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Noradrenaline modifies arterial reflection phenomena and left ventricular efficiency in septic shock patients: A prospective observational study☆

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ABSTRACT

Purpose: To determine whether noradrenaline alters the arterial pressure reflection phenomena in septic shock patients and the effects on left ventricular (LV) efficiency.
Material and methods: Thirty-seven septic shock patients with a planned change in noradrenaline dose. Timing and magnitude (Reflection Magnitude and Augmentation Index) of arterial reflections were evaluated. Total, steady, and oscillatory LV power (also expressed as fraction of the total power), subendocardial viability ratio (SEVR), energy efficiency and transmission ratios were used as a marker of LV efficiency.
Results: An incremental change in noradrenaline increased Reflection Magnitude [0.28(0.09) to 0.31(0.1], Augmentation Index [−6.4(23.6) to 4.8(20.7)%], and LV total power [0.79(IQR:0.47–1) to 0.98(IQR:0.57–1.27) W], all $p < 0.001$; whereas decreased arrival time of reflected waves [from 95(87 to 121) to 83(79 to 101)ms; $p < 0.001$]. Variables of LV performance showed a decreased efficiency: oscillatory fraction and energy efficiency ratio increased [20.9(5.7) to 22.8(4.9)%, and 8.2(1.7) to 10.1(2) mW.min.litre^{-1}; $p < 0.001$, respectively]; and energy transmission ratio and SEVR decreased [73.8(9.9) to 72(9.8)% and 146(IQR:113–188) to 143 (IQR:109–172)%, $p = 0.003$ and $p = 0.041$, respectively].
Conclusions: Noradrenaline increased reflection phenomena, increasing LV workload and worsening LV performance in septic shock patients. These conditions could explain the detrimental effects during long-term use of noradrenaline.

1. Introduction

Profound vasoplegia and depressed myocardial contractility are the hallmark of the cardiovascular disorders in septic shock [1]. In this context, vasopressors aimed to correct arterial hypotension are usually necessary to restore the organ perfusion pressure [2]. However, even if the vasopressors are needed for sustaining arterial pressure during resuscitation, their impact may potentially be detrimental if they increase left ventricular (LV) workload or if LV function is already impaired, as described in septic shock patients [3].

Arterial wave reflection is a physiological phenomenon and the major component of the cardiac afterload [4,5]. These arterial reflections are responsible for the pulse pressure amplification and the differences in the pressure waveform from central aorta to the peripheral arterial system [5]. They also determined the systolic boost and the progressive reduction in LV ejection associated with aging [5]. Both the magnitude and timing of arterial reflections affect to the LV ejection: during systole,

Abbreviations: AI, Augmentation index; C_{art}, Arterial compliance; Ea, Effective arterial elastance; EER, Energy efficiency ratio; ETR, Energy transmission ratio; LV, Left ventricle; MAP, Mean arterial pressure; Q, Blood flow; P, Central pressure; Pfw, Amplitude of the forward pressure waveform; Pbw, Amplitude of the backward pressure waveform; RI, Reflection index; RM, Reflection magnitude; R_T, Total vascular resistance; SEVR, Subendocardial viability ratio; T, Cardiac period; T_d, Diastolic time interval; T_s, Systolic time interval; W_{fwd}, Hydraulic power in the forward wave; W_{osc}, Oscillatory left ventricular power; W_{std}, Steady left ventricular power; W_{tot}, Total left ventricular power; Zc, Characteristic impedance; τ, Diastolic time Interval; $\%W_{osc}$, Oscillatory left ventricular power fraction..

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reflections lead to an increased LV workload; whereas in diastole, they exert a beneficial effect increasing coronary perfusion pressure [5].

Although the impact of vasopressors during septic shock have been usually studied considering the arterial circulation mainly represented by mean arterial pressure (MAP) and systemic arterial resistance [6, 7], a proper evaluation of noradrenaline effects would require a broader description of the arterial system, including the impact of the arterial wave reflections and considering their effects on LV performance [3]. The particular combination of LV dysfunction and vasoplegia may make patients more susceptible with septic shock to the effects of arterial wave reflections when using noradrenaline.

We therefore designed this study to determine whether noradrenaline modifies the arterial pressure propagation and reflection phenomena in septic shock patients, and how this could affect LV efficiency. We hypothesised that the effects of noradrenaline would depend on the magnitude and timing of the arterial wave reflections: a beneficial effect is expected if they affect mainly during the diastole (enhancing coronary perfusion pressure), or detrimental if they increased LV workload affecting predominately during systole.

