is now good evidence that this should be a research focus of high priority.

These findings are reminiscent of the discovery of the importance of glycemic control in the critically ill population. There was a time when glycemic control was virtually ignored until the detrimental effects of hyperglycemia were documented (11), and the benefits of glycemic control were clearly defined (12, 13). Obviously, we now consider proper management of this factor as a marker of an institution's ability to organize itself and deliver current, evidence-based practice.

In light of the growing evidence of impaired outcomes with dysnatremias, we are led to the natural and important question: Is sodium control destined to be the next core measure?

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Understanding the Divergent Effects of Norepinephrine on Cardiac Output: Go With the Flow*

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The mantra of "preload, afterload, contractility, heart rate and rhythm" is repeatedly used on ICU rounds as hemodynamic principles are applied to complex patients. However, translating these concepts from the physiology laboratory to the clinical setting is challenging. During the past decade, two concepts related to preload have increasingly demonstrated their relevance to patient management. In this issue of *Critical Care Medicine*, Maas and colleagues (1) combine these concepts to explain why norepinephrine increases cardiac output in some patients but decreases it in others.

The first concept is the venous return curve, originally developed by Guyton (2). Analogous to other equations, venous return (flow) to the right heart equals the pressure gradient for flow divided by the resistance to flow (**Fig. 1**). The pressure gradient for venous return is the difference between the mean capillary filling pressure and the right atrial pressure. Increases in venous return can occur by increasing the mean systemic filling pressure, decreasing the right atrial pressure, or decreasing the venous vascular resistance. As shown in Figure 1, cardiac output is the point where the venous return curve and the Frank–Starling cardiac function curve intersect (inflow and outflow are equal). In the past, it has been difficult to measure venous function curves. Over the past decade, this group has developed and verified measurement of mean systemic filling pressure (equivalent to mean capillary filling pressure) and venous resistance during mechanical ventilation by using stepwise increases in airway pressure to increase right atrial pressure while monitoring cardiac output noninvasively through a pulse contour method (3–5).

The second concept is the use of stroke volume variation (SVV) to assess the position of the heart on the cardiac function

***See also p. 143.**

Key Words: cardiac output; mean systemic filling pressure; norepinephrine; stroke volume variation; venous return curve

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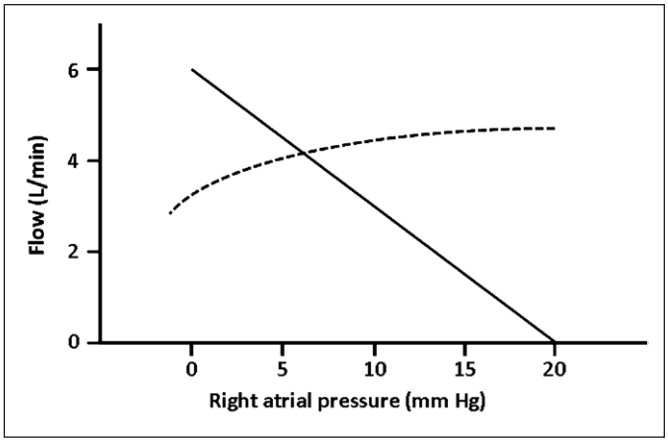

Figure 1. The venous return curve (*solid line*) and the Frank–Starling cardiac function curve (*dashed line*). When right atrial pressure equals the mean circulatory filling pressure, there is no gradient for venous return, resulting in zero flow. In this diagram, this occurs at a pressure of 20 mm Hg. As right atrial pressure decreases below this value, venous return linearly increases with a slope equal to the venous vascular resistance. The cardiac function curves demonstrate how cardiac output increases with right atrial pressure. The intersection of the two curves defines the equilibrium when venous return and cardiac output are equal. In this diagram, the equilibrium occurs when right atrial pressure is 6 mm Hg and cardiac output is 4 L/min.

curve. Classically, preload is the end-diastolic stretch of the myocardial fibers, but preload is usually assessed in the clinical setting by end-diastolic filling pressures, which vary with myocardial compliance. As a result, filling pressures do not predict the response to a fluid challenge (6). Static measures of preload have increasingly been replaced by dynamic measures such as systolic pressure variation, pulse pressure variation, and SVV, which are based on the concept that changes in intrathoracic pressure with respiration will result in changes in stroke volume as the heart moves along the Frank–Starling cardiac function curve in response to changes in cardiac filling (7). Studies have demonstrated improved outcome in surgical and critically ill patients when fluid administration is titrated to dynamic measures, such as maintaining SVV below a threshold value (8, 9).

