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Impact of norepinephrine on right ventricular afterload and function in septic shock—a strain echocardiography study

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Background: In this observational study, the effects of norepinephrine-induced changes in mean arterial pressure (MAP) on right ventricular (RV) systolic function, afterload and pulmonary haemodynamics were studied in septic shock patients. We hypothesised that RV systolic function improves at higher doses of norepinephrine/MAP levels.

Methods: Eleven patients with septic shock requiring norepinephrine after fluid resuscitation were included <24 hours after ICU arrival. Study enrolment and insertion of a pulmonary artery catheter was performed after written informed consent from the next of kin. Norepinephrine infusion was titrated to target mean arterial pressures (MAP) of 60, 75 and 90 mmHg in a random sequential order. At each target MAP, strain—and conventional echocardiographic—and pulmonary haemodynamic variables were measured. RV afterload was assessed as effective pulmonary arterial elastance, (E_{pa}) and pulmonary vascular resistance index, (PVRI). RV free wall peak strain was the primary end-point.

Results: At highest compared to lowest norepinephrine dose/MAP level, RV free wall peak strain increased from −19% to −25% (32%, $P = .003$), accompanied by increased tricuspid annular plane systolic excursion (22%, $P = .01$). At the highest norepinephrine dose/MAP, RV end-diastolic area index (16%, $P < .001$), central venous pressure (38%, $P < .001$), stroke volume index (7%, $P = .001$), mean pulmonary artery pressure (19%, $P < .001$) and RV stroke work index (15%, $P = .045$) increased, with no effects on PVRI or E_{pa}. Cardiac index did not change, assessed by thermodilution ($P = .079$) and echocardiography ($P = .054$).

Conclusions: Higher doses of norepinephrine to a target MAP of 90 mm Hg improved RV systolic function while RV afterload was not affected.

1 | INTRODUCTION

Septic shock is defined as a subset of sepsis, characterised by, after adequate volume resuscitation, the need of vasopressors in order to maintain a normal mean arterial pressure (MAP) ≥65 mmHg.[1] Myocardial dysfunction is commonly seen in sepsis also involving the right ventricle (RV). The number of studies on RV function in sepsis by conventional echocardiography is limited. Using American Society of Echocardiography criteria,[2] an RV dysfunction has been

described in septic shock.[3,4] Furthermore, it was recently shown that the incidence of isolated right and combined right and left ventricular dysfunction in sepsis/septic shock were 47% and 53%, respectively.[5]

Norepinephrine administration increases arterial pressure due to its vasoconstrictor effect and is recommended as the first-choice vasopressor in this group of patients.[6] Concerns have been raised regarding a potentially negative effect of norepinephrine on myocardial function due to a norepinephrine-induced increase in left ventricular (LV) afterload.[7] The RV afterload is frequently elevated

in sepsis due to increased pulmonary vascular resistance (PVR)[8] particularly in septic patients with associated acute lung injury requiring mechanical ventilation.[9] Norepinephrine has the potential to further increase RV afterload by an alpha-mediated pulmonary vasoconstriction in septic patients.[10,11] On the other hand, norepinephrine may increase RV systolic function by its β_1-receptor agonistic effect.[12] In addition, norepinephrine has been shown to increase both RV and LV preload, by alpha-mediated constriction of systemic venous capacitance vessels causing an increase in intrathoracic blood volume.[13]

Strain echocardiography is a relatively new and promising method for assessment of myocardial systolic function, as it can differentiate between active and passive (scar) movement of myocardial segments. Speckle-tracking echocardiography measures the relative movement of myocardial greyscale alterations (speckle patterns) and can thereby quantify systolic deformation, strain, describing percentage changes in myocardial segment length. The most frequently used strain variable is global longitudinal strain (GLS), which has been introduced for the detection of LV dysfunction.[14] In sepsis, strain imaging has the ability to detect impaired LV[15,16] systolic function not appreciated by conventional echocardiography.

