Effects of norepinephrine on mean systemic pressure and venous return in human septic shock

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Objectives: **Norepinephrine exerts venoconstriction that could increase both the mean systemic pressure and the resistance to venous return, but this has not yet been investigated in human septic shock. We examined the relative importance of both effects and the resulting effect on venous return when decreasing the dose of norepinephrine.**

Setting: **Intensive care unit.**

Patients: **Sixteen septic shock patients.**

Measurements: **For estimating the venous return curve, we constructed the regression line between the pairs of cardiac index (pulse contour analysis) and central venous pressure values. These values were measured during 15-sec end-inspiratory and end-expiratory ventilatory occlusions performed at two levels of positive end-expiratory pressure, in view of widening the range of cardiac index:central venous pressure measurements and increasing the accuracy of the regression line. The x-axis intercept of the regression line was used to estimate the mean systemic pressure and the inverse of the slope of the regression line to quantify resistance to venous return. These measurements were obtained before and after decreasing the dose of norepinephrine. Passive leg raising was performed before and after decreasing the dose of norepinephrine.**

Main Results: **Decreasing the dose of norepinephrine from 0.30 (0.10–1.40) to 0.19 (0.08–1.15) μg/kg/min decreased the mean systemic pressure from 33 ± 12 mm Hg to 26 ± 10 mm Hg ($p = .0003$). The slope of the multipoint cardiac index:central venous pressure relationship increased ($p = .02$). The resistance to venous return decreased, i.e., 1/slope decreased. Simultaneously, cardiac index decreased from 3.47 ± 0.86 L/min/m^2 to 3.28 ± 0.76 L/min/m^2 ($p = .04$), indicating a decrease in venous return. Passive leg raising increased cardiac index to a larger extent after (8% ± 4%) than before (1% ± 4%) decreasing norepinephrine ($p = .001$), suggesting an increase in unstressed blood volume at the lowest dose of norepinephrine.**

Conclusions: **In septic shock patients, decreasing the dose of norepinephrine decreased the mean systemic pressure and, to a lesser extent, the resistance to venous return. As a result, venous return decreased. (Crit Care Med 2012; 40:0–0)**

Key Words: mean systemic pressure; norepinephrine; septic shock; venous return

Acute circulatory failure during septic shock is characterized by decreased vascular tone and/or by low cardiac output. Norepinephrine exerts powerful arterial vasoconstrictive effects allowing to restore the mean arterial pressure (1). In this regard, it is the vasoconstrictive drug of choice during septic shock (2). Beyond arterial vasoconstriction, norepinephrine also induces other important hemodynamic effects. Recent studies showed that norepinephrine can also increase cardiac preload (3, 4) and cardiac output in case of preload dependence (3). In animals with endotoxinic shock, the use of catecholamines is associated with a lesser amount of delivered fluid (5). These studies hypothesized that norepinephrine increased cardiac preload by increasing the venous return. Indeed, because it could stimulate the α1-adrenergic receptors of the veins, norepinephrine could stress the walls of the venous reservoir and increase the upstream pressure of the venous return, i.e., the mean systemic pressure (3, 4). However, through venoconstriction, norepinephrine could also increase the resistance to venous return, what might counteract the effect of increased mean systemic pressure on venous return. In a porcine model of endotoxinic shock, Datta and Magder (6) elegantly demonstrated that norepinephrine increased the mean systemic pressure without modifying the resistance to the venous return, leading to an increase in venous return. Nevertheless, the respective effects of norepinephrine on mean systemic pressure and resistance to venous return have never been investigated in human septic shock.

This is what we aimed at investigating in the present study. For estimating the mean systemic pressure and the resistance to venous return, we used a method derived from that described by Maas and co-workers (7) and which takes advantage from the hemodynamic effects of heart–lung interactions (8). The novelty of this method is that it allows assessing the features of the venous return in the absence of cardiac arrest. Indeed, by recording pairs of cardiac index (CI) and central venous pressure (CVP) values during various conditions of ventilation, it allows estimating a venous return curve. We hypothesized that decreasing the dose of norepinephrine in septic shock patients would decrease the mean systemic pressure and the resistance to venous return. Based upon the observation of Datta and Magder (6), we expected a stronger effect on the mean systemic pressure than on resistance to venous return, such that decreasing the dose of norepinephrine would eventually result in a decrease in venous return.