The current study by Maas and colleagues examined the effect of an incremental norepinephrine infusion titrated to increase mean arterial pressure by 20 mm Hg in postoperative cardiac surgery patients. Norepinephrine increased cardiac output in six of the 16 patients but decreased it in the remaining ten patients. As expected for a vasoconstrictor, norepinephrine increased systemic vascular resistance, venous vascular resistance, and mean systemic filling pressure in all patients. In addition, there was a small increase in central venous pressure, but this was smaller than the increase in mean systemic filling pressure so that the gradient for venous return consistently increased. In the absence of any direct cardiac effects (no change in the cardiac function curve), the anticipated effect on venous return (and therefore cardiac output) could be either an increase (due to the increased gradient for venous return) (10) or a decrease (due to the increased resistance to venous return).

However, norepinephrine also shifted the cardiac function curve. As an inotrope, norepinephrine shifts the cardiac function curve upwards and to the left, but as an arterial vasoconstrictor, increased afterload may have the opposite effect (directly on the left ventricle, and, by increasing left atrial pressure and pulmonary vascular resistance, on the right ventricle as well). Because norepinephrine has potentially opposing changes on both venous return and on cardiac function, the net effect on cardiac output would seem unpredictable.

However, the authors demonstrated that SVV >8.7% reliably predicted an increased cardiac output in response to norepinephrine. Since SVV is a measure of how stroke volume varies with changes in preload, patients with high SVV are operating on the steep portion of the cardiac function curve. Because the effect of norepinephrine on mean systemic pressure generally exceeds the effect on venous vascular resistance, the increased preload with norepinephrine resulted in a significant increase in cardiac output in this group of patients. In contrast, patients with low SVV are operating on the flat portion of their cardiac function curves, and the negative effect of increased afterload likely exceeded the small benefit of augmented venous return, thereby decreasing cardiac output.

One potential implication of this study is to use norepinephrine to increase blood pressure and cardiac output in patients with high SVV. However, patients with high SVV generally respond to fluid administration, which should normally be preferred to vasopressor agents. In patients with low SVV, this study suggests that inotropic agents rather than vasopressor agents should be used to treat hypotension. However, arterial pressure was at an acceptable level before norepinephrine, so the further increase with norepinephrine may have exaggerated the adverse effects of increased afterload. Patients in this study had normal cardiac output at baseline. In contrast, patients with poor ventricular function may be more adversely affected by the increased systemic afterload from norepinephrine. The venous return curve focuses attention on the right ventricle, but many critically ill patients have right ventricular dysfunction where effects on pulmonary vascular resistance rather than venous return may be dominant or have left ventricular dysfunction where a right ventricular venous return curve may be less relevant. Finally, the study was performed in patients after cardiac surgery. The choice of vasopressors is most challenging in sepsis, where norepinephrine similarly can increase or decrease cardiac output (11). In future studies, applying these techniques in multiple different settings, particularly in combination with newer techniques for assessment of contractility and ventricular afterload, will increase our understanding of the complex physiology of our critically ill patients and thereby improve outcomes.

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Sepsis and Ventilator-Induced Lung Injury: An Imperfect Storm*

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Inflammatory mediators are primary candidates as biomarkers for the development and prognosis of acute respiratory distress syndrome (ARDS), with studies conducted at both the molecular and protein levels into established as well as newly identified potential targets (1). However, inflammatory biomarkers that are both sensitive and specific remain elusive. New evidence suggesting a divergence between inflammatory mediator expression and pathogenesis, particularly in the context of ventilator-induced lung injury (VILI), may contribute some explanation.

ARDS follows direct exposure to an insult such as an infective pathogen, or follows indirectly, as a secondary complication of a distant inflammatory process (2). Respiratory epithelium, endothelium, and in situ macrophages respond to these stimuli through the release of inflammatory mediators such as the cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6, and chemokines such as IL-8, resulting in the recruitment and activation of systemic leukocytes, particularly neutrophils. Inflammatory activation and neutrophil chemotaxis further contribute to damage of the respiratory epithelium culminating in diffused alveolar damage, increased permeability, interstitial and alveolar edema, and both cellular and protein infiltration and accumulation followed by surfactant dysfunction, increased surface tension, and early changes in lung mechanics.

