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Editorial

EDITORIAL

Norepinephrine improves cardiac function during septic shock, but why?

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Septic shock is associated with vasoplegic hypotension.[1] Norepinephrine, a potent α-adrenergic vasopressor, is recommended as the first-line vasopressor for the treatment of hypotension based on the Surviving Sepsis Guidelines.[2] Whilst norepinephrine infusions often restore organ-perfusion pressure, the obligatory increase in arterial pressure sometimes decreases cardiac output by increasing the left ventricular afterload, compromising global tissue perfusion. Myocardial depression is frequently present in patients with septic shock, but becomes evident in some patients only after the correction of hypotension.[3,4] Interestingly, nitric-oxide-synthase inhibition in septic shock restored arterial pressure, but decreased cardiac output and was associated with increased mortality.[5] Accordingly, it is thus crucial to determine the cardiovascular effects of norepinephrine in septic shock. If norepinephrine increased arterial pressure whilst simultaneously decreasing cardiac output, its beneficial effects would be diminished.

Relevant to this concern, Hamzaoui and colleagues[6] report in this issue of the *British Journal of Anaesthesia* the effects of norepinephrine on cardiac function in the early phase of septic shock. The authors used echocardiography to evaluate cardiac function in 38 patients who remained hypotensive despite fluid resuscitation. Measurements were performed at baseline with a mean arterial pressure (MAP) of 56 (7) mm Hg and after reaching a target MAP of 80 (9) mm Hg. The authors observed that several echocardiographic indices of left ventricular systolic and diastolic function and right ventricular systolic function increased by 10–15%. Importantly, these improvements in cardiac functional indices were also associated with an increase in both stroke volume and cardiac output. Although these findings lend support to the use of norepinephrine in the management of hypotension in patients in septic shock, they do not define the mechanism by which cardiac performance improved.

Several mechanisms could underlie these positive inotropic effects (Fig. 1). First, the increase in diastolic arterial pressure would improve coronary artery perfusion in patients who were previously hypotensive. Whilst myocardial ischaemia is seldom implicated in myocardial depression of sepsis, a low diastolic pressure in vasodilatory shock might compromise myocardial perfusion. In this study, the baseline diastolic pressure was low, but within an acceptable range (45 (6) mm Hg). Second, the increase in arterial pressure also increases left ventricular afterload, which might induce the Anrep response. The Anrep response is a physiological response of the ventricle to an increased load involving increased phosphorylation of the calcium channels between the transverse tubules and the sarcolemma, and resulting in an increased intrinsic contractility. Third, norepinephrine has not only strong α-adrenergic stimulating effects, but also a limited β-adrenergic effect. This β_1-adrenergic effect could increase myocardial contractility by increasing calcium flux. Interestingly, there was no associated tachycardia, in opposition to what is observed when other vasopressors with associated β-adrenergic effects are used, such as dopamine and epinephrine.[7–9] This positive inotropic effect would be blunted or non-existent in patients treated previously with β-blockers. Fourth, left ventricular systolic performance, whilst influenced by arterial pressure, is also determined by ventriculo-arterial coupling. Ventriculo-arterial coupling refers to the relation between the left ventricular contractility (end-systolic elastance) and the arterial vascular stiffness (arterial elastance). Importantly, poor left ventricular performance and