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PATIENTS AND METHODS

Patients. This study was conducted in the 15-bed medical intensive care unit of a University Hospital. It was approved by the Institutional Review Board of our institution (Comité pour la protection des personnes Ile-de-France VII). A deferred informed consent was asked from the patient's surrogate as soon as possible. As he/she recovered consciousness, a deferred informed consent was asked from the patient. If the patient or his/her next of kin refused to consent, patient's data were not entered into analysis. All patients were suffering from a septic shock and received norepinephrine. Patients were included in the study if they met all of the following criteria:

1. Decision of the attending physician to decrease the dose of norepinephrine due to an improvement of the hemodynamic status.
2. Mechanical ventilation in the volume assist–control mode (ventilators Evita 2 or 4, Dräger, Lübeck, Germany).
3. State of consciousness allowing to perform 15-sec expiratory and inspiratory occlusions. This was assessed by the visual observation of the airway pressure curve displayed by the ventilator.
4. Hemodynamic stability for at least 30 mins, as defined by no change in the mean arterial pressure and in cardiac output of >10%.
5. Hemodynamic monitoring by a PiCCO2 device (Pulsion Medical Systems, Munich, Germany).

Patients could not participate if they were <18 yrs old or pregnant and if a passive leg raising was contraindicated (head trauma, venous compression stockings) (9).

Hemodynamics Measurements. All patients had an internal jugular vein catheter and a thermistor-tipped arterial catheter (PV2024, Pulsion Medical Systems, Munich, Germany) in the femoral artery that was connected to the PiCCO2 monitoring device for measuring CI (through transpulmonary thermodilution and pulse contour analysis). The pressure sensors connected to the arterial and venous lines were referenced to the right atrium, i.e., on the axillary line, 5 cm below the sternal angle (10), and zeroing was performed against atmospheric pressure. Airway pressure was measured at the proximal extremity of the endotracheal tube. Arterial pressure, CVP, and airway pressure were continuously computerized using the HEM 4.2 data acquisition software (Notocord, Croissy sur Seine, France). The beat-to-beat values of stroke volume derived from pulse contour analysis performed by the PiCCO2 device were computerized by using the PiCCOWin 4.0 software (Pulsion Medical Systems, Munich, Germany). These beat-to-beat values of stroke volume were then averaged over a 2-sec period, and CI was calculated over this period. Calibration of pulse contour analysis–derived estimation of stroke volume was performed by using transpulmonary thermodilution, with injection of three cold saline boluses (15 mL each) (11).

Through transpulmonary thermodilution, the PiCCO2 device also allowed measuring the global end-diastolic volume and the cardiac function index. The global end-diastolic volume is the volume of blood contained in the four cardiac cavities at end-diastole. It is considered as a marker of preload (12). The cardiac function index is an estimation of the left ventricular systolic function (13, 14).

At the beginning of the study, demographic data of each patient were collected. The most recent arterial blood gas analysis and arterial blood lactate were also collected. Finally, ventilator settings and measurements, modalities of sedation, use of renal replacement therapy, and administration of other vasoactive drugs were recorded.

Method Used for Estimating the Mean Systemic Pressure and the Resistance to Venous Return. The mean systemic pressure and the resistance to venous return were determined by constructing an estimated venous return curve through the hemodynamic effects of heart–lung interactions before and after decreasing the dose of norepinephrine. The principle of this method has been previously described (7) and was modified for the purpose of this study. According to the model described by Guyton et al (15), the venous return curve is the relationship between points with right atrial pressure as an x coordinate and venous return as a y coordinate. Under the steady state, CVP could be equated to the right atrial pressure and CI could be equated to the venous return (7). The aim of the method we used was to construct a venous return curve by obtaining a series of points with various cardiac output and CVP values. For this purpose, we simultaneously recorded CI and CVP during end-inspiratory and end-expiratory ventilatory occlusions. Indeed, end-inspiratory occlusion is supposed to decrease CI and to increase CVP while, conversely, end-expiratory occlusion is supposed to increase CI and to decrease CVP. Aiming at enlarging the range of CI and CVP values, we performed end-inspiratory and end-expiratory occlusions at a different level of positive end-expiratory pressure (PEEP). First, at PEEP = 5 cm H_2O, a 15-sec expiratory occlusion was performed followed, after the time required for stabilization of hemodynamic variables, by a 15-sec inspiratory occlusion. Then, the PEEP was increased in order to reach a plateau pressure of 30 cm H_2O (16). At this PEEP level and after stabilization of the hemodynamic variables, the 15-sec expiratory and inspiratory occlusions were repeated. A second set of these four ventilatory occlusions was repeated immediately after the first one (expiratory and inspiratory occlusions at PEEP = 5 cm H_2O and expiratory and inspiratory occlusions at plateau pressure = 30 cm H_2O).

