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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