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Systolic-dicrotic notch pressure difference can identify tachycardic patients with septic shock at risk of cardiovascular decompensation following pharmacological heart rate reduction

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Abstract

Background: During sepsis, heart rate (HR) reduction could be a therapeutic target, but identification of responders (non-compensatory tachycardia) and non-responders (compensatory for 'fixed' stroke volume [SV]) is challenging. We tested the ability of the difference between systolic and dicrotic pressure ($SDP_{difference}$), which reflects the coupling between myocardial contractility and a given afterload, in discriminating the origin of tachycardia.

Methods: In this *post hoc* analysis of 45 patients with septic shock with persistent tachycardia, we characterised features of haemodynamic response focusing on $SDP_{difference}$, classifying patients according to variations in arterial dP/dt_{max} after 4 h of esmolol administration to maintain HR <95 beats min^{-1}. A cut-off value of 0.9 mm Hg ms^{-1} was used for group allocation.

Results: After reducing HR, arterial dP/dt_{max} remained above the cut-off in 23 patients, whereas it decreased below the cut-off in 22 patients (from 0.99 [0.37] to 0.63 [0.16] mm Hg ms^{-1}; mean [SD], $P<0.001$). At baseline, patients with decreased dP/dt_{max} after esmolol had lower $SDP_{difference}$ than those with higher dP/dt_{max} (40 [19] *vs* 53 [16] mm Hg, respectively; $P=0.01$). The $SDP_{difference}$ remained unchanged after esmolol in the higher dP/dt_{max} group (49 [16] mm Hg), whereas it decreased significantly in patients with lower dP/dt_{max} (29 [11] mm Hg; $P<0.001$). In the latter, the HR reduction resulted in a significant cardiac output reduction with unchanged SV, whereas in patients with higher dP/dt_{max} SV increased (from 48 [12] to 67 [14] ml; $P<0.001$) with maintained cardiac output.

Conclusions: A decrease in $SDP_{difference}$ could discriminate between compensatory and non-compensatory tachycardia, revealing a covert loss of myocardial contractility not detected by conventional echocardiographic parameters and deteriorating after HR reduction with esmolol.

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Editor's key points

- A substantial number of patients with septic shock is resistant to pharmacological treatment of tachycardia with esmolol.
- The difference between systolic and dicrotic pressure ($SDP_{difference}$) might be helpful in discriminating the origin of tachycardia.
- This study showed that in patients with a lower $SDP_{difference}$ tachycardia was compensatory for a state of reduced left ventricular contractility.
- A low $SDP_{difference}$ in patients with septic shock with tachycardia might indicate a high risk of decompensation in case of pharmacological reduction in heart rate.
- Larger studies are required to reveal if the $SDP_{difference}$ might discriminate septic patients that are more likely to benefit from heart rate reduction.

Elevated heart rate (HR) persisting 24 h after adequate volume resuscitation and commencement of vasopressors identifies a particularly severe subset of patients with septic shock with poor prognosis.[1,2] Tachycardia directly contributes to poor outcome by impairing left ventricular (LV) diastolic function,[3] increasing cardiac workload, and reducing ventricular efficiency by altering ventricular–arterial (V–A) coupling (V–AC).[4–6] Therefore, reducing HR could be a reasonable therapeutic target in a specific population of septic patients. However, it remains challenging to distinguish between the compensatory origin of tachycardia (low stroke volume [SV]) and non-compensatory elevated HR (maladaptive sympathetic overstimulation), making it difficult to establish which patient will benefit from pharmacological control of HR and who eventually will be harmed by this treatment.[2,7–9]

In a cohort of patients with septic shock with persistent tachycardia, we previously analysed the relationship between myocardial performance and afterload, before and after reducing HR with esmolol.[5] Using conventional haemodynamic and echocardiographic variables, we found that HR reduction was associated with increased SV despite unchanged LV ejection fraction (LVEF) and more importantly a decreased arterial dP/dt_{max} ($_{art}dP/dt_{max}$), a surrogate of LV intrinsic contractility.[10] In this study, we concluded that reduction in HR allowed a higher SV despite lower contractility, potentially attributable to better LV filling pattern or improved V–AC (or both) through a reduction in arterial elastance (Ea), the latter induced either by HR reduction *itself* and by a direct effect of esmolol on arterial vasculature.[5] Interestingly, improved myocardial performance was confirmed by changes in the relationship between systolic arterial pressure (SAP), MAP, and dicrotic notch pressure (DNP) on arterial pressure waveform.[5] In fact, the difference between SAP and DNP ($SDP_{difference}$) is the result of the coupling between myocardial contractility and a given afterload, and its decrease may indicate conditions where V–AC is worsening (decoupling) because of an excessive afterload for that level of LV contractility.[11–13] As the question if such positive haemodynamic response to esmolol (i.e. increased SV despite decreased $_{art}dP/dt_{max}$ after reducing HR) occurred similarly in all patients or, conversely, if a pattern of unresponsiveness to esmolol could be identified, we performed a *post hoc* analysis to test the ability of the difference between SAP and DNP to discriminate between compensatory and non-compensatory origin of elevated HR, and thus in detecting a cardiovascular state at high risk of decompensation in case of HR reduction with esmolol.

