Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock*

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Objective: **To investigate the effect of norepinephrine on static (right atrial pressure, pulmonary artery occlusion pressure) and dynamic (pulse pressure variation and arterial systolic pressure variation) preload indicators in experimental hemorrhagic shock.**

Design: **Prospective controlled experimental study.**

Setting: **Animal research laboratory.**

Subjects: **Six anesthetized and mechanically ventilated dogs.**

Interventions: **Dogs were instrumented for measurement of arterial blood pressure, pulmonary artery catheter derived variables including right atrial pressure, pulmonary artery occlusion pressure, and cardiac output. Simultaneously, pulse pressure variation and systolic pressure variation were calculated. Pulse pressure variation is the difference between the maximal and the minimal value of pulse pressure divided by the mean of the two values and is expressed as a percentage. Systolic pressure variation is the difference between the maximal and the minimal systolic pressure and is expressed as an absolute value. After baseline measurements, hemorrhagic shock was induced by a stepwise cumulative blood withdrawal of 35 $mL \cdot kg^{-1}$ of body weight. A second set of hemodynamic measurement was made 30 mins after bleeding. The third set was made 30 mins later under norepinephrine.**

Measurements and Main Results: **Mean arterial pressure and cardiac output decreased after hemorrhage ($p < .05$), whereas right atrial pressure and pulmonary artery occlusion pressure remained unchanged. Baseline pulse pressure variation and systolic pressure variation increased significantly with hemorrhage, from 12% (9%) to 28% (11.5%) ($p < .001$) and from 12.5 (6.5) to 21 (8.2) mm Hg ($p < .05$), respectively. Norepinephrine induced a significant increase of cardiac output and a significant decrease of pulse pressure variation and systolic pressure variation but did not significantly change right atrial pressure or pulmonary artery occlusion pressure values. Stroke volume was correlated to pulse pressure variation and systolic pressure variation but was not correlated to right atrial pressure or pulmonary artery occlusion pressure.**

Conclusion: **Our study confirms the superiority of dynamic variables (pulse pressure variation and systolic pressure variation) over static ones (right atrial pressure and pulmonary artery occlusion pressure) in assessing cardiac preload changes in hemorrhagic shock. However, norepinephrine could significantly reduce the value of these dynamic variables and mask a true intravascular volume deficit possibly by shifting blood from unstressed to stressed volume. (Crit Care Med 2005; 33:2339–2343)**

KEY WORDS: norepinephrine; pulse pressure; systolic pressure variation; cardiac preload; hemorrhagic shock

Adequate use of fluid therapy in critically ill patients is a crucial task for intensive care physicians. However, reduction of cardiac preload in intensive care unit patients is usually subtle, and routine triggers of fluid expansion such as hypotension and tachycardia are often unreliable (1). Although frequently used, cardiac filling pressures such as central venous pressure and pulmonary artery occlusion pressure (PAOP) poorly reflect patients' volume status and are often misleading in the assessment of fluid responsiveness (2). Conversely, the value of dynamic variables using arterial pressure waveform analysis in mechanically ventilated patients is increasingly emphasized (3). Indeed, the magnitude of arterial systolic and pulse pressure variability (SPV and PPV) was found to be a good predictor of fluid responsiveness in experimental and clinical setting (4–9) and was more accurate than static measurement of central venous pressure or PAOP (7, 10, 11). Moreover, for both variables, fixed threshold values were proposed to discriminate between responders and nonresponders to fluid challenge (7, 9).

In clinical practice, fluid expansion is commonly coadministered with catecholamines to improve cardiovascular function in hemodynamically instable patients. As catecholamines could have a direct effect on regional vascular capacitance, they would alter SPV and PPV values and interfere with the prediction of the response to fluid expansion. Indeed, norepinephrine (NE) and other potent vasoconstrictors have been shown to induce a shift of venous blood from unstressed to stressed vascular bed (12–14). An obvious downside of this possibility is that these drugs will be used instead of true fluid

*See also p. 2437.