In this issue of *Critical Care Medicine*, Uematsu and co-workers (3) present findings from a murine model of mild systemic sepsis following cecal ligation and puncture (CLP) with lung injury exacerbated by high tidal volume (Vt = 40 mL/kg), zero positive end-expiratory pressure injurious mechanical ventilation. The study compares systemic sepsis or VILI with their cumulative "two-hit" attack and reports inflammatory mediator (interleukin-6, TNF-α and chemokine, keratinocyte-derived chemokine) concentrations in both serum and epithelial lining fluid, and lung function (arterial oxygenation and respiratory compliance). Although CLP and high Vt ventilation independently increased both systemic plasma and epithelial lining fluid cytokines, increased alveolar protein and diminished respiratory function were only achieved by injurious ventilation. Systemic priming by CLP prior to high Vt ventilation did not increase this alveolar protein level or worsen respiratory function despite increases in both systemic and epithelial lining fluid cytokines exceeding additive levels achieved by CLP and high Vt. Pretreatment with the anti-inflammatory dexamethasone reduced systemic cytokine production, but did not affect epithelial lung fluid cytokines, protein, or respiratory function. The authors conclude that these results suggest dissociation between systemic and pulmonary cytokines in CLP-primed high Vt injurious ventilation, as well as between cytokine levels and lung function. These findings reiterate emerging evidence for alternative mechanisms of injury in VILI which differentiate these conditions from ARDS, which is predominantly mediated via an inflammatory cascade (4, 5). The VILI paradigm attributes equivalent, if not a predominant, cause of injury to mechanotransduction and stress failure of the plasma membrane rather than direct inflammatory damage. Investigations by D'Angelo and colleagues

***See also p. 151.**

Key Words: acute lung injury; acute respiratory distress syndrome; cytokines; inflammatory biomarkers; ventilator-induced lung injury

Dr. Bersten is a board member of Southern Medical Diagnostics, Signostics, and has consulted for Southern Medical Diagnostics. He has received grant support from National Health and Medical Research Council, Intensive Care Foundation, and has patents: inventor on patents relating to a lung biomarker test, royalties: with Oh's Intensive Care Manual, and stocks/options in Signostics. Dr. Dixon has not disclosed any potential conflicts of interest.

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Cardiac Output Response to Norepinephrine in Postoperative Cardiac Surgery Patients: Interpretation With Venous Return and Cardiac Function Curves*

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Objective: We studied the variable effects of norepinephrine infusion on cardiac output in postoperative cardiac surgical patients in whom norepinephrine increased mean arterial pressure. We hypothesized that the directional change in cardiac output would be determined by baseline cardiac function, as quantified by stroke volume variation, and the subsequent changes in mean systemic filling pressure and vasomotor tone.

Design: Intervention study.

Setting: ICU of a university hospital.

Patients: Sixteen mechanically ventilated postoperative cardiac surgery patients.

Interventions: Inspiratory holds were performed at baseline-1, during increased norepinephrine infusion, and baseline-2 conditions.

Measurements and Main Results: We measured mean arterial pressure, heart rate, central venous pressure, cardiac output, stroke volume variation and, with use of inspiratory hold maneuvers, mean systemic filling pressure, then calculated resistance for venous return and systemic vascular resistance. Increasing norepinephrine by 0.04 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased mean arterial pressure 20 mm Hg in all patients. Cardiac output decreased in ten and increased in six patients. In all patients mean systemic filling pressure, systemic vascular resistance and resistance for venous return increased and stroke volume variation decreased. Resistance for 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 cardiac output decrease ($p = 0.002$) and was unchanged in the patients with a cardiac output increase. Baseline stroke volume variation was higher in those in whom cardiac output increased ($14.4 \pm 4.2\%$ vs. $9.1 \pm 2.4\%$, $p = 0.012$). Stroke volume variation >8.7% predicted the increase in cardiac output to norepinephrine (area under the receiver operating characteristic curve 0.900).