During each occlusion, we recorded the extreme values of CI (averaged over a 2-sec period, minimal for inspiratory occlusions, maximal for expiratory occlusions) reached at the end of the 15-sec occlusions and the value of the CVP recorded in the same time. An example of the effects of the end-expiratory and end-inspiratory occlusions on CI and CVP is shown in Fig. 1. Each ventilatory occlusion allowed obtaining a couple of measurements of CVP and CI. Each pair of measurements was reported on a graph connecting the CI (y-axis) and the CVP (x-axis). From the eight pairs of measurements (CI:CVP) obtained for each dose of norepinephrine, the regression line was computed by using the least-squares method (Excel, Microsoft, Redmond, WA). This regression line could be equated to the venous return line (7). Then, the mean systemic pressure was estimated as the pressure corresponding to the x-intercept of the regression line, as described in the model proposed by Guyton et al (15). The resistance to the venous return was estimated from the inverse of the slope of the regression line.

From the value of the mean systemic pressure, it was also possible to calculate the resistance of the different parts of the vascular bed as:

- - Indexed systemic resistance = (mean arterial pressure – CVP)/CI.
- - Indexed arterial resistance = (mean arterial pressure – mean systemic pressure)/CI.
- - Indexed resistance to venous return = (mean systemic pressure – CVP)/CI (7).

An example of the regression line with the estimation of the mean systemic pressure before and after the decrease in the dose of norepinephrine is shown on Fig. 2.

Study Design. At baseline, a first set of hemodynamic measurements was performed, including arterial pressure, CVP, CI, global end-diastolic volume, and cardiac function index. The continuous monitoring of the arterial pressure, CVP, airway pressure, stroke volume, and CI was started. The effects of a passive leg raising test on the pulse contour analysis–derived CI were assessed, as previously described (17, 18).

Two sets of four ventilatory occlusions were then performed, as previously described. This allowed estimating the mean systemic pressure and the resistance to venous return at baseline dose of norepinephrine.

After performing these eight ventilator occlusions, the dose of norepinephrine was decreased, according to the objectives of the physician in charge. The hemodynamic variables were allowed to stabilize, as assessed by the absence of variation of mean arterial pressure by >10% over a 30-min period. Transpulmonary thermodilution was repeated. Afterwards, another series of the eight ventilatory occlusions was repeated at a decreased dose of norepinephrine to estimate the mean systemic pressure and the resistance to venous return. All other treatments were kept unchanged during the decrease in norepinephrine dose.

