

Norepinephrine in Sepsis: Looking beyond Vasoconstriction!

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Sir,

Norepinephrine (NE) is essentially a potent vasopressor agent administered in septic shock to alleviate the hypotension emanating from an impaired arterial tone, as recommended by the surviving sepsis guidelines. Albeit the restoration of the tissue-perfusion pressure with NE infusion, an associated elevation in the afterload presents a potential of adversely affecting the ventricular output. Moreover, in addition to the peripheral vasoplegic properties, the inflammatory mediators predispose to myocardial depression and increased pulmonary vascular resistance (PVR). Therefore, there has been a recent interest in studying the consequences of NE infusion on the biventricular performance, as ventricular dysfunction incurs a poorer prognosis following sepsis.

Two recent studies have addressed this concern and assessed the cardiac effects of NE in a structured manner.^{1,2} Hamzaoui et al. demonstrated an inotropic effect of NE infusion in early phase of septic shock considering an improved echocardiographic profile of both the left ventricle and right ventricle (RV) function.¹ However, the understanding of the mechanisms behind an augmented ventricular performance, particularly RV, remained clouded in absence of data on preload and afterload parameters. The subsequent study by Dalla et al. formally evaluated RV preload, afterload, and function in background of a NE infusion in septic shock.² The study outlined an improvement of RV function without an increase in the PVR or the RV afterload. These findings are noteworthy considering the contradictory literature on effects of NE on the pulmonary vasculature in NE-dependent vasodilatory shock, with some studies depicting an elevated PVR³ while the more recent studies do not suggest accentuated PVR with NE in a setting of septic shock.⁴

A nuanced perspective on the diverse actions of NE based on the receptors activated is warranted to comprehend the results of these studies. The α -adrenergic stimulation results in an increased diastolic pressure and an augmented coronary perfusion, which could account for an improved ventricular performance. Moreover, Anrep effect can also explain this enhancement in ventricular function. The α -adrenoceptors activation also results in an accentuated preload owing to the reduction of the systemic vascular capacitance.⁵ On the contrary, β_1 -adrenergic stimulation in the cardiomyocytes bestows an independent positive inotropic effect. It is noteworthy that the effects of NE on PVR are compounded by the combination of α -mediated increase and β -mediated decreased pulmonary vascular tone.²⁻⁴ Considering the aforementioned points, a NE infusion is expected to improve the ventriculoarterial coupling, which is deleteriously affected in sepsis. However, the varying degree of the sepsis-induced β_1 -adrenoceptors downregulation, the extent of preload-responsiveness and the

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dynamic interplay of vascular resistances depending on the NE infusion dosages compound the cardiac effects of NE in septic patients.

To conclude, NE administration in septic patients should be conceptualized as a combination of resultant cardiac and vascular consequences, in order to attain a reasonable level of cardiovascular stability and tissue-perfusion. The consolidated effect of NE on ventricular contractility, upstream vascular resistances, and ventriculoarterial coupling is complex and needs to be closely monitored with serial echocardiographic examinations in order to prudently titrate the drug infusion to target systemic pressures while avoiding the long-term sequel of an accentuated myocardial workload.

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