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Chapter 10

Cardiac output response to norepinephrine in postoperative cardiac surgery patients: interpretation with venous return and cardiac function curves

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Abstract

Norepinephrine can either increase or decrease cardiac output, but the determinants have not been studied in ICU patients. The aim of the study was to explain these effects with the use of Guytonian venous return and cardiac function curves. In sixteen mechanically ventilated postoperative cardiac surgery patients inspiratory holds were performed at baseline-1, during increased norepinephrine infusion and baseline-2 conditions. We determined mean arterial pressure, central venous pressure, cardiac output, stroke volume variation and mean systemic filling pressure, resistance for venous return and systemic vascular resistance. Increasing norepinephrine by $0.04 \pm 0.02 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ increased mean arterial pressure 20 mmHg in all patients. Cardiac output decreased in 10 and increased in 6 patients. In all patients mean systemic filling pressure, systemic vascular resistance and resistance for venous return increased and stroke volume variation decreased. Resistance to venous return and systemic vascular resistance increased more ($p = 0.019$ and $p = 0.002$) in the patients with a cardiac output decrease. Heart rate decreased in the patients with a decline in cardiac output and was unchanged in the patients with a cardiac output increase. Baseline stroke volume variation was higher in those in whom cardiac output increased (14.4 ± 4.2 versus $9.1 \pm 2.4\%$, $p = 0.012$). Stroke volume variation $> 8.7\%$ predicted the increase in cardiac output to norepinephrine (ROC AUC 0.900). In conclusion, the change in cardiac output induced by norepinephrine is determined by the balance between volume recruitment (as determined by mean systemic filling pressure) and change in resistance for venous return and baseline heart function. Furthermore, the response of cardiac output on norepinephrine can be predicted by baseline stroke volume variation.

Introduction

Norepinephrine (NE) is the vasopressor of choice in septic shock¹ because of its ability to maintain vasomotor tone, but it is also recommended as treatment for resistant cardiogenic shock.^{2,3} However, the effect of NE on cardiac output (CO) is highly variable. Both increases and decreases in CO can be seen in response to NE in patients with both septic shock⁴⁻¹⁰ and without.^{11,12} Cardiovascular mechanisms used to explain these effects include increases in cardiac contractility, cardiac preload, coronary perfusion and afterload^{5,13,14} as recently described in humans with septic shock.¹⁰

Central to these arguments is that changes in effective circulating blood and venous return occur independent of changes in contractility. Potentially, the final CO change in response to NE must be determined by the balance between the increased preload effects of increasing peripheral vasomotor tone versus the increased afterload effect of increasing mean arterial pressure (Pa). Furthermore, the resistance to venous return (Rvr) may also be increased by NE owing to venoconstriction. But until now no studies have been done in humans that describe the effects of NE based on effective circulating blood volume (by measurements of mean systemic filling pressure (Pmsf)), Rvr, total systemic resistance (Rsys), and the intersection of venous return and cardiac function curves. Recently, we showed that it is possible to measure Pmsf and Rvr at the bedside in intensive care patients.¹⁵ Furthermore, using the same measurement techniques, we described the hemodynamic effects of dobutamine in piglets.¹⁶

The aim of the study was to determine the effects of NE on the determinants of the CO change and to explain these effects with the use of Guytonian venous return and cardiac function curves. We hypothesized that NE could increase CO by increasing effective circulating volume by recruitment from venous capacitance vessels (increase in Pmsf) or decrease CO by either an increase in venous resistance decreasing venous return or an increase in left ventricular afterload (increase in Rsys).

Materials and methods

Patients. The study was approved by the hospital ethics committee of Leiden University Medical Center and was carried out in Leiden. The Institutional Review Board of University of Pittsburgh approved review and analysis of the data. We included 16 patients planned for elective coronary artery bypass surgery or mitral valvuloplasty. All patients signed informed consent on the day before surgery. Patients with previous myocardial infarction, left ventricular ejection fraction < 45%, aortic insufficiency, aortic aneurysm or extensive peripheral arterial occlusive disease were not considered for the study. The protocol was started during the first postoperative hour after admission to the ICU. Sedation was maintained with propofol (3.2 mg·kg⁻¹·h⁻¹) and sufentanil (0.17 µg·kg⁻¹·h⁻¹). The patients were mechanically ventilated in airway pressure release ventilation mode (Evita 4, Dräger AG, Lübeck, Germany) adjusted to achieve normocapnia (arterial pCO₂ between 40 and 45 mmHg) with tidal volumes of 7.3 ± 1.3