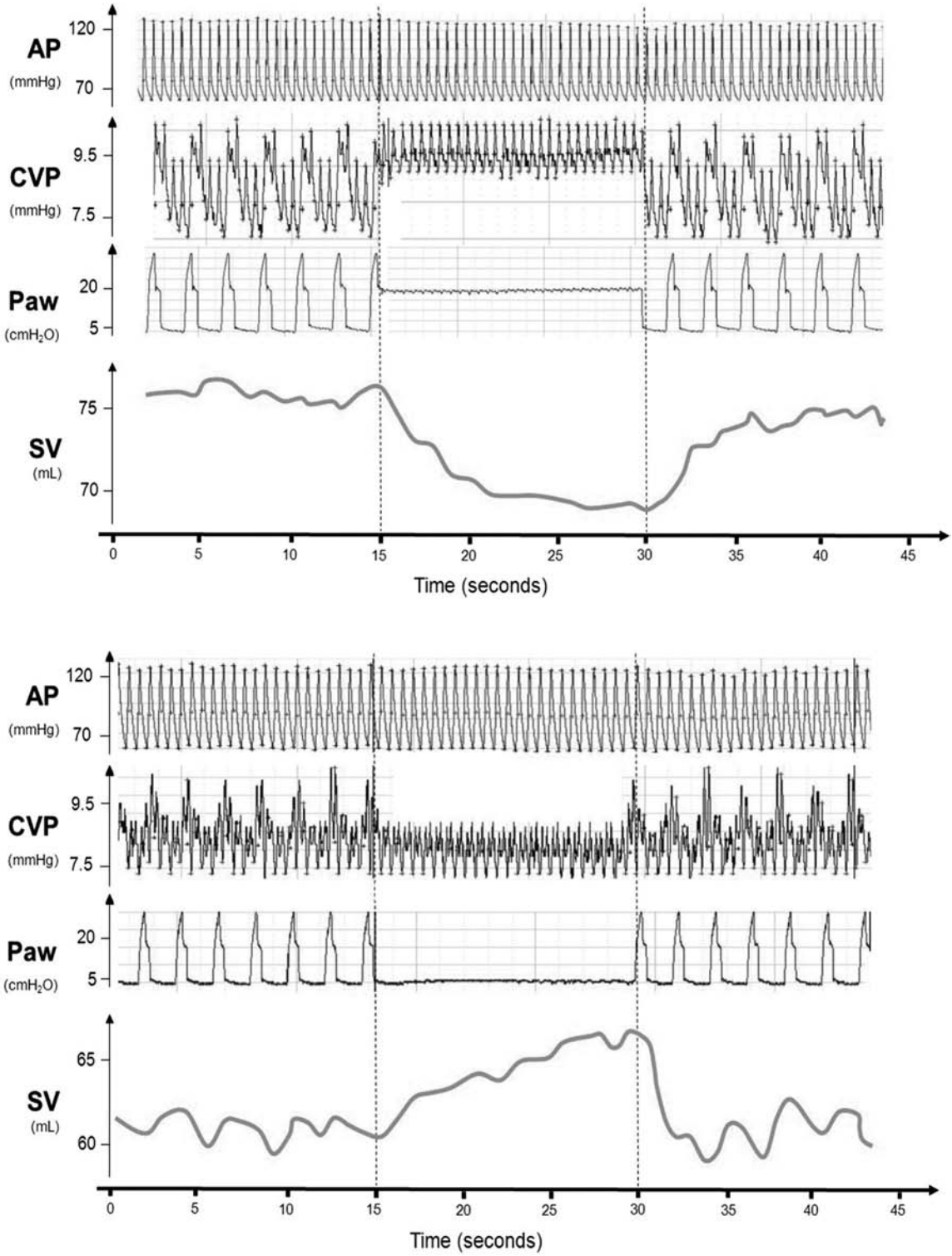

Figure 1. Example of the hemodynamic changes observed during an inspiratory occlusion (*top*) and an expiratory occlusion (*bottom*). *AP*, arterial pressure; *CVP*, central venous pressure; *Paw*, airway pressure; *SV*, stroke volume.

Data Analysis. Data are expressed as mean ± SD, median [interquartile range], or frequency (n, %), as appropriate. All quantitative data were normally distributed except for lactate, the ratio of arterial oxygen tension over oxygen inspired fraction, PEEP and the plateau pressure, the dose of norepinephrine, the resistance to venous return, and the inverse of the slope of venous return (Anderson–Darling tests). The statistical comparisons between the two times of the study were performed using a paired Student's t test or a Wilcoxon test, as appropriate. Statistical significance was defined by a $p < .05$. The statistical analysis was performed using MedCalc 11.6.0 software (MedCalc, Mariakerke, Belgium).

RESULTS

Patients. Sixteen patients were included in the study between January and

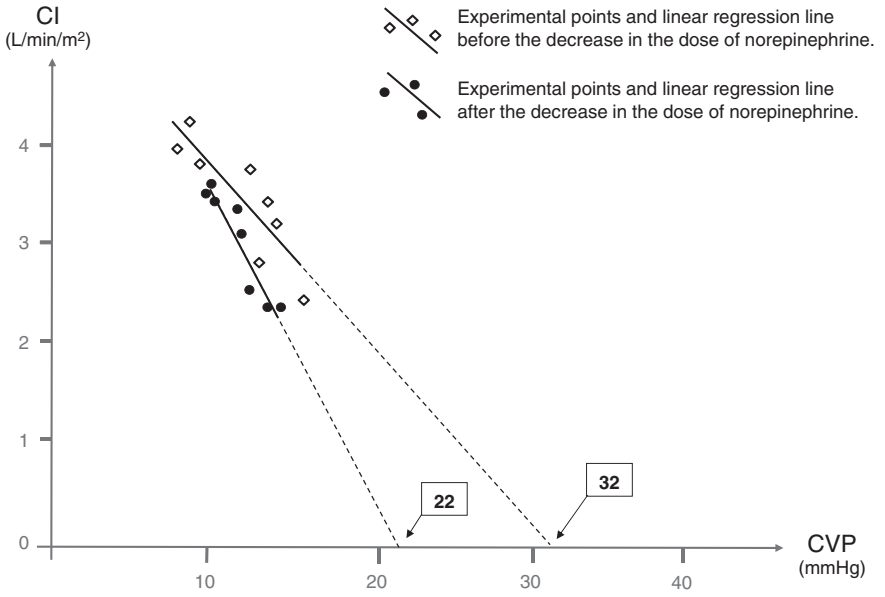

Figure 2. Example of the estimation of the venous return curves in a patient in whom norepinephrine was decreased from 1.5 to 0.7 μg/kg/min. The extrapolation of the regression lines to the x-axis allowed estimating the mean systemic pressures. *CI*, cardiac index; *CVP*, central venous pressure.