2. Material and methods

This observational study was conducted in the medico-surgical intensive care unit of the Hospital SAS de Jerez and approved by our Institutional Research Ethics Committee (Comité de Ética de la Investigación de Cádiz, CIF: Q-9150013B). Written informed consent was obtained from all patient's relatives. The STROBE guidelines for reporting observational studies were used during the redaction of this manuscript [8].

2.1. Patients

We prospectively included patients from 24 June 2016 to 4 August 2017 during the first 72 h after diagnosis of septic shock [2], equipped with a radial artery catheter and monitored with an esophageal Doppler, for whom the attending physician decided to modify the noradrenaline infusion to achieve a MAP according to each patient's clinical condition. Patients with cardiac arrhythmia or pacemakers were excluded. All patients were sedated and their lungs ventilated in volume-controlled mode.

2.2. Hemodynamic monitoring

Continuous hemodynamic monitoring was performed with an esophageal Doppler (CardioQ-Combi™, Deltex Medical, Chichester, UK). The radial arterial catheter was connected to a pressure transducer (TruWave®, Edwards Lifesciences LLC, Irvine, CA, USA), and zeroed to atmospheric pressure. Optimal damping of the arterial waveform was checked by fast-flushing the line. Hemodynamic variables were continuously recorded and 1-min averaged.

2.3. Carotid-femoral pulse wave velocity

Pulse wave velocity represents the propagation speed of the arterial pulse through the arterial system and it is considered the gold-standard measurement of arterial stiffness and an independent predictor of cardiovascular mortality [9]. Pulse wave velocity was calculated using the carotid-to-femoral transit time and the foot-to-foot method using the SphygmoCor system (AtCor Medical, Sydney, Australia) [10]. The carotid-to-femoral distance was assessed using 80% of the direct distance between the carotid and femoral measuring points [10]. At least two consecutive measurements were obtained. If these differed ≥1 $m.s^{-1}$, a third measurement was obtained and the average value was used.

2.4. Arterial wave separation analysis

Central aortic pressure was estimated from the carotid pressure waveform using from high-fidelity applanation tonometry (SPT-301; Millar Instruments, Houston, TX, USA) [11, 12]. Time-integrated mean pressure and diastolic pressure from the invasive radial artery were used to calibrate carotid tracings [13].

Radial pressure and aortic blood flow waveforms obtained from Doppler system were resampled from 180 to 128 Hz for analysis with the tonometric pressure waveform. At least 10 s of the carotid, radial pressure and Doppler flow waveforms were ensemble-averaged, foot-to-foot aligned using the maxima of the second-derivative, and linearly interpolated to the duration of the cardiac cycle (in milliseconds) to provide a representative waveform for analysis. A description of the study setup and signal processing is described in Fig. 1 and Additional file 1, Fig. S1.

Central pressure waveform (P) was separated in its forward and backward components, according to the method proposed by

