

The Contrasting Effects of Dopamine and Norepinephrine on Systemic and Splanchnic Oxygen Utilization in Hyperdynamic Sepsis

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Objective.—To compare the effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in patients with hyperdynamic sepsis.

Design.—A randomized short-term, interventional study.

Setting.—An intensive care unit of a university hospital.

Patients.—Twenty septic patients with a cardiac index greater than $3.2 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and either a mean arterial pressure (MAP) less than 60 mm Hg or a systemic vascular resistance index less than $1200 \text{ dyne}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$.

Methods and Interventions.—Patients were randomized to receive an infusion of either dopamine or norepinephrine titrated to increase the MAP to greater than 75 mm Hg. The hemodynamic profile, oxygen delivery, oxygen consumption (determined by indirect calorimetry), and gastric intramucosal pH (pHi) (determined by gastric tonometry) were determined at baseline and after 3 hours of achieving the target MAP.

Results.—Dopamine increased the MAP largely by increasing the cardiac index whereas norepinephrine increased the MAP by increasing the systemic vascular resistance index while maintaining the cardiac index. Although oxygen delivery and oxygen consumption increased in both groups of patients, the pHi increased significantly in those patients treated with norepinephrine whereas the pHi decreased significantly in those patients receiving dopamine ($P < .001$, for corrected 3-hour value).

Conclusions.—This study suggests that dopamine may cause an uncompensated increase in splanchnic oxygen requirements in septic patients. Norepinephrine, however, may have a more favorable hemodynamic profile and improve splanchnic tissue oxygen utilization in sepsis.

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THE REPORTED incidence of the sepsis syndrome in US hospitals has increased 139% in the last decade.¹ The use

of immunosuppressive therapy, an aging population, improved survival of individuals with debilitating illnesses, and invasive medical procedures are thought to have contributed to this increase.²⁻⁴ Despite initial optimism, antiendotoxin and anticytokine therapy appears to have little role in the treatment of sepsis.⁴ Broad-spectrum antibiotics and fluid resuscitation therefore remain the cornerstone of treatment in patients with sep-

tic syndrome and septic shock. However, despite adequate fluid resuscitation, many septic patients remain hypotensive with evidence of inadequate tissue oxygen utilization.⁵ Inotropic agents are almost always used in this situation to increase blood pressure and improve tissue oxygen delivery. Dopamine is considered by many to be the inotropic agent of choice in this situation.^{2,5}

The oxygen utilization abnormality in sepsis may be due to the combined effects of a low mean perfusion pressure together with capillary endothelial damage, resulting in sluggish capillary flow, microcapillary occlusion, and functional arteriovenous shunting.^{6,7} Recent data suggest that in septic patients dopamine may increase splanchnic oxygen requirements and increase functional arteriovenous shunting.⁸ Segal and coworkers⁹ demonstrated in a hemorrhagic animal model that dopamine hastened the onset of splanchnic ischemia. Norepinephrine is less thermogenic than dopamine and has differing hemodynamic effects in septic patients.¹⁰⁻¹² However, due to the fear of excessive vasoconstriction, this agent has not been widely used.¹⁴ We hypothesized that in hyperdynamic sepsis norepinephrine may have a more desirable effect on splanchnic microcapillary flow and tissue oxygen utilization than does dopamine. The aim of this study was to compare the short-term effects of an infusion of dopamine and norepinephrine on the hemodynamic profile and systemic and splanchnic oxygen utilization in patients with hyperdynamic sepsis.

METHODS

This study was conducted in an intensive care unit of a university hospital. The study protocol was approved by the university review board. Patients were eligible for entry if they met the following criteria: a definable sepsis syndrome, positive blood cultures, and standard criteria for sepsis. Patients were excluded if they had a cardiac index less than $3.2 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ or a systemic vascular resistance index less than $1200 \text{ dyne}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{m}^{-2}$, a mean arterial pressure (MAP) less than 60 mm Hg, or were on mechanical ventilation. Patients were also excluded if they had a central venous catheter with a positive bacterial culture, a central venous catheter with a positive blood culture, or if they had a central venous catheter with a positive blood culture. In addition, patients were excluded if they had a central venous catheter with a positive blood culture, a central venous catheter with a positive blood culture, or if they had a central venous catheter with a positive blood culture.