RV systolic function can also be evaluated with strain echocardiography by assessment of RV free wall strain. In sepsis/septic, shock it has been shown that RV free wall peak strain is considerably reduced[15,16] and that severely reduced RV free wall strain was associated with increased 6-month mortality.[15]

Our aim was to investigate the immediate effects of changes in norepinephrine infusion rates/MAP levels on RV systolic function and RV afterload, in patients with septic shock, by the combined use of strain echocardiography and a pulmonary artery thermodilution catheter for assessment of pulmonary haemodynamics. We tested the hypothesis that higher norepinephrine infusion rates/MAP levels improve RV systolic function in patients with norepinephrine-dependent septic shock despite the potential increase in RV afterload.

2 | METHODS

The study was approved by the Regional Ethical Review Board in Gothenburg (www.epn.se) (protocol 325-15, approved 20 June 2015). The study was registered at ClinicalTrials.gov (NCT02640846, in 29 December 2015). Data from the first part of this protocol are presented. Written informed consent was obtained from the patient's next of kin.

2.1 | Study population

We included 11 patients admitted with septic shock to the general intensive care unit (ICU), Sahlgrenska University Hospital, Gothenburg, between August 2016 and April 2018 according to the Sepsis-3 criteria.[1] The inclusion criteria were: (a) verified infection, (b) a Sequential Organ Failure Assessment (SOFA) score > 2, (c) the need

> **Editorial Comment**
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> In this small observational study of patients with early septic shock, titrating noradrenaline to target a mean arterial pressure of 90 mm Hg compared to 60 mm Hg improved echocardiographic measures of right ventricular systolic function without changing right ventricular afterload or cardiac index. The hypothesis that increased noradrenaline/mean arterial pressure levels are associated with positive inotropic effects needs to be confirmed in a larger patient cohort enabling potential mechanisms to be further explored.

for treatment with norepinephrine to maintain MAP > 65 mmHg after fluid resuscitation to achieve a stroke volume variation < 12% (PiCCO™, Pulsion Ltd, Germany), (d) sinus rhythm, (e) serum lactate > 2 mmol/l, (f) controlled mechanical ventilation with no breathing efforts (no muscle relaxants) and (g) age > 18 years. The fluid management of the patients was at the discretion of the attending intensivist in charge. The exclusion criteria were: (a) severe circulatory instability refractory to treatment, (b) poor quality of echocardiographic images, (c) patients having a pacemaker, premorbid heart disease, previous cardiac surgery and (d) severe tricuspid or mitral regurgitation. All patients were sedated with fentanyl and propofol infusion.

2.2 | Measurements of pulmonary and systemic haemodynamics

Systolic (SAP), mean (MAP) and diastolic arterial blood pressure were measured invasively by a radial artery catheter. Each patient underwent a catheterisation with a 7.5-F pulmonary artery catheter (PAC) (Baxter Healthcare, Irvine CA) for the purpose of the study protocol. Cardiac output (CO) and stroke volume were measured by thermodilution technique (PAC) (mean of three 10-mL ice-cold saline injections) and indexed to the body surface area to receive cardiac index (CI) and stroke volume index (SVI). The coefficient of variation for CO measurements was < 10% in all patients. Heart rate (HR), arterial blood pressure, systolic and mean pulmonary arterial pressure (MPAP) and central venous pressure (CVP) were continuously measured. Pulmonary capillary wedge pressure (PCWP) was measured intermittently. The transducers were referenced to the midaxillary line. Pulmonary (PVRI) and systemic vascular resistance indices (SVRI), as well as right (RVSWI) and left (LVSWI) ventricular stroke work indices were calculated according to standard formulas.

Effective arterial elastance (E_a) was measured as $0.9 \times SAP/SVI$[17] The formula for effective pulmonary arterial elastance (E_{pa}) is: $(PAPes - PCWP)/SVI$,[18] where PAPes is end-systolic pulmonary artery pressure. If PAPes is approximated by MPAP, as suggested by Morimont et al,[18] then E_{pa} can be calculated as: $(MPAP-PCWP)/SVI$.[18]

E_{pa} incorporates all elements of total RV afterload, including vascular resistance, arterial compliance and characteristic impedance.

