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WHAT'S NEW IN INTENSIVE CARE

Norepinephrine in septic shock

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Introduction

Norepinephrine (NE) is both an alpha1- and beta1-agonist, and is therefore able to increase vascular tone and contractility [1]. Recent guidelines recommend NE as the first-line vasopressor in septic shock [2]. However, because septic shock is a syndrome that results from a variable combination of decreased venous return, myocardial depression and decreased vascular tone, the place for NE in initial resuscitation is not straightforward.

There is no doubt that prolonged hypotension contributes to the mortality of sepsis [3], but several issues, such as when to start NE, or the optimal mean arterial pressure (MAP) target in different contexts, are still controversial [4]. This is particularly relevant since NE has a wide spectrum of effects on the cardiovascular system (Fig. 1) that could eventually increase or decrease systemic, regional or microcirculatory blood flow depending on factors such as dose, pre-existing comorbidities, preload status, severity and stage of disease, and interaction with other processes of care [1].

When to start norepinephrine

The recent Hour-1 Bundle supported by the Surviving Sepsis Campaign recommends starting vasopressors within the first hour of resuscitation if initial fluid loading does not restore minimum MAP [5]. Indeed, NE infusion can be safely started before intensive care unit (ICU) admission, even in intermediate care without intensivist supervision [6].

Early administration of NE can increase cardiac output through an increase in venous return and thus cardiac preload, but also by increasing contractility [7]. Two recent studies showed that early use of NE is associated with less fluid administration and improved outcome [8, 9]. Moreover, in a retrospective study, early initiation of NE was associated not only with less positive fluid balance but also with a shorter duration of hypotension and NE requirements [10]. In hypotensive fluid-responsive patients, NE may thus be used as an adjunct to fluids to increase cardiac output and perfusion pressure, although the exact place and timing have yet to be determined.

Norepinephrine and cardiac performance

As NE improves cardiac systolic function in the early stage of septic shock, increased left ventricular afterload does not necessarily result in a decrease in stroke volume even in patients with low left ventricular ejection fraction (< 45%) [7]. In addition to the beta1-agonist effects of NE, restoration of coronary perfusion pressure through an increase in diastolic arterial pressure, which may be particularly low in the context of vasodilatory shock [1], might contribute to a beneficial effect of NE on cardiac function. This is especially relevant for patients with coronary artery disease, who represent a large proportion of patients admitted for septic shock. Whether NE can still be beneficial for cardiac function when administered in advanced septic shock, with potential desensitization of beta1 receptors, has yet to be demonstrated.

In the early phase of septic shock, ventriculo–arterial (V–A) coupling, an important determinant of cardiovascular performance, may be impaired in more than 80% of the patients [11]. This uncoupling results in worsening cardiac energetics and performance. Guinot et al. showed that NE can improve V–A coupling and stroke volume in hypotensive post-cardiac surgery patients, although stroke volume was found to increase only in patients with preserved coupling [12].

Dynamic arterial elastance (Eadyn) also provides insight into the cardiovascular state [13]. Eadyn is a functional marker of V–A coupling that can help to indicate or adjust NE therapy. In patients with septic shock, Guinot et al. [13] demonstrated that Eadyn predicts a