Study Maneuvers

Patients were enrolled in the study if they were in the intensive care unit of a university hospital and had a central venous catheter with a positive bacterial culture, a central venous catheter with a positive blood culture, or if they had a central venous catheter with a positive blood culture. Patients were enrolled in the study if they were in the intensive care unit of a university hospital and had a central venous catheter with a positive bacterial culture, a central venous catheter with a positive blood culture, or if they had a central venous catheter with a positive blood culture. Patients were enrolled in the study if they were in the intensive care unit of a university hospital and had a central venous catheter with a positive bacterial culture, a central venous catheter with a positive blood culture, or if they had a central venous catheter with a positive blood culture.

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METHODS

This study was conducted in the critical care unit of a teaching hospital. The study protocol was approved by the university review board. Patients were eligible for entry into this study if they had a definable source of infection and/or positive blood cultures, met the standard criteria for sepsis,³ and after adequate fluid resuscitation (pulmonary capillary wedge pressure >12 mm Hg) had a cardiac index greater than 3.2 L·min⁻¹·m⁻² and either a systemic vascular resistance index (SVRI) less than 1200 dyne·s·cm⁻⁵·m⁻² or a mean arterial pressure (MAP) less than 60 mm Hg, and who were undergoing mechanical ventilation. Patients requiring dialysis, patients with active upper gastrointestinal bleeding, and patients unlikely to survive longer than 24 hours following initiation of the study were excluded. In addition, patients who required an inspired oxygen concentration greater than 70% to maintain an arterial oxygen saturation of greater than 90% were also excluded from the study.

Study Maneuvers

Patients were studied within 24 hours of developing sepsis. A nasogastric tonometer (Tonometrics Inc, Hopkinton, Mass) was inserted, and its position was confirmed radiologically. To improve the accuracy of the measurement of the gastric intramucosal pH (pHi), all patients received intravenous ranitidine. If not already in situ, a 7.5F flow-directed hemodilution pulmonary artery catheter with a fast-response thermistor (Baxter, Irvine, Calif) was inserted.

Patients were fluid resuscitated to achieve a pulmonary capillary wedge pressure of greater than 12 mm Hg. To minimize changes in oxygen uptake unrelated to the intervention, patients were sedated with a midazolam and morphine infusion, and a vecuronium infusion was used for neuromuscular blockade. In addition, the patients were not turned or suctioned, and they did not receive physiotherapy or have a roentgenographic examination during the study period. Ventilation was adjusted to maintain an arterial pH greater than 7.29 and an arterial saturation greater than 90%. No changes in ventilator settings were permitted during the study period.

Patients were randomized using a random-number generator to receive an infusion of dopamine or norepinephrine. After baseline measurements were obtained, the vasoactive agent was titrated during a period of 20 minutes to achieve a MAP greater than 75 mm Hg (and in the case of dopamine, the dose was also titrated to keep the pulse rate less than

Table 1.—Patient Demographic Data (Mean±SD)

	Norepinephrine	Dopamine*
Age, y	46±7	46±4
Sex, M:F	6:4	5:5
Hemoglobin level, g/L	103±6	95±3
White blood cell count, ×10 ⁹ /L	8.1±2.1	14.1±2.7
Serum urea nitrogen level, mmol/L (mg/dL)	10.0±2.9 (28±8)	10.7±3.6 (30±10)
Acute Physiology and Chronic Health Evaluation II score	18±1	17±2

*No significant differences between groups.

Table 2.—Patients' Clinical Data

Age, y	Diagnosis	Outcome
Norepinephrine		
35	Pneumococcal pneumonia	Alive
32	Pneumococcal pneumonia	Dead
39	<i>Pseudomonas</i> pneumonia	Dead
45	<i>Klebsiella</i> pneumonia	Alive
62	Urosepsis, pneumonia	Alive
67	Urosepsis, gram-negative septicemia	Alive
68	Urosepsis, gram-negative septicemia	Dead
49	Pulmonary tuberculosis, gram-negative septicemia	Dead
32	Pancreatitis, gram-negative septicemia	Dead
38	Cellulitis, septicemia	Alive
Dopamine		
40	Pneumococcal pneumonia	Dead
64	Pneumococcal pneumonia	Alive
29	Pneumococcal pneumonia	Dead
42	Gram-negative pneumonia	Dead
92	Gram-negative pneumonia	Dead
27	Glioma, gram-negative septicemia	Alive
78	Myeloma, gram-negative septicemia	Dead
62	Acute renal failure, gram-negative septicemia	Dead
64	Urosepsis, gram-negative septicemia	Alive
54	Adult respiratory distress syndrome, gram-negative septicemia	Alive

150 beats per minute). The use of other vasoactive agents was not permitted during the study period. Each patient was studied once and did not cross over to the other limb of the study. Once the desired MAP was achieved no alteration in rate of infusion of the inotropic agent or fluid was permitted until the end of the study period.