Methods

Study design

This was a *post hoc* analysis of a prospective observational study[5] undertaken in an 18-bed multidisciplinary ICU (Policlinico Umberto I, 'La Sapienza', University of Rome), approved by an institutional review board and registered on ClinicalTrials.gov (NCT02188888). In that study, we analysed 45 patients with septic shock with an HR ≥95 beats min^{-1} after at least 24 h of resuscitation (according to current guidelines[14]) and requiring norepinephrine (NE) to maintain a MAP ≥65 mm Hg. After enrolment, patients were treated with a continuous esmolol infusion to achieve and maintain a target HR between 80 and 94 beats min^{-1} during their entire ICU stay.[5] Haemodynamic and echocardiographic variables (and NE requirements) were determined at baseline (before esmolol initiation) and after 4 h of esmolol infusion. All patients were sedated with remifentanil and propofol, and received volume-controlled mechanical ventilation. Fluid challenges were performed to maintain central venous pressure (CVP) ≥8 mm Hg and pulmonary artery occlusion pressure (PAOP) ≥12 mm Hg. Exclusion criteria were age <18 yr, pregnancy, cardiac dysrhythmias, valvular heart disease, and concomitant administration of inotropic agents.[5]

Haemodynamic measurements

For further details on the study design, please refer to the original study.[5] Systemic haemodynamic monitoring included pulmonary artery (7.5 Fr; Edwards Lifesciences, Irvine, CA, USA) and radial artery catheterisation connected to the pressure transducer TruWave system (Edwards Lifesciences); MAP, CVP, mean pulmonary arterial pressure, and PAOP were measured at end-expiration; HR was measured from continuous electrocardiographic recording. We estimated cardiac output (CO) and SV by using the MostCare® haemodynamic monitor (Vytech, Padua, Italy), which utilises the pressure recording analytic method (PRAM) to provide continuous beat-to-beat monitoring of SV.[15] In addition to SV, as per the design of the original study, true measures were automatically obtained from the analysis of the radial arterial pressure waveform contour; these measures were SAP, DNP, MAP, diastolic arterial pressure, and $_{art}dP/dt_{max}$. After data acquisition, we calculated the difference between systolic and dicrotic

pressure ($SDP_{difference}$). As for the original study,[5] Ea was calculated by applying the formula MAP/SV.[16–19] Cardiac power output (CPwO) was calculated as CPwO=MAP×CO/451.[20]

Echocardiography

Two-dimensional real-time echocardiographic studies were performed to firstly exclude aortic valve diseases, and then to assess LVEF and tricuspid annular plane systolic excursion (TAPSE), using a wide-angle phased-array digital sector scanner and a 5 MHz multiplane transoesophageal probe (T6H, HD7 XE; Philips, Eindhoven, Netherlands). Echocardiographic studies were performed by a trained echocardiographer.

Statistical analysis

There was no *a priori* sample size calculation for this sub-study performed. Despite an improved SV, in the whole study population of the original prospective study we reported a decrease in $_{art}dP/dt_{max}$ (from 1.08 [0.32] to 0.89 [0.29] mm Hg ms^{-1}), but not in LVEF, indicating a decrease in LV contractility after HR reduction.[5] To detect a possible HR compensatory response to a state of a covert reduction in LV contractility before esmolol administration, the presently *post hoc* analysis was performed by dividing patients into two groups according to the decrease below an arbitrary cut-off value of $_{art}dP/dt_{max}$. We chose such cut-off value taking into account the mean value of $_{art}dP/dt_{max}$ observed in the original study after HR control.[5] An $_{art}dP/dt_{max}$ greater than (high $_{art}dP/dt_{max}$) or less than (low $_{art}dP/dt_{max}$) 0.9 mm Hg ms^{-1} 4 h after esmolol administration was used for group allocation.

Statistical analysis was performed with IBM® SPSS 20.0 statistical software (SPSS, Chicago, IL, USA). Continuous variables are presented as mean (standard deviation), or median (25th–75th inter-quartile range) as appropriate, and categorical variables as number and percentage (%). Differences in the haemodynamic patterns of patients with $_{art}dP/dt_{max}$ greater or lower than 0.9 mm Hg ms^{-1} with attention to $SDP_{difference}$ were analysed before and after reducing HR with esmolol. Within-group differences (comparing baseline *vs* after 4 h of esmolol infusion) and between-groups comparisons according to dP/dt_{max} at each time point (at baseline or after 4 h) were made by means of χ^2 with Yates correction, or unpaired Student's *t*-test, or Fisher's exact test and Mann–Whitney *U*-test, as appropriate. Statistical significance was established at a two-tailed *P*-level <0.05. Owing to the lack of previous clinical data, the analyses performed were exploratory and no *ex ante* power analysis was feasible.