2.3 | Conventional echocardiography

A transthoracic 2D echocardiographic examination was performed with a 5-MH transducer (Vivid E9, General Electric Medical System, Horten, Norway) immediately after each haemodynamic measurement (see above). The three standard echocardiographic views were recorded over three cardiac cycles, irrespective of the respiratory cycle. Standard measurements of LV systolic function included LV volumes, ejection fraction (LVEF) by the modified Simpson's rule, time velocity integral in the LV outflow tract (TVI-LVOT) and stroke volume (SV) ($\pi \times$ LVOT radius$^2 \times$ TVI-LVOT). TVI-LVOT were assessed over the respiratory cycle to assess stroke volume variation, at baseline, calculated as ($SV_{max}-SV_{min}$)/ [($SV_{max} + SV_{min}$) $\times$ 0.5]. For assessment of RV systolic function, tricuspid annular plane systolic excursion (TAPSE) by M-mode and tricuspid lateral annulus tissue Doppler systolic velocity (S') were measured,[2] as well as RV end-diastolic area index (RVEDAI).

2.4 | Strain echocardiography

Strain measurements were performed offline in the four-chamber, long-axis and two-chamber views. All offline analyses were performed by an investigator (KD), blinded to the MAP level, experienced in speckle tracking analysis using the EchoPAC workstation version 201(GE Medical Systems). The free RV wall (three segments) and each of the LV walls were analysed. From the analysis, we calculated the longitudinal strain of the RV free wall peak strain and the GLS for the LV, as well. Myocardial strain is presented as fractional change (%) in length between two time points, end-diastole (L_0) and end-systole (L) and calculated as: ($L - L_0$)/$L_0 \times$ 100. Negative values of strain indicate myocardial shortening. Impaired RV function was defined as a RV free wall peak strain> −24%.[19]

2.5 | Experimental protocol

After the insertion of the pulmonary artery catheter the norepinephrine dose was adjusted to obtain a target mean arterial pressure (MAP) of 75 mmHg (baseline). Measurement of systemic and pulmonary haemodynamics, as well as, an echocardiographic examination was performed twice at this target MAP. All patients were then subjected to target MAP:s of 60 and 90 mmHg, in a random order, for a period of at least 10 minutes, excluding wash-in/wash-out periods, by decreasing/increasing the infusion rate of norepinephrine (Figure 1). The wash-in/wash-out periods lasted for approximately 5-10 minutes. One of the investigators performed the haemodynamic measurements and dose adjustments and another the echocardiographic examination, both blinded to each other's findings. At the end of each period, haemodynamic and echocardiographic measurements were performed. Fluid infusion rates and ventilatory settings were not changed during the experimental procedure.

2.6 | Statistical analysis

From the two baseline measurements, the intra-observer agreement for each of the variables, RV free wall peak strain and LV global longitudinal strain, was assessed by the coefficients of variation for paired observations. Inter-observer variation was not assessed. The mean of the first and second measurements at baseline were calculated (baseline). The primary outcome variable was RV free wall peak strain. To detect a norepinephrine-induced 30% relative change in RV free wall peak strain at the highest compared to lowest norepinephrine dose/MAP level, 11 patients were needed at a power of 0.8, a significance level of 0.05 and at a RV free wall strain of −20 with a SD of 5.[23] An analysis of variance (ANOVA) for repeated measurements was used to evaluate the haemodynamic and echocardiographic effects of norepinephrine-induced variations in mean arterial pressure. A probability level (P-value) of less than .05 was considered to indicate statistical significance. Data are presented as
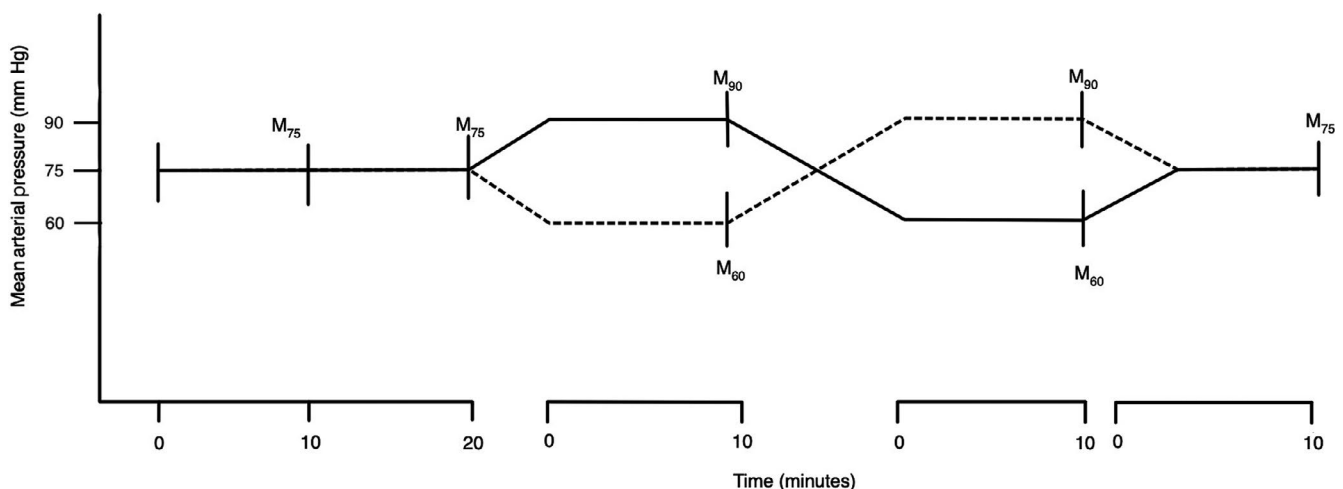

