

COMMENTARY

Norepinephrine: more of a neurohormone than a vasopressor

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See related research by Hamzaoui *et al.*, <http://ccforum.com/content/14/4/R142>

Abstract

Septic shock causes unpredictable cardiovascular responses through adrenoceptor-mediated changes in cardiac function and vascular responsiveness. The use of norepinephrine should be regarded as neurohormonal augmentation therapy to defend decompensating haemodynamic function rather than as a rescue therapy to treat shock. Recent trials represent a perceptible change in clinical practice to preferentially use norepinephrine early in resuscitation to defend the mean arterial pressure and to use norepinephrine as a neurohormone rather than as a vasopressor.

In the previous issue of *Critical Care*, Hamzaoui and colleagues present an observational study on the haemodynamic effects of norepinephrine in septic patients with life-threatening hypotension [1]. Within 6 hours of admission to the intensive care unit, a threshold mean arterial pressure (MAP) ≤ 65 mmHg was selected to commence an infusion of norepinephrine, regardless of the degree of prior volume resuscitation. Measurements of cardiac index and derived indices of preload (end-diastolic global volume index) and stroke volume variation were made at baseline and following augmentation of MAP with norepinephrine. The patients were further categorised according to baseline left ventricular ejection fraction and whether they were able to achieve the target MAP. The investigators found that norepinephrine significantly increased MAP to a median value of 75 mmHg, which was associated with significant increases in cardiac output and indices of stroke volume and preload. This effect was consistent independent of

baseline left ventricular ejection fraction – apart from those patients with left ventricular ejection fraction $< 45\%$, who attained MAP > 75 mmHg. The authors concluded that the early administration of norepinephrine directed at achieving a target systemic perfusion pressure was achievable through parallel increases in cardiac output and preload.

Although Hamzaoui and colleagues' study is observational and single-centred in a relatively small population of septic patients using derived indices from pulse contour analysis to quantify changes in preload and contractility [1], the results are consistent with physiological models that define the protean haemodynamic effects of endogenous catecholamines, specifically norepinephrine, under homeostatic and pathological conditions.

Norepinephrine is the predominant endogenous sympathetic amine acting in all populations of adrenoceptors [2]. There is a common misperception that this amine is predominantly an α -agonist. Norepinephrine exhibits sympathetic activity over an expanding population of adrenoceptors on the circulation (α_{1A} and α_{1B} , α_{2A} , α_{2B} and α_{2C} , β_1 , β_2 and β_3), acting centrally on the myocardium, on the arterial (conduit) circulation and on the venous (capacitance) circulation [3]. Haemodynamic function at any point in time represents the balance between the two circulations, so that changes in one are represented by compensatory changes in the other [4,5].

Under pathological conditions such as septic shock, qualitative and quantitative changes in cardiac function and vascular responsiveness result in unpredictable cardiovascular responses between and within individuals, initially as a compensated high output or vasodilated state to a decompensated low output or vasoplegic state. Teleologically, this represents exhaustion of endogenous neurohumoral responses induced by pathological processes or an overwhelmed host response. In this context, the use of exogenous infusions of catecholamines, such as norepinephrine or epinephrine, should be seen as neurohormonal augmentation therapy to defend decompensating haemodynamic function rather than as a rescue therapy to treat shock [6].

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This understanding is somewhat at variance to traditional clinical practice, supported by current guidelines that recommend haemodynamic resuscitation follows a step-wise approach – initial fluid loading, followed by the use of an inotrope to improve cardiac output, followed by a vasopressor to squeeze the circulation to augment the perfusion pressure [7].

Three recently published randomised controlled trials comparing the effects of catecholamines in severe sepsis have demonstrated equivalence in haemodynamic responses without adverse effects on organ function or mortality [8-10]. Of the three catecholamines studied, norepinephrine was associated with the lowest incidence of drug-specific side effects compared with epinephrine (hyperlactataemia and hyperglycaemia) and dopamine (arrhythmias). On the basis of these studies and a recent commentary [11], norepinephrine appears to be the initial agent of choice. Furthermore, these trials represent a perceptible change in clinical practice to preferentially use catecholamines early in resuscitation to defend MAP as the principal haemodynamic endpoint, although it is acknowledged that there is little evidence or agreement on an optimal perfusion pressure in septic shock [12].

The justification for selecting MAP is based on pragmatic reasons – MAP is easy and accurate to measure – as well as it being an aggregate index of organ perfusion pressure. However, as there is little direct relationship between perfusion pressure and venous return, which remains difficult to measure under clinical conditions, clinicians rely on the assumption that parallel changes in the arterial and venous circulations will occur.

The use of norepinephrine as a neurohormonal augmentation therapy by Hamzaoui and colleagues demonstrated inotropic and vasopressor responses in a heterogeneous population of patients with severe sepsis using current monitoring techniques [1]. These data are consistent with established biological and basic science evidence, and provide additional strength to the argument for viewing norepinephrine as a neurohormone rather than as a vasopressor and to recommend its early use as the first-line agent for life-threatening hypotension.

Abbreviations

MAP, mean arterial pressure.

Competing interests

The author declares that he has no competing interests.

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