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Norepinephrine exerts an inotropic effect during the early phase of human septic shock

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Abstract

Background: We conducted this study to investigate whether norepinephrine increases cardiac contractility when administered during the early phase of septic shock.
Methods: We studied 38 patients with septic shock who had been resuscitated for <3 h and whose mean arterial pressure (MAP) remained <65 mm Hg. Echocardiographic variables were obtained before (T_0) and after either initiation or an increase in the dose of a norepinephrine infusion to increase MAP to ≥ 65 mm Hg (T_1). We collected left ventricular ejection fraction (LVEF), velocity-time integral of the left ventricular outflow tract (VTI), tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus (S_a) and of the lateral mitral annulus (S_m), and tricuspid annular plane systolic excursion (TAPSE).
Results: There were significant ($P<0.05$) increases from T_0 to T_1 in MAP [mean (SD): from 56 (7) to 80 (9) mm Hg], LVEF [from 49 (13) to 56 (13)%], VTI [from 18 (5) to 20 (6) cm], S_m [from 10.8 (5.1) to 12.1 (5.0) cm s^{-1}], TAPSE [from 1.8 (0.5) to 2.0 (0.5) cm], and S_a [from 13.0 (5.6) to 15.1 (6.4) cm s^{-1}]. In the subgroup of 15 patients with LVEF ≤45%, significant increases in VTI [from 16 (8) to 18 (7) cm] and in LVEF [from 36 (7) to 44 (10)%] were observed.
Conclusions: Norepinephrine administration during early resuscitation in patients with septic shock increased the cardiac systolic function despite the presumed increase in left ventricular afterload secondary to the increased arterial pressure. Whether such an effect persists over time remains to be evaluated.
Clinical trial registration: NCT02750683.

Keywords: echocardiography; left ventricular function; norepinephrine; septic shock

Norepinephrine (NE) is a potent vasopressor used in septic shock to reverse hypotension resulting from a deeply depressed arterial tone. However, there is concern over a negative effect of NE on cardiac function through an increase

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Editor's key points

- Some of the effects of norepinephrine in sepsis may be related to β_1-adrenergic effects, but few specific data are available.
- In this study of patients with septic shock, early administration of norepinephrine was associated with increased arterial pressure and echocardiographic indices of cardiac function, suggesting increased myocardial contractility.
- Possible mechanisms include increased coronary perfusion, direct myocardial β_1-adrenergic effects, or possibly, increased preload.
- Data were restricted to before and after restoration of arterial pressure, and it is not known whether these effects would persist.
- The study was not designed to evaluate continuing cardiovascular effects or clinical outcomes.

in left ventricular afterload,[1] especially when cardiac function is already impaired. Nevertheless, by restoring arterial tone NE may restore diastolic arterial pressure (DAP), hence the coronary perfusion of the left ventricle.[2] This might reduce some degree of the ischaemic myocardial dysfunction that can occur in patients with prior coronary artery disease and low DAP. In addition, NE may exert a positive effect on cardiac contractility through β_1-adrenergic stimulation.[3] Although sepsis-induced downregulation of β_1-adrenergic receptors may occur,[4 5] it may be relatively late,[6] and thus, not observed when NE is administered early. However, the effects of early administration of NE on cardiac systolic function in human septic shock have not been studied specifically.

The aim of this study, therefore, was to test the hypothesis that early administration of NE in septic shock patients with severe hypotension might enhance left ventricular systolic function.

Methods

This prospective observational study was performed between October 2014 and January 2016 in two 15-bed intensive care units. The study was approved by the institutional review board of our institution (Comité de Protection des Personnes, Paris-Ile-de-France VII). Informed patient (or next-of-kin) consent was obtained from all patients. Our study was registered in ClinicalTrials.gov (NCT02750683).