Conclusions: The change in cardiac output induced by norepinephrine is determined by the balance of volume recruitment (increase in mean systemic filling pressure), 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. (*Crit Care Med* 2013; 41:143–150)

Key Words: cardiac output; cardiac surgery; mean systemic filling pressure; norepinephrine; vascular resistance

Norepinephrine (NE) is the vasopressor of choice in septic shock (1) 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 shock (4–10) 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 re-

*See also p. 352.

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sponse to NE must be determined by the balance between the increased preload effects of increasing peripheral vasomotor tone vs. the increased afterload effect of increasing mean arterial pressure (MAP). 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]), resistance to venous return, total systemic vascular resistance, 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 systemic vascular resistance).

MATERIAL 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 the 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 $mg \cdot kg^{-1} \cdot h^{-1}$) and sufentanil (0.17 $\mu g \cdot kg^{-1} \cdot h^{-1}$). The patients were mechanically ventilated in airway pressure release ventilation mode (Evita 4, Dräger AG, Lübeck, Germany) adjusted to achieve normocapnia (arterial P_{CO_2} between 40 and 45 mm Hg) with tidal volumes of 7.3 ± 1.3 $mL \cdot kg^{-1}$, a respiratory rate of 12 min^{-1}, and 5 cmH_2O positive end-expiratory pressure. All patients were in sinus rhythm. Hemodynamic stability was achieved using fluids (60 $mL \cdot h^{-1}$) 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 hrs after surgery and was discharged from the ICU on the first postoperative day.

Physiological Monitoring

MAP 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, CA). 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, 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 MAP, PCV, and CO over the final 3 secs for a set of four inspiratory-holds of 12 secs at airway plateau pressures of 5, 15, 25, and 35 cm H_2O. The inspiratory-hold maneuvers were separated by 1-min intervals to reestablish the initial hemodynamic steady state. During these inspiratory holds, when airway pressure increased, PCV increased concomitantly, whereas CO and MAP decreased with a delay of three to four beats resulting in a plateau between 7 and 12 secs 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 (**Fig. 1**).

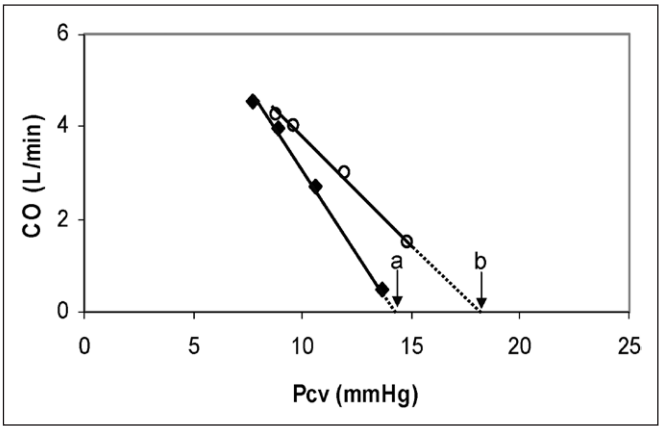

Figure 1. Venous return curve plotted for one patient after four inspiratory hold maneuvers. At increasing values of airway pressure, central venous pressure (PCV) increases and cardiac output (CO) decreases. Mean systemic filling pressure (PMSF) is the value of PCV, when cardiac output is extrapolated 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*).

Protocol

After stabilization of the patient in the ICU, series of baseline-1 measurements were done of MAP, PCV, CO, and PMSF. Next, continuous NE infusion rate was increased to induce a 20 mm Hg increase in MAP, and after 15 mins the series of measurements were repeated. The observation period ended with baseline-2 measurements 15 mins after retuning to a NE infusion rate equal to baseline-1 condition.

Data Analysis and Statistics

The venous return data (PCV vs. 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 MAP and PCV and CO (systemic vascular resistance = [MAP–PCV]/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 (RVR = [PMSF–PCV]/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 cutoff values are reported as 95% confidence intervals. All values are given as mean ± 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 yrs, 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 ± 0.03 $\mu g.kg^{-1}.min^{-1}$) at baseline. Except for dobutamine, which was given to one patient in low dosage (1 $\mu g.kg^{-1}.min^{-1}$), no other vasoactive medication was given. **Table 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 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced an increase of MAP with 19.7 ± 8.7 mm Hg.