Results

Of the 45 patients included in the original study (age ranging from 24 to 90 yr), 22 patients (48.9%) experienced a decrease in $_{art}dP/dt_{max}$ below the cut-off (0.9 mm Hg·ms^{-1}) 4 h after reducing HR with esmolol, with a percentage of changes *vs* baseline of −35 (33)% (*P*<0.001). Conversely, 23 patients (51.1%) maintained an $_{art}dP/dt_{max}$ >0.9 mm Hg ms^{-1} (variation from baseline −4 [27]%; *P*=0.43). Sixteen out of 23 patients in the high $_{art}dP/dt_{max}$ survived until 28 days, whereas only 6 of 22 patients with low $_{art}dP/dt_{max}$ survived until 28 days (69.6% *vs* 27.3%, respectively; *P*=0.005). Baseline characteristics and ICU length of stay were not different between patients with high or low $_{art}dP/dt_{max}$ (Table 1).

Haemodynamic and echocardiographic variables and NE requirements

In both groups, the target HR reduction was achieved in all patients within 4 h of starting esmolol infusion. As shown in Table 2, baseline systemic haemodynamic, LVEF and TAPSE, and Ea and NE requirements were comparable between groups.

At baseline, the only significant difference between groups was the $SDP_{difference}$ (53 [16] mm Hg in high $_{art}dP/dt_{max}$ *vs* 40 [19] mm Hg in patients with low $_{art}dP/dt_{max}$ after HR reduction; *P*=0.01). Whilst the group of patients with high $_{art}dP/dt_{max}$ after esmolol maintained similar values of $SDP_{difference}$ after HR reduction (49 [16] mm Hg), those with low dP/dt_{max} after esmolol showed a significant reduction in $SDP_{difference}$ (to 29 [11] mm Hg), resulting in a larger $SDP_{difference}$ between groups after esmolol administration (*P*<0.001). Such finding was the net result of a significant reduction in SAP in the presence of similar values of DNP in the group with low values of $_{art}dP/dt_{max}$ after HR reduction, whereas the group with higher dP/dt_{max} after esmolol maintained unchanged the SAP and the DNP values (Table 2).

Compared with baseline values, the HR reduction caused a significant decrease of the CO only in the group of patients with low $_{art}dP/dt_{max}$ after esmolol administration (CO reduction from 5.0 [1.3] to 4.4 [1.0] L min^{-1}). This effect was the net result of significantly lower HR in the presence of unchanged SV. However, in patients with high values of $_{art}dP/dt_{max}$ after esmolol administration, we found a significantly increased SV (from 48 [12] to 67 [14] ml) with consequently maintained CO (even non-significantly increased) despite the reduction in HR. As a result, CPwO increased significantly only in patients with high $_{art}dP/dt_{max}$ after esmolol (from 0.54 [0.13] to 0.75 [0.27] W; *P*<0.05) (Table 2).

Table 1 Patient characteristics. Patients were divided into two groups, according to changes in peripheral artery dP/dt_{max} with a cut-off value greater than (high dP/dt_{max}) or smaller than (low dP/dt_{max}) 0.9 mm Hg ms^{-1} after reducing HR with esmolol. Data are given as mean with standard deviation (SD) or median (25th–75th inter-quartile range [IQR]); P<0.05. SAPS II, Simplified Acute Physiology Score II; *t*, Student's *t*-test; *U*, Mann–Whitney *U*-test; χ, χ^2 test.

Patient characteristics	High $_{art}dP/dt_{max}$ after esmolol (*n*=23)	Low $_{art}dP/dt_{max}$ after esmolol (*n*=22)	P-value
Age (yr), mean (SD)	60.4 (18.3)	58.1 (17.8)	0.671 (*t*)
Sex (M/F), *n*	13/10	19/3	0.06 (χ)
SAPS II, mean (SD)	49.1 (6.3)	51.5 (7.4)	0.247 (*t*)
ICU length of stay (days), median (IQR)	14 [10–22]	13 [8–22]	0.609 (*U*)

Table 2 Haemodynamic, echocardiographic, and arterial waveform analysis measures. Patients were divided into two groups, according to changes in values of peripheral artery dP/dt_{max} with a cut-off value greater than (high $_{art}dP/dt_{max}$) or less than (low $_{art}dP/dt_{max}$) 0.9 mm Hg ms^{-1} after reducing HR with esmolol. Data are presented as mean and standard deviation (SD). $_{art}dP/dt_{max}$, arterial peripheral dP/dt_{max}; CO, cardiac output; CPwO, cardiac power output; DAP, diastolic arterial pressure; DNP, dicrotic notch pressure; Ea, arterial elastance; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary arterial pressure; NE, norepinephrine; PAOP, pulmonary arterial occlusion pressure; SAP, systolic arterial pressure; SV, stroke volume; TAPSE, tricuspid annular plane solid excursion. $SDP_{difference}$=SAP−DNP. *Statistically significant 'within-group' difference ($P<0.05$) comparing baseline *vs* values recorded at 4 h after esmolol infusion; in bold are highlighted statistically significant differences between groups.