We included adult patients with septic shock who had a mean arterial pressure (MAP) <65 mm Hg (measured by an intra-arterial catheter) within the first 3 h after the start of resuscitation. In the two units, no fixed predefined fluid management protocol is used. Instead, fluid management is personalized and decided by the physician in charge and in consideration of the patient's past medical history, clinical signs, and dynamic indices of fluid responsiveness when available or results of a fluid challenge, according to the current European recommendations.[7] For every patient, early initiation of NE was decided by the physician in charge on the basis of lifethreatening hypotension even if hypovolaemia had not been totally resolved, as recommended.[8]

Before starting the study, patients could have received NE already, but the desired target value of MAP had not yet been achieved. For every patient included (time T_0), NE was either initiated or its dose increased in order to achieve the desired MAP target value ($\geq$65 mm Hg, or more in the event of a history of chronic hypertension). Time T1 was defined as the time when the desired MAP target was achieved. If a change of the associated therapy (fluid administration, ventilator settings, and other drugs) was decided by the attending physician, the patient was not included.

Data collection

Clinical information, the volume of fluids administered before inclusion, use of mechanical ventilation, the time interval between the start of resuscitation and T_0, and the time interval between T_0 and T_1 were noted.

Haemodynamic data

At T_0 and at T_1, we recorded heart rate (HR), systolic arterial pressure (SAP), DAP, MAP, and the blood lactate concentration.

Transthoracic echocardiographic data

Transthoracic echocardiographic (TTE) examination was performed at T_0 and T_1 with a 3.75 MHz probe using a CX50 Philips (Philips Healthcare, DA Best, Holland) and a Vivid i (GE Healthcare, Freiburg, Germany) machine. There was one echocardiographic operator in each intensive care unit, both of them (O.H., M.J.) physicians with a national echocardiographic diploma and $\geq$3yr training.

Patients were in supine flat or lateral supine positions depending on their respiratory tolerance. Two-, four-, and five-chamber apical views were used in order to determine the left ventricular ejection fraction (LVEF), calculated by the biplane method of disc summation (modified Simpson's rule), and the following other indices of right or left ventricular systolic function: tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus (S_a), tricuspid annular plane systolic excursion (TAPSE) measured by M-mode echocardiography, and tissue Doppler imaging of mean systolic velocity of the lateral mitral annulus (S_m). We also collected the velocity-time integral of the flow in the left ventricular outflow tract (VTI), and we calculated cardiac output (CO) by multiplying the heart rate by the stroke volume. The latter was calculated as the product of VTI by the area of the left ventricular outflow tract. We also collected the left ventricular end-diastolic area (LVEDA) from the four-chamber apical view, the peak early (*E*) and late (*A*) transmitral flow velocity, tissue Doppler imaging of the mean early diastolic velocity (E') of the lateral mitral annulus, and the ratios *E*/*A* and *E*/*E*'. All the variables were averaged over three beats, or over five beats in the event of atrial fibrillation.

We also calculated an estimate of the effective arterial elastance (E_a). The E_a is generally calculated using the following formula: 0.9 $\times$ aortic end-systolic pressure/stroke volume.[9] As we inserted the arterial catheter in the femoral artery, and given the low pulse wave amplification phenomenon between the aorta and the location of catheter's tip (normally close to the iliac artery), we made the reasonable assumption that the SAP approximated the aortic end-systolic pressure, so that the estimated E_a was calculated as 0.9 $\times$ SAP/stroke volume. We also estimated the left ventricular end-systolic elastance (E_{es}) by applying the estimation previously proposed by Robotham and colleagues:[10] estimated $E_{es}=E_a/(1/\text{LVEF})-1$.

Statistical analysis

In order to calculate the number of patients needed for our study, we estimated from the previous literature[11] that an increase of 5% in LVEF from T_0 to T_1 was clinically relevant, and taking into account an α-risk of 5% and a β-risk of 20%, at least 34 patients needed to be included.

The distribution of the data was evaluated using the Kolmogorov-Smirnov test. Data are expressed as the mean (SD) or as the median [interquartile range], as appropriate. Paired comparisons for numerical variables were performed using Student's paired t-test except for variables with a non-normal distribution (Wilcoxon test). The intra-observer and the inter-observer reproducibility was assessed in 10 randomly selected patients for LVEF, VTI, E, A, E', S_m, S_a, LVEDA, and TAPSE. Each variable was obtained twice by the same observer and the coefficient of variation calculated. The statistical analysis was performed with MedCalc 8.1.0.0 (Mariakerke, Belgium). A P-value <0.05 was considered statistically significant.

