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Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study

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Abstract *Objectives:* To compare the effects of norepinephrine and dobutamine to epinephrine on hemodynamics, lactate metabolism, and gastric tonometric variables in hyperdynamic dopamine-resistant septic shock. Design: A prospective, intervention, randomized clinical trial. Setting: Adult medical/surgical intensive care unit in a university hospital.
Patients: 30 patients with a cardiac index (CI) > 3.5 l · min^{-1} · m^{-2} and a mean arterial pressure (MAP) ≤ 60 mmHg after volume loading and dopamine 20 μg/kg per min and either oliguria or hyperlactatemia.
Interventions: Patients were randomized to receive an infusion of either norepinephrine-dobutamine or epinephrine titrated to obtain an MAP greater than 80 mmHg with a stable or increased CI.
Measurements and main results: Baseline measurements included: hemodynamic and tonometric parameters, arterial and mixed venous gases, and lactate and pyruvate blood levels. These measurements were repeated after 1, 6, 12, and 24 h. All the patients fulfilled the therapeutic goals. No statistical difference was found between epinephrine and norepinephrine-dobutamine for systemic hemodynamic measurements. Considering metabolic and tonometric measurements and compared to baseline values, after 6 h, epinephrine infusion was associated with an increase in lactate levels (from 3.1 ± 1.5 to 5.9 ± 1.0 mmol/l; $p < 0.01$), while lactate levels decreased in the norepinephrine-dobutamine group (from 3.1 ± 1.5 to 2.7 ± 1.0 mmol/l). The lactate/pyruvate ratio increased in the epinephrine group (from 15.5 ± 5.4 to 21 ± 5.8; $p < 0.01$) and did not change in the norepinephrine-dobutamine group (13.8 ± 5 to 14 ± 5.0). Gastric mucosal pH (pHi) decreased (from 7.29 ± 0.11 to 7.16 ± 0.07; $p < 0.01$) and the partial pressure of carbon dioxide (PCO_2) gap (tonometer PCO_2 – arterial PCO_2) increased (from 10 ± 2.7 to 14 ± 2.7 mmHg; $p < 0.01$) in the epinephrine group. In the norepinephrine-dobutamine group pHi (from 7.30 ± 0.11 to 7.35 ± 0.07) and the PCO_2 gap (from 10 ± 3.0 to 4 ± 2.0 mmHg) were normalized within 6 h ($p < 0.01$). The decrease in pHi and the increase in the lactate/pyruvate ratio in the epinephrine group was transient, since it returned to normal within 24 h.
Conclusions: Considering the global hemodynamic effects, epinephrine is as effective as norepinephrine-dobutamine. Nevertheless, gastric mucosal acidosis and global metabolic changes observed in epinephrine-treated patients are consistent with a markedly inadequate, although transient, splanchnic oxygen utilization. The metabolic and splanchnic effects of the combination of nore-

pinephrine and dobutamine in hyperdynamic dopamine-resistant septic shock appeared to be more predictable and more appropriate to the current goals of septic shock therapy than those of epinephrine alone.

Key words Septic shock · Catecholamines · Intramucosal pH · Lactic acidosis · Splanchnic circulation · Tonometry

Introduction

Currently, a clear recommendation for a specific catecholamine regimen in septic shock is lacking. After volume resuscitation, catecholamines are usually required to achieve an adequate systemic perfusion pressure. Dobutamine and/or dopamine often fail to restore adequate perfusion pressure. There is ample evidence that either epinephrine or the combination norepinephrine-dobutamine are able to increase arterial pressure without deleterious effect or with favorable effects on oxygen delivery in septic shock [1–7]. Nevertheless, both the gastrointestinal tract and the liver may be inadequately perfused despite the presence of normal systemic measures of the adequacy of tissue oxygenation [8]. Dahn et al. [9] demonstrated that splanchnic perfusion in patients with sepsis increases to the same extent as cardiac output, although splanchnic oxygen consumption increases to a greater extent than whole-body oxygen consumption, thus making the gut vulnerable to ischemia. Evidence is accumulating that gastrointestinal function, particularly splanchnic bed perfusion and the integrity of the gut mucosa, occupies a key position in the perpetuation and pathogenesis of multiple organ failure [8].

