

Heart rate reduction may be a major determinant of vascular tone in esmolol-treated septic shock patients – although still remains to be confirmed!

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Introduction

Over the last decade, the regulation of the autonomic nervous system by β_1 -adrenoreceptor antagonists in septic shock patients has been the subject of growing literature. In 2013, Morelli *et al.* published a randomized, controlled, open-label, single-center phase 2 trial investigating the efficacy of intravenous esmolol, a short acting β_1 -blocker titrated to lower heart rate (HR) in septic shock patients with severe tachycardia. This study found that esmolol was associated with a reduction in HR to the specified target range (80–94 bpm), maintained cardiac output, increased systemic vascular resistances along with a subsequent reduction in norepinephrine dose requirements (1). The mechanisms by which esmolol reduced norepinephrine requirement in this trial remain unclear. Indeed, although mean blood pressure (MBP) is the result of the product of cardiac output and systemic vascular resistance, vessels exhibit an extremely low density of β_1 -adrenoreceptors (2).

Study design and findings

In a recent study, Andrea Morelli *et al.* hypothesized that the esmolol-related reduction in HR would increase diastolic filling time and consequently stroke volume (SV) in septic shock. Such increase in SV could be associated with decreased arterial Elastance (Ea) and, thus, with

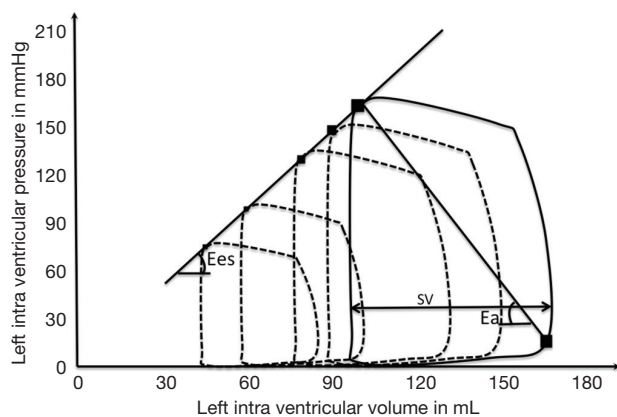
improved vascular tone, thereby explaining the reduction in norepinephrine requirement to maintain adequate MBP. In this single center trial, adult patients with septic shock were included if they had persistent tachycardia >94 bpm at 24 hours of optimal resuscitation. Patients who required inotropic agents, or had significant valvular disease or arrhythmia, were excluded. Before and at 4 hours of intravenous esmolol titration to maintain HR in the range of 80 to 94 bpm, central and pulmonary hemodynamics, cardiac output, beat-to-beat estimation of SV (derived from arterial pressure waveforms), left ventricle ejection fraction by echocardiography, and Ea were recorded. All patients received identical resuscitation management (fluid, catecholamine, sedation) although inotropic drugs were not allowed during the study. Forty-five of the 116 screened patients were included, of which 73% were male. Patients had a mean SAPSII score of 54 ± 17 , a mean length of ICU stay of 18 ± 17 days, and a 28-day survival rate of 49%. Compared to baseline, at 4-hours of esmolol infusion, Ea significantly decreased while SV increased and the dose of norepinephrine was reduced. *Table 1* displays the main hemodynamic data reported in this study.

Commentary

Morelli *et al.* showed that in adults with septic shock and persistent tachycardia, intravenous treatment with esmolol

Table 1 Main hemodynamic and beat-to-beat waveform data

Parameters	Before esmolol initiation	Four hours after esmolol infusion	P
Heart rate (bpm)	115±11	88±9	<0.001
Cardiac output ^{thermodilution} (L·min ⁻¹)	5.4±1.3	5.1±1.4	0.11
Cardiac output ^{waveform analysis} (L·min ⁻¹)	5.1±1.3	5.0±1.3	0.77
Stroke volume ^{thermodilution} (mL)	48±14	59±18	<0.001
Stroke volume ^{waveform analysis} (mL)	47±12	59±16	<0.001
Mean blood pressure (mmHg)	80±12	75±10	0.005
Systemic vascular resistances (Dyn.s ⁻¹ .cm ⁻⁵)	1,234±293	1,102±260	0.001
Ea ^{thermodilution} (mmHg·L ⁻¹)	2.0±0.6	1.55±0.5	<0.001
Ea ^{waveform analysis} (mmHg·L ⁻¹)	2.2±0.7	1.7±0.5	<0.001
Left ventricular ejection fraction (%)	52±11	53±11	0.17
Mean arterial pressure-dicrotic pressure (mmHg)	9.4±9	4.3±8	<0.0001
Norepinephrine dosage (µg·kg ⁻¹ ·min ⁻¹)	0.7±0.7	0.58±0.55	0.01

**Figure 1** Pressure volume relationship during a preload reduction test. Ees, end elastance slope; Ea, Arterial elastance; SV, stroke volume.

was associated with a reduction in both HR and the need for norepinephrine. These authors suggested that the observed reduction in the dose of norepinephrine to maintain MBP >65 mmHg was a consequence of improved vasomotor tone, as indirectly assessed by changes in Ea.