ml·kg⁻¹, a respiratory rate of 12·min⁻¹ and 5 cmH₂O positive end-expiratory pressure. All patients were in sinus rhythm. Hemodynamic stability was achieved using fluids (60 ml·hour⁻¹) and catecholamines. During the study interval, no changes were made in vasoactive drug therapy, except for the protocolized increase in NE dosage, and all patients were hemodynamically stable. Every patient experienced full recovery from anesthesia within 8 hours after surgery and was discharged from intensive care unit on the first postoperative day.

Physiological monitoring. Pa was measured with a radial artery catheter and central venous pressure (Pcv) was measured with a venous catheter inserted in the right internal jugular vein. Both catheters were connected to a pressure transducer (PX600F, Edwards Lifesciences, Irvine, California, USA). Zero levels of blood pressures were referenced to the intersection of the anterior axillary line and the fifth intercostal space. Airway pressure was measured at the proximal end of the endotracheal tube with an air-filled catheter connected to a transducer, balanced at zero level against ambient air. Beat-to-beat CO, stroke volume and stroke volume variation (SVV) were obtained by Modelflow pulse contour analysis (Modelflow, FMS, Amsterdam, The Netherlands) as previously described and validated by us.¹⁷⁻²⁰ Modelflow was calibrated with the averaged result of three measurements with the bolus lithium indicator dilution method (LiDCO Ltd, Cambridge, UK) at the beginning of the protocol. For the lithium dilution method an injection of lithium chloride (0.3 mmol) is given in the central venous catheter, and the resulting arterial lithium-time curve is recorded by withdrawing blood past a lithium sensor attached to the patient's radial artery line. Pressures were recorded online using a data acquisition program on a personal computer.

Determination of Pmsf. Previously we described the bedside determination of Pmsf in detail.¹⁵ Summarizing, we measured steady-state Pa, Pcv and CO over the final 3 seconds for a set of four inspiratory holds of 12 seconds at airway plateau pressures of 5, 15, 25 and 35 cm H₂O. The inspiratory hold maneuvers were separated by 1-minute intervals to reestablish the initial hemodynamic steady state. During these inspiratory holds, when airway pressure increased, Pcv increased concomitantly, whereas CO and Pa decreased with a delay of three to four beats resulting in a plateau between 7 and 12 seconds after start of the inflation. Next, a venous return curve was constructed by plotting the values of the four pairs of Pcv and CO against each other. Pmsf was defined as the Pcv after fitting a linear line through these data points and extrapolating CO to zero (figure 10.1).

Protocol. After stabilization of the patient in the intensive care unit, series of baseline-1 measurements were done of Pa, Pcv, CO and Pmsf. Next, continuous NE infusion rate was increased to induce a 20 mmHg increase in Pa and after 15 minutes the series of measurements were repeated. The observation period ended with baseline-2

measurements 15 minutes after returning to a NE infusion rate equal to baseline-1 condition.

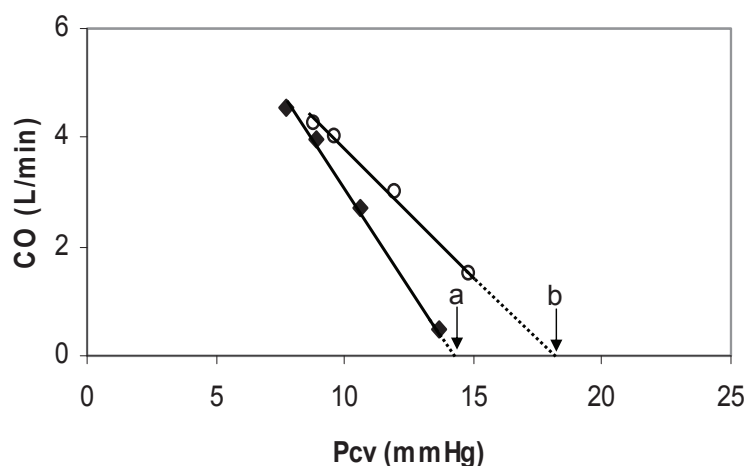


Figure 10.1 Example of a venous return curve

Venous return curve plotted for 1 patient after 4 inspiratory hold maneuvers. At increasing values of airway pressure, central venous pressure (Pcv) increases and cardiac output (CO) decreases. Mean systemic filling pressure (Pmsf) is the value of Pcv, when cardiac output is extrapolated to zero (marked with an arrow). Measurements were performed during baseline conditions (closed diamonds, straight line, Pmsf indicated by a) and after norepinephrine dosage increase (open circles, dotted line, Pmsf indicated by b).