Increasing NE resulted in a decrease in CO in ten patients and an increase in CO in six patients (Table 1). In the patients with a CO decrease, NE was increased from 0.04 ± 0.04 to 0.09 ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$; in the patients with a CO increase, NE was increased from 0.04 ± 0.04 to 0.08 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The dose of NE during baseline conditions as well as the dose during NE did not differ between both groups. The ten patients that decreased CO on NE had a significantly higher rise in PCV, systemic vascular resistance, and RVR during NE (p values 0.042, 0.002, and 0.019 respectively) compared to the six patients that increased CO on NE. Furthermore, these ten patients had a decline in heart rate (HR) ($p = .002$) and a stable stroke volume, whereas the group of six 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 increase had at baseline a significantly 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% confidence interval 0.647–0.987, $p = 0.0001$) was found and a cutoff 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 (**Fig. 2*A*** 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.

CO Increase by NE

In six patients CO increased during NE. We schematically constructed an averaged venous return curve and a cardiac function curve for these patients (Fig. 2*A*) based on the average values of PCV, PMSF, and CO (Table 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

TABLE 1. Pooled Results for 16 Patients at Start (Baseline-1), After Increasing Norepinephrine Dosage, and 15 Mins After Decreasing the Norepinephrine Infusion to Original Dosage (Baseline-2)

	Baseline-1	NE	Baseline-2	*p*
All patients (*n* = 16)				
MAP (mm Hg)	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 ($L \cdot min^{-1}$)	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 (mm Hg)	7.61 ± 2.07	8.55 ± 2.35	7.58 ± 2.13	<0.001
PMSF (mm Hg)	21.44 ± 6.12	27.57 ± 7.39	21.98 ± 5.34	<0.001
PVR (mm Hg)	13.60 ± 5.66	19.02 ± 6.20	14.26 ± 5.16	0.001
RVR (mm $Hg \cdot min \cdot L^{-1}$)	3.14 ± 0.94	4.72 ± 1.64	3.22 ± 0.99	<0.001
RSYS (mm $Hg \cdot min \cdot L^{-1}$)	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)				
MAP (mm Hg)	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 ($L \cdot min^{-1}$)	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 (mm Hg)	7.57 ± 2.30	8.03 ± 2.68[e]	7.37 ± 2.25	0.064
PMSF (mm Hg)	19.80 ± 5.27	23.57 ± 4.62	19.22 ± 4.40	0.014
PVR (mm Hg)	12.23 ± 4.36	15.55 ± 4.34	11.85 ± 4.02	0.024
RVR (mm $Hg \cdot min \cdot L^{-1}$)	2.97 ± 0.57	3.58 ± 0.64[cf]	2.82 ± 0.73	0.026
RSYS (mm $Hg \cdot min \cdot L^{-1}$)	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[a]	0.009
Patients with CO decrease after NE Group B (*n* = 10)				
MAP (mm Hg)	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 ($L \cdot min^{-1}$)	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 (mm Hg)	7.57 ± 1.93	8.86 ± 2.22[e]	7.65 ± 2.06	<0.001
PMSF (mm Hg)	22.40 ± 6.11	29.97 ± 7.88	23.51 ± 4.94	0.005
PVR (mm Hg)	14.77 ± 5.52	21.10 ± 6.38	15.86 ± 4.54	0.010
RVR (mm $Hg \cdot min \cdot L^{-1}$)	3.29 ± 1.00	5.41 ± 1.68[cf]	3.48 ± 0.93	0.001
RSYS (mm $Hg \cdot min \cdot L^{-1}$)	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[a]	<0.001

NE = norepinephrine; MAP = 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 groups A and B: [a]$p = 0.012$; comparing norepinephrine values between groups A and B: [b]$p = 0.001$, [c]$p = 0.009$; comparing change in value induced by norepinephrine between groups A and B: [d]$p < 0.001$, [e]$p = 0.042$, [f]$p = 0.019$, [g]$p = 0.002$, [h]$p = 0.003$.

