

Effects of perfusion pressure on tissue perfusion in septic shock

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Objective: To measure the effects of increasing mean arterial pressure (MAP) on systemic oxygen metabolism and regional tissue perfusion in septic shock.

Design: Prospective study.

Setting: Medical and surgical intensive care units of a tertiary care teaching hospital.

Patients: Ten patients with the diagnosis of septic shock who required pressor agents to maintain a MAP \geq 60 mm Hg after fluid resuscitation to a pulmonary artery occlusion pressure (PAOP) \geq 12 mm Hg.

Interventions: Norepinephrine was titrated to MAPs of 65, 75, and 85 mm Hg in 10 patients with septic shock.

Measurements and Main Results: At each level of MAP, hemodynamic parameters (heart rate, PAOP, cardiac index, left ventricular stroke work index, and systemic vascular resistance index), metabolic parameters (oxygen delivery, oxygen consumption, arterial lactate), and regional perfusion parameters (gastric mucosal P_{CO_2} , skin capillary blood flow and red blood cell velocity, urine output) were measured.

Increasing the MAP from 65 to 85 mm Hg with norepinephrine resulted in increases in cardiac index from 4.7 ± 0.5 L/min/m² to 5.5 ± 0.6 L/min/m² ($p < 0.03$). Arterial lactate was 3.1 ± 0.9 mEq/L at a MAP of 65 mm Hg and 3.0 ± 0.9 mEq/L at 85 mm Hg (NS). The gradient between arterial P_{CO_2} and gastric intramucosal P_{CO_2} was 13 ± 3 mm Hg (1.7 ± 0.4 kPa) at a MAP of 65 mm Hg and 16 ± 3 at 85 mm Hg (2.1 ± 0.4 kPa) (NS). Urine output at 65 mm Hg was 49 ± 18 mL/hr and was 43 ± 13 mL/hr at 85 mm Hg (NS). As the MAP was raised, there were no significant changes in skin capillary blood flow or red blood cell velocity.

Conclusions: Increasing the MAP from 65 mm Hg to 85 mm Hg with norepinephrine does not significantly affect systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion. (Crit Care Med 2000; 28:2729–2732)

KEY WORDS: sepsis; sepsis syndrome; septic shock; norepinephrine; systemic hypotension; regional blood flow; gastric tonometry; lactate; arterial pressure; tissue oxygenation; laser-Doppler

Septic shock is characterized by hypotension, which is not reversed despite aggressive fluid resuscitation. Nitric oxide (1, 2), prostacyclin (3, 4), and bradykinins (5) are among the substances that cause decreases in arteriolar tone and vasodilation during septic shock. In addition, experimental studies suggest that sepsis results in down-regulation of adrenergic receptors, which may attenuate the response to endogenous and exogenous catecholamines (6). Impaired vascular reactivity has also been described in septic shock (7, 8), leading to the hypothesis that organ perfusion may be pressure dependent in this syndrome.

The primary vasoactive agents used in clinical practice to augment vascular tone are catecholamines. Of these agents, norepinephrine has been reported to improve renal and splanchnic perfusion in patients with septic shock (9, 10). However, the recommended end points with regard to mean arterial pressure (MAP)

vary considerably, ranging from 60 mm Hg, which represents the point at which organ perfusion becomes pressure dependent, to levels of 80 mm Hg to 90 mm Hg (10–12). The benefit of titrating catecholamine infusions to higher levels of arterial pressure has never been demonstrated and may adversely affect organ perfusion by inducing excessive vasoconstriction. Accordingly, the purpose of this study was to examine the effect of titrating norepinephrine to different levels of MAP on systemic and regional indices of perfusion.