Study Measurements

A data set was collected at baseline and repeated 3 hours later. Each data set included complete blood cell count, arterial blood lactate concentration, a hemodynamic and oxygenation profile, and a pHi measurement. Hemodynamic data included pulmonary arterial pressure, heart rate, central venous pressure, MAP, pulmonary capillary wedge pressure, cardiac output, and right ventricular ejection fraction. Cardiac output determinations were made using 10 mL of injectate at 0°C and cardiac output computer (Explorer, Baxter). Arterial blood and mixed venous blood were sampled simultaneously with the cardiac output measurements for determination of blood gas values (ABL3, Radiometer, Copenhagen, Denmark) and

hemoglobin saturation (OSM 3 Hemoximeter, Radiometer). Oxygen delivery and systemic vascular resistance were calculated using a standard formula. All flow and volume measurements were indexed to body surface area. Hemoglobin concentration was measured using a Coulter analyzer (Coulter Electronics, Hialeah, Fla). Arterial blood specimens for lactate determination were analyzed using an enzymatic method (2300 Stat Analyzer, YSI Inc, Yellow Springs, Ohio). The normal range of plasma lactate for our laboratory is 1.2 to 2.2 mmol/L. The Acute Physiology and Chronic Health Evaluation II score was used as an index of disease severity.

Gastrointestinal oxygenation was indirectly assessed by measuring the pHi using a nasogastric tonometer (Tonometrics Inc). The tonometer is a nasogastric tube with a silicone balloon that is freely permeable to carbon dioxide at its distal end. Gastric intramucosal pH as measured by tonometry has been validated by direct measurement using microelectrodes,¹⁵ and the measurements obtained reflect the adequacy of splanchnic aerobic metabolism.¹⁶ The normal pHi is 7.39±0.03 (mean±SD).¹⁷ The balloon of

shock. However, resuscitation, remain hypotensive. Inadequate tissue perfusion. Vasoactive agents are his situation to and improve tissue perfusion. Dopamine is considered an inotropic agent.

abnormality in the combined perfusion pressure and endothelial damage. Capillary flow, and functional shunt. Recent data on patients receiving dopamine show increased oxygen requirements. Vasoconstrictive effects on arterial perfusion. Dopamine and norepinephrine have similar effects on peripheral vasoconstriction. Dopamine may have a more pronounced effect on splanchnic microcirculation. Oxygen utilization. The aim of this study was to compare the short-term effects of dopamine and norepinephrine on hemodynamic and splanchnic oxygenation in hyper-

Table 3.—Hemodynamic and Oxygenation Data of Patients Treated With Norepinephrine or Dopamine (Mean±SEM)

	Norepinephrine (n=10)			Dopamine (n=10)			Changes at 3 Hours, P*
	Baseline	3 Hours	P	Baseline	3 Hours	P	
Heart rate, beats/min	105±5	102±3	.20	121±4	139±3	.001	.002
Mean arterial pressure, mm Hg	65±4	67±4	<.001	63±2	87±3	<.001	.60
Mean pulmonary arterial pressure, mm Hg	27±3	31±2	.03	29±2	34±3	.005	.70
Pulmonary capillary wedge pressure, mm Hg	15±1	16±1	.20	15±1	16±1	.10	.70
Cardiac index, L·min ⁻¹ ·m ⁻²	4.2±0.5	4.7±0.4	.01	4.2±0.4	5.3±0.7	.008	.05
Right ventricular ejection fraction	28.6±3.2	31.1±3.0	.008	28.4±3.4	33.3±3.7	.02	.50
Left ventricular stroke work index	29±4	44±7	.007	25±4	37±5	<.001	.50
Systemic vascular resistance index, dyne·s·cm ⁻⁵ ·m ⁻²	1110±109	1405±107	.005	1035±77	1221±130	.10	.50
Oxygen delivery index, ml·min ⁻¹ ·m ⁻²	498±77	590±66	.01	673±54	703±89	.02	.70
Oxygen consumption index, ml·min ⁻¹ ·m ⁻²	145±21	149±22	.05	183±29	221±38	.001	.20
Intramuscular pH	7.16±0.07	7.23±0.07	.008	7.24±0.04	7.18±0.05	.02	.001
Lactate, mmol/L	1.8±0.5	1.9±0.43	.60	2.2±0.4	2.1±0.4	.60	.60