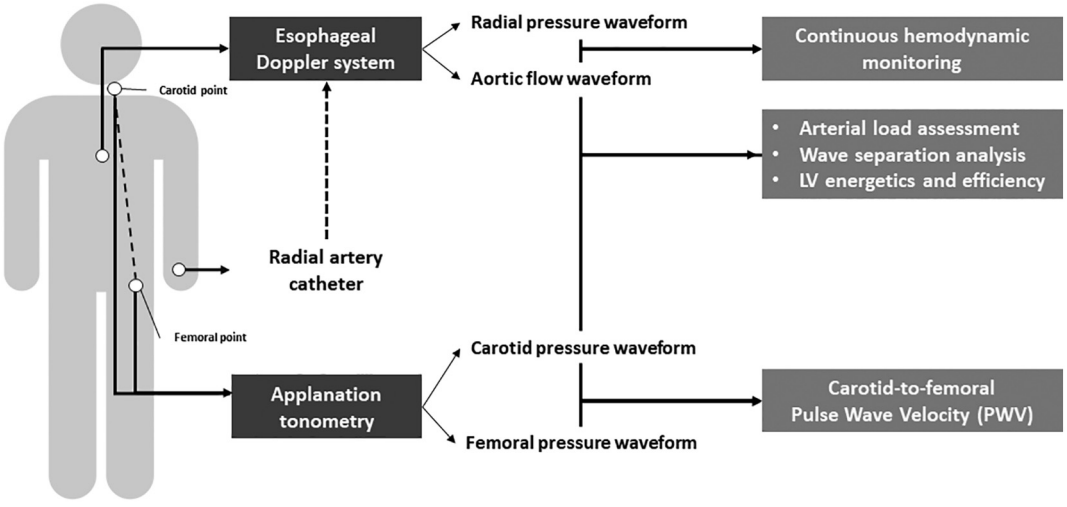

Fig. 1. Signal processing and analysis. Carotid and femoral arteries were identified, and measurement points were marked with a dermographic pen. Then the distance between carotid to femoral points were measured. The carotid-to-femoral distance used for pulse wave velocity (PWV) calculation was determined using the 80% of the actual distance (dashed line). Pulse wave velocity was estimated calculating the distance from the beginning of systole (using the electrocardiogram as the fiduciary signal) to foot of the carotid and femoral pressure waveforms. The averaged tonometric carotid waveform was used as a surrogate of the central pressure waveform for pulse waveform analysis.

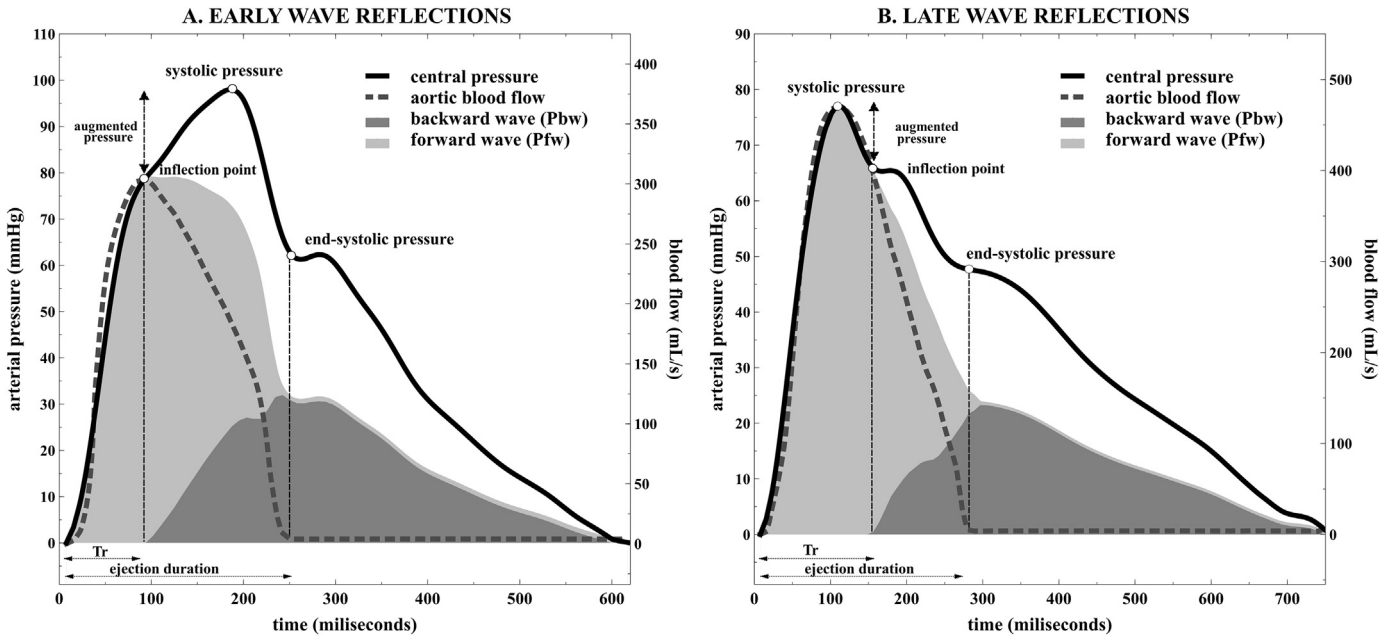

Fig. 2. Pulse wave waveform analysis. *Left*: typical features of the central arterial pressure waveform in a patient with early arterial wave reflections. Time to arrival of reflected wave (Tr) occurs during early systole, increasing pulse pressure, and creating a positive augmentation index. *Right*: a patient with late arterial wave reflections, which they mainly contribute during diastolic period. In this case, augmentation index is negative. Light and dark shaded areas correspond to the forward and backward pressure waveforms, respectively. For illustrative purposes foot value of pressure at each wave was subtracted equalizing all pressure feet at zero. Reflection Magnitude (RM) represents the ratio between the amplitudes of backward and forward waveforms, whereas Reflection Index (RI) expresses the ratio between amplitudes of the backward and the measured arterial waveforms.