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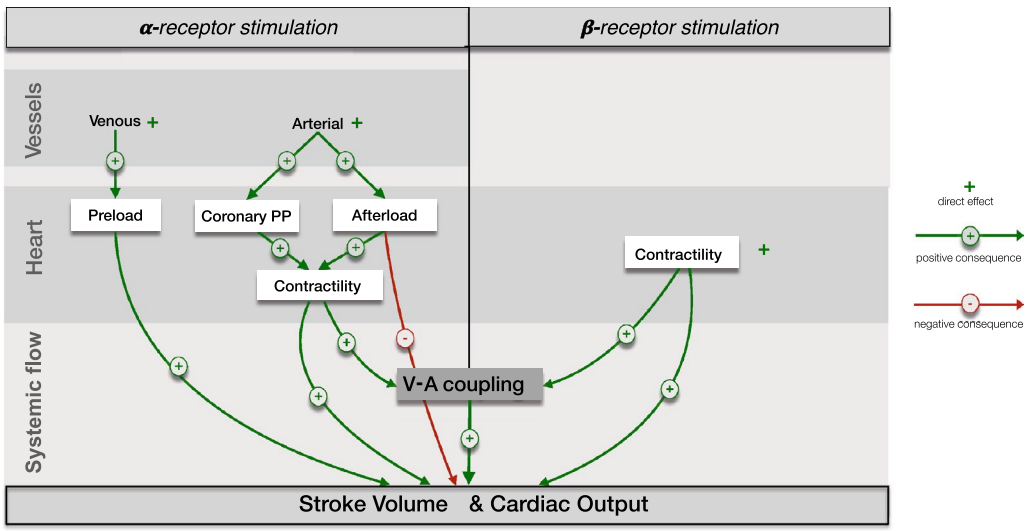

Fig. 1 Schematic representation of the potential mechanisms by which norepinephrine can modulate cardiac output and stroke volume through alpha- or beta-receptor stimulation in septic shock. *PP* perfusion pressure, *V-A* ventriculo-arterial coupling

decrease in MAP in response to a decrease in NE dosage, suggesting its potential in helping clinicians to individualize vasopressor therapy and maintain NE at the lowest necessary infusion rate.

Norepinephrine and tissue perfusion

NE can improve regional and microcirculatory flow by increasing perfusion pressure above the autoregulation threshold in hypotensive patients, but can also decrease flow by excessive vasoconstriction in high doses. This is particularly true for the microcirculation, where the final effect depends on the basal status of microcirculatory flow [1]. Unfortunately, monitors for assessing the effect of NE on regional or microcirculatory flow are not universally available. Therefore, until new research is published, current practice should be to adjust NE infusion to the lowest dose maintaining a MAP ≥ 65 mmHg and adequate global perfusion parameters.

Immunologic effects of norepinephrine

Norepinephrine, via both its alpha- and beta-adrenergic effects, may induce immunoparalysis. Where alpha-adrenergic receptors are linked to both pro- and anti-inflammatory actions, beta-adrenergic stimulation exerts anti-inflammatory effects [14]. Both in vitro and in vivo data suggest that NE has substantial anti-inflammatory effects and promotes bacterial growth that can be significantly mitigated by the use of beta-blockers. The clinical relevance in shock states, however, is unknown. In the early phase of shock resuscitation, adequate tissue perfusion and antibiotics may prevail over potential anti-inflammatory effects.

When and how to discontinue norepinephrine support

In septic shock patients with combined NE and vasopressin (VP) support, the discontinuation of VP first may result in faster development of hypotension then when NE is discontinued first [15]. Because NE decreases the release of VP, discontinuation of VP during NE infusion might result in persistently depressed VP levels, resulting in hypotension. The potential role of monitoring Eadyn to guide the reduction of NE infusion [15] appears more impractical than bedside clinical testing.

Directions for further hemodynamic research

Following current recommendations, NE is initially adjusted to maintain a MAP ≥ 65 mmHg, but guidelines have established no superior limit, and MAP is typically managed in the range of 65–85 mmHg in the usual clinical setting. However, minor changes in the rate of NE infusion within these limits could significantly influence a range of cardiac function-related parameters including preload, afterload, contractility and V–A coupling, with potential detrimental consequences. Thus, it appears necessary to test a two-step NE titration strategy in septic shock: the first step aimed at achieving a minimum organ perfusion pressure, and then further adjustments focused on the dose associated with the best cardiac performance. In addition, the optimal criteria for initiation

of NE should be addressed, with a focus on the relationship between heart rate and diastolic blood pressure as an indirect assessment of the severity of vascular tone depression.

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Compliance with ethical standards

Conflict of interest
The authors declare no conflict of interest.

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