Results

All data except the dose of NE, the volume of fluids received before inclusion, and the time intervals between the start of resuscitation and T_0 and between T_0 and T_1 were normally distributed.

Patient characteristics

Thirty-eight patients with septic shock (24 males, 14 females) were included. The mean age [range] was 68 [30–91] yr; mean simplified acute physiology score (SAPS2) score at admission was 55 (20). The main patients' characteristics at T_0 are displayed in Table 1.

At T_0, 16 patients (42%) were already receiving NE, with a median dose of 0.23 [0.20–0.40] μg kg^{-1} min^{-1}. At T_1, all the patients were receiving NE, with a median dose of 0.45 [0.20–0.80] μg kg^{-1} min^{-1}. The median time elapsed between T_0 and T_1 was 97 [65–120] min. The median length of stay was 9 [4–22] days, the median duration of NE administration was 4 [3–8] days (Table 1), and the mortality rate at discharge from the intensive care unit was 38%, and at day 28 it was 39%.

Haemodynamic variables

In the whole group, all the components of arterial blood pressure increased significantly between T_0 and T_1, whereas blood lactate significantly decreased (Table 2).

Echocardiographic variables

For the LVEF, VTI, Sm, Sa, E, E', A, LVEDA and TAPSE, the intra-observer reproducibility defined as the coefficient of variation was 3.2 (3.1%), 6.6 (4.6%), 5.3 (4.4%), 5.2 (5.8%), 4.2 (3.2%), 4.2 (5.2%), 4.1 (3.8%), 3.8 (3.0%) and 4.0 (3.0%), respectively. The inter-observer reproducibility was 3.5 (2.9%), 3.2 (3.1%), 8.2 (7.1%), 7.4 (6.3%), 3.7 (2.5%), 6.2 (5.0%), 6.2 (3.1%), 3.4 (3.1%), and 8.7 (7.5%) respectively.

From T_0 to T_1, VTI, LVEF, S_m, TAPSE, S_a, E, A, and E' increased significantly (Table 3 and Fig. 1). The LVEDA and the E/A and E/E' ratios did not change.

In the subgroup of patients (n=15) with baseline LVEF <45%, from T_0 to T_1, VTI increased from 16 (6) to 18 (7) cm (P<0.05) and LVEF from 36 (7) to 44 (10%) (P<0.05), but S_m, TAPSE, and S_a did not change significantly (Table 4 and Fig. 2).

Table 1 Baseline characteristics of patients (*n*=38). SAPS2, simplified acute physiology score

Characteristics	Whole population (*n*=38)
Age [yr; mean (range)]	68 (30–91)
SAPS2 [mean (SD)]	55 (20)
Sex (female/male)	14/24
Co-morbidities [*n* (%)]	
Ischaemic heart disease	8 (21)
Hypertension	21 (55)
Diabetes	8 (21)
Source of infection [*n* (%)]	
Lung	15 (40)
Urinary tract	6 (15)
Abdomen/biliary tract	8 (21)
Other sources	9 (24)
Time elapsed between start of resuscitation and T_0 (min; median [interquartile range])	120 [90–240]
Volume of fluids administered (ml;median [interquartile range])	1500 [1000–2000]
Mechanical ventilation [*n* (%)]	22 (57)
Patients receiving norepinephrine [*n* (%)]	16 (42)
Length of stay (days; median [interquartile range])	9 [4–22]
Duration of norepinephrine administration (days; median [interquartile range])	4 [3–8]

Finally, from T_0 to T_1, the estimated E_a increased significantly from 1.30 (0.45) to 1.75 (0.72) mm Hg ml^{-1} and the estimated E_{es} increased significantly from 1.31 (0.61) to 2.31 (1.03) mm Hg ml^{-1}.

