Commentary

Beta-blockers in septic shock: a magnifying glass on the relation heart vessel

Calypso Mathieu, Laurent Zieleskiewicz, Marc Leone

Service d'anesthésie et de réanimation, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, Aix Marseille Université, Marseille, France
Correspondence to: Marc Leone, MD, PhD. Service d'anesthésie et de réanimation, Chemin des Bourrely, Hôpital Nord, 13015, Marseille, France. Email: marc.leone@ap-hm.fr.

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Beta-blocker therapy is a promising treatment in patients with septic shock. During septic shock, catecholamine plasma concentrations are increased due to endogenous production. Despite this increase, exogenous supply remains useful in order to achieve an adequate perfusion pressure, leading to organ perfusion (1). However, the persistent elevation of catecholamine plasma concentrations was associated with increased mortality (2). Excessive adrenergic stimulation is harmful to the heart (3). In animal studies, esmolol, a selective beta-1-adrenergic blocker, improves cardiac contractility, stroke volume (SV) and vascular responsiveness to norepinephrine (4-6). In patients with septic shock who were initially stabilized, Morelli *et al.* showed that esmolol infusion reduced heart rate, increased SV and reduced norepinephrine requirements (7). In this seminal study, the use of esmolol resulted in an impressive decrease in mortality.

In a recent, prospective observational study, the same group determined the relationship between esmolol-induced heart rate reduction and arterial elastance (E_a) (8). After 24 hours of resuscitation, 45 septic shock patients with an heart rate above 95 beats per minute and requiring norepinephrine to maintain a mean arterial pressure (MAP) above 65 mmHg were included. The exclusion criteria were age <18 years, cardiac dysrhythmias, need for an inotropic agent, significant valvular heart disease, and pregnancy were. Esmolol infusion was titrated to obtain a heart rate between 80 and 94 beats per minute. Compared to baseline, the use of esmolol was associated with reductions in E_a (2.19±0.77 *vs.* 1.72±0.52 mmHg·L^{-1}; P<0.001), MAP (80±12 *vs.* 75±10 mmHg; P=0.005), arterial dP/dt_{max} (1.08±0.32 *vs.* 0.89±0.29 mmHg·ms^{-1}; P=0.0009) and norepinephrine dosage (0.7±0.7 *vs.* 0.58±0.55 µg·kg^{-1}·min^{-1}; P=0.01). In parallel, SV significant increased (48±14 *vs.* 59±18 mL; P<0.001), confirming previous findings. The cardiac output (5.4±1.3 *vs.* 5.1±1.4 L·min^{-1}; P=0.11) and the left ventricular ejection fraction (LVEF) [(52±11)% *vs.* (53±11)%; P=0.17] remained unchanged. The authors conclude that the esmolol-induced heart rate reduction effectively improved E_a. This improvement was accompanied by an adequate systemic perfusion in those patients.

We have to congratulate Morelli and his team for their in-depth assessment of the effects of beta-blockers in septic shock patients. They were among the first ones to show the feasibility of this initially provocative concept. They pursue their crusade by refining each of their findings. The merit of the present study was to consider the relation between heart and vessel in patients with septic shock. The authors remind us that the cardiac function closely depends on the vascular response to the initial insult and treatments (8). At the bedside, the cardiac function analysis should never been disconnected from the vascular state.

According to the concept of ventriculo-arterial coupling, the cardiovascular performance depends on the interaction between heart pump and arterial system (9). Left ventricular elastance (E_{es}) reflects cardiac contractility, independently of loading conditions. On a pressure-volume loop, E_{es} is defined as the slope of the relationship between end-systolic pressure (P_{es}) and end-systolic volume, at different load levels. E_a reflects afterload of the left ventricle. It depends on the peripheral resistance, total vascular compliance, impedance, and systolic and diastolic time intervals. E_a is estimated by the ratio of left ventricular P_{es} to SV (P_{es}/SV) (10). P_{es} is accurately predicted by multiplying peak

arterial systolic pressure (P_{sys}) by 0.9 (10).

E_{es}/E_a ratio is a reliable index of ventriculo-arterial coupling (11). When left ventricle and arterial system are optimally coupled, E_{es}/E_a is close to 1. This results in a maximal stroke work. Myocardial efficiency is defined as the amount of external work performed for myocardial oxygen consumed. It is maximal if E_{es}/E_a ratio tends to 2 (12). Below the value of 1, a ventriculo-arterial decoupling is suggested. Tachycardia exacerbates abnormal ventricular-arterial coupling in heart failure (13). The patients with septic shock display ventriculo-arterial decoupling resulting in impaired left ventricular performance (14).

In septic shock, beta-blockers probably improve cardiac dysfunction by reducing excessive adrenergic stimulation. Reducing heart rate increases the diastole duration, optimizing ventricular filling. The global effect is an increase in SV. Showing that SV also improved by a reduction in E_a, Morelli *et al.* provided a new contribution in order to better understand the potential benefit of beta-blockers in the patients with septic shock (8). Beta-blockers may limit the ventriculo-arterial decoupling, and thus improve the left ventricular mechanical efficiency.

However, these results should be confirmed by further studies. One limitation of the study is the estimation of E_a. It is validated by P_{es}/SV where P_{es} can be approached by $P_{sys} \times 0.9$ (10). In the present study, E_a is calculated using the MAP/SV ratio. Other limitations include the use of central venous pressure or pulmonary artery occlusion pressure for assessing the need for fluid. For a well-identified reason, the target of heart rate was not achieved in all patients.

In routine, echocardiography is often used to estimate LVEF (15). However, LVEF is a load-dependent index, which does not reflect only cardiac contractility. The interaction between the heart and the arterial system, explored through ventriculo-arterial coupling, is a key determinant of cardiovascular performance. At the bedside, its implementation is challenging because the pressure-volume loops are not easily constructed. New technologies should make it possible to estimate the ventriculo-arterial coupling, including the non invasive single-beat determination of E_{es} (16) or the pressure recording analytic method (17).

In septic shock, the rate of mortality remains high in an unacceptable way. In next years, a strategy would be to provide individualized treatments. At the bedside, correcting a ventriculo-arterial decoupling may result in a directed use of specific drugs. If the decoupling is related to decreased cardiac contractility, inotropes are indicated. If decoupling is primarily due to increased E_a among septic patients with tachycardia, the use of beta-blockers could be an option. Beta-blockers will improve cardiac efficiency, reduce myocardial oxygen requirements and prevent myocardial insult. There is an imminent need that other groups confirm those findings.

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Footnote

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