FIGURE 1 Schematic drawing of the experimental procedure. In six patients, the sequence of target mean arterial pressure (MAP) was 75, 90, 60 mmHg (full line) and in the remaining five patients the sequence was 75, 60, 90 mmHg (dashed line)

mean ± standard deviation (SD). Statistical analysis was performed using SPSS for Mac version 21.

3 | RESULTS

Eleven patients were included in the study, 7 male and 4 females, with a mean age of 63 ± 10 (Table 1). All patients were studied within 24 hours after the ICU arrival (12 ± 6 hours). The mean SAPS 3 score and SOFA score on ICU arrival were 62 ± 12 and 10 ± 3, respectively. Patient characteristics, clinical data, sources of infection and mortality are presented in Tables 1 and 2. None of the patients received any vasopressor or inotropic drug other than norepinephrine. Our data were normally distributed, as tested by the Kolmogorov-Smirnov test.

3.1 | Haemodynamic variables

The doses of norepinephrine to obtain target MAP:s of 60, 75 and 90 mmHg were 0.16 (0.10-0.40), 0.36 (0.18-0.59) and 0.49 (0.23-0.69) µg/kg/min, respectively. Highest compared to lowest norepinephrine dose/MAP level was accompanied by increases in SVI (7%, $P = .001$, ANOVA), MPAP (19%, $P < .001$), PCWP (50%,

TABLE 1 Patient characteristics

	n = 11
Age (years)	63 ± 10
Body surface area (m²)	1.8 ± 0.3
ICU length of stay (days)	6.8 ± 4.1
SAPS III score on ICU arrival	62 ± 12
SOFA score on ICU arrival	10 ± 3
Serum lactate on admission (mmol/L)	4.7 ± 2.2
ICU mortality (%)	9
30-d mortality (%)	27
Cause of sepsis, n (%)	
Abdominal sepsis, n (%)	6 (54)
Pneumonia, n (%)	1 (9)
Streptococcus septicemia, n (%)	2 (18)
Mediastinitis, n (%)	1 (9)
Necrotising fasciitis, n (%)	1 (9)
Respiratory variables	
Tidal volume (mL)	536 ± 133
Tidal volume/kg body weight	6.5 ± 1.4
PEEP (cm H₂O)	11 ± 2.6
FiO₂%	43 ± 16
Peak inspiratory pressure (cm H₂O)	23 ± 3.8

Note: Data are presented as means ± SD or proportions.
Abbreviations: ICU, intensive care unit; FiO_2, fraction of inspired oxygen; SAPS III, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment score; PEEP, Positive end expiratory pressure.

