Editorial Commentary

Norepinephrine, more than a vasopressor

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Provenance: This is an invited article commissioned by the Section Editor Guo-Wei Tu, MD, PhD (Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

Comment on: Hamzaoui O, Jozwiak M, Geffriaud T, *et al.* Norepinephrine exerts an inotropic effect during the early phase of human septic shock. Br J Anaesth 2018;120:517-24.

Submitted Jan 08, 2019. Accepted for publication Jan 27, 2019.
doi: 10.21037/atm.2019.01.76
View this article at: http://dx.doi.org/10.21037/atm.2019.01.76

In a recent study, Hamzaoui *et al.* (1) reported that early use of norepinephrine (NE) in patients with septic shock increased cardiac systolic function despite the increase in left ventricular afterload secondary to the rise in mean arterial pressure (MAP).

Background

NE is the alpha-adrenergic vasopressor of choice in septic shock (2) because of its ability to restore both arterial tone and the effective circulating volume. The latter would be the result of recruitment of unstressed volume from the venous capacitance vessels, with an increase in stressed volume, mean systemic filling pressure (Pmsf) and the driving pressure for venous return (Pvr) (3). In addition, by its beta-1 and alpha-1 adrenergic properties, NE also increases contractility of the myocardium (4). Nevertheless, an increase in left ventricular afterload and the resistance to venous return (Rvr) may ultimately decrease cardiac output (CO) (3).

NE and its effect on CO

Given the previous facts, the effect of NE on CO is highly variable and may depend on baseline cardiac preload status and on its inotropic effects. As an increase in preload also results in an increase in myocardial contraction force by the Starling mechanism (5), the real inotropic effect of NE is not easy to assess. In an early study by Goldberg *et al.* (6), the researchers showed an increase in right ventricular contractile force in thoracotomy patients, when infusing NE. In 1965 Cohn *et al.* observed that for a similar increase in MAP in a mixed group of patients with circulatory shock, the use of NE was associated with more pronounced increase in CO when compared to angiotensin, an agent lacking venoconstriction properties (7). In post-cardiac surgery patients, Maas *et al.* (3) found an increase in CO when increasing NE, associated with a decrease in stroke volume variation (SVV) from 14.4% to 11.9%, while patients that exhibited a decrease in CO were fluid unresponsive at baseline (SVV 9.1%). Hamzaoui *et al.* (1) showed a significant increase in LVEF and stroke volume, after adding or titrating NE to reach a MAP >65 mmHg in a subgroup of patients with septic shock and left ventricular ejection fraction (LVEF) <45%. In septic shock patients increasing the dose of NE reduces the effect of a passive leg raising on CO (8). Indeed, decreasing NE dose should lead to a decrease in Pmsf, Pvr and subsequently venous return and CO. This was confirmed in a recent study (9).

Likewise, titrating NE in fluid resistant hypotensive post cardiac surgery patients improved stroke volume and ventriculo-arterial (V-A) coupling (10). V-A coupling is another important determinant of cardiovascular performance. V-A coupling can be measured as the ratio of arterial elastance (Ea) to end-systolic ventricular elastance (Ees) (11). Ea is the expression of the total afterload

imposed on the left ventricle and represents the complex association of different arterial properties including wall stiffness, compliance and outflow resistance; Ees is a useful, relatively load independent index of myocardial contractility (11,12) although it is affected by baseline myocardial characteristics as stiffness, compliance, fibrosis, synchrony, and remodeling (13). The majority of patients with septic shock exhibit significant V-A decoupling independent of the commonly seen reduced Ea (14). The assessment of cardiovascular function by evaluation of the Ea/Ees ratio can offer an adjunctive perspective for understanding the pathophysiology of altered hemodynamic profiles. NE may have mainly inotropic effects in case of LV dysfunction and mainly vasoconstrictive effects in case of arterial dysfunction. Correction of either of these variables results in improvement of ventriculo-arterial coupling (*Figure 1*).

Methodology and reliability to assess cardiac function with echocardiography in ICU patients

LVEF is a classical measurement of cardiac function, representing how much blood is being pumped out of the left ventricle. Robotham *et al.* (15). more than 25 years ago suggested that LVEF reflects the coupling between left ventricular contractility and afterload. In the same direction, Jardin *et al.* (16) described that patients with a normal LVEF had a significantly lower systemic vascular resistance (SVR) than patients with impaired LVEF. Thus, LVEF reflects the fact that vasoplegia unmasks systolic cardiac dysfunction. In addition, LVEF can improve by an increase in end-diastolic volume due to fluid resuscitation and by decreased afterload due to low systemic resistance. Likewise LVEF decreases as afterload increases, the differences being greatest at low preloads (15). Therefore, LVEF is the result of an interaction between preload, contractility and afterload, and its normality does not rule out myocardial depression (15).

Systolic function can be assessed by tissular Doppler imaging (TDI) through its systolic mitral annulus velocity (Sm), reflecting the peak velocity of shortening of the myocardial fibers oriented in the longitudinal direction. In an experimental study, A'roch *et al.* (17) found no change in Sm when venous return of the inferior vena cava was stopped (inflated balloon), but it increased with inotropic drugs. Likewise, Amà *et al.* (18) observed a significant increase in Sm after a volume challenge in cardiac surgery patients with conserved ejection fraction, and no changes in Sm after an increase in afterload with phenylephrine. Nonetheless, Oki *et al.* (19) showed a significant decrease of Sm when afterload was increased in healthy volunteers. Thus, TDI Sm appears being more sensible to increases in venous return, afterload and inotropic drugs than to decreases on venous return (17-19).