MATERIALS AND METHODS

The protocol was approved by the Institutional Research Board of Saint Vincents Hospital and Medical Center, and written informed consent was obtained from the proxies or closest relatives of all patients admitted to the study. The study population included 10 patients admitted to the medical or surgical intensive care unit who met the following inclusion criteria: a) an identified site of infection; b) a systemic inflammatory response as indicated by a temperature $>38.2^\circ\text{C}$ or $<36.8^\circ\text{C}$, a heart rate >90 beats/min, a respiratory rate >20 breaths/min, or the need for

mechanical ventilation; c) MAP < 60 mm Hg despite fluid resuscitation to a pulmonary artery occlusion pressure (PAOP) >12 mm Hg; and d) the requirement for norepinephrine to maintain MAP ≥ 60 mm Hg (13). Patients with a need for varying doses of pressors or inotropic agents during the study period, other than norepinephrine, were excluded.

Heart rate (HR) was monitored continuously. Arterial pressure was monitored via an arterial catheter in either the radial or femoral artery. All patients were catheterized with a pulmonary artery catheter. Serial measurements of HR, MAP, PAOP, and central venous pressure were made. Transducers were referenced to the midaxillary line and all pressures were taken at end-expiration. Cardiac index (CI) was measured by thermodilution using measurements that varied by $<10\%$. Oxyhemoglobin saturation and content were measured with a co-oximeter (IL-282, Instrumentation Laboratories, Lexington, MA). Arterial, mixed venous, and tonometrically measured CO_2 tensions were determined by a blood gas analyzer (Nova Biomedical Stat Profile 5, Waltham, MA). Arterial lactate levels were determined by the enzymatic method (Vitros 950 lactate analyzer, Johnson & Johnson, Rochester, NY). Derived hemodynamic variables were calculated from standard formulae: systemic vascular resistance index (SVRI) (dyne·sec/

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$\text{cm}^5\cdot\text{m}^2$) = (MAP – central venous pressure / CI) \times 80; systemic oxygen delivery ($\dot{V}\text{O}_2$) (mL/min/m²) = arterial oxygen content \times CI; systemic oxygen consumption ($\dot{V}\text{O}_2$) (mL/min/m²) = arteriovenous oxygen content difference \times CI; left ventricular stroke work index (g·m/m²) = CI / HR \times (MAP – PAOP) \times 0.0136.

A tonometric nasogastric tube was inserted into the stomach (TRIP NGS Catheter, Tonometrics, Worcester, MA), after which radiographic confirmation of catheter position was obtained. All patients were placed on intravenous famotidine. Phosphate-buffered solution was used to improve the accuracy of the measurements (14). Intraluminal Pco_2 was measured from 1.5-mL samples that were aspirated from the catheter balloon anaerobically after discarding the first 1 mL. The mucosal Pco_2 measurement was multiplied by the appropriate equilibration factor provided by the manufacturer. Laser-Doppler measurements of skin red blood cell flow and velocity were recorded from the ventral surface of one forearm (ALF21R Advance Laser Flowmeter, Advance Company, Tokyo, Japan). To measure urine output, drainage from a Foley catheter was emptied before and after the measurement periods.

Ventilator settings were adjusted to a tidal volume of 8–10 mL/kg at a rate set to meet the patients' ventilatory requirements with an oxygen saturation of >90%. All patients were treated with 250-mL aliquots of 5% albumin or 6% hetastarch to attain a PAOP of 12 mm Hg. Patients were transfused with packed red blood cells if, at study admission, the hemoglobin was <9 g/dL. Patients were sedated with lorazepam or propofol; however, no additional sedation, antipyretics, or vasoactive drugs were administered during the study period.

After entering into the study, the patient's norepinephrine dose was adjusted to attain a MAP of 65 mm Hg. After a titration and equilibration period of 45 mins, an additional 60 mins then elapsed during which no alterations in other vasoactive medications were permitted. Hemodynamic data were then collected and arterial lactate, blood gases, urine output, tonometric data, and laser-Doppler measurements were recorded. The norepinephrine dose was then increased to attain a MAP of 75 mm Hg during a 45-min period, and measurements were repeated after an additional 60-min period of hemodynamic stability. Finally, the norepinephrine dose was increased to attain a MAP of 85 mm Hg, and data were again collected after the two periods.