$P < .001$) CVP (38%, $P < .001$), SVRI (47%, $P < 0.001$), LVSWI (39%, $P < .001$) and RVSWI (15%, $P = .045$), and a decrease in PVRI/SVRI ratio (35%, $P < .001$). PVRI or heart rate was not affected by the norepinephrine infusion rate/MAP level. Neither CO ($P = .075$) nor CI ($P = .079$) changed significantly comparing the highest to the lowest norepinephrine dose/MAP level. E_a increased by 36% ($P < .001$), while E_{pa} was not significantly affected by the norepinephrine/MAP level (−15%, $P = .133$). All patients were in sinus rhythm during the performance of the experimental protocol (Table 3, Figure 3A-D).

3.2 | Echocardiographic variables

At baseline (75 mmHg), the ventilator-induced variation in SV, assessed by echocardiography was 9.2 ± 4.5%. Data on RV free wall peak strain and RVEDAI are missing from one patient. Impaired RV function, was seen in 7/11 (64%) patients at baseline (75 mmHg). Highest compared to lowest norepinephrine dose/MAP level was accompanied by improved RV systolic function as reflected by a change in RV free wall peak strain from −19 ± 4 to −25 ± 5 ($P = .003$, ANOVA), a 22% increase in TAPSE ($P = .010$) and a 18% increase of tricuspid annular systolic velocity S′ ($P = .029$). RVEDAI increased significantly by 16% ($P < .001$) and SVI increased by 17% ($P = .012$). Neither CO ($P = .066$), CI ($P = .054$) nor LVEDV ($P = .070$) changed significantly at higher doses of norepinephrine/MAP levels. LV ejection fraction or LV GLS were not affected with higher doses of norepinephrine/MAP levels (Table 4, Figure 2, Figure 3A-D).

The intra-observer coefficient of variation for paired measurements of RV free wall peak strain and LV global longitudinal strain were 10% and 6%, respectively.

4 | DISCUSSION

The main findings were that RV function improved with increasing doses of norepinephrine, as assessed both by strain and conventional echocardiography. Furthermore, neither PVRI nor effective pulmonary arterial elastance (E_{pa}), a measure of the total RV afterload, was affected by norepinephrine in contrast to the pronounced increase in SVRI and systemic arterial elastance (E_a). The selective systemic vasoconstrictive effect of norepinephrine was supported by the fall in the PVR/SVR ratio. In addition, norepinephrine caused an increase in CVP and RVEDA index, strongly suggesting an increase in RV preload. This, together with a potential inotropic effect and the lack of norepinephrine-induced increase in PVR, could explain the norepinephrine-induced improvement in RV function and SVI.

It has previously been shown that the RV free wall strain in patients without cardiopulmonary disease ranges between −24% and −29 with a mean of −27 ± 2%.[19] In the present study, 64% of the patients had a RV free wall strain > −24%, with a mean of −21 ± 5% at baseline (75 mmHg), suggesting that RV function was compromised, confirming previous strain echocardiographic studies on patients with severe sepsis.[15,16]

TABLE 2 Clinical data of the nine septic shock patients

Patient	Age	Sex	Underlying disease	Infection	ICU mortality	30-d mortality
1	77	F	Ovarial carcinoma, hypertension,	Abdominal sepsis (C. Albicans)	Died	Died
2	64	M	Hypertension	Intestinal ischemia	Survived	Survived
3	69	F	Cholangiocarcinoma	Gastrointestinal perforation (*Escherichia Coli*)	Survived	Survived
4	52	M	None	Abdominal sepsis (beta-haemolytic streptococcus group A)	Survived	Survived
5	69	F	Ovarial carcinoma, hypertension	Bowel perforation (*E. Coli*, streptococcus anginosus, bacteroides fragilis)	Survived	Survived
6	63	M	Alcohol abuse	Gastrointestinal perforation (*E. Coli*)	Survived	Died
7	66	F	Hypertension, COPD	Septicemia (streptococcus aureus)	Survived	Survived
8	66	M	Oesophageal carcinoma	Mediastinitis (Enterococcus feacium, Stenotrophomonas)	Survived	Survived
9	70	M	Multiple sclerosis, hypertension, diabetes type II	Necrotising fasciitis (Bacteroides thetaiotomicron, enterococcus feacium	Survived	Died
10	51	M	Hypertension	Pneumonia (Influenza A, Coronavirus, HCU1)	Survived	Survived
11	43	M	Trauma	Septicemia (Stafylococcus aureus, Streptococcus mitis)	Survived	Survived