Westerhof et al. [14].

$$Pfw = [P(t) + Zc^{*}\ Q(t)]/2$$

$$Pbw = [P(t) - Zc^{*}\ Q(t)]/2$$

Zc represents the characteristic impedance, calculated as described below [5, 15]; Pfw is the forward waveform generated by the interaction of the ejected blood flow (Q) and the physical properties of the aortic root traveling towards the peripheral arterial system; and Pbw is the net backward waveform, which is the composite result of the multiple collisions of Pfw with different peripheral reflection sites in the arterial bed returning to the heart [14]. The measured central pressure, therefore, results from the summation of Pfw and Pbw (Fig. 2).

2.5. Assessment of arterial wave reflections

The impact of arterial reflections on LV afterload was assessed by the augmentation index (AI) as:

$$AI(\%) = \text{augmented pressure}/\text{central pulse pressure}$$

Where augmented pressure is the difference between the first and second peak of central pressure, and central pulse pressure the difference between systolic and diastolic of central pressure. AI sign will then depend on the arrival time of Pbw (Fig. 2).

We also evaluated the influence of arterial reflections during cardiac ejection relating the amplitude of Pbw and Pfw as (Fig. 2) [16]:

$$\text{Reflection magnitude (RM)} = \text{Pbw amplitude}/\text{Pfw amplitude}$$

$$\text{Reflection Index (RI)} = \text{Pbw amplitude}/(\text{Pbw amplitude} + \text{Pbw amplitude})$$

Since not only the magnitude is important but also the timing of reflections, the arrival time of the reflected wave (Pbw_t) was also calculated from the beginning of the central pressure to the foot of Pbw and normalised to the cardiac period (T) for comparison. Examples of pulse wave analysis in a patient with early and late reflections are shown Fig. 2.

2.6. Arterial load assessment

The arterial system was characterised by a 3-element Windkessel model [16], consisting of:

2.6.1. Total vascular resistance (R_T)

$$R_T = (\text{MAPc/esophageal} - \text{Doppler cardiac output})^{*}\ 80$$

With MAPc being the pressure-time integral of central pressure.

2.6.2. Arterial compliance (C_{art}) [17]

$$C_{art} = (\text{esophageal} - \text{Doppler cardiac output/heart rate})/[(K^{*}\ (P_1 - P_2)]$$

K represents the ratio of the total area under the central pressure and the diastolic area, and P_1 and P_2 are the maximum central pressure after dicrotic notch and the diastolic pressure, respectively.

2.6.3. Characteristic impedance (Zc)

Calculated as the slope of the early pressure-flow relationship as the ratio between the initial part of the central pressure wave (from its foot to the first systolic shoulder), and the peak of the aortic blood flow [5]

The effective arterial elastance (Ea) was used as a lumped parameter accounting for both mean and pulsatile LV load [18]:

$$Ea = R_T/[t_s + \tau^{*}\left(1 - e^{-td/\tau}\right)$$

Where t_s and t_d are systolic and diastolic periods, respectively, and τ the diastolic time constant ($\tau = R_T{}^{*}C_{art}$) [18].

2.7. Left ventricular energetics

Left ventricular energetics were analyzed from the pressure and flow waveforms (Additional file 1, Fig. S2). The total LV power (W_{tot}) transferred to the systemic circulation was calculated as the time-averaged integral of the instantaneous product of pressure and flow during the whole cardiac period:

$$W_{tot} = \frac{1}{T}\int_0^T P(t)Q(t)dt$$

The product of mean pressure by mean flow, or steady power (W_{std}), corresponds to the energy that maintains cardiac output and represents the fraction of W_{tot} useful for organ perfusion [4, 19, 20].

$$W_{std} = \overline{P} * \overline{Q}$$

The oscillatory power (W_{osc}) refers to the energy lost in pulsatile phenomena due to cardiac contractions:

$$W_{osc} = W_{tot} - W_{std}$$

The contribution of kinetic energy was considered negligible [4].