Data analysis and statistics. The venous return data (Pcv versus CO) were fitted using a least-squares method. The extrapolation of the regression line to zero CO determines Pmsf. Total vascular systemic resistance was calculated as the ratio of the pressure difference between Pa and Pcv and CO ($R_{\text{sys}} = (P_a - P_{\text{cv}})/\text{CO}$). The resistance downstream of Pmsf was taken to reflect resistance for venous return and calculated as the ratio of the pressure difference between Pmsf and Pcv and CO ($R_{\text{vr}} = (P_{\text{msf}} - P_{\text{cv}})/\text{CO}$). The pressure gradient for venous return (Pvr) was defined as the pressure difference between Pmsf and Pcv. After confirming a normal distribution of data with the Kolmogorov-Smirnov test, differences in parameters during baseline condition (mean of baseline-1 and baseline-2) and the condition with increased NE infusion rate were analyzed using paired t-tests. SVV as predictor of the NE-induced change in CO was analyzed using a receiver operating characteristic curve. The precision of the receiver operating characteristic analysis for the area under the curve, sensitivity, specificity and cut-off values are reported as 95% confidence intervals. All values are given as mean \pm SD. A p-value < 0.05 was considered statistically significant.

Results

Sixteen patients were included in the study with a mean age of 64 ± 11 years, mean weight 90 ± 17 kg, and mean length 176 ± 8 cm. All patients underwent coronary artery bypass surgery, except one patient who had a mitral valvuloplasty. All patients had low dosages of NE ($0.04 \pm 0.03 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) at baseline. Except for dobutamine

which was given to one patient in low dosage ($1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), no other vasoactive medication was given.

Table 10.1 shows the pooled results of baseline measurements before (baseline-1), during increased NE infusion rate and after return to original NE dose (baseline-2). There were no significant differences in hemodynamic values between baseline-1 and baseline-2. An average increase in NE dosage of $0.04 \pm 0.02 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ induced an increase of Pa with $19.7 \pm 8.7 \text{ mmHg}$. Increasing NE resulted in a decrease in CO in 10 patients and an increase in CO in 6 patients (table 10.1). In the patients with a CO decrease, NE was increased from 0.04 ± 0.04 to $0.09 \pm 0.06 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; in the patients with a CO increase, NE was increased from 0.04 ± 0.04 to $0.08 \pm 0.02 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The dose of NE during baseline conditions as well as the dose during NE increase did not differ between both groups. The 10 patients that decreased CO on NE had a significantly higher rise in Pcv, Rsys and Rvr during NE (p-values 0.042, 0.002 and 0.019 respectively) compared to the 6 patients that increased CO on NE. Furthermore, these 10 patients had a decline in HR ($p = 0.002$) and a stable stroke volume, while the group of 6 patients with an increase in CO had a stable HR and an increase in stroke volume ($p = 0.001$). The patients with a CO decrease during NE had at baseline a significant lower SVV ($p = 0.012$) as well as a lower SVV during NE ($p = 0.001$) compared to the patients with a CO increase during NE.

When predicting CO response to NE based on SVV, a receiver operating characteristic curve with an area under the curve of 0.900 (95% CI 0.647-0.987, $p = 0.0001$) was found and a cut-off SVV value of 8.7% with a sensitivity and specificity of 100% and 70%, respectively.

Discussion

Our study shows that NE-induced increases in arterial pressure can be associated with either an increase or a decrease in CO in stable postoperative cardiac surgery patients depending on baseline ventricular responsiveness. Those patients with a greater baseline SVV increased their CO in response to a NE-induced increase in arterial pressure.

The physiologic explanation for these divergent CO responses in a group of otherwise similar patients rests in the differential effects NE had on venous return and ventricular function between these two subgroups of patients. To illustrate this point, we plotted venous return curves (based on the inspiratory hold maneuvers) and an estimation of a cardiac function curve for both CO-increasing and CO-decreasing patients (figure 10.2A and B). We used SVV as a measure of the steepness of the cardiac function curve.²¹ Because the heart can only pump into the arteries that which it receives and the heart has minimal reservoir capacity venous return matches CO very closely over a few heart beats.²² Thus, the intersection of the cardiac function and venous return curves at the time of study reflects steady-state CO and its change if either of these relations varies. These points are expanded upon below.