Variable mean (SD)		High $_{art}dp/dt_{max}$ after esmolol (n=23)	Low $_{art}dp/dt_{max}$ after esmolol (n=22)	P-value
CO (L min^{-1})	Baseline	5.3 (1.3)	5.0 (1.3)	0.59
	4 h	5.7 (1.1)	4.4 (1.0)*	<0.001
SV (ml)	Baseline	48 (12)	46 (13)	0.59
	4 h	67 (14)*	50 (12)	<0.001
HR (beats min^{-1})	Baseline	113 (10)	116 (11)	0.33
	4 h	87 (10)*	90 (6)*	0.19
MAP (mm Hg)	Baseline	80 (12)	82 (13)	0.72
	4 h	76 (11)	74 (8)*	0.40
SAP (mm Hg)	Baseline	122 (19)	115 (17)	0.24
	4 h	117 (18)	101 (12)*	0.001
DAP (mm Hg)	Baseline	60 (11)	65 (13)	0.16
	4 h	55 (10)*	59 (8)*	0.12
DNP (mm Hg)	Baseline	68 (14)	75 (15)	0.14
	4 h	69 (13)	72 (10)	0.34
$SDP_{difference}$ (mm Hg)	Baseline	53 (16)	40 (19)	0.01
	4 h	49 (16)	29 (11)*	<0.001
MPAP (mm Hg)	Baseline	29 (9)	30 (7)	0.44
	4 h	27 (8)	27 (6)	0.96
PAOP (mm Hg)	Baseline	17 (4)	17 (3)	0.29
	4 h	16 (3)	17 (4)	0.29
CVP (mm Hg)	Baseline	12 (3)	13 (4)	0.30
	4 h	12 (4)	12 (3)	0.85
TAPSE (cm)	Baseline	1.6 (0.5)	1.5 (0.6)	0.36
	4 h	2.1 (0.6)*	2.0 (0.6)*	0.34
LVEF (%)	Baseline	54 (12)	50 (9)	0.14
	4 h	55 (12)	52 (9)	0.30
CPwO (W)	Baseline	0.54 (0.13)	0.52 (0.16)	0.65
	4 h	0.75 (0.27)*	0.51 (0.31)	<0.001
Ea (mm Hg L^{-1})	Baseline	1.77 (0.51)	1.92 (0.56)	0.35
	4 h	1.17 (0.26)*	1.69 (0.39)*	<0.001
$_{art}dP/dt_{max}$ (mm Hg ms^{-1})	Baseline	1.14 (0.22)	0.99 (0.37)	0.13
	4 h	1.09 (0.23)	0.63 (0.16)*	<0.001
NE dose (μg kg^{-1} min^{-1})	Baseline	0.59 (0.47)	0.66 (0.58)	0.70
	4 h	0.50 (0.41)	0.54 (0.57)	0.79

The Ea was similar at baseline and decreased significantly in both groups after esmolol infusion. However, the reduction in Ea was significantly larger in the group with high $_{art}dP/dt_{max}$ after esmolol (from 1.77 [0.51] to 1.17 [0.26] mm Hg·L^{-1}; $P<0.05$) than in the group with low $_{art}dP/dt_{max}$ after esmolol (from 1.92 [0.56] to 1.69 [0.39] mm Hg·L^{-1}; $P<0.05$; $P<0.001$ between groups). After reducing HR, LVEF remained unchanged, whereas TAPSE significantly increased in both groups (Table 2). At baseline, logistic regression analysis indicated that $SDP_{difference}$ significantly differentiates the two groups (high and low $_{art}dP/dt_{max}$): P=0.025; confidence interval (CI): 1.00–1.08; 68% of patients correctly classified; area under the curve (AUC)=0.731; $P<0.018$ with a cut-off value of 37 mm Hg (Fig. 1a). Similarly, after reducing HR, logistic regression analysis indicated that $SDP_{difference}$ significantly discriminates the two groups (high and low $_{art}dP/dt_{max}$): P=0.001; CI: 1.05–1.22; 80% of patients correctly classified; AUC=0.854; $P<0.001$ with a cut-off value of 34 mm Hg (Fig. 1b).