This study has substantial limitations that prevent any definite conclusions regarding the mechanisms underlying the esmolol-associated reduced need for norepinephrine. First, it was designed as an uncontrolled observational study. Thus, only information on association and not on causality may be provided. At the very least, the authors should have designed alternate sequences of 'on and off' esmolol administration. The ultra-short half-life of esmolol would have permitted such design. Secondly, the generalizability

of these findings is unclear. Indeed, almost 40% of these patients had persistent tachycardia after 24 hours of optimal resuscitation. Other recent trials, e.g., PROCESS and ARISE, reported mean HR values of 114 and 104 bpm at baseline, 97 and 94 bpm at 6 hours, and of 95 and 90 bpm at 24 hours. Accordingly, in the general septic shock population, there are much fewer patients with persistent tachycardia than that observed in the trials by Morelli *et al.* (3-6). Third, the indirect and imprecise assessment of vasomotor tone may not allow definite conclusions.

Septic shock is characterized by ventriculo-arterial uncoupling defined as systolo-diastolic biventricular dysfunction as well as vascular hyporesponsiveness to endogenous vasopressors (7). Ventriculo-arterial coupling (VAC) is described using the Pressure-Volume curves recorded from an intraventricular conductance catheter. Left ventricular inotropism can be investigated experimentally, by varying preload or afterload, drawing a series of Pressure Volume loops defining the End Systolic Pressure (ESP) Volume Relationship (*Figure 1*). The slope of this relationship, called End Elastance slope (Ees), is a reliable marker of load-independent cardiac function. ESP is a function of cardiac contractility, with SV and afterload roughly representing vasomotor tone in the aorta. Thus, Ea is defined by the slope of the relationship between SV and ESP, and can be estimated by the ESP/SV ratio. There is a linear relationship between systolic blood pressure and ESP, *i.e.*, $ESP = 0.9 \text{ SAP}$ (8). Hence, Ea can be estimated as equal to 0.9 SBP/SV (*Figure 1*). Ea is dependent on various factors including peripheral vascular resistances, arterial compliance, arterial impedance and systolic-diastolic

interval times (9). VAC may be estimated by the Ea/Ees ratio (10). In healthy humans, the optimal value for Ea/Ees ratio is around 1, and a value of Ea/Ees ratio >1.36 reflects ventriculo-arterial uncoupling (9). As described above, ventriculo-arterial uncoupling may result from a decrease in Ea (e.g., vasoplegia in septic shock) and/or decrease in Ees (cardiogenic shock or septic cardiomyopathy). Morelli *et al.* assessed Ea using two relatively independent methods. They estimated SV from a single beat-to-beat analysis of the arterial catheter and from the thermodilution cardiac output. However, for Ea calculation, surprisingly, the authors used mean blood pressure as the numerator and not systolic blood pressure, which allows, as seen above, a better approximation of ESP. Mean blood pressure is far from reflecting ESP. Finally, these authors failed to appropriately assess VAC since they only estimated Ea and did not record the Ea/Ees ratio, although this was in fact performed in a previous study (11).

In addition, given the decrease in mean blood pressure, it is very difficult to link the reduction in norepinephrine requirement to esmolol effects on SV and Ea. Matching the MBP between the two time measurements would have strengthened the results on norepinephrine requirement. This methodological bias may also impact other hemodynamic parameters, particularly on the MBP-P_{dic} variable.

Morelli *et al.* further suggested that the anti-inflammatory effects of esmolol may also contribute to the observed changes in Ea. However, they failed to provide any supporting data, and one may argue that anti-inflammatory effects would unlikely have occurred this swiftly, i.e., after only four hours of treatment (12-15).

In summary, the study by Morelli *et al.* found that, in selected septic shock patients with persistent tachycardia, esmolol infusion may effectively control HR, improve stroke volume and Ea. Unfortunately, methodological biases in the assessment of vasomotor tone prevented any bona fide explanation on the mechanisms by which esmolol reduced the need for norepinephrine.

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Footnote

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