Table 10.1 Pooled results for 16 patients at start (Baseline-1), after increasing norepinephrine dosage (NE) and 15 minutes after decreasing the norepinephrine infusion to original dosage (Baseline-2).**All Patients (n = 16)**

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	81.60 ± 10.16	101.85 ± 9.81	82.80 ± 13.60	< 0.001
HR (min ⁻¹)	74.4 ± 14.0	70.1 ± 13.8	75.7 ± 14.1	0.003
CO (l•min ⁻¹)	4.30 ± 0.78	4.09 ± 0.67	4.44 ± 0.80	0.043
SV (ml)	59.4 ± 13.3	60.4 ± 15.2	60.7 ± 15.6	0.825
Pcv (mmHg)	7.61 ± 2.07	8.55 ± 2.35	7.58 ± 2.13	< 0.001
Pmsf (mmHg)	21.44 ± 6.12	27.57 ± 7.39	21.98 ± 5.34	< 0.001
Pvr (mmHg)	13.60 ± 5.66	19.02 ± 6.20	14.26 ± 5.16	0.001
Rvr (mmHg•min•l ⁻¹)	3.14 ± 0.94	4.72 ± 1.64	3.22 ± 0.99	< 0.001
Rsys (mmHg•min•l ⁻¹)	17.42 ± 3.88	23.31 ± 4.09	17.35 ± 4.27	< 0.001
Rvr/Rsys	19.0 ± 7.9	20.4 ± 6.6	19.2 ± 6.9	0.305
SVV (%)	11.1 ± 4.0	7.9 ± 4.3	11.0 ± 4.7	< 0.001

Patients with CO increase after NE Group A (n = 6)

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	81.65 ± 13.67	98.41 ± 10.68	85.14 ± 19.27	0.010
HR (min ⁻¹)	73.2 ± 17.0	72.7 ± 16.1 ^h	73.0 ± 16.1	0.419
CO (l•min ⁻¹)	4.06 ± 0.93	4.31 ± 0.86 ^d	4.16 ± 0.80	0.004
SV (ml)	57.5 ± 16.9	61.4 ± 16.8	59.2 ± 17.1	0.001
Pcv (mmHg)	7.57 ± 2.30	8.03 ± 2.68 ^e	7.37 ± 2.25	0.064
Pmsf (mmHg)	19.80 ± 5.27	23.57 ± 4.62	19.22 ± 4.40	0.014
Pvr (mmHg)	12.23 ± 4.36	15.55 ± 4.34	11.85 ± 4.02	0.024
Rvr (mmHg•min•l ⁻¹)	2.97 ± 0.57	3.58 ± 0.64 ^{c, f}	2.82 ± 0.73	0.026
Rsys (mmHg•min•l ⁻¹)	18.83 ± 5.01	21.54 ± 4.36 ^g	18.97 ± 5.07	0.022
Rvr/Rsys	16.7 ± 6.0	17.1 ± 4.3	15.2 ± 3.4	0.355
SVV (%)	14.4 ± 4.2 ^a	11.9 ± 2.7 ^b	14.9 ± 3.7	0.009

Patients with CO decrease after NE Group B (n = 10)

	Baseline-1	NE	Baseline-2	p
Pa (mmHg)	82.52 ± 8.10	103.91 ± 9.19	82.22 ± 9.21	< 0.001
HR (min ⁻¹)	75.1 ± 12.8	68.6 ± 12.9 ^h	77.3 ± 13.4	0.002
CO (l•min ⁻¹)	4.46 ± 0.64	3.96 ± 0.52 ^d	4.61 ± 0.74	0.002
SV (ml)	60.5 ± 11.6	59.8 ± 15.1	61.6 ± 15.5	0.558
Pcv (mmHg)	7.57 ± 1.93	8.86 ± 2.22 ^e	7.65 ± 2.06	< 0.001
Pmsf (mmHg)	22.40 ± 6.11	29.97 ± 7.88	23.51 ± 4.94	0.005
Pvr (mmHg)	14.77 ± 5.52	21.10 ± 6.38	15.86 ± 4.54	0.010
Rvr (mmHg•min•l ⁻¹)	3.29 ± 1.00	5.41 ± 1.68 ^{c, f}	3.48 ± 0.93	0.001
Rsys (mmHg•min•l ⁻¹)	16.67 ± 2.34	24.37 ± 3.74 ^g	16.49 ± 2.96	< 0.001
Rvr/Rsys	20.3 ± 7.8	22.3 ± 7.2	21.5 ± 6.4	0.478
SVV (%)	9.1 ± 2.4 ^a	5.3 ± 2.9 ^b	8.7 ± 3.6	< 0.001