The complexity of right ventricle (RV) anatomy and geometry challenges the accurate assessment of right ventricular systolic function. TDI also has the potential to assess ventricular contractile function independent of the shape of the ventricle. The tricuspid lateral annular systolic velocity (Sa) can assess the longitudinal myocardial velocities as the tricuspid annulus descends toward the apex. Nonetheless, experimental models found that Sa is reduced by both, a decrease in preload and an increase in afterload (20), and that Sa increases with inotropes and fluid challenges (21). Thus, the magnitude of ejection phase myocardial velocities has been shown to be preload and afterload dependent (19). In the same direction, TAPSE (tricuspid annular plane systolic excursion), which represents longitudinal movement of the free wall of the RV base, correlates strongly with RV ejection fraction obtained by radionuclide angiography (22). Unfortunately, TAPSE also is limited by both preload and afterload dependency (23).

The ideal index of ventricular performance should be sensitive to contractile changes, independent of loading conditions, and easily obtained and reproducible (12). Through the analysis of the end-systole pressure volume relationship (ESPVR), the end systole elastance (Ees) is a relatively load independent parameter, combined with its adequate reflection of inotropic state (11). However, studies in animals and patients have shown that it cannot be relied on under all operating conditions because of load dependencies, despite being relatively load-independent over a specified range (12).

Conclusions

Several mechanisms contribute to preserve adequate cardiac function in patients with circulatory failure: appropriate preload, good contractility, and reduced afterload, as well as an optimal ventriculo-arterial coupling. In this setting, the study by Hamzaoui *et al.* (1) and earlier studies show that the use of NE, even early in the course of septic shock, has no significant deleterious effect on myocardial function even if MAP is significantly improved. Caution should however be taken when the patient is fluid unresponsive and thus already operating on the flat part of the Starling's curve.

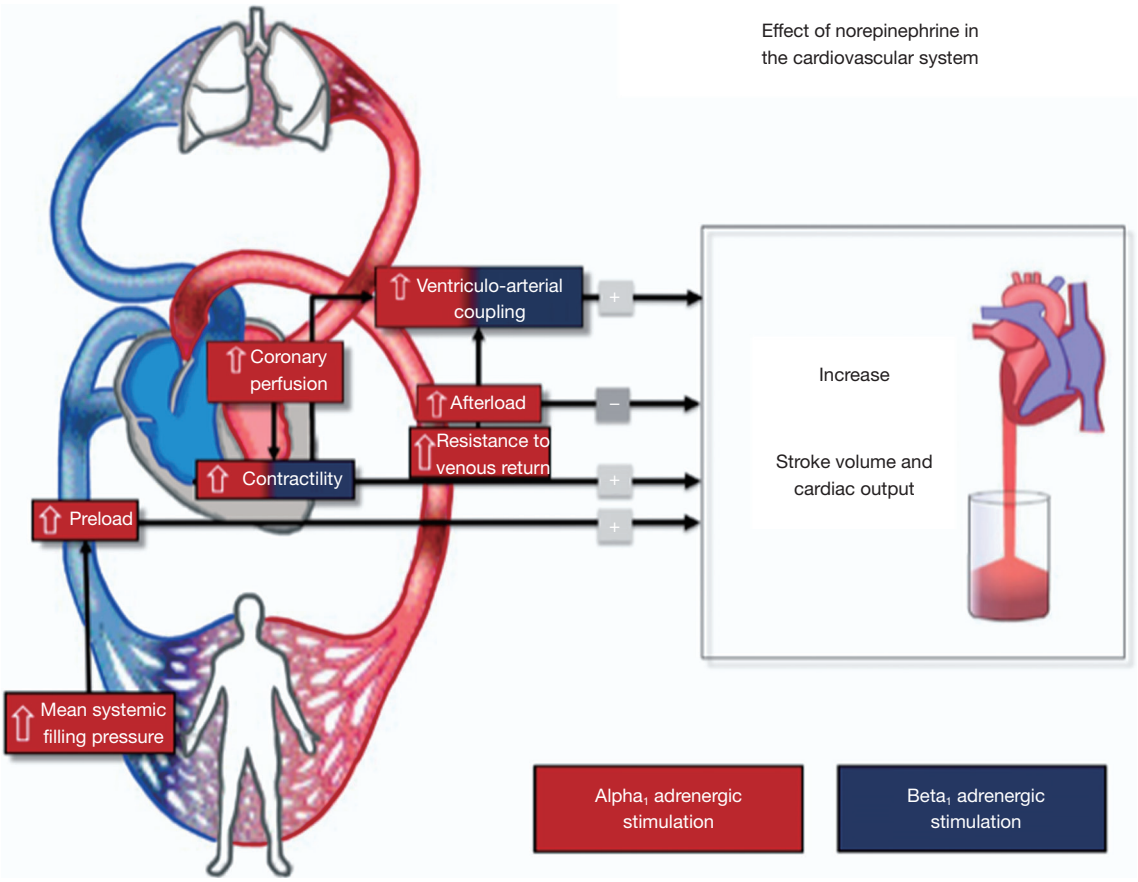

Figure 1 Main effect of Norepinephrine according to $alpha_1$ and $Beta_1$ adrenergic receptors.

Acknowledgements

The authors are grateful with M.D. David Carpio Cordero for the figure design.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Espinoza ED, Hernandez G, Bakker J. Norepinephrine, more than a vasopressor. Ann Transl Med 2019;7(Suppl 1):S14. doi: 10.21037/atm.2019.01.76