2.8. Left ventricular efficiency

The oscillatory power fraction ($\%W_{osc}$) represents the portion of W_{tot} wasted in oscillatory power and quantifies the efficiency of power dissipation of the arterial system. $\%W_{osc}$ was used as a measure of the optimization of ventriculo-arterial coupling [12, 19, 21].

$$W_{osc} = \frac{W_{osc}}{W_{tot}} * 100$$

We also calculated the LV power necessary for generating one unit of cardiac output for a given arterial load, as the energy efficiency ratio (EER) [22]:

$$EER = W_{tot}/Q$$

The subendocardial viability ratio (SEVR), or the ratio between the pressure-time integral during diastole and systole of the central pressure waveform, was used as an index of myocardial perfusion relative to cardiac load [23]. The systolic component of SEVR, also called as Tension Time Index, was used as an estimation of myocardial oxygen consumption (Additional file 1, Fig. S3) [24].

The energy transmission ratio (ETR) represents the LV power wasted because of arterial reflections:

$$ETR = W_{tot}/W_{fwd}$$

Where W_{fwd} is the hydraulic power in the forward wave calculated from the forward pressure and flow waves. ETR expresses the effect of arterial reflections on LV power: the lower the ETR, the higher the influence of arterial reflections reducing LV power [25].

2.9. Study protocol

Noradrenaline infusion rate was modified in steps of 0.03 μg Kg^{-1} min^{-1} and monitoring the response every 2–3 min (according to our institutional protocol), until achieving the desired MAP (≈65 mmHg or higher in patients with prior hypertension) [26]. All hemodynamic variables were measured before and after modifying noradrenaline dose. As we expected that studied variables will vary directly to noradrenaline modifications, changes over time were assessed from the lower to the higher dose for analysis purposes. No changes in ventilatory settings or sedatives were made.

2.10. Statistical analysis

The normality of data was tested using the Shapiro-Wilk test. Results are expressed as mean (SD) or median (IQR [range]). Differences between continuous variables before and after changes in noradrenaline dose were assessed by using a paired Student's *t*-test or a Wilcoxon test, as appropriate. A $P < 0.05$ was considered statistically significant. Statistical analyses performed using MedCalc 17.6.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

3. Results

Thirty-eight patients were included, one of them was excluded due to a poor quality of the tonometry record. The characteristics of the remaining patients are detailed in Table 1. noradrenaline was introduced in three patients, increased in eight, withdrawn in eight, and reduced in 18. Radial MAP increased from 63 (6) to 74 (6) mmHg ($P < 0.0001$) in the group of patients with an increment or introduction of noradrenaline infusion; and decreased from 90 (9) to 76 (6) mmHg ($P < 0.0001$) in those patients in which noradrenaline was decreased or withdrawn. Details of the changes during noradrenaline dose modifications can be found in the Additional file 1, Tables S1 and S2.

Analysing data from lower to the higher dose, noradrenaline was increased from 0.06 (0–0.13 [0–0.42]) to 0.15 (0.07–0.27 [0.02–0.50]) $\mu g^{-1}.Kg^{-1}.min^{-1}$ ($p < 0.0001$). This incremental change was associated with an increased arterial load and pulse wave velocity and altered magnitude and timing of arterial wave reflections: reflected waveform has a greater amplitude and arrived earlier. Both phenomena yielded to a larger influence during systole increasing LV afterload (Table 2). An example of the effects of changing noradrenaline dose in the shape of pressure and flow waves, arterial waveform analysis and LV energetic calculations is shown in Additional file 1, Fig. S4.

Noradrenaline also modified LV power and the energy dissipated by oscillations. According to the EER, the energy cost of generating one unit of cardiac output was larger with higher noradrenaline dose. Furthermore, a significant part of this power was wasted due to a greater impact of arterial reflections (lower ETR). Because of a higher myocardial

Table 1
Characteristics of the study population.