Abbreviations: COPD; chronic obstructive pulmonary disease

This study evaluated the direct effects of norepinephrine on RV free wall deformation by the use of speckle tracking echocardiography in patients with septic shock. Previous studies on the effects of norepinephrine on RV function in patients with septic shock are scarce. The effects of norepinephrine on systemic and pulmonary haemodynamics, as well as RV ejection fraction (RVEF), assessed by a fast-response pulmonary arterial thermodilution catheter, has previously been studied in patients with septic shock.[10,11] PVRI increased by 22%-40% when norepinephrine increased MAP from 50-55 to 75-90 mmHg. In their studies, RVEF was, however, not affected, despite this increase in RV afterload, and the authors suggested that NE improved RV function in those patients. Whether this norepinephrine-induced increase in RV performance was caused by an increase in RV coronary perfusion, an increase in RV preload or a positive β_1-receptor mediated inotropic effect, could not be assessed in their studies. Furthermore, the norepinephrine-induced increase in RV afterload could increase myocardial contractility by the Anrep effect, induced by an afterload increase.[20]

Ventricular strain is a load-dependent myocardial deformation variable, which is sensitive to changes in preload, as shown in a clinical strain echocardiographic study.[21] Furthermore, an increase in inotropic stimulation increases ventricular strain, also when preload and afterload are controlled.[22] In the present study, the NE-associated improvement in RV free wall strain was, most likely, caused by an increase in RV preload. A more or less, positive β_1-receptor-mediated inotropic effect could also contribute to the improved RV performance with norepinephrine. LV contraction may also contribute to RV ejection mediated through septal contraction.[23] Although we did not measure the degree of septal contraction in the present study, we believe it is unlikely that the improvement in RV systolic function, induced by norepinephrine, was caused by enhanced septal contraction, as norepinephrine did not induced changes in LV systolic function.

Our findings are in line with a recent study by Hamzaoui et al, evaluating the cardiac effects of norepinephrine in early human septic shock by conventional echocardiography.[24] Although their study was focused on LV function, the norepinephrine-induced increase in MAP from 56 to 80 mmHg induced significant increases in TAPSE and tricuspid lateral annulus tissue Doppler systolic velocity (*S'*), suggesting a norepinephrine-induced improvement in RV performance. Unfortunately, the authors did not provide information on pulmonary arterial pressure, PVRI, E_{pa}, RV preload, or whether or not hypovolemia was resolved in all patients.

The effects of norepinephrine on the tone of the pulmonary vasculature are complex due to the relation between the previously described α_1-mediated pulmonary vasoconstriction[25] and the

	Target mean arterial pressure			
	MAP 60 mmHg	MAP 75 mmHg	MAP 90 mmHg	ANOVA P-value
Mean arterial pressure (mmHg)	60 ± 1.2	75 ± 2.2	91 ± 2.5	NA
Systolic arterial pressure (mmHg)	95 ± 10	119 ± 13	144 ± 20	<.001
Norepinephrine (µg/kg/min) (IQR)	0.16 (0.1 - 0.4)	0.36 (0.18 - 0.59)	0.49 (0.23 - 0.69)	NA
Heart rate (beats per minute)	86 ± 12	84 ± 11	83 ± 13	.223
Cardiac output (L/min)	6.3 ± 1.8	6.6 ± 1.9	6.7 ± 2.1	.075
Cardiac index (L/min/m^2)	3.5 ± 1.1	3.7 ± 1.2	3.8 ± 1.2	.079
Stroke volume index (mL/m^2)	41 ± 13	43 ± 11	44 ± 13	.001
LVSWI (g × m/m^2)	28 ± 9	37 ± 14	59 ± 16	<.001
RVSWI (g × m/m^2)	8.0 ± 4.4	8.5 ± 4.5	9.2 ± 4.6	.045
Mean pulmonary arterial pressure (mmHg)	21 ± 4.6	23 ± 4.5	25 ± 5.0	<.001
Pulmonary capillary wedge pressure (mmHg)	10 ± 4	13 ± 4	15 ± 4	<.001
Central venous pressure (mmHg)	8 ± 3	9 ± 3	11 ± 3	<.001
PVRI (dynes × s/cm^5/m^2)	259 ± 92	241 ± 82	231 ± 79	.432
SVRI (dynes × s/cm^5/m^2)	1320 ± 465	1531 ± 429	1915 ± 625	<.001
PVRI/SVRI	0.20 ± 0.05	0.16 ± 0.05	0.13 ± 0.04	<.001
Effective arterial elastance (mmHg/mL/m^2)	2.24 ± 0.66	2.60 ± 0.62	3.04 ± 0.63	<.001
Effective pulmonary arterial elastance (mmHg/mL/m^2)	0.27 ± 0.09	0.25 ± 0.07	0.23 ± 0.08	.103