Discussion

In this study, we found that the early use of NE in patients with septic shock to target MAP values of ≥65 mm Hg improves left and right ventricle systolic function variables, increases cardiac output, and decreases blood lactate without increasing HR. The increase in LVEF and in VTI remained in the subgroup of patients with left ventricular dysfunction. To our knowledge, no previous clinical study has reported the cardiac effects of NE during the early phase of resuscitation of septic shock using TTE. This non-invasive method, which provides a detailed characterization of cardiac function,[12] is recommended to be performed as soon as possible in shock states.[7 13]

In the absence of an increase in cardiac contractility, LVEF should have decreased with NE from T_0 to T_1, because the left ventricular afterload, which is another important determinant of LVEF, probably increased with NE, as indicated by the marked increase in SAP and also suggested by the increase in the estimated E_a. Thus, the significant increase in LVEF with NE, in spite of the increased left ventricular afterload, strongly suggests that NE increased the left ventricular contractility. This is also suggested by the increase in the estimated E_{es}, although this calculated variable suffers from limitations (see below).

Norepinephrine has α- and β_1-adrenergic properties,[3] which may enhance cardiac contractility through two main mechanisms: (i) an indirect effect through the improvement of coronary perfusion via the increase in DAP (α-adrenergic

Table 2 Haemodynamic variables before (T_0) and after (T_1) initiation of norepinephrine (or increase in its dose) for the whole population (n=38). DAP, diastolic arterial pressure; HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine; SAP, systolic arterial pressure

Variable	T_0	T_1	P-value
NE dose (μg kg $^{-1}$ min^{-1}; median [25%–75% interquartile range])	0.23 [0.20–0.40]	0.40 [0.20–0.80]	<0.05
HR [beats min^{-1}; mean (SD)]	99 (20)	99 (23)	0.9
SAP [mm Hg; mean (SD)]	85 (12)	124 (15)	<0.05
DAP [mm Hg; mean (SD)]	45 (6)	60 (10)	<0.05
MAP [mm Hg; mean (SD)]	56 (7)	80 (9)	<0.05
Lactate [mmol litre^{-1}; mean (SD)]	3.2 (2.0)	2.5 (1.3)	<0.05

effect); and (ii) a direct effect on cardiomyocyte β_1-adrenergic receptors.

Firstly, NE can increase left ventricular contractility though an increase in DAP, which is the upstream pressure of coronary perfusion of the left ventricle. Our population included mostly old patients with multiple cardiovascular risk factors or with known ischaemic cardiomyopathy, or both, with a low DAP [45 (6) mm Hg] at T_0 that may have resulted in a decreased coronary perfusion. It can therefore be speculated that restoration of DAP might have contributed to restore the coronary perfusion and to improve the cardiac performance in some of our patients. Any invasive measurements of lactate concentration in the coronary sinus to assess the effect of NE on coronary perfusion more precisely were obviously unfeasible in this group of patients who primarily needed resuscitation for severe shock and life-threatening hypotension.

Secondly, NE has the potential to increase cardiac contractility owing to its β_1-adrenergic receptor stimulation.[3] Nevertheless, during sepsis, β_1-adrenergic stimulation of cyclic adenosine monophosphate may be impaired, with a resulting effect of myocardial hyporesponsiveness to catecholamines.[4 5] In this regard, dobutamine (a β_1-adrenergic agent) was shown not to increase the left ventricular end-systolic elastance in human septic shock.[14] However, in experimental sepsis, a biphasic change (an increase, then a decrease) in the density of β_1-adrenergic receptors, owing to a phenomenon called receptor internalization, was reported.[15] Similar results were found by Abi-Gerges and colleagues,[6] who reported time-dependent changes in the adenylcyclase pathway in cardiac myocytes, with an initial phase of early potentiation of the β_1-adrenergic response ('upregulation'), followed by a downregulation phase.[6] In our study, the mean time interval between the start of resuscitation and T_0 was short enough to account for a positive effect of NE on cardiac systolic function indices through β_1-adrenergic stimulation.

