septic shock patients. In addition, Stolk and colleagues limited their analyses of norepinephrine effects on the host response in sepsis patients 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).

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As evidence accumulates regarding its potentially deleterious effects, has 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 non-adrenergic 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 to 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).

Stolk and colleagues provide the first *in vivo* human evidence that norepinephrine exerts anti-inflammatory 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. While norepinephrine remains the best option for the management of vascular dysfunction in septic shock, efforts should be pursued to get the best from its

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wanted hemodynamic properties while limiting its unwanted immunological side effects.

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