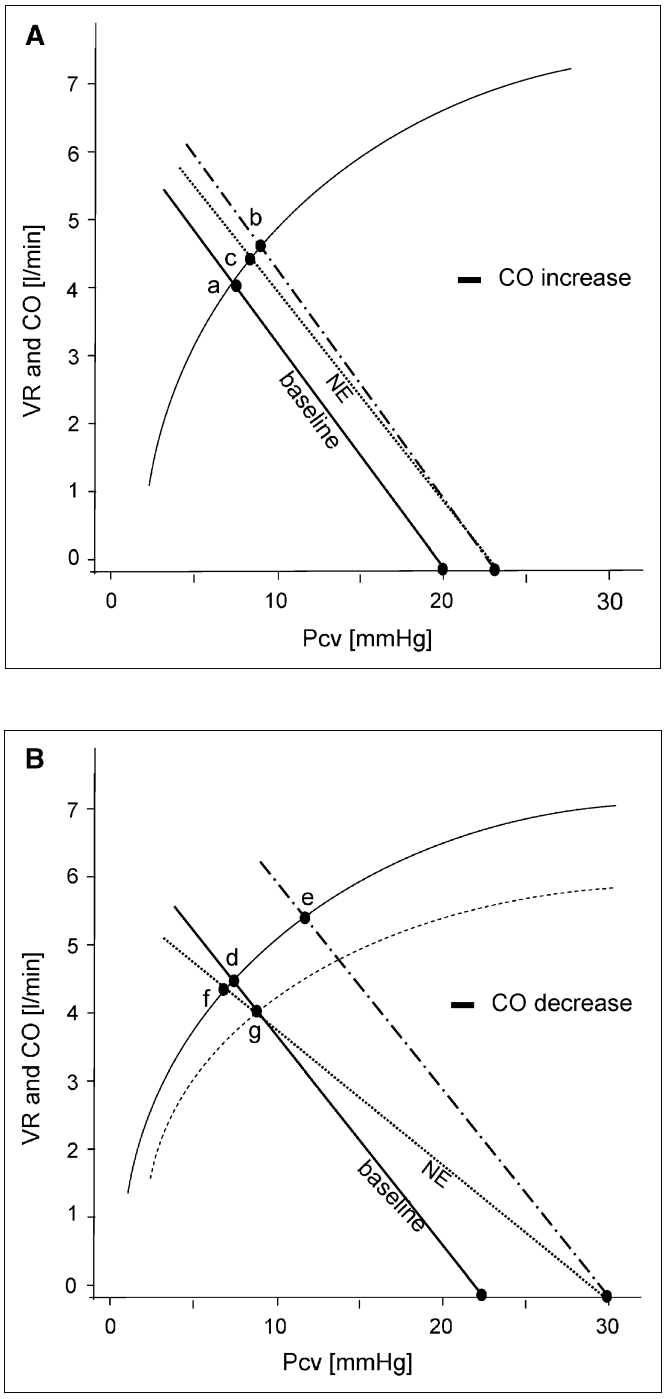

Figure 2. Schematic diagram of the effects of norepinephrine (NE). Venous return (VR) curve and cardiac output (CO) curve constructed from average values of central venous pressure (PCV), mean systemic filling pressure (PMSF), and CO for patients who increased CO (**A**) and decreased CO (**B**) after NE dose increase. The dots are the mean values derived from Table 1 for the CO-increasing and the CO-decreasing group. **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). **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.

blood volume, the increase in PMSF is the result of a volume shift from the unstressed to the stressed compartment (Fig. 2*A* 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 proportion 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 will 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 (Fig. 2*A*, 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 CO must be equal over time, the intersection of the venous return curve and the heart function curve determines CO (Fig. 2*A*, 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%–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 impaired output owing to the associated increased afterload. Because 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 MAP).

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 differ-

ent 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.

CO Decrease by NE

In the remaining ten patients in our study, NE caused CO to decrease. In Figure 2*B*, we indicate at least three mechanisms determining the change in venous return or CO 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 the 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 because 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 (Fig. 2*B*, 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 MAP. Similarly, CO decreased in hypotensive septic shock patients given nitric oxide synthase inhibition to raise MAP (27) 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 an 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 patients (29) and septic pigs (13). Still other studies demonstrated a NE-induced reduction in HR in healthy humans (30–32), normal and hypertensive subjects (33), 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 MAP 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 MAP was similar to that of the other subgroup 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 β-adrenergic receptor stimulation.

The differential effects of NE on CO in our study, together with an increase in MAP, 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 MAP. 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 suggest 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 MAP 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 gradi-

ent 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 MAP, 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, Pinsky (40) in intact canine showed PMSF by ventilatory maneuvers to be equal to PMSF by total circulatory stop flow. We (41) 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 study (18) 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 HRs, 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 MAP 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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