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Table 1. Effects of bleeding and norepinephrine on basic hemodynamic variables

	Baseline	Hemorrhage	Norepinephrine
HR, beats · min^{-1}	167 (35)	210 (44)[a]	153 (56)[b]
MAP, mm Hg	144 (42)	85 (46)[a]	153 (36)[b]
RAP, mm Hg	5.5 (4.2)	3.0 (4.2)	2.0 (4.0)
PAP, mm Hg	18.5 (16.1)	12.0 (9.3)	18.0 (15.0)
PAOP, mm Hg	6.0 (5.1)	4.5 (4.0)	3.5 (5.1)
CO, L · min^{-1}	4.68 (3.30)	1.98 (0.86)[a]	3.08 (1.72)[b,c]
SVR, dyne · sec · cm^{-5}	2367 (1475)	3313 (1900)[a]	3922 (2744)[b,c]
PVR, dyne · cm^{-5}	213 (182)	303 (245)[a]	428 (310)
pH	7.36 (0.05)	7.29 (0.12)[a]	7.24 (0.11)[c]
HCO_3^-, mmol/L	24.1 (3.1)	18.0 (4.7)[a]	15.8 (6.0)[c]

HR, heart rate; MAP, mean arterial pressure; RAP, right atrial pressure; PAP, pulmonary arterial pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

[a]$p < .05$ vs. baseline; [b]$p < .05$ vs. hemorrhage; [c]$p < .05$ vs. baseline. Values are median (interquartile range).

replacement, which may increase both cardiac work and vasoconstriction in an already compromised regional microcirculation. Accordingly, examining the interaction between NE infusion and dynamic variables of fluid responsiveness is important to optimize their interpretation in clinical practice.

In the current study we assessed the effects of NE infusion on SPV and PPV change in a dog model of hemorrhagic shock. Our goal was to determine whether NE could decrease the values of SPV and PPV and evaluate the magnitude of this effect. The effects of NE on conventional hemodynamic markers of cardiac preload (central venous pressure and PAOP) were also investigated.

MATERIALS AND METHODS

Animal Preparation. The experimental protocol was approved by the committee of ethics of the medical university of Monastir (Tunisia) and performed according to the Helsinki convention on the use and care of animals. In six dogs weighing 13.3 ± 2.5 kg, anesthesia was induced with 5 mg·kg^{-1} thiopental and maintained with additional doses of 1 mg·kg^{-1} intravenous thiopental to maintain depth of anesthesia defined as a slight but present corneal reflex and the absence of signs of pain or discomfort in the studied dogs. The range of total additional doses of thiopental administered for each dog was between 30 and 50 mg. The animals were intubated and submitted to volume-controlled mechanical ventilation set at respiratory rate of 30 breaths/min, and tidal volume was adjusted to keep $Paco_2$ between 30 and 35 mm Hg. Fio_2 was set at 0.5. Muscle relaxation was achieved with 0.1–0.2 mg·kg^{-1} intravenous pancuronium bromide. A 16-gauge Teflon arterial catheter was inserted into the femoral artery to measure arterial blood pressure and to withdraw arterial blood gases. A balloon thermistor-tipped 5-Fr catheter (Arrow International, Reading, PA) was inserted and floated through the femoral vein for the measurement of right arterial pressure (RAP), pulmonary artery pressure (PAP), PAOP, and cardiac output (CO). The blood temperature determined by means of the pulmonary artery catheter was maintained at normal ranges during the experiment using a warming pad. Pleural pressure was measured by the esophageal balloon method (latex balloon; length, 10 cm; circumference, 3.5 cm; thickness, 0.06 mm; volume, 0.4 mL of air; polyethylene catheter: inner diameter, 1.5 mm; outer diameter, 2.5 mm; length, 80 cm). Airway pressure was measured with a catheter connected to the tip of the endotracheal tube via an intermediate piece. Airway and esophageal pressure catheters were filled with normal saline and connected to a pressure transducer. To adjust chest wall compliance of dogs to human values, we used an inflated vest around the dog's chest. Inflation of the vest was maintained throughout the experiment to keep esophageal pressure/airway pressure ratio at approximately 50% (15). Spontaneous respiratory efforts were not allowed. This was ascertained through the stability of femoral and pulmonary arterial pressure profile and monitoring of pleural pressure variations.