Table 3 Echocardiographic variables before (T_0) and after (T_1) initiation of norepinephrine (or increase in its dose) for the whole population (n=38). CO, cardiac output; peak early (E) and late (A) transmitral flow velocity; E', tissue Doppler imaging of the mean early diastolic velocity of the lateral mitral annulus; LVEDA, left ventricular end-diastolic area; LVEF, left ventricular ejection fraction; S_a, tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus; S_m, tissue Doppler imaging of mean systolic velocity of the lateral mitral annulus; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity-time integral of the flow in the left ventricular outflow tract

Variable	T_0	T_1	P-value
CO [litres min^{-1}; mean (SD)]	6.3 (2.2)	7.0 (2.7)	<0.05
LVEF [%; mean (SD)]	49 (13)	56 (13)	<0.05
VTI [cm; mean (SD)]	18 (5)	20 (6)	<0.05
E [cm s^{-1}; mean (SD)]	81 (27)	92 (27)	<0.05
A [cm s^{-1}; mean (SD)]	75 (22)	86 (27)	<0.05
E' [cm s^{-1}; mean (SD)]	10 (3)	11 (4)	<0.05
E/A [mean (SD)]	1.1 (0.4)	1.1 (0.5)	0.8
E/E' [mean (SD)]	9.0 (4.9)	9.1 (6.9)	0.15
S_m [cm s^{-1}; mean (SD)]	10.8 (4.7)	12.1 (5.0)	<0.05
TAPSE [cm; mean (SD)]	1.8 (0.5)	2.0 (0.5)	<0.05
S_a [cm s^{-1}; mean (SD)]	13.0 (5.6)	15.2 (6.4)	<0.05
LVEDA [cm^2; mean (SD)]	28.9 (5.4)	29.8 (6.5)	0.12

In our study, the mean value of LVEF at T_0 was 49%, which is quite low in such a situation of low SAP, hence of low left ventricular afterload. This suggests some impairment of left ventricular contractility. In 15 out of the 38 patients (39%), LVEF was <45%, a result that is in perfect agreement with that reported by Vieillard-Baron and colleagues,[1] who found that 40% of patients with septic shock during the first day had an LVEF <45%. Importantly, the positive effect of NE on left ventricular function remained in this subgroup of 15 patients with low LVEF, in spite of the increase in SAP. This contradicts the idea that NE exerts a deleterious effect on left ventricular function because of its increasing effect on left ventricular afterload. Our results are in agreement with those of an experimental study of septic myocardial depression in rats. In that study, NE was shown to be as effective as epinephrine (at equipressor doses) to improve LVEF and cardiac contractility (assessed using a conductance catheter), whereas phenylephrine, a pure α-adrenergic agent, did not exert such effects.[16]

We measured LVEF to assess the cardiac systolic effects of NE because it is the most widely used echocardiographic variable to assess left ventricular systolic function.[17] We also measured S_m, S_a, and TAPSE, which have been introduced more recently to assess the left and right ventricular systolic function.[18–20] Although we used different techniques (tissue Doppler imaging, time-motion etc.), all the markers of the cardiac systolic function increased in our population, reinforcing our conclusion of increased cardiac systolic function with early administration of NE.

Several limitations of our study should be acknowledged.

This was a prospective but observational study, and the clinical management of patients was done exclusively by the physicians in charge. In this regard, the MAP reached at T_1 was 80 (9) mm Hg, that is, within a wide range of values >65 mm Hg, which is probably attributable to the fact that the MAP target was adjusted in consideration of several factors,

