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EDITORIAL

Beta-blockers in septic shock to optimize hemodynamics? Yes

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Septic shock represents one of the maximum physical stresses to the organism. The physiological response to stress includes increased release of catecholamines, leading to a stimulation of cardiac β1-adrenergic receptors thereby increasing heart rate and ventricular contractility in order to increase global and microvascular blood flow and oxygen delivery to vital organs. Yet there are adverse effects of adrenergic stimulation including tachyarrhythmias, increased cardiac oxygen consumption with risk of cardiac ischemia, and immune dysregulation. So while it sounds at first contradictory to stabilize the cardiovascular function by giving β-blocking agents to "brake" the system, there could be benefits. However, is beta-blockade in these clinical circumstances really a brake?

Dr. Morelli and coworkers present in a recent article in *Intensive Care Medicine* data on a cohort of 45 patients with the primary diagnosis of septic shock, in whom pulling this brake seems to improve cardiovascular function [1]. After initial hemodynamic stabilization over the first 24 h, patients who were tachycardic (heart rate more than 95 bpm) received a titrated esmolol infusion with the primary goal of reducing heart rate to 80–94 bpm within a time window of 4 h. Indeed, they achieved the intended reduction in heart rate, which could have primarily decreased cardiac output. However, the decreased heart rate was offset by increased ventricular filling time and volume, and decreased left ventricular afterload, ultimately resulting in increased stroke volume, obviously compensating for the decrease in heart rate. Interestingly, left ventricular ejection fraction remained unchanged. This, in combination with a decrease in arterial dP/dt_{max} and a concomitant reduction in the need for norepinephrine, strongly points toward a more economical cardiac function under β-blockade. This mechanism is illustrated in Fig. 1.

Similarly, β-blockade seemed paradoxical at first but was ultimately shown to be very effective in chronic heart failure [2]. To follow the automobile metaphor, β-blockade is more a shift to a higher gear, when revolutions per minute are becoming too high. This shift results in the same speed, but with greater fuel efficiency.

So the physiological concept of improving cardiac efficiency seems to work as well in selected patients with septic shock. This is a very important message, since a physiological rationale is one indispensable prerequisite for any new treatment concept. With all enthusiasm, we have to keep in mind that this study performed in a selected group of patients without known cardiac comorbidities was not a randomized controlled trial (RCT), nor was any patient-centered clinical outcome assessed. Second, management of preload has an influence on that treatment concept: the automobile metaphor of changing gears works only with adequate engine cubic capacity. The parallel of engine cubic capacity in patients is cardiac preload that must be in the upper range—otherwise diastolic filling would not increase, when slowing the heart rate—the major prerequisite for ejection fraction to remain stable leading to an increased stroke volume. Morelli and coworkers guaranteed high ventricular preload by keeping central venous pressure (CVP) ≥ 8 mmHg, and pulmonary arterial occlusion pressure (PAOP) ≥ 12 mmHg, following the current recommendations for the initial phase of fluid resuscitation in septic shock [3]. Using CVP and PAOP and in particular using those target values for guiding fluid therapy

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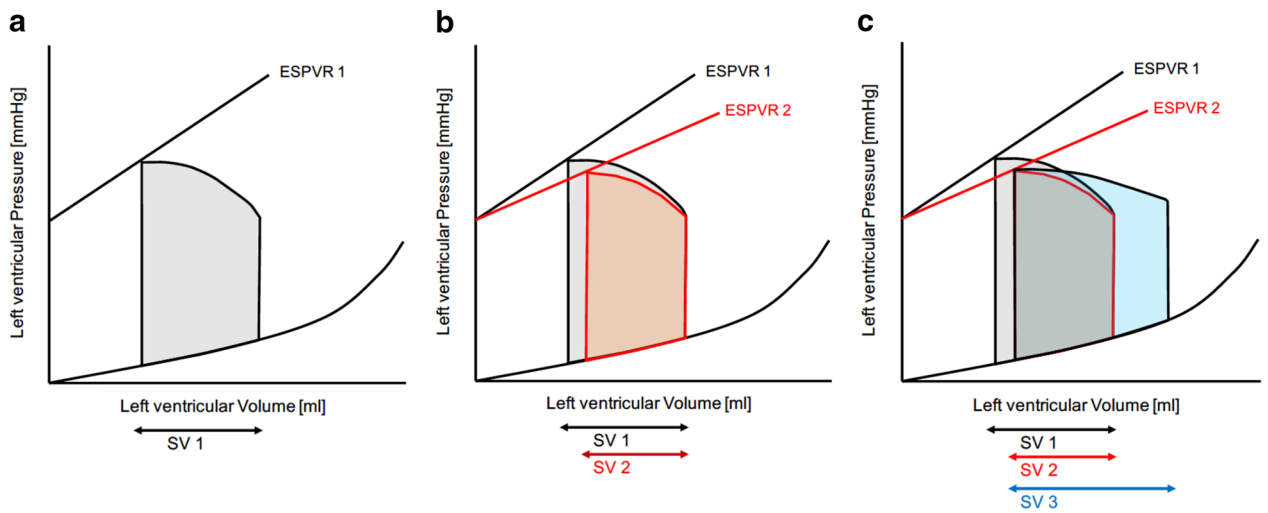