NE, norepinephrine; Pa, mean arterial blood pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; Pcv, central venous, pressure; Pmsf mean systemic filling pressure; Pvr, pressure gradient for venous return; Rvr, resistance to venous return; Rsys, systemic vascular resistance; Rvr/Rsys, location of Pmsf; SVV, stroke volume variation.

Comparing mean baseline value between Group A and B: ^a p = 0.012. Comparing norepinephrine values between Group A and B: ^b p = 0.001; ^c p = 0.009. Comparing change in value induced by norepinephrine between Group A and B: ^d p < 0.001; ^e p = 0.042; ^f p = 0.019; ^g p = 0.002; ^h p = 0.003

Cardiac output increase by norepinephrine. In 6 patients CO increased during NE. We schematically constructed an averaged venous return curve and a cardiac function curve for these patients (figure 10.2A) based on the average values of Pcv, Pmsf and CO (table 10.1). Two mechanisms determine the change in the venous return curve during NE: an increase in effective circulating blood volume as manifest by an increased Pmsf and an increase in Rvr. How can Pmsf increase during NE? This can occur due to a decrease in systemic vascular compliance or a decrease in systemic vascular unstressed volume. Changes in systemic vascular compliance in response to low dose NE are minimal; however, decreases in unstressed volume are more likely owing to blood flow redistribution away from high unstressed volume vascular beds.²³ Unstressed volume is the blood volume that is required to fill the circulatory system without causing intravascular pressure and stressed volume (the volume that stretches the vascular system to create the intravascular pressure, Pmsf).²³ Thus, as Pmsf increased during NE without a change in total blood volume, the increase in Pmsf is the result of a volume shift from the unstressed to the stressed compartment (figure 10.2A shift from point *a* to *b*). This recruitment of volume from unstressed to stressed volume can be the result of an increased arteriolar resistance to those parts of the circulation with a high proportions of unstressed volume (e.g. splanchnic circulation)²⁴ or a selective increase in venous smooth muscle tone.

An increase in venous smooth muscle tone will not only decrease unstressed volume, but also diminish the cross-sectional area of the venous vessels and increase Rvr, which will be manifest by the lower slope of the venous return curve during increased NE compared to baseline condition (figure 10.2A, point *c*). The increase in Pmsf with NE while Pcv was constant results in an increased Pvr. Although both Pvr and Rvr increased, the ratio (which defines venous return) increased during NE. Because venous return and cardiac output must be equal over time, the intersection of the venous return curve and the heart function curve determines cardiac output (figure 10.2A, points *a* and *c*). The heart function curve has to fit through these data points if there is no change in heart function.

The decrease in SVV from baseline to NE (14.4% to 11.9%) indicated that the patients shifted to a less steep part of their cardiac function curve. This change in ventricular responsiveness could have been due to either the increased filling or the impaired output owing to the associated increased afterload. Since CO increased in these patients, the most likely primary mechanism for the decrease in SVV is an increase in preload (an increase in venous return), resembling volume expansion, which, in this case, is achieved by recruitment of volume from the unstressed to the stressed compartment. Thus, in our patients who increased CO on NE, the likely working mechanism of NE is recruitment of intravascular volume resulting in an increase in Pmsf, which has a stronger effect than the associated increase in Rvr and left ventricular afterload (increased Pa).