September 2011. Their characteristics at baseline are listed in Table 1. No patient received another catecholamine than norepinephrine. Six patients (37%) were known as hypertensive before inclusion. All patients received sedation, and six received neuromuscular blocking agents. For six patients (37%), continuous veno-venous hemofiltration was in progress during the measurements. The mortality rate at day 28 was 62%.

Among the 233 patients who were hospitalized for septic shock in our unit over this period of time and in whom the dose of norepinephrine was decreased, 217 were excluded (35% because investigators were not available at that time, 34% because the degree of consciousness did not allow to perform the inspiratory and expiratory holds, 17% because of the absence of sufficient hemodynamic stability, and 14% because cardiac output was not monitored).

Hemodynamic Effects of the Ventilatory Occlusions on CVP and CI. The values of CI and CVP obtained during the different occlusions are listed in Table 2. The minimal values of CVP were obtained during the expiratory pause at a PEEP of 5 cm H_2O, both before and after the decrease in the dose of norepinephrine. The maximal values of CVP were obtained during the inspiratory pause at a plateau pressure of 30 cm H_2O, both before and after the decrease in the dose of norepinephrine. The difference between the maximal and minimal values of CVP was 4 mm ± 2 mm Hg at baseline and 4 mm ± 2 mm Hg after the decrease in the dose of norepinephrine (Table 2).

The maximal values of CI were obtained during the expiratory occlusion at a PEEP of 5 cm H_2O, both before and after the decrease in the dose of norepinephrine. The minimal values were obtained during the inspiratory occlusion at a plateau pressure of 30 cm H_2O, both before and after the decrease in the dose of norepinephrine (Table 2). The average ± SD difference between the maximal and minimal values of CI was 0.85 L/min/m² ± 0.47 L/min/m² at baseline and 0.90 L/min/m² ± 0.43 L/min/m² after the decrease in the dose of norepinephrine (Table 2). The minimal changes in cardiac index we observed (i.e., between the value during inspiratory pause at PEEP = 5 cm H_2O and the value during expiratory pause at PEEP = 5 cm H_2O) were 12% ± 9% before and 15% ± 9% after the norepinephrine dose.

There was a significant linear relationship between CI and CVP in every patient at baseline and after norepinephrine decrease (each $p < .05$) as shown by the mean ± SD coefficient of determination of the regression lines of 0.70 ± 0.15 before and 0.72 ± 0.12 after decreasing the dose of norepinephrine. A typical example is given in Fig. 2.

Hemodynamic Effects of the Decrease in the Dose of Norepinephrine. The dose of norepinephrine was significantly decreased from 0.30 [0.10–1.40] to 0.19 [0.08–1.15] μg/kg/min. The modifications of the hemodynamic variables induced by this intervention are listed in Table 3. A mean time of 45 mins ± 12 mins elapsed between the decrease in the dose of norepinephrine and the second set of measurements. Mean arterial pressure decreased by 15% ± 8%. Heart rate was not significantly modified. CI decreased from 3.47 ± 0.86 L/min/m² to 3.28 ± 0.76 L/min/m². The increase in CI induced by the passive leg raising maneuver performed after the decrease in the dose of norepinephrine was larger than that observed before decreasing the dose of norepinephrine (+8% ± 4% vs. +1% ± 4%, respectively) (Table 3).

After the decrease in the dose of norepinephrine, the estimated mean systemic pressure decreased from 33 ± 12 mm Hg to 26 ± 10 mm Hg (Table 3, Fig. 3). Simultaneously, the inverse of the slope of the venous return curve decreased from 6.2 (interquartile range 4.4–8.0) to 5.0 (3.6–6.5) mm Hg·min·m²/L ($p = .01$) (Table 3). Finally, the venous return resistance (from 6.5 [4.4–8.2] to 5.2 [3.7–7.1] mm Hg·min·m²/L), arterial resistance, and systemic resistance decreased (Table 3).

Table 1. Patients characteristics at baseline

Age (yrs)	67 ± 16
Male gender (n, %)	8 (50%)
Simplified Acute Physiologic Score II	65 ± 21
Lactate (mmol/L)	2.0 [1.3–3.6]
Pao_2/FIo_2 (mm Hg)	174 [160–189]
Tidal volume (mL/kg)	7.1 ± 1.2
Respiratory rate (/min)	26 ± 7
PEEP (cm H_2O)	8 [5–10]
Plateau pressure at PEEP = 5 cm H_2O (cm H_2O)	21 [19–23]
PEEP for obtaining plateau pressure = 30 cm H_2O (cm H_2O)	15 [9–15]
Compliance of the respiratory system (mL/cm H_2O)	31 ± 10

PEEP, positive end-expiratory pressure.
Data are expressed as mean ± SD, median [interquartile range], or frequency (%); n = 16.