Cumulative data on the use of epinephrine in septic shock in a total of 54 patients suggest that epinephrine improves oxygen transport values to supranormal or normal values, without causing adverse cardiac or peripheral constrictive effects and without altering mortality [10]. The receptor profile of epinephrine is complex, and its pharmacologic effects depend largely on the dose. At low doses, epinephrine acts predominantly on the peripheral β_1- and β_2-adrenergic receptors. However, as the dose of epinephrine is increased, the α_1-adrenergic receptor-mediated vasoconstrictor effects predominate. Despite identical receptor targets, norepinephrine (α_1 and β_1 agonists) in combination with low doses of dobutamine (β_1 and β_2 agonists) might have different results on peripheral activity, particularly when the dose is increased. Recent studies [11, 12] have suggested that β_2 agonists like dobutamine and dopexamine improve splanchnic perfusion in critically ill patients. Moreover, norepinephrine and dobutamine are less thermogenic than epinephrine [13, 14] and may have a more desirable effect on the adequacy of splanchnic oxygenation. There is still a lack of clinical studies which compare, in a randomized manner, what combinations of inotropes and/or vasopressors are most suitable in optimizing the systemic and regional hemodynamics in hyperdynamic septic shock patients. Therefore, we designed this prospective, randomized study to compare the systemic hemodynamic as well as metabolic and splanchnic effects of epinephrine and norepinephrine-dobutamine in dopamine-resistant septic shock.

Table 1 Characteristics of study groups. Values are mean ± SD or numbers of patients. (*APACHE* Acute Physiology and Chronic Health Evaluation, *OSF* number of organ system failures)

	Epinephrine (n = 15)	Norepinephrine-dobutamine[a] (n = 15)
Age (years)	54 ± 10	56 ± 9
Sex, M:F	10:5	11:4
APACHE II score	23 ± 4.6	24 ± 5.8
OSF score	2.7 ± 0.6	2.6 ± 0.6
Primary illness	9 medical 6 surgical	8 medical 7 surgical
Source of infection	Pulmonary 10 Abdominal 4 Soft tissue 1	Pulmonary 9 Abdominal 5 Meningitis 1
Oliguria (n)	12	11
Hyperlactatemia (n)	13	13

[a] No significant differences between groups

Materials and methods

Study design and patient population

The study received the approval of the local ethics committee and written informed consent was obtained from the patient's closest relative. The present study included 30 consecutive patients with hyperdynamic septic shock as defined by the ACCP/SCCM conference consensus committee [15]. Patients were eligible for entry into the study if they had a definable source of infection and/or positive blood cultures. Volume resuscitation was considered optimal when, at a given level, infusion of additional fluids was no longer accompanied by an increase in cardiac index (CI). To be included in the study after optimal volume resuscitation and treatment with dopamine up to a dose of 20 μg/kg per min, the patients had to have the following (baseline): (1) mean arterial pressure (MAP) $\leq$ 60 mmHg, (2) signs of altered perfusion as oliguria (< 30 ml/h) or an increased lactate level (> 2.5 mmol/l), and (3) a CI > 3.5 $l \cdot min^{-1} \cdot m^{-2}$.

The clinical characteristics of the two study groups are summarized in Table 1. At the time of inclusion, there was no difference between the two groups for severity scores and hemodynamic, tonometric, and metabolic parameters (baseline values) (Tables 1, 2, 3).

Hemodynamic and metabolic parameters

Heart rate (HR) was monitored continuously. Routine clinical monitoring of patients included a thermodilution pulmonary artery catheter, with fiberoptic continuous monitoring of mixed venous oxygen saturation (Oximetrix, Abbott, Chicago, Ill., USA) and a radial or a femoral artery catheter. The zero reference level for the supine position was the mid-chest level and pressure was measured at the end of expiration. Serial measurements of HR,

MAP, mean central venous pressure (CVP), mean pulmonary artery pressure (MPAP), and pulmonary artery occlusion pressure (PAOP) were taken. Cardiac output was measured in triplicate by injecting 10 ml 5% dextrose at room temperature into the proximal port of the pulmonary artery catheter. Cardiac output was computed from the thermodilution curves using a cardiac output computer. CI, oxygen delivery index (DO_2I), and oxygen consumption index (VO_2I) were calculated using standard formulae. There was no additional volume loading and no change in ventilator parameters or catecholamine dose during the first hour of the study. Blood gases and tonometric specimens were measured with a blood gas analyzer standardized to saline measurements (Ciba Corning, Halsted, Essex, UK).