Fig. 1 Pressure–volume loops of the left ventricle are depicted. **a** Pressure–volume loop prior to β-blockade; **b** β-blockade leads to a decrease of inotropy, which is reflected by the reduced angle of the ESPVR 2. Accordingly, the resulting SV 2 is diminished; **c** if venous return to the left ventricle is high enough, the prolonged duration of diastole caused by heart rate reduction will allow increased left ventricular filling, which, in combination with decreased afterload, will result in an increased SV 3. *SV* stroke volume, *ESPVR* end-systolic pressure volume relation

are currently very controversial, primarily because using these targets could lead to fluid overload associated with worse outcome in septic shock [4, 5]. So the important, conceptual cardiovascular question still needs to be answered: how much preload is necessary for safe and effective β-blockade in septic shock?

Beta-blockade has been associated with reduced mortality during septic shock in experimental studies and in two preliminary human RCTs [6–8]. A recent small pilot RCT ($n = 90$) in China suggested benefit of the combination of esmolol and milrinone in sepsis for control of heart rate and possibly survival (but the absolute risk reduction was an unlikely 30 %) [6]. Retrospective cohort studies suggest that chronic use of beta-blockers prior to ICU admission improves short-term survival [9]. A recent systematic review of beta-blockade in sepsis suggests some benefit, but there is still work to do because of the lack of large RCTs—most studies are small and uncontrolled case series/cohorts [7]. In addition to its beneficial effects on cardiac dynamics, beta-blockade may exert beneficial pleiotropic effects including blunting the inflammatory response, metabolic changes, and sepsis-associated coagulopathy [10–14]. Furthermore, beta-blockade may increase microcirculatory/small vessel blood flow in a small cohort ($n = 25$) of patients with sepsis [10]. Interestingly, norepinephrine requirements were significantly decreased by esmolol; however, there was no control group so we cannot be sure these were not just improvements with time.

Animal model studies show marked changes in immune gene expression—primarily anti-inflammatory effects—after β-blockade with esmolol, so some of the benefit of β-blockade could be in fact immune-mediated, and not related to the potentially beneficial cardiovascular physiology effects we discussed herein [12, 13]. For example, eight genes with common promoter sequences for NFKB and/or BRCA1 were modulated by esmolol [13]. Analysis of a human database identified the upregulation of CAMP ($p = 0.032$) and TNFSF10 ($p = 0.001$) genes in septic patients compared with healthy controls [13]. In another animal model, esmolol decreased NFKB activation, increased Akt and endothelial nitric oxide synthase phosphorylation, while lowering inducible nitric oxide synthase expression in cardiac and vessel tissues [11]. Esmolol also improves LPS-induced ventricular dysfunction [14]. Thus, esmolol has impressive immune modulation in animal models that may be important in human sepsis, too.

So at this stage, it cannot be anticipated whether this treatment concept will finally lead to an improvement in outcome in real life. However, the therapeutic concept of "setting the brake" by β-blockade seems deceptively simple and could be effective in carefully chosen septic shock patients (excluding those with hypovolemia, known complex cardiac comorbidities, tachyarrhythmias, hemodynamic instability despite vasopressor treatment, or systolic cardiac dysfunction). These data must stimulate further research, especially well-designed, well-powered RCTs.

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EDITORIAL

Beta-blockers in septic shock to optimize hemodynamics? No

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Cardiac assessment in the critically ill septic patient has become increasingly sophisticated [1]; yet, the relationship between the heart and systemic arterial system remains an area of unfulfilled hope, with precise evaluation continuing to elude the practicing clinician. The concept of "cardiovascular (CV) performance or efficiency" is an attractive one, a tool promising to bridge the knowledge gulf that currently exists [2]. That said, its clinical application is challenging. First, there seems to be a lack of consensus as to which parameters best represent CV performance, whether it be stroke volume (SV), stroke work (SW), work efficiency, or the ventriculo arterial coupling (V-A coupling) [3]. Second, pragmatic methods for measuring some theoretical parameters, such as unstressed ventricular volume (V_0), end-systolic pressure (P_{es}), and arterial compliance (C_{art}), are still lacking, let alone the challenge of the time-variable nature of these parameters.