Age (years)	61 (11)
Gender (male/female)	28/9
Weight (kg)	83.5 (17.6)
Height (cm)	171 (9)
APACHE II score at admission	22 (7)
SOFA score at admission	11 (3)
Plasma lactate level at admission ($mg.dl^{-1}$)	22.4 (17.1–49.4 [8.8–167])
Days from ICU admission to study inclusion	1.5 (0.5–3 [0–3])
30-day mortality rate, n (%)	11 (29.7%)
Postsurgical admission	17 (46%)
Anaelgesia, sedative drugs and inotropes	
Fentanyl, n; dose ($\mu g.kg^{-1}.h^{-1}$)	7; 2.3 (0.5)
Remifentanil, n; dose ($\mu g.kg^{-1}.min^{-1}$)	29; 0.18 (0.06)
Midazolam, n; dose ($mg.kg^{-1}.h^{-1}$)	10; 0.10 (0.04)
Dobutamine, n; dose ($\mu g.kg^{-1}.min^{-1}$)	3; 4 (1)
Ventilatory settings	
Tidal volume ($ml.Kg^{-1}$ predicted body weight)	7 (6–8 [6–9])
Respiratory rate ($breaths.min^{-1}$)	20 (18–20 [16–22])
Total PEEP (cmH_2O)	7 (6–8 [3—12])
Source of infection, n	
Abdominal	16
Pulmonary	18
Urological	2
Neurological	1

Values are expressed as mean (SD), median (IQR [range]) or number (proportion).
APACHE: Acute Physiology And Chronic Health Evaluation; FiO_2: inspired oxygen fraction; ICU: intensive care unit; PEEP: positive end-expiratory pressure; SaO_2: arterial oxygen saturation; SD: standard deviation; SOFA: Sequential Organ Failure Assessment.

Table 2
Arterial vascular mechanics and left ventricular hemodynamics during an incremental change in noradrenaline dose in septic shock patients.

	Lower dose of noradrenaline	Higher dose of noradrenaline	*P* value
Left ventricular hemodynamics			
Cardiac output; l.min^{-1}	5.87 (2.22)	5.89 (2.26)	0.873
Stroke volume; ml	68 (19)	70 (19)	0.200
Heart rate; beats.min^{-1}	86 (66 to 105)	80 (65 to 106)	0.012
Systolic arterial pressure; mmHg	101 (13)	125 (18)	<0.001
Diastolic arterial pressure; mmHg	55 (8)	62 (9)	<0.001
Mean arterial pressure; mmHg	72 (66–77 [46–90])	84 (77–94 [62–107])	<0.001
Radial mean pressure; mmHg	72 (66–78 [46–90])	84 (77–92 [61–107])	<0.001
Ejection duration; ms	241 (45)	249 (52)	0.002
Pulse pressure variation; %	6.4 (4.4–11.1 [2–34])	4.9 (3.4–8 [2−23])	<0.001
Arterial vascular mechanics			
R_T; dyn.cm.s^{-5}	1123 (440)	1345 (557)	<0.001
C_{art}; ml.mm.Hg^{-1}	1.73 (1.44–2.24 [0.50–6.44])	1.33 (1.04–1.76 [0.49–3.76])	<0.001
Zc; dyn.cm.s^{-5}	179 (144–236 [83–578])	236 (170–311 [86–591])	<0.001
Ea; mmHg.ml^{-1}	1.67 (0.63)	1.96 (0.74)	<0.001
PWV; m.s^{-1}	8.6 (2.6)	10.4 (3.6)	<0.001
Arterial waveform analysis			
Pfw amplitude; mmHg	43.4 (13.6)	55.2 (14.5)	<0.001
Pbw amplitude; mmHg	11.7 (4.1)	16.5 (5.9)	<0.001
Pbw_t; ms	95 (87–121 [71–248])	83 (79–101 [59–239])	<0.001
Normalised Pbw_t	0.14 (0.11–0.19 [0.07–0.48])	0.11 (0.09–0.14)	<0.001
Augmentation index; %	−6.4 (23.6)	4.8 (20.7)	<0.001
Reflection Magnitude	0.28 (0.09)	0.31 (0.10)	<0.001
Reflection Index	0.21 (0.05)	0.23 (0.06)	<0.001
Myocardial O_2 consumption			
Tension time index; mmHg.s	20.7 (17.5–23.8 [9.7–32.1])	26.3 (20.2–32.6 [13.9–47.3])	<0.001
Left ventricular power and efficiency			
W_{tot}; W	0.79 (0.47–1 [0.27–1.82])	0.98 (0.57–1.27 [0.39–1.96])	<0.001
W_{std}; W	0.65 (0.32)	0.76 (0.33)	<0.001
W_{osc}; W	0.17 (0.10–0.22 [0.05–0.48])	0.22 (0.16–0.26 [0.08–0.56])	<0.001
$\%W_{osc}$; %	20.9 (5.7)	22.8 (4.9)	<0.001
Energy efficiency ratio; mW.min.l^{-1}	8.2 (1.7)	10.1 (2)	<0.001
Energy transmission ratio; %	73.8 (9.9)	72 (9.8)	0.003
Subendocardial viability ratio; %	146 (113–188 [81–324])	143 (109–172 [78–318])	0.041