Table 2. Values of central venous pressure and cardiac index recorded during the ventilatory occlusions at different positive end-expiratory pressure levels before and after the decrease in the dose of norepinephrine

	Expiratory Occlusion With Positive End-Expiratory Pressure = 5 cm H_2O	Inspiratory Occlusion With Positive End-Expiratory Pressure = 5 cm H_2O	*p* (Inspiratory vs. Expiratory)	Expiratory Occlusion With Plateau Pressure = 30 cm H_2O	Inspiratory Occlusion With Plateau Pressure = 30 cm H_2O	*p* (Inspiratory vs. Expiratory)
Central venous pressure (mm Hg)						
Before decreasing the norepinephrine dose	9 ± 4	11 ± 5	**<.001**	10 ± 4	13 ± 5	**<.001**
After decreasing the norepinephrine dose	7 ± 4	9 ± 4	**<.001**	9 ± 4	11 ± 4	**<.001**
p (after vs. before)	**.03**	**.002**		**.03**	**.02**	
Cardiac index (L/min/m²)						
Before decreasing the norepinephrine dose	3.60 ± 0.87	3.17 ± 0.95	**<.001**	3.44 ± 0.81	2.74 ± 0.92	**<.001**
After decreasing the norepinephrine dose	3.42 ± 0.77	2.91 ± 0.86	**<.001**	3.22 ± 0.68	2.52 ± 0.74	**<.001**
p (after vs. before)	**.05**	**.02**		**.01**	**.04**	

Data are expressed as mean ± SD; n = 16. *p* values in bold <.05.

DISCUSSION

This study shows that decreasing norepinephrine in septic shock patients modifies both the upstream pressure of the venous return and the resistance to venous return. Indeed, the decrease in the dose of norepinephrine decreased the estimated mean systemic pressure and decreased the resistance to venous return to a lesser extent. As a result, the venous return decreased.

Hemodynamic Effects of Norepinephrine. Norepinephrine is the first-line vasopressor that is generally used in septic shock (2). By stimulating the α1-adrenergic receptors of peripheral arteries, it exerts a potent arterial vasoconstriction. This allows a rapid restoration of arterial pressure (19) and might increase the coronary blood flow (20). Norepinephrine might also exert an inotropic effect through β1- and, to a lesser extent, α1-adrenergic stimulation (21). The effects of norepinephrine on the venous compartment have been less explored. In the present study, decreasing the dose of norepinephrine was associated with a decrease in cardiac preload as assessed by a decrease in global end-diastolic volume and in CVP. These results are in line with those of two recent studies of our group showing that norepinephrine may increase cardiac preload (3, 4). This was confirmed in the present study in which we observed that decreasing norepinephrine decreased the global end-diastolic volume. However, our previous studies did not directly investigate the physiologic determinants of venous return, namely the mean systemic pressure and the resistance to venous return.

Effects of Norepinephrine on the Mean Systemic Pressure. The present study suggests that norepinephrine exerts some potent effect on the mean systemic pressure, which is the upstream pressure of the venous return (15). Indeed, we observed that decreasing the dose of norepinephrine induced a significant leftward shift of the relationship between CVP and CI, suggesting a decrease of estimated mean systemic pressure. This result is consistent with the few animal studies conducted on this topic (6, 22). The effect of decreasing the dose of norepinephrine on mean systemic pressure can easily be explained by a decrease in the α1-adrenergic venous stimulation. The venous system is made of compliant and thin-walled vessels that represent a physiologic reservoir that can be recruited by sympathetic stimulation. Indeed, the α1-adrenergic stimulation increases the stress against the vessel walls and thus increases the intravascular pressure. Through this mechanism, norepinephrine increases the stressed blood volume and decreases the unstressed volume, that is to say the blood volume participating to the venous return (23). This effect of norepinephrine on the stressed blood volume has been described in previous animal studies showing a decrease in venous capacitance (24, 25).

Table 3. Evolution of hemodynamic variables before and after the decrease in the dose of norepinephrine