Group differences were analyzed using repeated-measures analysis of variance (ANOVA) with the Greenhouse-Geisser adjustment; because of the small sample size, an extension for linear trends was also examined. Differ-

ences were considered significant at $p < .05$. Data are presented as mean \pm SE.

RESULTS

Seven men and three women were entered into the study (Table 1). Four patients had pneumonia and six had an intra-abdominal source of sepsis. Two patients were anuric and on continuous venovenous hemofiltration during the study. Patients were studied within the first 24 hrs of their course but after initial hemodynamic stabilization. One patient was receiving dobutamine, and five patients were receiving low-dose dopamine. The average Acute Physiology and Chronic Health Evaluation (APACHE) II score was 29 ± 3 at the time of entry. Three patients survived to the 30-day follow-up.

The dose of norepinephrine was 23 ± 22 $\mu\text{g}/\text{min}$ to maintain a MAP of 65 mm Hg, 31 ± 25 $\mu\text{g}/\text{min}$ to maintain a MAP of 75 mm Hg, and 47 ± 39 $\mu\text{g}/\text{min}$ to maintain a MAP of 85 mm Hg (Table 2). The highest dose of norepinephrine required by an individual patient to maintain a MAP of 65 mm Hg was 53 $\mu\text{g}/\text{min}$, to maintain a MAP of 75 mm Hg was 65 $\mu\text{g}/\text{min}$, and to maintain a MAP of 85 mm Hg was 115 $\mu\text{g}/\text{min}$. There was an increase in CI from 4.7 ± 0.5 L/min/m² to 5.5 ± 0.6 L/min/m² as the norepinephrine dose was increased to attain a MAP of 85 mm Hg. This was not a statistically significant difference by ANOVA, but it did exhibit a significant linear trend ($p < 0.03$; Table 2). As the norepinephrine infusion was increased, SVRI increased from 998 ± 94 dyne·sec/cm⁵·m² at 65 mm Hg to 1065 ± 101 dyne·sec/cm⁵·m² at 75 mm Hg and to 1216 ± 159 dyne·sec/cm⁵·m² at 85 mm Hg, which exhibited a significant linear trend ($p < 0.046$). Increasing the dose of norepinephrine was associated with significant changes in HR but not in PAOP. A significant increase in left ventricular stroke work index was observed that primarily reflected an increase in pressure work.

Increases in oxygen delivery and consumption at each level of MAP were observed, but the linear trend was only significant for oxygen delivery (Table 3). Mixed venous oxygen saturation and arterial lactate levels were unchanged throughout the study. Changes in skin capillary blood flow were not significant, and erythrocyte velocity also did not change with increasing doses of norepinephrine (Table 4). There were modest

Table 1. Characteristics of 10 patients with septic shock

Age (yrs)	68 \pm 12
APACHE II	29 \pm 2.7
M/F	7/3
Dobutamine/dopamine	1/5
Cause of sepsis	
Cholecystitis	3
Pneumonia	4
Urosepsis	1
Colitis	2

Data for age and Acute Physiology and Chronic Health Evaluation (APACHE) II score are presented as mean \pm SE.

increases in gastric intramucosal Pco_2 that were not statistically significant, and there were no changes in the arterial-intramucosal Pco_2 gradient at the different levels of arterial pressure. No changes in urinary output were observed as MAP was increased.

DISCUSSION

Norepinephrine is frequently used to improve arterial pressure in patients with septic shock who remain hypotensive after fluid infusion. The dose of norepinephrine used in our study is in the mid-range of infusion rates reported in previous studies, where MAP levels of >80 mm Hg were achieved (10, 15, 16). Both β - and α -adrenergic receptors are stimulated with norepinephrine. However, the primary hemodynamic effect of this drug is to increase SVR and thereby increase MAP. Increases in cardiac output are usually modest but may occur, as was observed in our study, and can contribute to an increase in MAP as also evidenced in our study (17, 18).