Over a quarter of a century ago, in the effort to match the heart function and the arterial load from an evolutionary viewpoint, Elzinga and Westerhof postulated that to attain minimum ventricular size a mammalian heart evolved with its working point quite close to optimum power and optimum efficient, and that a specific heart rate is required to guarantee sufficient pressure during diastole [4]. A decade prior to this, Sunagawa et al. predicted that maximal SW results when the end-systolic elastance (E_{es}) of the ventricle and arterial load (E_a, effective arterial elastance) are equal $E_a/E_{es} = 1$ [5, 6].

The E_a/E_{es} ratio has been used in various studies as a means to reflect V-A coupling [2, 7, 8]. In these studies, a high E_a/E_{es} ratio is taken to imply V-A uncoupling. E_a has a determinative effect on V-A coupling if ventricular contractility, hence E_{es}, is constant. On the basis of the pressure–volume relationship, Sunagawa et al. predicted, using the ratio of left ventricular P_{es} to SV, that E_a remains constant under a given steady-state vascular impedance load [5]. Hence, this gives rise to

$$E_a = \frac{P_{es}}{SV}$$

Although such measurements originally required invasive pressure recordings, now hemodynamic monitoring techniques allow for estimation of E_a by measuring SV noninvasively. E_a can be expressed as a function of systemic vascular resistance (SVR), heart rate (HR), and C_{art}. P_{es} is higher than mean arterial pressure (MAP) in humans, and it is expressed as follows:

$$P_{es} = MAP + \Delta P$$

As MAP is the product of SVR and cardiac output (CO), it follows that

$$P_{es} = (SVR \times CO) + \Delta P$$

$$P_{es} = (SVR \times SV \times HR) + \Delta P$$

$$\frac{P_{es}}{SV} = (SVR \times HR) + \frac{\Delta P}{SV}$$

Since P_{es}/SV is E_a, and $\Delta P/SV$ is a measure of arterial stiffness ($1/C_{art}$), hence

$$E_a = (SVR \times HR) + \frac{1}{C_{art}}$$

Hence, E_a can be approximated as $MAP/SV + 1/C_{art}$.

The above equations state that E_a consists of two components: a steady component (SVR × HR) and a pulsatile component ($1/C_{art}$) [7]. Using regression analysis,

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Segers et al. not only confirmed the above relationship in a heart–arterial interaction model but also found that the first component contributes three times more to E_a than the second [9], such difference probably being lower in septic patients with vasoplegia.

Morelli et al. recently suggested that the short-acting β-blocker esmolol improves CV efficiency in selected septic patients, e.g., those who remained tachycardic after initial resuscitation and still requiring norepinephrine infusion [10]. They hypothesized that these findings could partially explain the better prognosis associated with such therapy observed in a previous study targeting the same population [11]. Unfortunately, Morelli and colleagues may have failed to make the leap across the gap of understanding the CV efficiency in their study on several fronts.

First, there is no agreement for the choice of best parameters to reflect CV efficiency and that is very much left to investigators [3]. Morelli's group evaluated E_a [10], as an indirect marker of E_a/E_{es} ratio, assuming that E_{es} remains constant [10]. They understood the decrease in E_a observed after esmolol infusion as a better CV efficiency, leading to an increase in SV. However, E_a/E_{es} does not correlate linearly with SW and CV efficiency which have been reported to decrease with increasing or decreasing E_a/E_{es} ratio [12]. Optimal SW and CV efficiency have been reported with an E_a/E_{es} of 1 and between 0.5 and 0.66, respectively [12].

Second, most investigators used the dicrotic notch or 90 % of peak systolic pressure (P_{dic}) in their calculations, and Morelli's estimation of E_a is based on MAP, calculating the ratio between MAP and SV. Not only does this lead to an underestimation of E_a but also arterial stiffness ($1/C_{art}$) is excluded from the calculations. That said, they also reported the difference between MAP and P_{dic} using the MostCare® hemodynamic monitor. Whereas this difference is negligible in healthy subjects, this is higher in septic patients as a result of decrease in vascular tone and was partially restored after esmolol in Morelli's study [10].