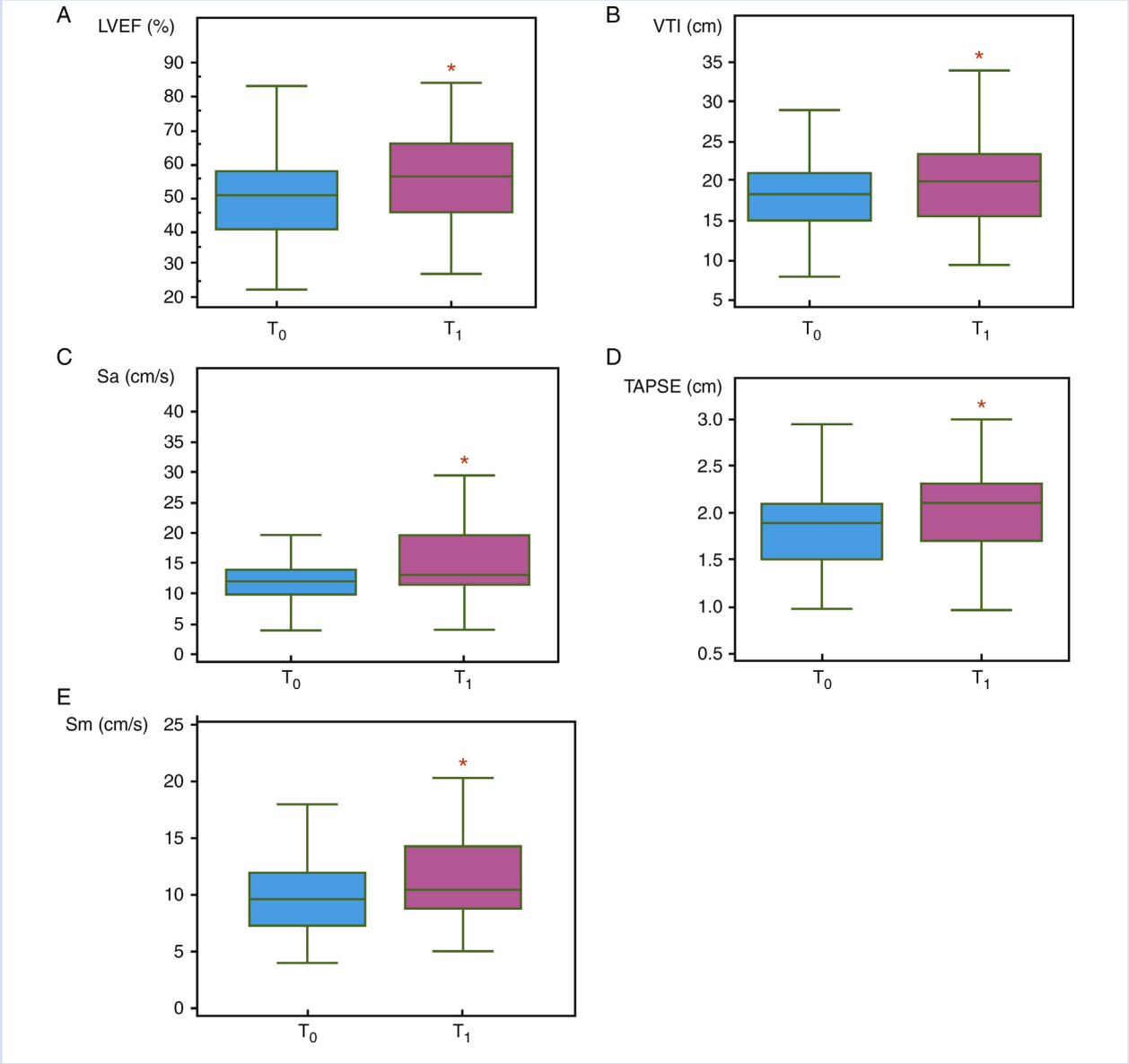

Fig 1. Box-and-whisker plots of left ventricular ejection fraction (LVEF; A), velocity-time integral of the flow of the left ventricular outflow tract (VTI; B), tissue Doppler imaging of the systolic motion of the tricuspid annulus (S_a; C), tricuspid annular plane systolic excursion (TAPSE; D), and tissue Doppler imaging of mean systolic velocity of the mitral annulus (S_m; E) before (T_0) and after (T_1) restoration of a mean arterial pressure >65 mm Hg with norepinephrine in the whole population (n=38). *P<0.05.

including a history of chronic hypertension (55% of our patients), individual clinical responses, and the presence of other cardiovascular risk factors suggestive of atherosclerosis.[21]

In spite of the presence of early left ventricular dysfunction in some patients, the physicians in charge did not administer dobutamine, considering that it was urgent first to correct the severe hypotension with NE, as is recommended in septic shock[8] and in cardiogenic shock[22] states. Obviously, our study cannot suggest that NE is superior to dobutamine to treat early sepsis-induced myocardial depression because we did not compare NE with dobutamine. It is possible that dobutamine at this stage would also have increased cardiac systolic function indices, because dobutamine is considered a more powerful β_1-adrenergic agent than NE in sepsis.[23] It should be stressed, however, that unlike NE, dobutamine has the potential to decrease DAP, and eventually, the coronary perfusion pressure owing to its vascular β_2-adrenergic properties.