Tonometric measurements

Gastric mucosal pH (pHi) was calculated with a tonometric technique. The tonometer (Tonometrics, Hopkinton, USA) was inserted by either the nasogastric or the orogastric route, and its position in the stomach was confirmed radiologically. The tonometer balloon was filled with 2.5 ml 0.9% saline and sufficient time (1 h) was allowed for the partial pressure of carbon dioxide (PCO_2) of the gastric mucosa to equilibrate with the saline. Simultaneous anaerobic samples of the saline and arterial and mixed venous blood were obtained and immediately analyzed for saline PCO_2 and arterial blood bicarbonate (HCO_3). Tonometric specimens were collected in a luer-lock syringe (5 ml B-D, Plastipak, Becton Dickinson, USA). Gastric pHi was calculated using the following modifications of the Henderson-Hasselbalch equation: $pHi = 6.1 + \log 10\ (\text{arterial } HCO_3)/(F \times 0.03 \times \text{tonometric saline } PCO_2)$ where F is a time-dependent factor for partially equilibrated samples and supplied by the tonometer manufacturer. All patients received histamine receptor (H_2) blocking agents by a continuous infusion (50 mg bolus of ranitidine followed by a continuous infusion of 10 mg/h). During the study, nasogastric tubes were not on continuous aspiration and intravenous sodium bicarbonate and enteral feedings were not given.

Metabolic measurements

For lactate determination, arterial blood samples were collected in fluoride oxalate-containing tubes and placed on ice. Lactate was measured by an enzymatic colorimetric method adapted to automatic analyzer Wako (Biochem Systems, France) and the higher limit of normal was 2 mmol/l.

For pyruvate, arterial blood samples were placed on ice and immediately deproteinized by addition of 2 ml perchloric acid (1 mol/l) for 2 ml of whole blood. Pyruvate was measured by an enzymatic ultraviolet method. A control group of 20 patients in the ICU without shock or hypoxia and with normal lactate values was studied with the same sample protocol.

Therapeutic protocol

After meeting inclusion criteria, each patient received either epinephrine or norepinephrine-dobutamine, according to the randomization code. Epinephrine and norepinephrine infusions were started at 0.3 μg/kg per min and dobutamine was infused at a fixed dose of 5 μg/kg per min. The infusion rate of epinephrine and norepinephrine was titrated on MAP at 5-min intervals to obtain a MAP > 80 mmHg with a stable or increased CI. Between baseline and the first hour, the ventilator settings and dopamine infusion rate were kept constant. After the first hour, dopamine was stopped and the titration of epinephrine or norepinephrine was increased to obtain the same MAP, if necessary.

Baseline measurements included hemodynamic parameters, tonometric parameters after 60 min of time equilibration, arterial and mixed venous gases, and lactate and pyruvate blood levels. These measurements were repeated after 1 (H_1) 6 (H_6) 12 (H_{12}), and 24 h (H_{24}).

Statistical analysis

Data are reported as mean ± SD. Baseline values were compared using an unpaired, two-tailed *t*-test. The difference between the epinephrine and the norepinephrine-dobutamine group was tested using a two-way analysis of variance (repeated time measurements and drug as independent variables). A repeated measures one-way analysis of variance was used to evaluate within-group differences. When the *F* value was statistically significant, a paired *t*-test with the Bonferroni correction was used. A p value of < 0.05 was considered significant.

Results

Hemodynamic measurements are given in Table 2. At H_1, all patients fulfilled the therapeutic goals. MAP and CI increased in all patients ($p < 0.01$). No arrhythmias occurred. Oliguria was reversed in 9 patients in the epinephrine group and in 10 patients in the norepinephrine-dobutamine group. No statistical difference in systemic hemodynamic measurements were found between the epinephrine and norepinephrine-dobutamine patients.

The metabolic and tonometric measurements are given in Table 3. Compared to baseline values, arterial lactate concentrations at H_6 increased in the epinephrine group ($p < 0.01$), while it decreased in norepinephrine-dobutamine group ($p < 0.01$). Lactic acidosis in the epinephrine group was transient, since it recovered within 24 h. The lactate/pyruvate ratio increased in the epinephrine group ($p < 0.01$) and did not change in the other group. The blood pyruvate concentration did not change during the study in the two groups. We observed a normal lactate/pyruvate ratio of 8.4 ± 1.7 in the control group without shock.

The pHi decreased and the PCO_2 gap increased in the epinephrine group ($p < 0.01$). In the norepinephrine-dobutamine group, pHi and the PCO_2 gap rapidly returned to normal values ($p < 0.01$). The decrease in pHi in the epinephrine group was transient and returned to normal within 24 h (Fig. 1).