Measurements. All hemodynamic variables were transduced and recorded on a multiple-channel recorder (Life Scope 12, Nihon Kohden, Japan). All measurements were taken in supine position with zero reference level at the midchest. Lead II of the electrocardiographic signal was also recorded. Cardiac output was measured using standard thermodilution technique and expressed as the mean of three measurements with 5 mL of ice-cold saline. Stroke volume (SV) was calculated as CO/heart rate adjusted to animal weight. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulas.

PPV and SPV calculation was performed over three consecutive respiratory cycles including five to seven heart beats each. The magnitude of the change in pulse pressure during a respiratory cycle was calculated as described by Michard et al. (8)

$$PPV = PPmax - PPmin/(PPmax + PPmin) \times 100 \quad [1]$$

where PPmax and PPmin are the maximal and minimal pulse pressures over this cycle. SPV was calculated as the mean difference between the maximum and minimum systolic blood pressure during one respiratory cycle. SPV was expressed in absolute values (mm Hg) as follows:

$$SPV = SPmax - SPmin \quad [2]$$

The final PPV and SPV included in the analysis were the average of the three values obtained over the three respiratory cycles.

Data were obtained from printed charts at 12.5 mm·sec^{-1}.

Experimental Protocol. After instrumentation, animals were allowed to stabilize for 30 mins before any experimental procedure. Baseline measurements including all the variables described previously were obtained twice at 10-min intervals to be sure that the animals were hemodynamically stable. Then blood was withdrawn with a total of 35 mL·kg^{-1} by stepwise cumulative volumes of 5 mL·kg^{-1} each. The procedure lasted approximately 30 mins and less if mean arterial pressure decreased below 50 mm Hg or >50% of baseline value. A second set of hemodynamic measurements was made after blood withdrawal. Then, NE was introduced and titrated to achieve baseline mean arterial pressure or ≥10% of baseline. After stabilization, a third set of hemodynamic measurement was obtained under NE infusion, approximately 30 mins after the second set.

At the end of the study, all animals were killed with intravenous potassium chloride while they were under surgical anesthesia with thiopental.

Statistics. All hemodynamic variables were analyzed as continuous variables and expressed as median with interquartile range. The variables were compared at the end of blood withdrawal period and under NE infusion to baseline values using the Wilcoxon signed-rank nonparametric test. Linear correlation were tested using Spearman rank method. Statistical significance was determined at the level of .05.

RESULTS

Changes in baseline basic hemodynamic data with hemorrhage and NE are presented in Table 1. Hemorrhage (median blood volume loss, 420 mL; range, 310–470) induced a significant decrease of MAP (144 [42] vs. 85 [36] mm Hg; $p < .05$) and CO (4.68 [3.30] vs. 1.98 [0.96] L·min^{-1}; $p < .05$) with a significant increase in SVR and HR, whereas RAP and PAOP remained unchanged. Under NE (median infusion rate