	Before	After	*p*
Dose of norepinephrine (μg/kg/min)	0.30 [0.10–1.40]	0.19 [0.08–1.15]	**<.0001**
Heart rate (beats/min)	90 ± 21	89 ± 18	.352
Central venous pressure (mm Hg)	9 ± 5	8 ± 5	**.023**
Mean arterial pressure (mm Hg)	91 ± 9	77 ± 7	**<.0001**
Cardiac index (L/min/m²)	3.47 ± 0.86	3.28 ± 0.76	**.045**
Cardiac index variation during a passive leg raising test (%)	1 ± 4	8 ± 4	**.001**
Mean systemic pressure (mm Hg)	33 ± 12	26 ± 10	**.0003**
Inverse of the slope of the venous return curve (mm Hg·min·m²/L)	6.2 [4.4–8.0]	5.0 [3.6–6.5]	**.01**
Resistance to venous return (mm Hg·min·m²/L)	6.5 [4.4–8.2]	5.2 [3.7–7.1]	**.01**
Arterial resistance (mm Hg·min·m²/L)	18.3 [14.9–22.2]	16.4 [12.1–19.7]	**.048**
Systemic resistance (mm Hg·min·m²/L)	25.3 [17.8–27.4]	21.0 [19.4–24.5]	**.001**
Global end-diastolic volume index (mL/m²)	819 ± 204	774 ± 171	**.032**
Cardiac function index (/min)	4.7 ± 1.6	4.7 ± 1.6	.481

Data are expressed as mean ± SD or median [interquartile range]; n = 16. Heart rate, central venous pressure, mean arterial pressure, and cardiac index were averaged over 12 secs during normal ventilation.

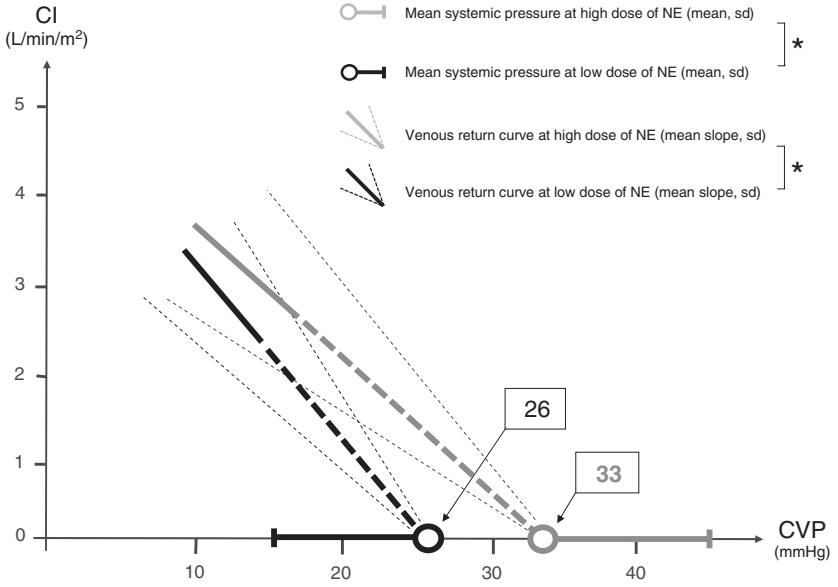

Figure 3. Changes in the mean systemic pressure and in the slope of the venous return curve induced by the decrease in the dose of norepinephrine (*NE*). *CI*, cardiac index; *CVP*, central venous pressure. *$p < .05$

The passive leg raising test mobilizes part of the unstressed venous blood volume and transfers it toward the cardiac cavities. The fact that CI increased more during passive leg raising at the lower dose of norepinephrine provides an additional argument for an increase in the unstressed blood volume. This is also in keeping with a previous study showing that increasing the dose of norepinephrine decreased the effects of passive leg raising on CI (3).

Effects of Norepinephrine on the Resistance to Venous Return. Our results suggest a decreased resistance to venous return when one decreases the dose of norepinephrine in septic shock patients. Indeed, we observed a significant decrease in the resistance to venous return estimated by two different ways: the inverse of the slope of the venous return curve (multipoint CI:CVP relationship) and the single-point resistance to venous return = (mean systemic pressure – CVP)/CI (Table 3). The effects of norepinephrine on the resistance to venous return have not been that much described. In pigs, Datta and Magder (6) demonstrated that norepinephrine does not change the resistance to venous return while it increases the mean systemic pressure. In a canine model, Imai and colleagues (26) showed that norepinephrine decreases the resistance to venous return, and the authors explained this result by the β-adrenergic effect of norepinephrine. Species differences concerning the distribution of α and β adrenergic receptors could explain these conflicting results.

In turn, we observed that the decrease in the dose of norepinephrine induced a decrease in cardiac output, i.e., venous return. This suggests that the decrease in resistance to venous return was exceeded by the decrease in the mean systemic pressure, such that the venous return decreased.