Discussion

In the present *post hoc* study, we observed that, in patients with septic shock with elevated HR and high vasopressor requirements, the difference between systolic and dicrotic pressure ($SDP_{difference}$) was effective in revealing a pre-existing condition of V–A decoupling as a result of a covert loss of myocardial contractility, which was not detected at baseline by values of LVEF and $_{art}dP/dt_{max}$. In patients with lower $SDP_{difference}$, tachycardia was compensatory for a state of reduced LV contractility. From a clinical perspective, lower values of $SDP_{difference}$ may indicate a cardiovascular state at high risk of decompensation in case of pharmacological HR reduction.

Our *post hoc* analysis of the original study was based on the observation that, despite an improved SV after HR reduction in the whole population, a reduction in $_{art}dP/dt_{max}$ (but not in LVEF) indicated an overall decrease in LV contractility.[5] This

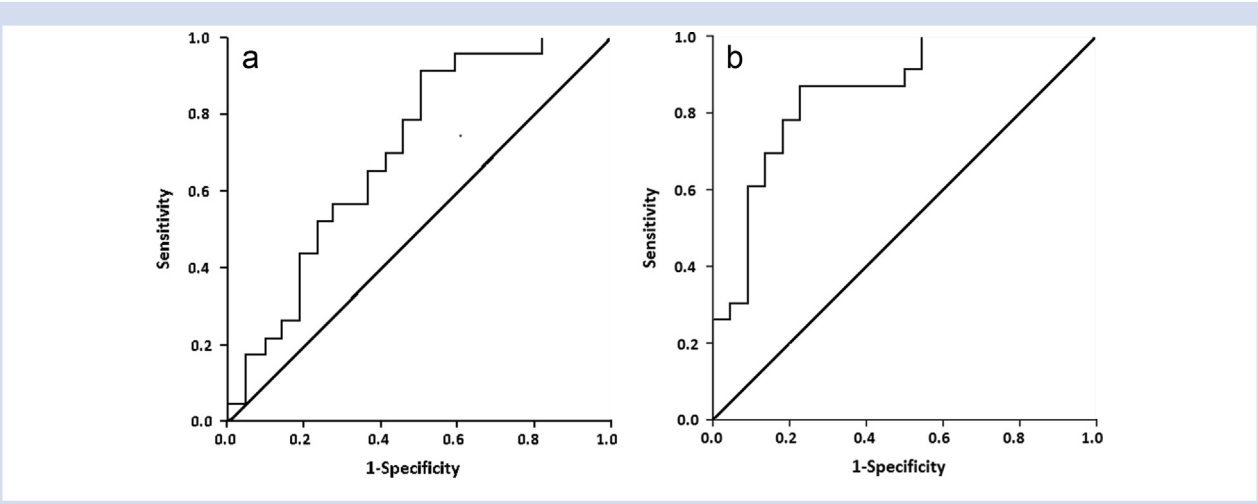

Fig 1. Receiver operating characteristic (ROC) curves for $SDP_{difference}$ and its correlation with arterial dP/dt_{max} 4 h after esmolol administration. (a) ROC curve for $SDP_{difference}$ at baseline: confidence interval (CI)=1.006–1.087; 68% patients correctly classified; area under the curve (AUC)=0.731; $P<0.018$. (b) ROC curve for $SDP_{difference}$ after 4 h of esmolol administration: CI=1.05–1.22; 80% of patients correctly classified; AUC=0.854; $P<0.001$.

may be the result of improved overall myocardial performance with LV generation of higher SV despite lower contractility, consistent with better LV filling pattern or an improved V–AC. Indeed, an HR reduction with a concomitant increase in SV allowing the maintenance of CO implies an economisation of cardiac workload and oxygen consumption.[5] However, we even hypothesised that in several patients the reduction in $_{art}dP/dt_{max}$ was the consequence of a direct negative effect of esmolol on LV contractility with tachycardia compensating for a state of covert systolic dysfunction. Based on this latter assumption, we retrospectively divided the population into two groups according to changes in $_{art}dP/dt_{max}$, as LVEF in the original study did not vary. By doing so, we noticed that only the baseline value of $SDP_{difference}$ (not $_{art}dP/dt_{max}$ or LVEF) was statistically significantly different between groups, suggesting that $SDP_{difference}$ might detect alterations in LV contractility better than other variables, such as LVEF and $_{art}dP/dt_{max}$.