Note: Data are presented as mean ± SD.

Abbreviations: MAP, mean arterial pressure; IQR, interquartile range; NA, not applicable; LVSWI, left ventricular stroke work index; RVSWI, right ventricular stroke index work index; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

FIGURE 2 Shows four-chamber recordings of RV free wall longitudinal strain from a septic shock patient at norepinephrine-induced changes in target mean arterial pressure of 60, 75 and 90 mmHg, respectively [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 (A-D) Shows the individual data on the effects of norepinephrine-induced changes in mean arterial pressure on (A) right ventricular (RV) end-diastolic area index (RVEDAI), (B) RV free wall strain, (C) RV afterload measured as effective pulmonary arterial elastance (E_{pa}) and (D) pulmonary vascular resistance index (PVRI). Increasing doses of norepinephrine increased RV preload and improved RV systolic function (=more negative values of RV free wall strain), while E_{pa} and PVRI were not affected. Data on RV free wall peak strain and RVEDAI are missing from one patient
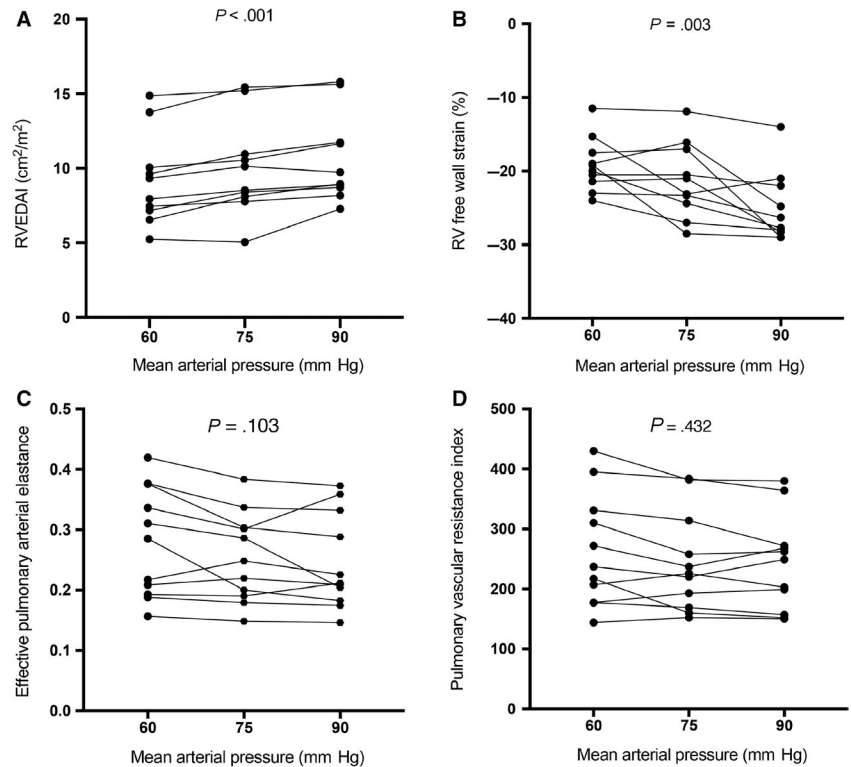