Estimation of the Mean Systemic Pressure. The method we used for estimating the mean systemic pressure was derived from that described in the pioneer study of Maas and co-workers (7) and in the subsequent publications of the same team (27, 28). The strength of this method is that it allows estimating the mean systemic pressure in human beings by simply using the cardiopulmonary interactions and, importantly, in the absence of cardiac arrest. This renders this method particularly attractive for exploring the venous return features in critically ill patients. For inducing simultaneous changes in CVP and CI, we used both inspiratory (7, 27, 28) and expiratory ventilatory occlusions. This allowed widening the range of the induced changes in CVP and CI in an attempt to improve the precision for constructing the regression line. As a result, the minimal changes in CI we measured (between inspiratory and expiratory occlusions at PEEP = 5 cm H_2O) were far above the precision of pulse contour analysis for measuring CI (29, 30). In this regard, the relationship between CI and CVP in every patient before and after norepinephrine decrease was significant (each $p < .05$) and tight. This supports the use of a linear model for studying the CI vs. CVP relationship, as previously hypothesized (7) and as performed here.

It should be noted that our method, as well that used by Maas et al (7), only *estimates* mean systemic pressure and does not directly measure it. This estimation is based on the extrapolation of the venous return curve to the x-axis, assuming that the relationship between venous return and CVP is linear in its extrapolated portion. Nevertheless, there are no physiological arguments to suggest that it should not be true (15).

The range of mean systemic pressures we observed in our patients was in the same range than reported in human studies (7, 31, 32) but higher than observed in previous animal studies (6, 22, 28, 33–35). This might be related to difference in the hemodynamic status during the measurement and, more importantly, to species difference. Supporting the latter hypothesis, Maas and co-workers reported significantly lower values of mean systemic pressure in piglets than in cardiac surgery patients while they used the same method to assess it. The values of estimated mean systemic pressure we found were slightly higher than the values reported by Maas and co-workers in their cardiac surgery patients (29 mm Hg) (28). This could be explained by the fact that our patients received higher doses of norepinephrine than these of Maas et al. In addition, it is likely that our stabilized septic shock patients had received higher amounts of fluids than in the latter study (28).

Our results could also be read in light of another theory than that of Guyton. Some authors previously suggested that norepinephrine could exert various venoconstrictive effects depending on the territory (36, 37). In this regard, one could hypothesize that decreasing the dose of norepinephrine electively relieved venoconstriction of the lower limbs, leading to a relative decrease in the intrathoracic blood volume. However, we did not measure the volume of blood contained into the different body venous compartments, and this prevents a critical evaluation of this alternative hypothesis for interpreting our results.

Other Hemodynamic Effects of Norepinephrine. In the present study, decreasing the dose of norepinephrine decreased arterial pressure. The cardiac function

index, a surrogate of left ventricular ejection fraction (14), did not change. Given the physiological relationship between left ventricular ejection fraction and left ventricular afterload (38), the fact that the cardiac function index did not change while systolic arterial pressure decreased suggests that decreasing the dose of norepinephrine decreased the left ventricular contractility.

Limitations and Implications. The main limitation of the present study is related to the characteristics of the studied population, namely a population of already resuscitated patients. We wanted to focus on the disease where norepinephrine is mostly prescribed along with fluid therapy, i.e., septic shock. Therefore, one cannot be certain that the effects we observed could be extrapolated to other clinical circumstances. For instance, one can suppose that in patients with deep hypovolemia, the venous capacitance would have been already lowered by hypovolemia. Similarly during cardiogenic shock, the venous capacitance is likely reduced by the endogenous adrenergic stimulation. In such circumstances, one could hypothesize that norepinephrine would have a very small effect on the venous capacitance and would increase the resistance to venous return to a larger extent, eventually leading to a decrease in venous return. However, the results of a previous study conducted in patients with deep hypotension and in whom norepinephrine was increased do not argue in favor of this hypothesis (3). Because of the duration of the experimental protocol, we preferred to include hemodynamically stable patients and thus to study the changes induced by a decrease in the dose of norepinephrine. Indeed, the relatively long time required for recording the data and for stabilization of hemodynamic variables after the change in norepinephrine dose would have exposed our patients to an obvious risk of prolonged hypotension. Nevertheless, the lack of a group of patients in whom the dose of norepinephrine was increased, as a control group, is a limitation of the present study.

Even though we studied the effects of a decrease of the dose of norepinephrine, the study provides indirect arguments supporting the view that introducing or increasing the dose of norepinephrine would induce an increase in mean systemic pressure. Similarly, introducing or increasing norepinephrine could increase the resistance to venous return but to a lower extent than it increases the mean systemic pressure. As a consequence, the introduction or the increase in the doses of norepinephrine would increase venous return and cardiac output. This hypothesis deserves further studies.

In conclusion, in septic shock patients, decreasing norepinephrine exerts some significant effect on the different components of systemic venous return. In our study, the decrease in the dose of norepinephrine was responsible for a decrease in venous return due to the decrease in mean systemic pressure which was more pronounced than the concomitant decrease in resistance to venous return.

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