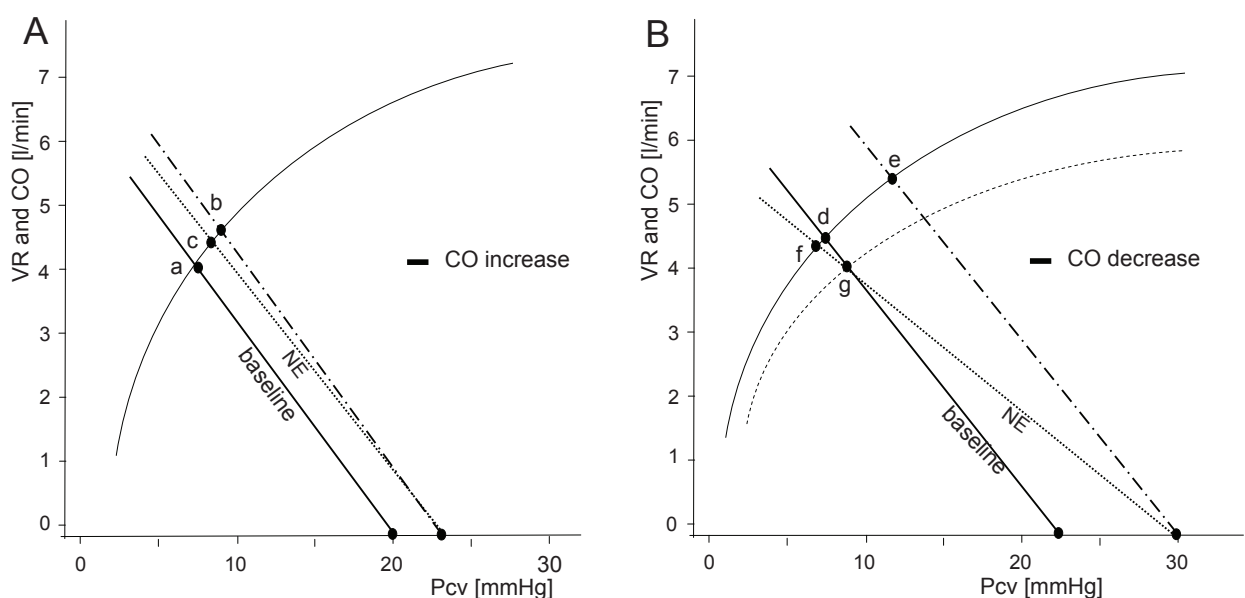


Figure 10.2 Effects of norepinephrine explained with venous return and cardiac output curves

Venous return (VR) curve and cardiac output (CO) curve constructed from average values of central venous pressure (Pcv), mean systemic filling pressure (Pmsf) and CO for patients who increased CO (A) and decreased CO (B) after norepinephrine (NE) dose increase. The dots are the mean values derived from table 2 for the CO-increasing and the CO-decreasing group.

Panel A: a. indicates working point of the circulation during baseline condition; b. indicates volume effect of generalized venoconstriction on CO by NE; c. indicates additional effect of venoconstriction on resistance to venous return (Rvr).

Panel B: d. indicates working point of the circulation during baseline condition; e. indicates volume effect of generalized venoconstriction on CO by NE; f. indicates additional effect of venoconstriction on Rvr; g. indicates effect of decreased heart function.

Such vasopressor-induced recruitment of blood volume from the unstressed compartment was previously described in dogs given α -adrenoceptor agonists (methoxamine hydrochloride and UK 14304-18).²⁵ Similarly, in pigs with normal cardiac function, NE indeed shifted the venous return curve to the right (and increased Pmsf), without affecting Rvr, which increased venous return and thus CO.¹³ Recently, an increase in cardiac preload (defined as left ventricular end-diastolic area) was found in septic shock patients when NE infusion was started or infusion rate increased.^{5,10} It is not clear from those studies if the increased end-diastolic volume was due to increased venous return, cardiac dilation due to increased afterload or both. Potentially, in sepsis, the unstressed volume could act as a reservoir, from which blood volume can be recruited. Considering the marked vasodilation and excess blood flow often seen in resuscitated patients in septic shock, this assumption seems reasonable. Monnet *et al.*¹⁰ also suggested that in states where vasoconstriction is predominant, such as cardiogenic and hypovolemic shock, NE would not alter preload significantly and thus could have different effects on CO. Indeed, NE infusion was associated with an unchanged CO in other studies in cardiogenic shock^{11,26}, in head trauma and in septic patients.¹² The latter two studies gave no individual patient data. Thus, it remains speculative if CO was indeed stable

in these patient groups or that their study group also consisted of both CO-increasing and CO-decreasing patients.