We previously showed that NE increases cardiac preload and cardiac output and decreases cardiac preload dependence.[24 25] Such cardiac preload effects are assumed to be related in part to the α-adrenergically mediated decrease in systemic venous capacitance.[26 27] Our patients were included in the early phase of septic shock, even when hypovolaemia was not totally resolved, as recommended in the event of life-

Table 4 Echocardiographic variables before (T_0) and after (T_1) initiation of norepinephrine (or increase in its dose) for the subgroup of patients with LVEF <45% (n=15). Peak early (E) and late (A) transmitral flow velocity; E', tissue Doppler imaging of the mean early diastolic velocity of the lateral mitral annulus; LVEF, left ventricular ejection fraction; S_a, tissue Doppler imaging of mean systolic velocity of the lateral tricuspid annulus; S_m, tissue Doppler imaging of mean systolic velocity of the lateral mitral annulus; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity-time integral of the flow in the left ventricular outflow tract

Variable	T_0	T_1	P-value
LVEF [%; mean (SD)]	36 (7)	44 (10)	<0.05
VTI [cm; mean (SD)]	16 (6)	18 (7)	<0.05
E [cm s^{-1}; mean (SD)]	83 (30)	91 (30)	0.11
A [cm s^{-1}; mean (SD)]	73 (13)	79 (23)	0.17
E' [cm s^{-1}; mean (SD)]	9.6 (3.1)	9.9 (2.6)	0.58
E/A [mean (SD)]	1.0 (0.4)	1.2 (0.6)	0.9
E/E' [mean (SD)]	9.6 (5.3)	10.4 (6.8)	0.22
S_m [cm s^{-1}; mean (SD)]	9.2 (3.7)	9.9 (4.0)	0.11
TAPSE [cm; mean (SD)]	1.8 (0.6)	1.8 (0.5)	0.5
S_a [cm s^{-1}; mean (SD)]	10.7 (3.7)	12.3 (4.1)	0.08

threatening hypotension by the Surviving Sepsis Campaign guidelines published at the time of the patients' inclusion in the study.[8] Therefore, in spite of prior fluid administration (median value of 1500 ml), we cannot exclude some degree of preload dependence in our patients, hence an additional preload effect of NE on VTI. Obviously, such an effect cannot fully account for the increase in LVEF, which essentially depends on left ventricular afterload and contractility, and only a little on left ventricular preload.[10] Moreover, the latter effect could be significant only in the event of very low cardiac preload.[10] Even if we did not precisely assess cardiac preload in our study, the absence of a significant (P=0.12) increase in LVEDA from T_0 to T_1 is not in favour of a preload effect of NE. However, we cannot exclude the possibility that including a larger number of patients would have resulted in a significant increase in LVEDA. Furthermore, the E/E' ratio, which is assumed to estimate the left ventricular filling pressure,[28] was in the normal range at baseline and did not increase with NE. However, E/E' is not a very accurate estimate of left ventricular filling pressure when it is between 8 and 15,[29] as it was for most of our patients. We thus cannot totally exclude the possibility that NE had increased left ventricular preload, hence VTI, in preload-dependent patients. Nevertheless, such an effect was unlikely to have occurred in patients with low LVEF, who are supposed to be preload -independent.