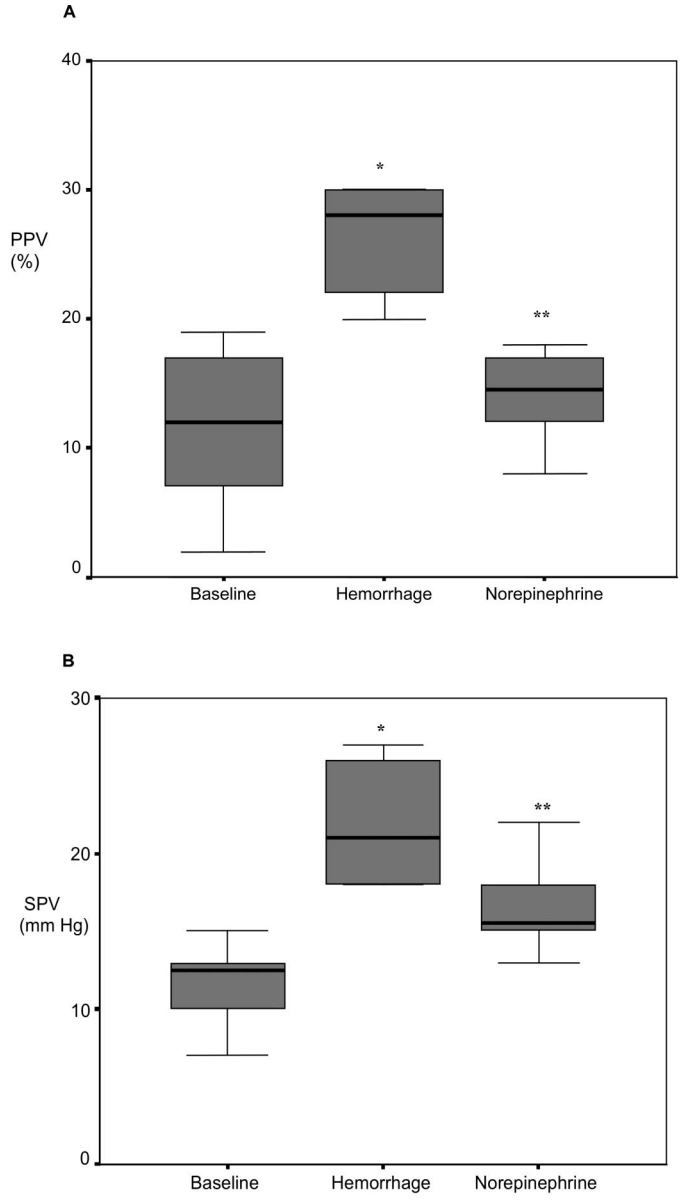

Figure 1. Box plots showing changes in comparison with baseline in pulse pressure variation (*PPV, A*) and arterial systolic pressure variation (*SPV, B*) following hemorrhage and treatment with norepinephrine. The line in each box indicates the median. The upper and lower limits of each box indicate the 75th and 25th percentiles, respectively. The error bars above and below each box represent the 90th and 10th percentiles, respectively. *$p < .05$ vs. baseline; **$p < .05$ vs. hemorrhage.

0.001 $\mu g \cdot kg^{-1} \cdot min^{-1}$), MAP increased significantly and reached baseline values. In addition, treatment of bled animals with NE induced a significant increase in CO and a further increase in SVR. However, under NE, CO remained significantly lower than its value at baseline. Neither RAP nor PAOP significantly changed with NE compared with values obtained after bleeding. Baseline PPV and SPV increased significantly with hemorrhage, from 12% (9%) to 28% (11.5%) ($p < .001$) and from 12.5 (6.5) to 21 (8.2) mm Hg ($p < .05$), respectively. With NE, both indexes decreased to levels not significantly different from baseline values (14.5% (6.2%) and 15.5 (4.5) mm Hg, respectively, for PPV and SPV; p not significant, Fig. 1). Changes in stoke volume index were inversely correlated with PPV ($r^2 = .71$, $p < .001$) and with SPV ($r^2 = .41$, $p < .05$, Fig. 2). PPV and SPV were correlated with each other ($r^2 = .53$; $p < .01$), but no correlation was observed between these indexes and RAP or PAOP.

DISCUSSION

In the present study we compared several indicators of cardiac preload in bled anesthetized dogs treated with NE. Pressure preload variables derived from the pulmonary artery catheter (RAP and PAOP) did not significantly change in response to hemorrhage or to NE infusion. Under the experimental conditions, neither RAP nor PAOP changes correlated with changes of SV. Conversely, PPV and SPV increased significantly after bleeding, and their changes correlated significantly with that of SV. However, the increase of PPV and SPV after bleeding was completely blunted under NE treatment without any apparent change of intravascular volume.