Cardiac output decrease by norepinephrine. In the remaining 10 patients in our study NE caused CO to decrease. In figure 10.2B we indicate at least three mechanisms determining the change in venous return or cardiac output with NE. These include the same two as for the other group, namely an increase in Pmsf (shift from point *d* to *e*) and Rvr (shift to point *f*), plus specifically for this group a decrement in the heart function curve (shift to point *g*). As in the increased CO with NE group, the increase in Pmsf is probably caused by same mechanisms, namely an increase in effective blood volume by recruitment of blood from unstressed to stressed volume concomitant with an increased Rvr. Importantly, the slope of the venous return curve (Rvr) changes significantly more with NE in the CO decrease group as compared to the CO increase group. Despite the increase in Pmsf in the CO decrease group (point *e*), venous return decreased because of larger rise in Rvr (i.e. the flattening of the slope of the venous return curve, point *f*) resulted in a decrement in the ratio of Pvr to Rvr and since venous return = Pvr/Rvr , these changes explain the resultant CO decrease.

Plotting the cardiac function curve and the intersection with the venous return curve revealed the third mechanism for the effects of NE on CO. Because Pmsf and Pcv both increased with NE, a shift of the working point downward to the steeper part on the same cardiac function curve cannot be the explanation for the decrease in CO in these patients. Also, the decrease in SVV is inconsistent with this explanation. The fall in CO can only be explained by a decrement in the cardiac function curve, as manifest by a less steep slope and reaching a lower plateau than it had at baseline (figure 10.2B, dashed heart function curve, point *g*). Thus, in patients that decrease CO on NE, the negative impact of increased left ventricular afterload becomes the dominant process. That initial baseline SVV, a measure of ventricular responsiveness, also identified these patients from those whose CO increased, not only supports this mechanism but also suggests that simple bedside measures can be used to predict the response to NE-induced increased vasomotor tone on CO. Others have reported similar findings. Desjars *et al.*⁷ observed a fall in CO in septic patients in response to a NE-induced increased Pa. Similarly CO decreased in hypotensive septic shock patients given nitric oxide synthase inhibition to raise Pa²⁷ and in patients with cardiogenic shock where the decrease was attributed to mitral valve insufficiency.¹¹

Importantly, in our patients who decreased CO with NE, they also displayed HR reduction. This finding resulted in a stroke volume unchanged. HR changes in response to NE have been reported before but the changes are variable. No decrease in HR was reported in septic shock patients treated with NE.^{5,8,10,28,29} In fact, HR increased during NE infusion in both septic shock patients²⁹ and septic pigs.¹³ Still other studies demonstrated a NE-induced reduction³⁰⁻³² in HR in healthy humans³⁰⁻³², normal and

hypertensive subjects³³ and in several animal studies.^{14,34-36} The HR reduction in all these studies was attributed to a baroreceptor-mediated central sympathetic withdrawal triggered by the NE-induced increased blood pressure.^{34,36} However, such baroreceptor-induced change in HR is accompanied by vasodilation of veins and arterioles.³⁷ Thus a decrease in vascular resistance might also be expected. Presumably, the NE-induced increased vascular smooth muscle tone overrides the decrement in sympathetic tone because Pa increased. Still, it is difficult to explain why our subjects who decreased their CO in response to NE also manifest this HR reduction because the increase in Pa was similar to that of the other sub-group whose CO increased similarly. Another possible explanation is a chemoreceptor-mediated response, but this mechanism is more effective in hypotensive than in hypertensive states.³⁷ Direct stretch of the right atrium by an increase in stressed volume (the Bainbridge reflex) cannot explain the HR reduction, because it induces the opposite effect.³⁷ Finally, if anything, any direct effect of NE should be an increase in HR due to direct beta adrenergic receptor stimulation.

The differential effects of NE on CO in our study, together with an increase in Pa, are remarkably similar to those reported earlier for the hemodynamic response to aortic cross clamping prior to aortic aneurysm repair. The immediate effect of abdominal aortic cross clamping is to increase Pa. However, in those subjects with preserved ventricular pump function the decreased vascular bed perfusion reduces unstressed volume increasing both Pmsf and CO, whereas in those with impaired ventricular pump function, although Pmsf also increases the increased afterload results in a decrement in CO.³⁸