We could not provide a precise estimation of E_{es} from echocardiographic measurements using the method of Chen and colleagues[30] recently applied to patients with septic shock by Guarracino and colleagues.[31] We only provided an estimation of E_{es} from the application of a formula previously proposed by Robotham and colleagues,[10] a formula that suffers from limitations. Among these limitations is the way to calculate E_a, which is included in the estimated E_{es} formula. For calculation of E_a, we approximated the aortic end-systolic pressure by the SAP. Such an approximation is reasonable because we measured SAP at the tip of an arterial catheter inserted in the femoral artery and thus at a location close to the aorta. Even if we could not accurately assess the left ventricular contractility, it is hard to believe that NE did not increase the left ventricular contractility because not only the estimated E_{es} increased but also, more simply, the LVEF increased despite the increase in arterial blood pressure, and presumably, in left ventricular afterload.

We did not evaluate the long-term effects of NE on cardiac function. Thus, we cannot be sure that the beneficial cardiac effects of NE observed when the desired MAP target was achieved would persist over time. Finally, the subgroup of patients with low LVEF (<45%) at T_0 is small, but the results found in this subgroup are nevertheless worth reporting, although they need to be confirmed in larger groups of patients.

In conclusion, NE administration during early resuscitation of patients with severe septic shock increased echocardiographic indices of cardiac systolic function despite the presumable increase in left ventricular afterload secondary to the increase in arterial pressure. These findings suggest that NE increased cardiac contractility during the early phase of resuscitation of human septic shock. Whether such a beneficial effect persists over time remains to be evaluated.

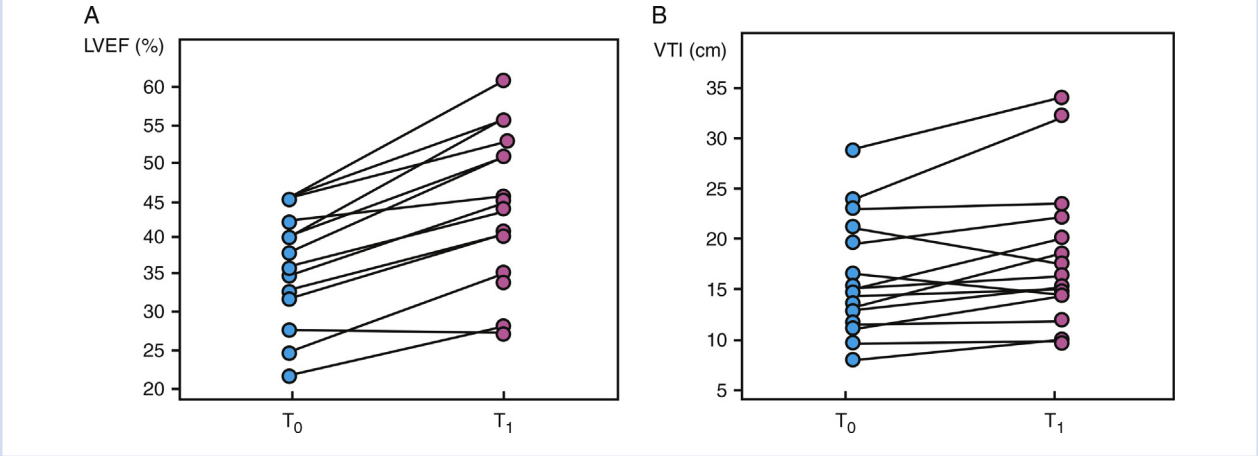

Fig 2. Individual responses of left ventricular ejection fraction (LVEF; A) and velocity-time integral of the sub-aortic flow (VTI; B) before (T_0) and after (T_1) restoration of a mean arterial pressure >65 mm Hg with norepinephrine in patients with an LVEF <45% at T_0 (n=15).

Authors' contributions

Conceived the study: O.H., C.R., J.-L.T.
Data collection: O.H., M.J., T.G., B.S., D.P., F.J., X.M., P.T.
Data analysis and interpretation: O.H., M.J., T.G., B.S., D.P., F.J., X.M., P.T., J.-L.T.
Drafted the manuscript: O.H., J.-L.T.
All authors read and approved the final manuscript.

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Declaration of interest

J.-L.T. and X.M. are members of the medical advisory board of Pulsion.

All the other authors have no conflict of interest to declare.

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