Consistent with the accumulating evidence, our results demonstrated the little value of RAP and PAOP in estimating cardiac preload, indicating clearly that a more accurate system is required that can effectively evaluate the need for fluid expansion (16–18). Recent studies have suggested that changes in arterial pressure induced by mechanical ventilation provide a reliable estimation of cardiac preload (18, 19). Respiratory variation of pulse pressure and systolic pressure was found to be a more reliable indicator of cardiac preload and fluid responsiveness than central venous pressure or PAOP (9). Our data confirm these findings, as among the four variables studied only PPV and SPV changed significantly following bleeding and NE infusion. A recent review comparing different indicators of cardiac preload found that static variables (RAP, pulmonary occluded pressure, right ventricular end-diastolic volume, and left ventricular end-diastolic area) had less capability of predicting fluid responsiveness in critically ill patients than dynamic indexes (inspiratory decrease in RAP, expiratory decrease in arterial systolic pressure, PPV, and respiratory changes in aortic blood velocity) (16). Whether PPV and SPV have the same accuracy in estimating fluid challenge responsiveness remains unresolved. Based on the fact that PPV is less affected than SPV by chest transmission of pleural pressure to the aorta, it has been suggested that PPV is a more specific predictor of changes in left ventricular stroke volume than SPV. In mechanically ventilated patients with acute circulatory failure related to sepsis, Michard et al. (9) demonstrated a closer correlation between PPV and volume expansion-induced changes in cardiac index than between PPV and changes in cardiac index. Although we did not perform fluid challenge to our animals, the significant elevation of PPV and SPV following bleeding suggests that both indexes could be used as surrogates to pre-

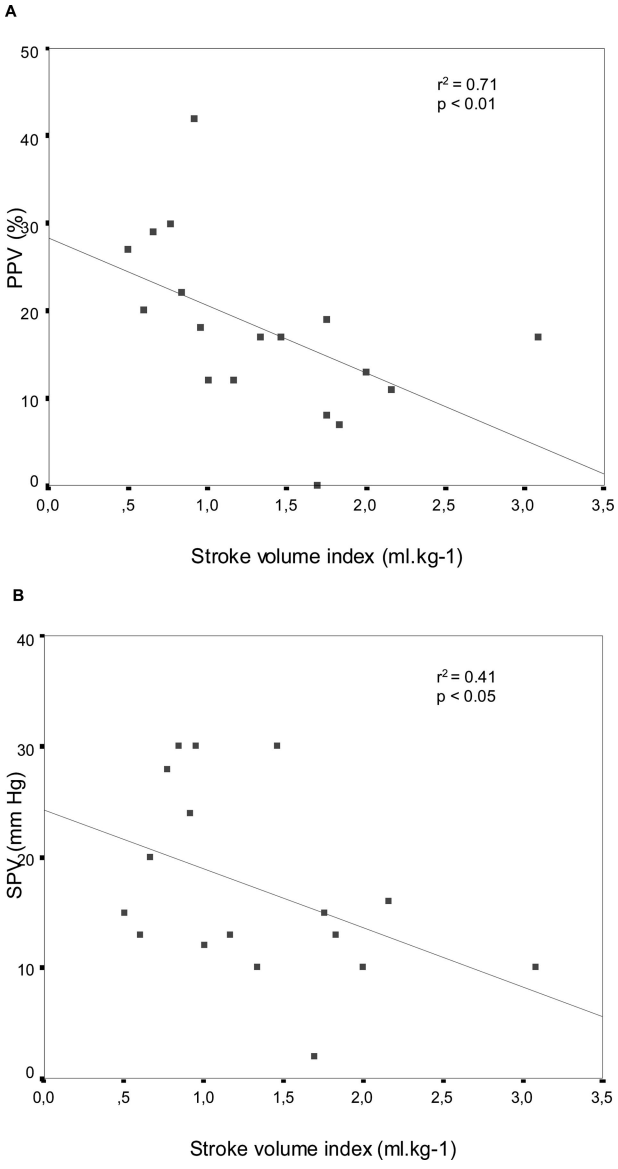

Figure 2. Correlation between pulse pressure variation (*PPV*, *A*) and arterial systolic pressure variation (*SPV*, *B*) and stroke volume index using pooled values for the group of six dogs. Regression lines and correlation coefficients are shown.