Clinical implications of our study. In a hypotensive patient, maintenance of organ perfusion pressure while still sustaining an adequate CO is critical. Thus, the clinician has the choice between fluid loading and vasoactive medication. Our study allows an insight in the mechanisms by which NE may alter CO. In some patients administration of NE mimics the effect of fluid loading on CO and in others the CO declines because a disproportional increase in Rvr reduces venous return and because of decreased contractile reserve. Our data further suggests that in postoperative cardiac surgery patients a SVV > 8.7% is associated with an increased CO in response to NE. In the hypotensive critically ill patient the clinician can therefore choose either fluid loading, administration of NE, or both to attempt to restore cardiovascular sufficiency, depending on the fluid responsiveness of the patient. Importantly, not only does a SVV < 8.7% in our study predict that NE will decrease CO but also that this is associated with a decrease in HR and cardiac function. In these patients, if one must simultaneously increase Pa and CO, the addition of an inotropic agent, like dobutamine, could be indicated. In pigs we showed that dobutamine decreases Pcv by an increase in cardiac function, leading to an increase in the pressure gradient for venous return. Together with a decrease in Rvr this results in an increase in CO.¹⁶ Although further study in patients with more diverse

clinical conditions, like trauma and sepsis, needs to be done before such a simplified approach can be assumed to universally inform clinical decision-making, the approach we describe above can be used in studying those populations as well.

From a clinical perspective, increasing CO is not always the goal of resuscitation. In the hyperdynamic hypotensive patient, restoration of Pa, in order to improve vital organ perfusion pressure, despite a reduction in CO, is often an acceptable strategy. Finally, avoidance of peripheral edema is another potential goal of balanced resuscitation. In that regard, both NE and fluid loading increase Pmsf, and thus the hydrostatic pressure in the capillaries and venules, increasing the potential for peripheral edema formation. Accordingly, using NE to avoid peripheral edema is not supported by the results of these studies. Theoretically, NE may have possible salutary effect on capillary filtration coefficient, if arterial vasoconstriction decreases capillary pressure. Furthermore, NE-induced vasoconstriction might lead to reduced blood flow through some capillary beds all together, reducing global capillary filtration pressure. However, these effects of NE on peripheral edema formation are beyond the scope of this study.

Limitations and assumptions. We only studied 16 patients, though their responses were very specific and the data reached statistical significance. Thus, we doubt that increasing the number of study patients would reduce the differences found. Still some of the differences in calculated parameters may have reached statistical significance with a larger patient cohort, although the directional changes would unlikely reverse. In this study population, a change in NE dose was not clinically indicated, as the patients had adequate CO and blood pressure. Restoring blood pressure in a previously hypotensive patient may result in different responses than those observed in our normotensive patients. However, no human study has been previously reported of the effects of NE on Pmsf and resistance to venous return. For this explorative study, we therefore chose a stable group of highly instrumented patients to describe the effects of NE. Future studies will need to examine the effect of NE on CO during hypotension due to sepsis, hypovolemia and impaired ventricular function and after volume resuscitation.

Pmsf measured with the inspiratory hold technique has not been validated by comparing it with Pmsf by total circulatory stop-flow.³⁹ However, Pinsky⁴⁰ in intact canine showed Pmsf by ventilatory maneuvers to be equal to Pmsf by total circulatory stop-flow. We⁴¹ recently showed in pigs that flow measured with a flow probe around the pulmonary artery, with a flow probe around the aorta and with Modelflow pulse contour were interchangeable. Furthermore, we found that estimations of Pmsf with the inspiratory hold technique using a flow probe around the aorta and pulse contour Modelflow method were interchangeable. We did not recalibrate the Modelflow after increasing NE dose because in a previous multicenter study¹⁸ in cardiac surgery patients, we showed that a single calibration of Modelflow was adequate and that vasoactive drugs did not affect the ability to track changes in CO thus induced.

We assumed venous compliance to be constant during baseline and NE conditions. There are no human studies examining the effect of NE on venous compliance, but NE infusion in cats did not alter venous compliance.⁴²

Our patients were mechanically ventilated without spontaneous breathing efforts and they had regular heart rates, all prerequisites for a reliable estimation of the venous return curves, Pmsf, CO and SVV. These prerequisite conditions make our analysis not directly applicable to other patient groups.

Conclusions

NE-induced increased Pa can either increase or decrease CO. The effect of NE on CO is a balance between increasing effective circulatory blood volume, venoconstriction and increased left ventricular afterload in stable postoperative cardiac surgery patients. Larger SVV correlates with increasing CO in response to NE.

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