*Difference between the 3-hour values of dopamine and norepinephrine, correcting for baseline values

the tonometer was filled with 2.5 mL of normal saline and allowed to equilibrate (starting 90 minutes before each data set) with the gastric mucosa. Once equilibrated, the balloon was aspirated, and the carbon dioxide tension of the fluid was determined using the ABL3 blood gas analyzer. The pHi was then calculated by substituting the partial pressure of carbon dioxide and arterial bicarbonate concentration into the Henderson-Hasselbalch equation.^{16,17}

Systemic oxygen uptake was measured by using a portable system of indirect calorimetry (Deltatrac Metabolic Monitor, Datex Instrumentation Corp, Helsinki, Finland). This system measures oxygen and carbon dioxide concentrations in inspired and expired gases during each minute and then calculates carbon dioxide production and oxygen uptake for the minute. This system has been shown to be accurate, reproducible, and sensitive.¹⁸ The metabolic monitor was calibrated before each measurement. After 5 minutes of stabilization, oxygen uptake was measured for a period of 20 minutes. The average coefficient of variation for each 20-minute period for the 20 patients studied was 7.8%.

Statistics

At the end of the data collection, summary statistics were compiled to allow a description of the study population. The baseline and 3-hour data for each group of patients was compared using the paired Student's *t* test. The baseline and 3-hour (corrected for baseline differences) data between the groups were compared using the unpaired Student's *t* test. Unless otherwise stated, all data are expressed as the mean±SEM.

RESULTS

Twenty patients were studied, 10 in each group. The patients' clinical and demographic data are presented in

Tables 1 and 2. The mean infusion rate of dopamine was 26±3.8 µg/kg per minute, and that of norepinephrine was 0.18±0.06 µg/kg per minute. The patients' hemodynamic and oxygenation data are presented in Table 3. There were no significant differences in any of the baseline parameters between the two groups of patients.

Dopamine increased the MAP by 38%, largely due to an increase in the cardiac index. In contradistinction, norepinephrine increased the MAP by 37%, predominantly due to an increase in the SVRI. Although oxygen delivery and oxygen consumption increased in both groups of patients, the pHi increased significantly in those patients treated with norepinephrine whereas the pHi decreased significantly in those patients receiving dopamine. The difference in the 3-hour pHi between the two groups of patients was significant (*P*<.001).

COMMENT

In this study, we demonstrated that dopamine increased both systemic oxygen delivery and oxygen consumption in patients with hyperdynamic sepsis. Yet, despite an increased oxygen delivery, the pHi, a surrogate marker of tissue oxygenation, decreased. In contrast, norepinephrine resulted in a significant increase in pHi, despite a less significant increase in systemic oxygen delivery. These findings suggest that dopamine increased splanchnic oxygen utilization, which was uncompensated for by the increased oxygen delivery consequent on the drugs' inotropic and chronotropic effects, the net result being an increase in the splanchnic oxygen debt (as reflected by the decrease in pHi). Norepinephrine, however, appeared to have a more favorable effect on the balance between splanchnic oxygen delivery and oxygen utilization. The results of this study may therefore challenge many of the conven-

tional wisdoms concerning the use of inotropic agents in the management of hyperdynamic sepsis.^{2,5,9,12,21}

While a number of studies have investigated the effects of dopamine and/or norepinephrine on the hemodynamic profile and oxygen utilization pattern in hyperdynamic sepsis, none have simultaneously followed the changes in indexes of tissue oxygenation and at the same time independently measured oxygen consumption.^{5,10,13,22} Measurements of systemic oxygen delivery and oxygen consumption provide little information as to the adequacy of tissue oxygenation. This data must be interpreted in conjunction with indexes of tissue oxygenation. Furthermore, due to mathematical coupling (of systemic oxygen delivery with oxygen consumption), oxygen consumption should be measured independently.²³