Oxygen delivery increased in parallel with the increase in CI. There was a tendency to increased oxygen consumption in our study, but this may have reflected primarily the thermogenic effect of catecholamines on metabolic rate (19, 20). Alternatively, the increase in the calculated oxygen consumption may reflect the interaction of dependent variables (21). Lactate levels did not change, which suggests that increasing the degree of vasoconstriction as MAP was increased from 65 mm Hg to 85 mm Hg did not adversely affect systemic tissue perfusion. Similarly, there were no significant adverse effects on microcirculatory blood flow in the subcutaneous tissues as measured by laser-Doppler. The lack of any adverse effects related to vasoconstriction probably results from the fact that al-

though vascular tone increased as the norepinephrine infusion was increased, SVRI remained well within the normal range. This physiology contrasts with forms of shock in which cardiac output is decreased, where the primary effect of norepinephrine is to increase vascular resistance to levels in excess of the normal range and to potentially compromise tissue perfusion (22).

Norepinephrine has been reported to have variable effects on splanchnic blood flow in septic shock. In some cases,

splanchnic mucosal perfusion improved (9, 23), whereas in others, deterioration has been observed (18, 24). In our study, there was no significant change in gastric intramucosal PCO_2 and the arterial-intramucosal PCO_2 gradient as the norepinephrine dose was increased, suggesting that vasoconstriction associated with increasing the norepinephrine infusion did not redistribute blood away from the splanchnic circulation. This observation is consistent with experimental studies which suggest that adrenergic agents do

not significantly redirect blood flow away from the splanchnic circulation in septic shock (25).

There also was no change in urinary output observed in our study as the MAP was increased with norepinephrine. This pattern contrasts with several previous reports suggesting that norepinephrine improved renal function as measured by urinary flow and creatinine clearance (10, 16, 26). The difference between our study and those reports demonstrating improved renal function primarily reflects that fact that our baseline was a MAP of 65 mm Hg rather than the more hypotensive levels that characterized the previous studies. Indeed, in many of the previous reports the initial levels of MAP were in the range of 55 mm Hg, levels below the autoregulatory threshold for renal blood flow (27).

The goal of vasopressor therapy is to improve arterial pressure while avoiding excessive vasoconstriction. The minimum acceptable level of MAP that is most commonly cited is 60 mm Hg. This level of MAP represents the point at which autoregulatory control of blood flow to the heart, kidneys, and brain ceases, resulting in pressure-dependent organ blood flow (28–30). In patients with hypertensive disease or atherosclerotic disease, the autoregulatory curve may be shifted to the right, requiring higher pressures to maintain organ perfusion. The ability to autoregulate blood flow may also be altered by organ injury as has been demonstrated in acute renal failure and in head injury (31, 32). Alterations in vascular reactivity with septic shock may also potentially alter the relationship between blood flow and organ perfusion, resulting in a wider range of pressure-dependent perfusion. These concerns have led to therapeutic protocols in which pressor therapy is titrated to levels of MAP between 80 mm Hg and 90 mm Hg (10, 11). Our study does not support the hypothesis that tissue perfusion is pressure dependent over the range of 65 mm Hg to 85 mm Hg and suggests little benefit in increasing the MAP to >65 mm Hg. Conversely, our data also suggest that in vasodilated patients with septic shock, the use of vasopressors to increase vascular tone toward more normal values of vascular resistance does not adversely affect tissue perfusion.

A limitation to our study is the small number of patients and short infusion period. Despite the sample size, significant changes in hemodynamic variables

Table 2. Changes in hemodynamic parameters as mean arterial pressure (MAP) is increased from 65 mm Hg to 85 mm Hg with norepinephrine

	MAP			F/LT
	65 mm Hg	75 mm Hg	85 mm Hg	
HR (beats/min)	97 ± 4	101 ± 4	105 ± 5	.02/.02
MAP (mm Hg)	65 ± 0.5	75 ± 0.4	86 ± 0.4	.0001/.0001
CI (L/min/m ²)	4.7 ± 0.5	5.3 ± 0.6	5.5 ± 0.6	.07/.03
PAOP (mm Hg)	14 ± 1	15 ± 1	16 ± 1	.18/.16
LVSWI (g·m/m ²)	45 ± 3	52 ± 5.5	63 ± 7	.01/.01
SVRI (dyne·sec/m ² ·cm ⁵)	998 ± 94	1065 ± 101	1216 ± 159	.09/.046
Norepinephrine (µg/min)	23 ± 22	31 ± 25	47 ± 39	.02/.016