From a physiological standpoint, in the absence of aortic valve diseases, the DNP on the arterial waveform is determined by the interactions between forward and reflection waves on the aorta. Although the forward wave (systolic) changes are related to the degree of myocardial contractility, the reflection waves are related to the structural and functional characteristics of the arterial network and on systolic/diastolic time intervals[21]; these afterload components can be summarised as Ea, finally reflecting the net arterial load on LV ejection.[4,5,21] Therefore, a delayed aortic valve closure (indicated by lower DNP, thus increased $SDP_{difference}$) reflects a lower afterload (i.e. Ea), increased myocardial contractility, or both, whereas an earlier aortic valve closure (decreased $SDP_{difference}$, as a result of higher DNP, decreased SAP, or both, with unchanged DNP) is associated with reduced myocardial contractility, increased arterial load, or both. Practically, the $SDP_{difference}$ can be proportional to the degree of V–AC, and its reduction could indicate worse cardiovascular performance. As a result, we hypothesise that changes in $SDP_{difference}$ correlate with different cardiovascular response to HR reduction with esmolol, discriminating between the compensatory and non-compensatory origins of tachycardia. Importantly, we found that baseline echocardiographic parameters, haemodynamic variables, and vasopressor dosages were similar between groups, except for lower baseline $SDP_{difference}$ in patients responding to esmolol with a decrease in $_{art}dP/dt_{max}$. Therefore, lower $SDP_{difference}$ at baseline may already identify patients with unfavourable LV loading conditions, as a result of an excessive afterload for that level of contractility and where tachycardia was a compensatory response for a covert state of reduced LV contractility.[4,5,22–24]

In contrast, in patients with higher $SDP_{difference}$ at baseline, HR reduction with esmolol did not affect LVEF, $_{art}dP/dt_{max}$, and $SDP_{difference}$ itself; in these patients, CO was maintained through an increase of SV (improved LV performance). Such improved haemodynamic profile after HR reduction is even confirmed by the increased values of CPwO observed in this group of patients. In contrast, in patients with lower baseline $SDP_{difference}$, the pharmacological HR reduction did not improve SV nor LVEF, but decreased CO, $_{art}dP/dt_{max}$, MAP, and SAP, resulting in a further reduction in $SDP_{difference}$. In these patients, CO was therefore maintained at the expense of higher HR because of 'fixed' SV, and esmolol administration unmasked a covert reduction of LV contractility and its inability to cope with increased afterload.[22]

Our findings should be interpreted considering both baseline and esmolol-induced differences in LV loading condition. In fact, improvements in myocardial performance could also be related to the ability of esmolol in further reducing arterial loading (lower Ea), and thus improving V–AC.[4,5,23–26] In the present *post hoc* analysis, baseline Ea was similar between groups and after esmolol decreased in both groups; however, such reduction was much more pronounced in patients with greater baseline $SDP_{difference}$ (roughly 34% absolute reduction *vs* 12% after esmolol). In patients with lower baseline $SDP_{difference}$, reducing the HR was not beneficial because esmolol caused a decrease in myocardial contractility (reduced $_{art}dP/dt_{max}$) coupled with a smaller reduction in Ea, indicating prevalent effect on myocardial contractility with less efficacy in lowering arterial load (Fig. 2).[5,25,26] In this condition, esmolol not only worsened V–A uncoupling contributing to poor outcome,[27–29] but even blunted

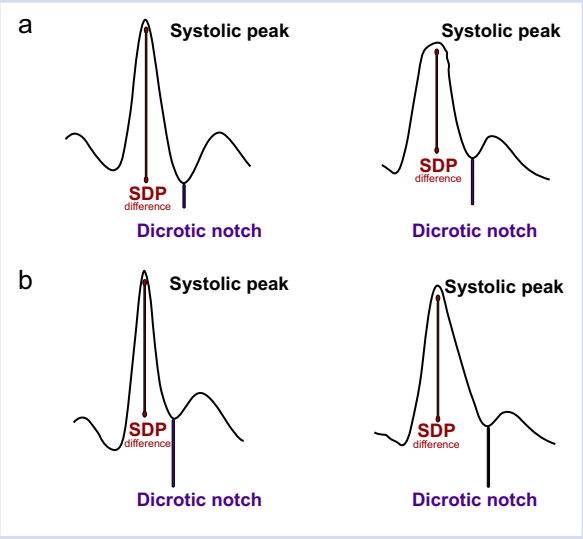

Fig 2. Different values of the difference between systolic and dicrotic pressures ($SDP_{difference}$) according to variations in the positions of the dicrotic notch pressure on arterial pressure waveform after esmolol administration in two of the enrolled patients. (a) Patient with values of arterial dP/dt_{max} below the cut-off after HR reduction, where the $SDP_{difference}$ decreases after esmolol administration (non-responder). The sharp pulse contour profile before HR reduction is the consequence of a reduction of left ventricular contractility,[27] which further deteriorates after HR reduction leading to ventricular–arterial uncoupling. (b) Patient with values of arterial dP/dt_{max} above the cut-off after HR reduction, where the $SDP_{difference}$ remains stable after esmolol administration (responder). In violet, the dicrotic notch. Red arrows represent $SDP_{difference}$ calculated as the difference between systolic peak and dicrotic notch pressure (purple).

a compensatory chronotropic response. It is important to note that HR reduction with esmolol did not apparently cause further cardiovascular derangement in both groups according to changes in conventional haemodynamic (MAP), echocardiographic (LVEF), and clinical (reduction in NE dosages) parameters.