We found that dopamine increased the MAP predominantly by increasing cardiac output whereas norepinephrine increased the MAP by increasing vascular tone, without compromising cardiac output. This suggests that in hyperdynamic sepsis dopamine acts largely by increasing flow whereas norepinephrine increases vascular resistance without compromising flow. These observations have been documented previously.^{5,11,13,22} At low doses, dopamine normally improves ventricular contractility and cardiac output by its β₁-adrenergic properties, and at high doses, it increases systemic vascular resistance by α₁-adrenergic receptor stimulation resulting in increased blood pressure. In hyperdynamic sepsis, however, the β₁-adrenergic properties of dopamine predominate regardless of dose.¹¹ The net effect is an increase in cardiac output and mean blood pressure, with the SVRI remaining unchanged or even decreasing slightly.¹¹⁻¹³ Norepinephrine, on the other hand, has both α₁-adrenergic and β₁-ad-

renergic properties dominating. In hyperdynamic sepsis, the net effect of norepinephrine is to increase afterload, thereby decreasing cardiac output.

Although dopamine increases splanchnic oxygen delivery, it could minimize directed splanchnic blood flow, probably because of the effects of dopamine on the splanchnic vasculature. Oxygen utilization in hyperdynamic sepsis is a dynamic process, and they found that splanchnic oxygenation improved with 37% surprisingly, however, splanchnic oxygen utilization was only 16% compared with normal. Vasaro et al²⁴ found that dopamine in eight patients with primary artery bypass grafting had a synthetic β₂-adrenergic and

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Changes at 3 Hours, p	
1	.002
1	.60
5	.70
5	.70
9	.05
1	.50
1	.60
1	.20
1	.20
1	<.001
1	.80

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dominating. In hyperdynamic sepsis, the
net effect of norepinephrine may be to
increase afterload (SVRI) with the
drugs' β_1 -adrenergic activity maintain-
ing cardiac output.

Although dopamine increased systemic
oxygen delivery by 23%, the pHi de-
creased. It could be argued that dopa-
mine directed flow away from the
splanchnic bed. This, however, seems im-
probable. Ruokonen and coworkers⁸ com-
pared the effects on dopamine and nore-
pinephrine on the pattern of splanchnic
oxygen utilization in patients with hy-
perdynamic sepsis using a dye dilution
technique and hepatic venous sampling.
They found that dopamine increased
splanchnic oxygen delivery by 65% com-
pared with 33% for norepinephrine. Sur-
prisingly, however, dopamine increased
splanchnic oxygen consumption by only
16% compared with 28% for norepineph-
rine. Uusaro et al²⁴ repeated this experi-
ment in eight patients following coro-
nary artery bypass surgery, using dopex-
amine (a synthetic catecholamine with
 β_2 -adrenergic and dopaminergic activity)

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as the inotropic agent. In this study, pHi measurements were also performed. Uusaro et al²⁴ found that splanchnic oxygen delivery and oxygen consumption increased, but the pHi decreased. These data are supported by a number of animal studies. In a dog model, Giraud and MacCannell²⁵ demonstrated that dopamine resulted in a net increase in splanchnic blood flow, but redistribution away from the gut mucosa occurred resulting in decreased splanchnic oxygen extraction. Similarly, in a hemorrhagic dog model, Segal and coworkers⁹ demonstrated that dopamine decreased the ability of the gut to extract oxygen and hastened the onset of gut ischemia.

We postulate that dopamine may increase gut mucosal oxygen needs and at the same time redistribute blood flow within the gut, resulting in reduced mucosal blood flow. The net effect would be to increase the mucosal oxygen debt.

It could be argued that the lack of a difference in arterial blood lactate concentration between the two groups of patients would not support our postulate. The arterial blood lactate level is

determined by the balance of whole-body production and liver metabolism.²⁶ Hepatic function and hepatic blood flow significantly influence blood lactate levels. A number of studies²⁷⁻²⁹ suggest that patients with sepsis demonstrate less hyperlactemia than do patients with cardiogenic or hypovolemic shock, possibly because of better hepatic perfusion. It is therefore conceivable that the increase in hepatic flow consequent on dopamine's effect on splanchnic flow may compensate for the drug's effect on lactate production.

In conclusion, this study suggests that dopamine may have a deleterious effect on the precarious balance between splanchnic oxygen delivery and utilization in septic patients. Norepinephrine, however, may improve splanchnic oxygen utilization in hyperdynamic sepsis. Considering the central role that gut ischemia may play in the genesis of multiple-system organ failure, these findings may be particularly important.³⁰ Further research is required to determine whether these pathophysiological findings affect patient outcome.

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