Third, confounders altering SVR, HR, vascular tone, preload, and contractility can all affect the estimations and interpretations of E_a and E_{es}. Like most other sepsis studies, Morelli's study was 'contaminated' with such confounders: interferences of catecholamines on SVR and increasing ventricular preload, the variation of underlying effects of sepsis on both the arterial tree as well as the left ventricle, and concomitant changes in ventricular elastance (E_{es}) that may possibly match changes in the measured E_a, maintaining V-A coupling within an acceptable range. For example it is known that with changing heart rates in normal subjects any changes in E_a are matched by corresponding changes in E_{es}, maintaining V-A coupling around 1.

Finally, their interesting assumption is that with no change in left ventricular ejection fraction (LVEF) or CO, E_a reduction is responsible for the increase in SV. Yet for an increase in SV there must also be a larger left ventricular end-diastolic volume for LVEF to remain the same. As a consequence, LV wall-stress would increase, then limiting improvement in CV performance. And HR has been shown to influence both end-diastolic and end-systolic volume [13]. Unfortunately, Morelli et al. did not report changes in LV size. Hence, there must be some change in ventricular function, even if it is an increase in preload that contributes to the results. Indeed, it is very difficult to change loading conditions without provoking reflex changes in ventricular contractility.

The range of hemodynamic measuring devices, including pulmonary artery catheter, thermodilution CO measuring devices, peripheral arterial pulse contour analysis, and echocardiography, attest to the enthusiasm of Morelli and colleagues [10]. However, their conclusions in regard to arterial elastance changes in septic patients when using esmolol raise too many uncertainties to be confident of the conclusions. Moreover, assuming that β-blockers could be useful in septic shock, and because of their negative inotropic effect, it is crucial to better understand in which patients such a drug could be efficient and not dangerous. In this regards, echocardiography should be key by its ability to detect severe septic cardiomyopathy (contraindication or non-indication to beta-blockers?) or hyperkinetic left ventricle (theoretical population of interest?) [14], which was not the case in the papers by Morelli's group [10, 11].

In conclusion, while the theoretical background is firmly laid, translating these concepts into practical use still requires lots of research since all the approximations and omissions previously discussed elevate doubts about the meaning of any results obtained and conclusions drawn. It is only fair to point out that such challenges bedevil most researchers in this field.

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Compliance with ethical standards

Conflicts of interest
Anthony McLean declares no conflict of interest. Fabio Silvio Taccone declares no conflict of interest. Antoine Vieillard-Baron declares no conflict of interest.

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EDITORIAL

Beta-blockers in septic shock to optimize hemodynamics? We are not sure

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In recent years, interest in the use of beta-blockade in sepsis has increased, bearing in mind that the septic heart may benefit from some protection against excessive adrenergic stimulation. Then, one trial suggested substantial improvement in survival following heart rate control by continuous infusion of esmolol, a short-acting selective beta-1 antagonist, in a highly selected group of septic shock with severe tachycardia [1]. The same group of researchers suggested potential positive effects on cardiac function from infusion of esmolol in a subsequent study in 45 septic shock with tachycardia above 95 bpm published in this issue [2]. In this study, esmolol-related decrease in heart rate was associated with increased stroke volume (SV). Owing to decreased cardiac contractility (as illustrated by the decrease in dP/dt_{max}), the preservation of SV can only result from increase in preload (related to the increase in diastolic time) or a decrease in afterload. Yet, the authors ascribed increase in SV to improved ventriculo-arterial coupling, as MAP/SV, an index of aortic elastance, improved while filling pressures were stable.

However, assessment of ventriculo-arterial coupling was indirect and relied on pulse wave analysis, thermodilution, and basic echocardiography, and most measurements are potentially subject to mathematical coupling of the data. Therefore, further studies using direct and independent assessments of cardiac-arterial coupling are needed before reliable conclusions can be made. Another major limitation was that arterial pressure was measured in peripheral arteries, thus underestimating central arterial pressure [3, 4]. This is due to the impact of reflected waves that are generated at branch points. Accordingly, the amplitude and timing of the central aortic waveform, which directly affects the heart and determines ventriculo-arterial coupling, differ from peripheral arterial traces that are commonly measured in ICU patients (Fig. 1). In addition, as vasodilation decreases the influence of reflected waves (Fig. 1), the discrepancies between central and peripheral waveforms are exacerbated with alterations in vascular tone such as observed in septic shock [5, 6]. The impact of the reflected waves was nicely illustrated by Bilo et al. [7] who restored a normal arterial trace by compressing the artery distally to the site of measurement, mimicking a restoration of arterial tone. In fluid-resuscitated endotoxemic pigs, Hatib et al. [5] nicely showed that peripheral systolic and mean arterial pressures markedly underestimated central aortic pressures, while diastolic pressure was reliably measured.