Data are presented as mean (SD) or as median (IQR [range]). *P* values refer to before vs. after noradrenaline dose change comparison.
R_T: total vascular resistance; C_{art}: arterial compliance; Zc: characteristic impedance; Ea: effective arterial elastance; PWV: arterial pulse wave velocity; Pfw: forward pressure waveform; Pbw: backward pressure waveform; Pbw_t: time to arterial reflection arrival; Normalised Pbw_t: time to arterial reflection arrival normalised to cardiac period; W_{tot}: left ventricular total power; W_{std}: left ventricular steady power; W_{osc}: left ventricular oscillatory power; $\%W_{osc}$: the fraction of total power (W_{tot}) wasted in oscillatory power (W_{osc}).

oxygen demand, a higher noradrenaline dose did not result in an overall benefit according to SEVR (Table 2).

4. Discussion

In this study, noradrenaline dose changes modified arterial pressure propagation and reflection phenomena affecting LV efficiency in septic shock patients. Considering changes from the lower to the higher dose, augmented arterial load and wave reflections led to a higher systolic workload imposed to left ventricle and a worse LV efficiency.

Arterial reflections represent the main component of the LV afterload [5]. These reflections are the consequence of the non-homogeneous and closed design of the cardiovascular system [14]. Therefore, when the heart contracts, a blood flow and pressure wave are created and propagated along the arterial tree. The measured arterial pressure waveform therefore results from the summation of the wave traveling from the heart to periphery and the backward waveforms returning from the periphery [14].

The reflected waves also interact with following cardiac contractions. The magnitude and timing of these reflections define the effects on LV performance [27]. While early wave reflections affect mainly during systole increasing LV workload and oxygen consumption, late reflected waves have a beneficial hemodynamic effect, as they predominantly increase diastolic pressure and myocardial perfusion pressure [28]. Pulse wave velocity and the effective distance to the main reflections locations are factors determining the magnitude and timing of arterial reflections [29]. An increase in arterial stiffness will therefore increase pulse wave velocity, reduce the arrival time of arterial reflections, and raise the LV systolic workload and oxygen consumption [27]. Since we can assume that no structural changes in arteries occurred in our study, factors increasing arterial stiffness and hence pulse wave velocity were mainly functional: a higher MAP level and an increased arterial load led to increase the speed of pulse wave propagation and raise the impact of arterial reflections on LV workload [29].

On the other hand, the heart can be considered as a source of energy that generates both pressure and flow [4, 5]. Ideally, the optimal transfer of this cardiac energy to the arterial system should be performed with a minimal loss [4], i.e., the maximal cardiac efficiency is achieved when all the energy is transmitted peripherally and the optimal stroke volume is obtained with the lowest energetic consumption [30]. However, because of the cardiac contractions, this energy is partially wasted due to arterial pulsations. Since oscillatory energy does not contribute to the forwarding flow to the peripheral organs, the lower $\%W_{osc}$ the better the LV efficiency in transforming the energy into steady pressure and flow for maintaining tissue perfusion [19, 20]. Moreover, as LV power is related to both cardiac function and arterial load, $\%W_{osc}$ represents a sort of index of the efficiency of the coupling between the heart and the arterial system, expressing how efficiently the energy generated by the heart is delivered into the arterial tree [4, 19-21]. Although the contribution of W_{osc} to W_{tot} is relatively small (10–15%) [4, 5], factors increasing arterial load also increase the oscillatory influence on W_{tot}. Furthermore, because the pulsatile component of the arterial load is substantially affected by reflection phenomena, the higher the influence of arterial reflections, the greater the energy wasted in pulsations [20, 21].

In our study, LV power changes should be interpreted considering variations in arterial load [21]. An increased LV power represents a compensatory response of the heart against a higher arterial load [20], probably induced by the Anrep response or by a noradrenaline-mediated inotropic effect [31]. However, LV efficiency depends not only on how much work is created but also on how this is performed. Therefore, an increased $\%W_{osc}$ and ETR associated with higher doses of noradrenaline imply an undesirable condition in terms of cardiovascular efficiency [21]. So, even if noradrenaline is necessary for restoring arterial pressure, the cost for such intervention is an increased myocardial workload and an impaired LV efficiency. For how long this situation can be sustained will eventually depend on the prior LV function and the clinical evolution of the septic process. However, if this situation persists and the heart is not able to cope with the increased workload, it may even further exacerbate or precipitate myocardial dysfunction [32].