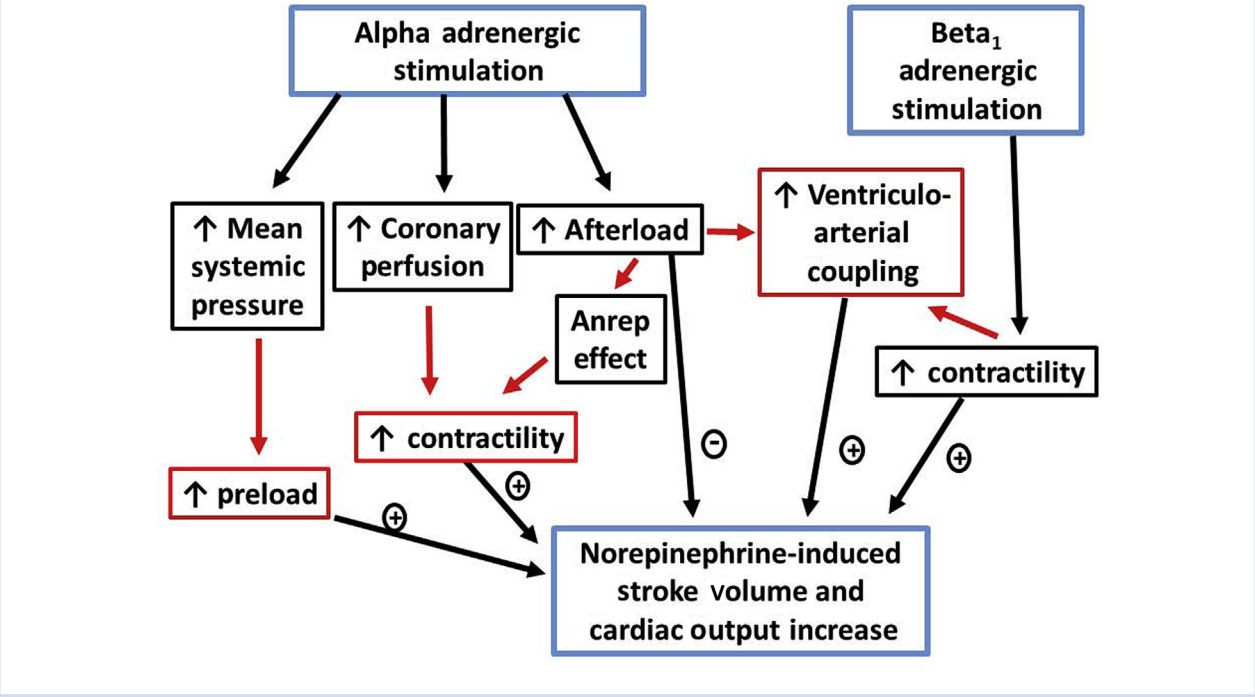

Fig 1. Mechanisms implicated in the norepinephrine-induced increase in stroke volume in early sepsis. Schematic representation of the potential mechanisms by which norepinephrine might increase cardiac output and stroke volume in septic patients. Blue boxes represent the primary receptor stimulation, black boxes their immediate effect, and red boxes the functional impact of those effects.

eventually left ventricular failure can occur if ventriculo-arterial coupling is either too large or too small, and this ratio is affected independently by both arterial elastance and end-systolic elastance. Thus, selected increases by arterial elastance induced by norepinephrine in the setting of reduced baseline arterial elastance could improve left ventricular ejection by restoring normal coupling quantified as an increased stroke volume despite a small increase in arterial pressure.

Patients with hypotensive septic shock commonly have reduced ventriculo-arterial coupling with a marked decrease in arterial elastance.[10] Norepinephrine has been shown to increase arterial elastance in septic patients who also displayed an increased cardiac output as the ratio of arterial to end-systolic elastance normalized.[11] A final mechanism by which norepinephrine might increase cardiac output is by increasing stressed circulatory blood volume. If norepinephrine increased stressed volume by decreasing unstressed circulatory volume, the mean systemic pressure would increase for an unchanged total blood volume. In patients who are preload responsive, this mechanism will increase the pressure gradient for venous return, increasing blood flow back to the heart, increasing cardiac output. Indeed, this mechanism has been shown to occur in sepsis and after cardiac surgery.[12,13] In non-preload responsive patients, although the mean circulatory filling pressure will increase, the right atrial pressure will increase similarly, such that cardiac output will remain unchanged.

Whilst the data presented by Hamzaoui and colleagues[6] do not allow differentiation between these potential mechanisms, many of these processes might jointly contribute to the final cardiovascular response to norepinephrine in the early phase of septic shock. If improvement in coronary perfusion is the main mechanism, this would be observed only during correction of severe hypotension. Reaching values higher than the auto-regulation threshold would expose the heart to the effects of increased afterload, and hence compromise the balance between myocardial oxygen requirements and oxygen delivery. If the Anrep effect contributed, such an effect is usually short lived (<60 min) and would disappear rapidly, again exposing the heart to the detrimental effects of increased afterload and adrenergic stimulation. The contribution of β-receptor stimulation is in line with data in experimental sepsis reporting an improvement in load-dependent and -independent indices of myocardial performance with norepinephrine.[14] Whilst it is unlikely that the increase in preload occurred in isolation, it might have contributed to the increase in cardiac output.[15] Indices of cardiac preload were not significantly increased, but the left ventricular end diastolic area tended to increase. One might expect the left ventricular preload to decrease if increased contractility was the sole mechanism for the observed response. In addition, most of the measured cardiac indices are load dependent and might thus have increased in response to the increase in cardiac preload more than if a reflection of a direct positive inotropic effect. Since these are dynamic changes often working in parallel, the increase in cardiac preload in response to norepinephrine infusion might not be observable in true hypovolaemic states when capacitance veins are already compressed by endogenous compensatory mechanisms. This highlights the need for concomitant fluid therapy in the early phase of septic-shock resuscitation.