Limitations

Additional limitations beyond those related to the original study design[5] include, firstly, the *post hoc* design. In this regard, to test our hypothesis (ability of $SDP_{difference}$ in discriminating the compensatory origin of tachycardia), we had to divide retrospectively the study population into two groups according to the changes of $_{art}dP/dt_{max}$ after esmolol administration. This exploratory evaluation was based on $_{art}dP/dt_{max}$ as it decreased significantly, whereas LVEF remained unchanged after esmolol administration. Notably, logistic regression analyses indicate that $SDP_{difference}$ was able to discriminate the two groups both at baseline and after reducing HR.

Secondly, although SAP and DNP were automatically calculated, caution should be exercised in interpreting the meaning of $SDP_{difference}$ as it may have been influenced by alterations in the physical characteristics of fluid-filled transduction systems and irregularity in the conducting tubes, which may affect the accuracy of pressure waveforms because of incorrect damping. However, this bias is mitigated by the characteristics of PRAM technology adopted in the MostCare haemodynamic monitor.[15,30] Indeed, after acquiring a single cardiac cycle, PRAM verifies the adequacy and accuracy of the radial pressure wave detected by sampling the signal at 1000 Hz. Through a specific dynamic filtering system, PRAM identifies and eliminates the single frequencies that may cause incorrect dumping, thus reducing the perturbative effects of the pressure transducers and their conducting tubes. It must be emphasised also that clinicians should not consider our preliminary findings for patients with aortic valve disease.

Thirdly, $_{art}dP/dt_{max}$ has to be interpreted only as a surrogate of LV contractility because it relies on the peripheral detection of the pulse wave. Such peripheral detection plays a crucial role in limiting the reliability of $_{art}dP/dt_{max}$ especially during septic shock, in which altered loading conditions and arterial wall characteristics may largely affect such variables.[10,31] In contrast, for similar reasons, the use of LVEF as echocardiographic index of LV contractility does not hold high specificity in patients with septic shock.[32,33]

Fourthly, to facilitate the bedside assessment of Ea, different approaches have been proposed and validated. As the superiority of one method over another in estimating Ea has not been demonstrated, both under dynamic conditions (i.e. changes in HR) and after pharmacological interventions, as for the original study,[5] we decided to use MAP in the formula for estimating Ea.

Finally, in the original study, high doses of esmolol were administered over a short time period.[5] Such study design carries higher risks of worsening haemodynamic instability, leading to increased NE requirements as a consequence of negative chronotropic effect and reduced myocardial contractility. A slower dose titration may lead to different results.

In conclusion, our preliminary results suggest that changes in $SDP_{difference}$ could be used to discriminate between compensatory and non-compensatory origins of tachycardia in patients with septic shock, possibly revealing a state of V–A uncoupling and a covert reduction of myocardial contractility not detected by conventional haemodynamic and echocardiographic parameters. If proved valid in larger prospective studies, this haemodynamic variable may facilitate a clinician's decision at bedside on which a population of patients with septic shock is more likely to benefit from HR reduction, avoiding, however, the pharmacological control of tachycardia in patients where it could be harmful.

Authors' contributions

Study design: AM, SMR
Data extrapolation: FS, CS
Data analysis/interpretation: AM, SMR, FS, GF, FEA, AV-B
Drafting of paper: AM, FS, CS, CE, FEA, SWR, GF, AV-B
Statistical analysis: SMR, MC
Critical review: CE, SWR, AM, FS, SMR, GF, FEA, AV-B
All authors read the paper and approved the final version, and have participated sufficiently in the work to take public responsibility for the whole content of the paper.

Declaration of interest

The authors declare that they have no conflicts of interest.