F, *p* value for repeated-measures analysis of variance (ANOVA) as MAP is increased from 65 mm Hg to 85 mm Hg; LT, *p* value for extension of ANOVA for linear trend; HR, heart rate; CI, cardiac index; PAOP, pulmonary artery occlusion pressure; LVSWI, left ventricular stroke work index; SVRI, systemic vascular resistance index.

Data are presented as mean ± SE.

Table 3. Indices of systemic oxygen metabolism as mean arterial pressure (MAP) is increased from 65 mm Hg to 85 mm Hg

	MAP			F/LT
	65 mm Hg	75 mm Hg	85 mm Hg	
$\dot{D}O_2$ (mL/min/m ²)	620 ± 59	670 ± 59	703 ± 74	.07/.02
$\dot{V}O_2$ (mL/min/m ²)	119 ± 12	138 ± 20	153 ± 20	.24/.11
$S\bar{v}O_2$ (%)	76 ± 3	76 ± 2	70 ± 2	.94/.76
Lactate (mEq/L)	3.1 ± 0.9	2.9 ± 0.8	3.0 ± 0.9	.55/.77

F, *p* value for repeated-measures ANOVA as MAP is increased from 65 mm Hg to 85 mm Hg; LT, *p* value for extension of ANOVA for linear trend; $\dot{D}O_2$, oxygen delivery; $\dot{V}O_2$, oxygen consumption; $S\bar{v}O_2$, venous oxygen saturation.

Data are presented as mean ± SE.

Table 4. Indices of regional perfusion as MAP is increased from 65 mm Hg to 85 mm Hg

	MAP			F/LT
	65 mm Hg	75 mm Hg	85 mm Hg	
Urinary output (mL)	49 ± 18	56 ± 21	43 ± 13	.60/.71
Capillary blood flow (mL/min/100 g)	6.0 ± 1.6	5.8 ± 1.2	5.3 ± 0.9	.59/.55
Red cell velocity (au)	0.42 ± 0.06	0.44 ± 0.06	0.42 ± 0.06	.74/.97
$PiCO_2$ (mm Hg)	41 ± 2	47 ± 2	46 ± 2	.11/.12
Pa- $PiCO_2$ (mm Hg)	13 ± 3	17 ± 3	16 ± 3	.27/.40

F, *p* value for repeated-measures analysis of variance (ANOVA) as MAP is increased from 65 mm Hg to 85 mm Hg; LT, *p* value for extension of ANOVA for linear trend; au, arbitrary units; $PiCO_2$, gastric intramucosal PCO_2 ; Pa- $PiCO_2$, arterial-gastric intramucosal CO_2 gradient.

Data are presented as mean ± SE.

were observed that were not evident in the perfusion-related variables. The infusion period was purposefully kept short to avoid the background effects of changes in the patients' underlying conditions. Although changes in lactate may take longer to equilibrate between interventions, it should be noted that there were no significant changes in lactate over the entire 6-hr study period (33, 34). Similarly, although the temporal relationship between changes in splanchnic blood flow and changes in arterial-intramucosal Pco_2 gradient is unclear, there was also no significant change in this parameter over the time of the study.

It is also important to note that the average age of patients in our study was 68 yrs, suggesting that our results should be applicable to an older, sicker patient population. However, only three patients had a previous history of hypertension, and it is possible that this group of patients may benefit from higher levels of arterial pressure. A confounding variable in our study was that many of the patients were receiving dopamine. This agent has been observed to significantly enhance renal blood flow in the face of adrenergic vasoconstriction and may have mitigated some of the effects of increased vasoconstriction associated with higher doses of norepinephrine (35, 36). Finally, our observations may not be applicable in patients in whom vascular resistance is increased with norepinephrine in excess of the normal range in an effort to increase arterial pressure.

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