Thus, the use of norepinephrine as inotrope in sepsis resuscitation would require that intravascular volume status be restored whilst MAP is not increased beyond some upper threshold. Importantly, since norepinephrine will decrease the unstressed circulatory blood volume, relying on norepinephrine alone as a temporising measure, whilst waiting for optimal fluid resuscitation, antibiotics, and source control efforts to have their long-term effects, is reasonable.

Another and even more philosophical consideration is whether these effects on cardiac function were beneficial. Whilst improvements in cardiac function and cardiac output were associated with a reduction in lactate levels, the increase in contractility combined with the increased afterload must markedly increase cardiac work, and thus, the myocardial oxygen consumption (MVO_2). In experimental sepsis, norepinephrine administration was associated with increased left ventricular pressure/volume area, a direct estimate of myocardial load, and thus MVO_2. Such an increased myocardial stress might not be beneficial if sustained. Indeed, β-adrenergic blockade in septic shock was shown to improve the left ventricular diastolic function,[16] although its long-term effects of survival need to be assessed.[17–19] To better understand whether or not these effects were at least transiently beneficial, these workers estimated the impact of norepinephrine on ventriculo-arterial coupling. Previous studies documented that patients in septic shock display ventriculo-arterial decoupling, which could partially explain the occult myocardial depression seen.[10] Hamzaoui and colleagues[6] showed improved ventriculo-arterial coupling with norepinephrine using indirect estimates of arterial and left ventricular end-systolic elastance. But, these data and data from Guinot and colleagues[11] need to be cautiously evaluated, because these indirect measures show wide variance, and these findings are merely associations. Still, in an animal study where ventriculo-arterial coupling was directly measured, norepinephrine improved ventriculo-arterial coupling,[14] suggesting that this increase in myocardial contractility reflected an improved cardiovascular status. In patients after cardiac surgery receiving norepinephrine to correct hypotension, Guinot and colleagues[20] observed an increase in stroke volume in 50% of patients. Interestingly, arterial elastance increased similarly in both stroke-volume responders and non-responders; however, ventriculo-arterial coupling was lower in stroke-volume responders. Only in those patients in whom norepinephrine restored normal ventriculo-arterial coupling did cardiac output also increase,[11] highlighting the important role of ventriculo-arterial coupling in determining the haemodynamic response to norepinephrine. One should also consider that these effects might depend on heart rate. In this study, heart rate remained constant at 95–100 beats min^{-1}. However, when higher heart rates are observed, the administration of the selective β_1-adrenoreceptor blocker, esmolol, improved ventriculo-arterial coupling by improving arterial elastance.[21] Accordingly, the beneficial effects of norepinephrine on ventriculo-arterial coupling might also be heart-rate dependent.

Finally, these patients were investigated within 3 h of initiation of resuscitation, and the effects of norepinephrine were evaluated immediately after reaching the target arterial pressure. Importantly, these beneficial haemodynamic effects of norepinephrine might not be sustained over time, as downregulation of β_1-adrenoreceptors is known to occur in the course of sepsis. Thus, the positive inotropic effects of norepinephrine might be short lived. Thus, without these positive inotropic effects, the septic heart might not be able to cope with increased afterload and may slowly decompensate.

In conclusion, in hypotensive patients in septic shock, the collective impact of norepinephrine on myocardial contractility, venous return, and ventriculo-arterial coupling appears to be highly beneficial during the initial phase of resuscitation, and helps sustain cardiac output and tissue perfusion. However, the long-term effects of the associated increased myocardial workload remain a concern, and physicians should try to use the lowest dose of drug to sustain a target arterial pressure with weaning off as soon as possible.

Declaration of interest

None declared.

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