Of note, the effects of heart rate manipulation reported by Morelli et al. [2] differed from data observed in middle-aged healthy individuals [8]. Using central measurements of aortic pressure and volumetric catheters to determine aortic volume, Stefanadis et al. [8] observed that pacing did not affect MAP, decreased systolic blood pressure while diastolic pressure was increased, and decreased the augmented pressure (the difference between central and peripheral systolic pressure). Interestingly, distensibility of the aorta increased and stiffness index decreased at high HR, indicating that Ea should decrease at high HR. To what extent the results of Morelli et al. suggesting a decrease in Ea and an improvement in ventriculo-arterial coupling were affected by the site of arterial pressure measurement remains to be determined. Of note, LVEF was unchanged, which suggests that ventriculo-arterial coupling was not improved to the extent suggested by peripheral arterial pressure

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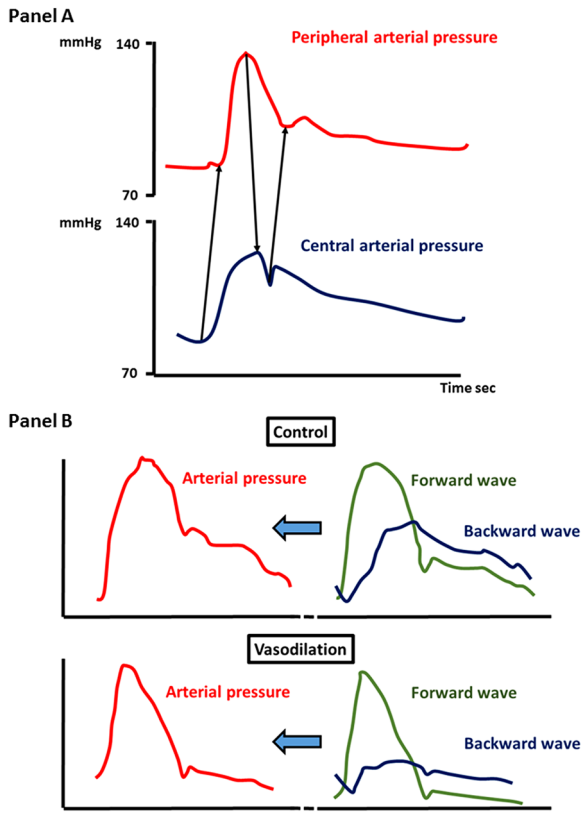

Fig. 1 Influence of reflected waves on arterial traces. **a** Central and peripheral aortic pressures: under the influence of reflected waves, central and peripheral arterial waveforms differ. Central aortic trace presents an earlier increase in the arterial pressure but the peak systolic pressure is slightly delayed and lower than in the periphery; the dicrotic notch occurs earlier and at a higher pressure than in the periphery (curves redrawn after Wang et al. [4]). **b** Impact of forward and backward waves on arterial traces: the measured arterial trace reflects a given point of the summation of forward and backward waveforms. Vasodilation alters reflection of waves and mostly decreases the impact of reflected waves. As a result the augmented pressure and dicrotic notch pressures are markedly decreased (adapted from Berger et al. [9])

measurements. Thus, whether esmolol-related heart rate reduction improved ventriculo-(central) arterial decoupling remains uncertain. However, the improvement in peripheral dicrotic notch–diastolic pressure gradient suggests that beta-blockade improved the reflection of waves. It still remains unclear whether this effect resulted from changes in arterial tone or in heart rate.

Finally, optimizing patients' hemodynamics not only improves cardiac efficiency, as evaluated in this study, but also improves tissue perfusion. Unfortunately, the reader is provided with minimal information on the issue of tissue perfusion. As cardiac output decreased by 5 % (a nonstatistically significant drop), oxygen delivery very likely decreased, as observed in the previous trial by the same researchers (−20 % decrease in oxygen delivery) [1]. Whether the negative impact of the decrease in oxygen delivery may be balanced by potentially beneficial effects on cardiac function remains speculative.

The net findings from the two trials performed by these researchers are that continuous infusion of esmolol may control heart rate without impairing stroke volume in a highly selected group of septic shock with severe tachycardia [1, 2]. Additional investigations are required to determine whether preserved stroke volume results from increased preload despite impaired contractility or from improved ventriculo-arterial coupling following decrease in afterload and Ea.

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