The combination of an impaired LV contractility and loss of vasomotor tone characterises the hemodynamic disorders of septic shock [1, 33]. Although noradrenaline titration is usually performed by targeting a minimum MAP level [2], eventually the overall benefit of noradrenaline in terms of cardiovascular efficiency will be a balance between the work required for pumping blood flow through the systemic circulation

and the energy wasted in W_{osc} [4, 20, 21, 34]. In this regard, one strength of our study is to analyse the effects of noradrenaline considering the influence of arterial reflections on the arterial circulation and the heart not as isolated systems, but from an integrative point of view. Moreover, since we analyzed the LV response to a noradrenaline-induced change in afterload, our assessment could be interpreted as a dynamic test defining the behaviour of the cardiovascular performance. From this perspective, even if noradrenaline is necessary for sustaining perfusion pressure, the imposed price is a greater afterload and an impaired LV efficiency. This unfavourable hemodynamic condition could help to explain the increased mortality described with the prolonged use or with high doses of noradrenaline [7, 35]. Consequently, a clinical recommendation could be drawn from our results: when using noradrenaline in septic shock, the heart must pay a price in terms of an increased myocardial workload and impaired LV efficiency. Even if this price could be assumable during early stages, when restoring organ perfusion is a clinical emergency, the physician should be aware about these harmful effects, especially in patients with previous LV dysfunction, and should try to use the lowest dose of noradrenaline to sustain MAP with the goal of withdrawing it as soon as patient's clinical condition permits Definitively, our study advocates for a more frequent assessment of noradrenaline requirement in septic shock, in the same way as sedatives in mechanically ventilated patients.

Finally, our study has some limitations. We used the carotid pressure as a surrogate for central pressure. Although this method has been recognised for estimating aortic pressure [11-13], it could present some significant differences, especially when calibrating using the radial pressure. However, diastolic and mean arterial pressures are relatively constant from the aorta to the radial artery, even after inducing vasodilation or during experimental septic shock [36, 37]. Furthermore, considering the clinical nature of our study, our estimation of the central pressure could be considered the best approach, as it does not rely on the assumptions of a mathematical transfer function. Second, in our study, cardiac output was not affected by changes in noradrenaline, which can be explained by the lack of preload-responsiveness. However, as noradrenaline could alter the distribution of the stressed/unstressed volumes and affect to the venous return [38], patients with a preserved preload-dependency could show not only changes in pressure but also in cardiac output. The results in this condition could be different from those observed in our study. Third, we have evaluated only the effects of noradrenaline, since it is the first-line vasopressor recommended for septic shock [2]. The impact of other vasopressors with a different hemodynamic profile, such as phenylephrine or vasopressin, has been not tested. However, although speculative, our results suggest that in septic shock patients, vasopressors with an inotropic effect would be preferable over those with no positive

effects on LV performance. Finally, we have focused only on the heart and the arterial circulation, without considering the impact on other systems, which it could have provided a more global perspective of the effects of noradrenaline. Furthermore, we did not evaluate whether the observed effects are sustained over time or whether they affected patient's long-term outcome.

5. Conclusions

Changes in noradrenaline dose in septic shock patients were associated with variations in arterial reflections and pulse wave velocity: an incremental change in noradrenaline augmented systolic workload imposed to left ventricle and worsened left ventricular efficiency. These unfavourable conditions could explain the long-term detrimental hemodynamic effects of noradrenaline observed in septic patients. Despite its physiological nature, the results of our study may not only improve our understanding of the mechanisms involved in the sepsis-induced cardiac dysfunction but may also use as a warning for the clinician when using noradrenaline for sustaining arterial pressure in septic shock patients.

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Competing interests

MIMG is consultant for Edwards Lifesciences and received Honoraria and/or Travel Expenses from Deltex Medical. AGC has received Honoraria from Edwards Lifesciences. A.G.C. have received lectures fees from Edwards Lifesciences. MC in the last 5 years has received Honoraria and/or Travel Expenses from Edwards Lifesciences, LiDCO, Cheetah, Bmeye, Masimo and Deltex Medical. The remaining authors have disclosed that they do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.07.027.

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