References

1. Domizi R, Calcinaro S, Harris S, et al. Relationship between norepinephrine dose, tachycardia and outcome in

septic shock: a multicentre evaluation. *J Crit Care* 2020; **57**: 185–90
2. Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013; **310**: 1683–91
3. Sanfilippo F, Corredor C, Arcadipane A, et al. Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis. *Br J Anaesth* 2017; **119**: 583–94
4. Guarracino F, Ferro B, Morelli A, Bertini P, Baldassarri R, Pinsky MR. Ventriculoarterial decoupling in human septic shock. *Crit Care* 2014; **18**: R80
5. Morelli A, Singer M, Ranieri VM, et al. Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study. *Intensive Care Med* 2016; **42**: 1528–34
6. Joulin O, Marechaux S, Hassoun S, Montaigne D, Lancel S, Neviere R. Cardiac force-frequency relationship and frequency-dependent acceleration of relaxation are impaired in LPS-treated rats. *Crit Care* 2009; **13**: R14
7. Liu P, Wu Q, Tang Y, Zhou Z, Feng M. The influence of esmolol on septic shock and sepsis: a meta-analysis of randomized controlled studies. *Am J Emerg Med* 2018; **36**: 470–4
8. Brown SM, Beesley SJ, Lanspa MJ, et al. Esmolol infusion in patients with septic shock and tachycardia: a prospective, single-arm, feasibility study. *Pilot Feasibility Stud* 2018; **4**: 132
9. Sanfilippo F, Santonocito C, Morelli A, Foex P. Beta-blocker use in severe sepsis and septic shock: a systematic review. *Curr Med Res Opin* 2015; **31**: 1817–25
10. Monge Garcia MI, Jian Z, Settels JJ, et al. Performance comparison of ventricular and arterial dP/dt_{max} for assessing left ventricular systolic function during different experimental loading and contractile conditions. *Crit Care* 2018; **22**: 325
11. Klein LW, Shahrrava A. The incisura. *Cardiol Rev* 2019; **27**: 274–8
12. Politi MT, Ghigo A, Fernandez JM, et al. The dicrotic notch analyzed by a numerical model. *Comput Biol Med* 2016; **72**: 54–64
13. Nichols WW, O'Rourke MF, Vlachopoulos C. *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. 6th Edn. Hachette: Hodder Arnold; 2011
14. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165–228
15. Scolletta S, Franchi F, Romagnoli S, et al. Comparison between Doppler-echocardiography and uncalibrated pulse contour method for cardiac output measurement: a multicenter observational study. *Crit Care Med* 2016; **44**: 1370–9
16. Cohen-Solal A, Caviezel B, Himbert D, Gourgon R. Left ventricular-arterial coupling in systemic hypertension: analysis by means of arterial effective and left ventricular elastances. *J Hypertens* 1994; **12**: 591–600
17. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983; **245**: H773–80
18. Morelli A, Sanfilippo F, Romano SM. Esmolol in septic shock: old pathophysiological concepts, an old drug, perhaps a new hemodynamic strategy in the right patient. *J Thorac Dis* 2016; **8**: 3059–62
19. Monge Garcia MI, Jian Z, Settels JJ, Hatib F, Cecconi M, Pinsky MR. Reliability of effective arterial elastance using peripheral arterial pressure as surrogate for left ventricular end-systolic pressure. *J Clin Monit Comput* 2019; **33**: 803–13
20. Fincke R, Hochman JS, Lowe AM, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. *J Am Coll Cardiol* 2004; **44**: 340–8
21. Morelli A, De Backer D. The ten principles behind arterial pressure. *Intensive Care Med* 2018; **44**: 911–4
22. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. *Crit Care Med* 2008; **36**: 1701–6
23. Boissier F, Razazi K, Seemann A, et al. Left ventricular systolic dysfunction during septic shock: the role of loading conditions. *Intensive Care Med* 2017; **43**: 633–42
24. Guarracino F, Bertini P, Pinsky MR. Cardiovascular determinants of resuscitation from sepsis and septic shock. *Crit Care* 2019; **23**: 118
25. Dekleva M, Lazic JS, Soldatovic I, et al. Improvement of ventricular–arterial coupling in elderly patients with heart failure after beta blocker therapy: results from the CIBIS-ELD trial. *Cardiovasc Drugs Ther* 2015; **29**: 287–94
26. Razzolini R, Tarantini G, Boffa GM, Orlando S, Iliceto S. Effects of carvedilol on ventriculo-arterial coupling in patients with heart failure. *Ital Heart J* 2014; **5**: 517–22
27. Yan J, Zhou X, Hu B, et al. Prognostic value of left ventricular-arterial coupling in elderly patients with septic shock. *J Crit Care* 2017; **42**: 289–93
28. Geri G, Vignon P, Aubry A, et al. Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis. *Intensive Care Med* 2019; **45**: 657–67
29. Tartière JM, Tabet JY, Logeart D, et al. Noninvasively determined radial dP/dt is a predictor of mortality in patients with heart failure. *Am Heart J* 2008; **155**: 758–63
30. Scolletta S, Bodson L, Donadello K, et al. Assessment of left ventricular function by pulse wave analysis in critically ill patients. *Intensive Care Med* 2013; **39**: 1025–33
31. Vaquer S, Chemla D, Teboul JL, et al. Influence of changes in ventricular systolic function and loading conditions on pulse contour analysis-derived femoral dP/dt_{max}. *Ann Intensive Care* 2019; **9**: 61
32. Repesse X, Charron C, Vieillard-Baron A. Evaluation of left ventricular systolic function revisited in septic shock. *Crit Care* 2013; **17**: 164
33. Sanfilippo F, Corredor C, Fletcher N, et al. Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: a systematic review and meta-analysis. *Crit Care* 2018; **22**: 183

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