TABLE 4 Echocardiographic variables

	Target mean arterial pressure			
	MAP 60 mmHg	MAP 75 mmHg	MAP 90 mmHg	ANOVA P-value
Right ventricular free wall peak strain,%	−19 ± 4	−21 ± 5	−25 ± 5	.003
Right ventricular end-diastolic area index (cm²/m²)	9.6 ± 3.9	10.3 ± 3.8	11.1 ± 3.9	<.001
Right ventricular end-systolic area index (cm²/m²)	4.6 ± 2.9	4.4 ± 3.2	4.5 ± 3.1	.835
TAPSE (mm)	18 ± 6	21 ± 7	22 ± 7	.010
Tricuspid S'(cm/sec)	11 ± 2	12 ± 2	13 ± 3	.029
Left ventricular global longitudinal strain, %	−15 ± 3	−17 ± 3	−17 ± 3	.122
Left ventricular ejection fraction, %	58 ± 9	58 ± 10	57 ± 16	.921
LVEDV (mL)	78 ± 25	87 ± 19	89 ± 22	.070
TVI-LVOT	17.4 ± 4.8	19.0 ± 5.4	20.5 ± 5.4	.003
Cardiac output (L/min)	5.6 ± 1.3	6.0 ± 1.4	6.3 ± 1.5	.066
Cardiac index (L/min/m²)	3.0 ± 0.8	3.2 ± 0.8	3.4 ± 0.9	.054
Stroke volume index (mL/m²)	36 ± 7	39 ± 9	42 ± 9	.012

Note: Data are presented as mean ± SD.

Abbreviations: LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; Tricuspid S', peak systolic velocity of the tricuspid annulus; TVI-LVOT, time velocity integral in the LV outflow tract.

β_1-mediated pulmonary vasodilatory effect.[26,27] Previous studies on the effects of norepinephrine on the pulmonary vascular bed in norepinephrine-dependent vasodilatory shock are scarce and contradictory. Some studies have shown that increasing doses of norepinephrine induce increases in PVRI in patients with norepinephrine-dependent septic shock,[10,11,28] while more recent studies

have shown that norepinephrine does not increase PVRI in norepinephrine-dependent septic or vasodilatory shock.[29-31] The major difference between those studies are that in the latter reports, norepinephrine induced an increase in cardiac output, which might have increased the endogenous release of vascular endothelial nitric oxide (NO) by a flow-dependent increase of vascular endothelial shear stress[32] counteracting the NE-induced α_1-mediated pulmonary vasoconstrictor response.

In the present study, increasing doses of norepinephrine induced no changes in LV systolic function, as assessed either by changes in LV ejection fraction or LV GLS. In spite of the norepinephrine-induced increase in LV filling pressure, which should potentially augment the preload-sensitive LV GLS,[21] such an increase was antagonised by the simultaneous increase in LV afterload, resulting in no net effect on LV GLS.[21] Our data do not support the findings from the recent study by Hamzaoui et al[24] They showed that norepinephrine administration during early (within 3 hours) resuscitation of septic shock patients, to increase MAP from 56 to 80 mmHg, increased LV ejection fraction. They attributed this beneficial effect of norepinephrine to a restoration of a low diastolic arterial pressure, which would improve coronary perfusion and LV performance and/or a norepinephrine-induced stimulation of upregulated β_1-adrenergic receptors.

The major limitation of the present study are the small number of patients, the prolonged inclusion window and the low inclusion ratio from screened patients with a risk for indication, selection and spectrum bias. Another limitation is that the lowest MAP (60 mmHg), used in the present study, is not supported by guidelines for management of septic shock (≥65 mmHg). Another limitation is that we only studied the acute effects of NE on cardiac function and pulmonary haemodynamics and we can therefore not draw conclusions on the potential long-term effects of norepinephrine on these variables in septic shock. The strength of this study is that data on RV and LV deformation, as well as, pulmonary and systemic haemodynamics, including pulmonary vascular resistance, RV and LV arterial elastance and RV and LV preload, were simultaneously obtained from the same patient.

We conclude that in this cohort of septic shock patients, variation in norepinephrine infusion rates to achieve target MAP:s in the range of 60-75 and 90 mmHg, appears to lead to increased RV free wall peak systolic strain findings, indicating better right ventricular systolic function at the higher norepinephrine infusion rates/MAP levels. The mechanisms behind this improvement could be an increase in RV preload, caused by a norepinephrine-induced venoconstriction and increased myocardial contractility, together with a neutral effect of norepinephrine on pulmonary vascular resistance and RV afterload.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.