dict response to fluid challenge. More important, however, is the fact that PPV and SPV values might be altered by vasopressors, which are frequently required in hypotensive patients. It has long been known that vasopressors can increase cardiac output in hemorrhagic shock by decreasing unstressed volume. Thus, our finding of a decrease in PPV and SPV with NE is consistent with this hypothesis. By constriction of the capacitance vessels, NE as other vasoconstrictors can shift blood from unstressed to stressed volume and, thereby, increase venous return (20–23). The mechanism includes lowering splanchnic venous outflow resistance and an increase in fractional blood flow to regions with fast time constants. Although catecholamines could have other effects on microvascular fluid balance that could decrease total blood volume (24), blood redistribution seems the predominant effect of NE. In animal studies, unstressed volume is estimated between 70% and 75% of the total blood volume, meaning that a large fluid reserve could be recruited by endogenous or exogenous vasoconstrictors (25, 26). The role of the spleen in this regard should also be considered, but its magnitude compared with blood redistribution effect remains to be determined. It is quite possible that the effect on the pressure variation was produced by changes in arterial elastance. Although Michard et al. (9) argued that diastolic and systolic pressures should be affected equally by changes in pleural pressure, this analysis has been challenged (3). Indeed, phase-dependent changes in arterial elastance with aortic volume and pleural pressure variations have been well described. Whether the NE effect could be explained by improved preload or elastance needs to be further investigated. This distinction would have been more evident in analyzing in our study the two components deltaDown and deltaUp of arterial pressure variation. Unfortunately, this was not performed in our experiment. Nonetheless, whatever the mechanism considered, the common consequence of NE infusion is a significant decrease of PPV and SPV in hemorrhagic shock without any fluid expansion. An almost 40% decrease of PPV was observed under NE infusion at the dose used in our study. This "autotransfusion" effect should be kept in mind when interpreting physiologic variables such as PPV and SPV in patients treated with NE or drugs with similar pharmacodynamic properties. In these patients, quantitative prediction of the response to fluid challenge using threshold values of PPV and SPV may be misleading as under these thresholds clinicians will maintain the use of vasopressors instead of fluid expansion. We believe that the appropriate approach in this situation is to try a reduction in vasopressors requirements by fluid loading with a close monitoring of PPV or SPV.

Some limitations of our study must be considered. First, although PPV and SPV are accurate methods for defining preload responsiveness, they are still surrogates of stroke volume variation. The relationship between stroke volume variation and these variables could vary with NE; unfortunately, we were unable to determine the direction of this interaction in our study since we did not monitor stroke volume variation. However, studies in which stroke volume variation and PPV or SPV were simultaneously measured have shown significant correlations between the increase in cardiac index caused by fluid challenge and all these variables (27, 28). It is possible that with its effect on arterial elastance, NE infusion will alter the quantitative but not the qualitative value of this relationship value. Second, our results may not be relevant for all hypotensive patients using vasoconstrictive drugs, in particular those with sepsis, because adrenergic affinity to catecholamines is markedly reduced during endotoxin shock (29, 30). In addition, the effect of endotoxemia on the distribution of total

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blood volume between stressed and unstressed compartments is not known. Although the magnitude of NE effects on PPV and SPV values in septic shock is difficult to predict, it is not uncommon in clinical practice to try reducing NE dose by fluid loading (31). Third, we need to distinguish volume responsive from the need for volume. For example, in a septic patient there could be advantages to maintaining the patient on NE with a lower blood volume because of potential benefits on capillary leak.

CONCLUSIONS

The main finding of this study was the demonstration that in an experimental model of hemorrhagic shock, NE treatment reduced PPV and SPV. Extrapolated to the clinical setting, these indexes could mask a true fluid loss in hypotensive mechanically ventilated patients under NE. Therefore, to reduce vasoactive substance requirements in hemodynamically instable patients, fluid challenge could be considered even when PPV and SPV values are in the "normal" range. Finally, it should be highlighted that these dynamic variables are useful only if there are no spontaneous respiratory efforts.

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