Six of 15 patients survived in the epinephrine group and 7 of 15 patients in norepinephrine-dobutamine group.

Discussion

With regard to systemic hemodynamics, the present study demonstrates that both epinephrine and norepinephrine-dobutamine improved arterial pressure and oxygen delivery in patients with septic shock after the failure of volume expan-

Table 2 Effects of epinephrine and norepinephrine-dobutamine on hemodynamic parameters[a] (mean ± SD) (*Ep* epinephrine, *Nor-Dob* norepinephrine-dobutamine, *Dop* dopamine, *MAP* mean arterial pressure, *HR* heart rate, *MPAP* mean pulmonary artery pressure, *PAOP* pulmonary artery occlusion pressure, *CI* cardiac index, DO_2I oxygen delivery index, VO_2I oxygen consumption index)

	Group	Baseline	H1	H6	H12	H24
Drug titration (μg/kg per min)	Ep	0	0.45 ± 0.09	0.52 ± 0.07	0.48 ± 0.08	0.36 ± 0.08
	Nor	0	0.44 ± 0.08	0.61 ± 0.08	0.64 ± 0.07	0.60 ± 0.07
	Dop	20 ± 0.5	20 ± 0.5	0	0	0
MAP (mmHg)	Ep	60 ± 8	89 ± 8*	93 ± 8*	96 ± 8*	89 ± 8*
	Nor-Dob	60 ± 8	87 ± 8*	86 ± 8*	90 ± 8*	86 ± 15*
HR (beats/min)	Ep	121 ± 19	114 ± 15	109 ± 11	115 ± 15	108 ± 19
	Nor-Dob	125 ± 15	130 ± 19	129 ± 15	117 ± 19	120 ± 15
MPAP (mmHg)	Ep	25 ± 7	31 ± 8*	29 ± 7	28 ± 8	26 ± 8
	Nor-Dob	26 ± 7	30 ± 7*	27 ± 8	25 ± 7	26 ± 7
PAOP (mmHg)	Ep	12 ± 7	13 ± 4	13 ± 7	11 ± 7	13 ± 7
	Nor-Dob	12 ± 4	9 ± 4	10 ± 7	10 ± 7	11 ± 7
CI ($l \cdot min^{-1}\ m^{-2}$)	Ep	4.0 ± 1	5.1 ± 1*	4.5 ± 1*	4.1 ± 1	4.1 ± 1
	Nor-Dob	4.0 ± 1	4.8 ± 1*	4.7 ± 1*	4.4 ± 1*	4.4 ± 1*
DO_2I ($ml \cdot min^{-1} \cdot m^{-2}$)	Ep	481 ± 152	632 ± 150*	608 ± 154*	605 ± 147*	612 ± 154*
	Nor-Dob	538 ± 150	662 ± 154*	665 ± 143*	630 ± 162*	632 ± 147*
VO_2I ($ml \cdot min^{-1} \cdot m^{-2}$)	Ep	141 ± 35	147 ± 42	156 ± 50*	143 ± 35	141 ± 31
	Nor-Dob	130 ± 31	141 ± 42	159 ± 46*	139 ± 31	143 ± 27

* $p < 0.01$ versus baseline
[a] No difference was observed between epinephrine and norepinephrine-dobutamine

Table 3 Effects of epinephrine and norepinephrine-dobutamine on metabolic and tonometric values (mean ± SD) (*Ep* epinephrine, *Nor-Dob* norepinephrine-dobutamine, *L/P ratio* lactate/pyruvate ratio, $PaCO_2$ arterial PCO_2, $PgCO_2$ gastric mucosal PCO_2)

	Group	Baseline	H1	H6	H12	H24
Arterial pH	Ep	7.35 ± 0.07	7.26 ± 0.07*	7.26 ± 0.11*	7.32 ± 0.07	7.38 ± 0.11†
	Nor-Dob	7.37 ± 0.11	7.33 ± 0.07	7.38 ± 0.07	7.40 ± 0.07	7.38 ± 0.11
Lactate (mmol/l)	Ep	3.1 ± 1.5	4.8 ± 1.5*	5.9 ± 1.0*	3.1 ± 1.0	2.4 ± 1.0†
	Nor-Dob	3.1 ± 1.5	3.1 ± 1.0	2.7 ± 1.0	2.6 ± 0.9	2.1 ± 1.4*
L/P ratio	Ep	15.5 ± 5.4	20 ± 5.4*	21 ± 5.8	18 ± 5.0*	14 ± 5.4†
	Nor-Dob	13.8 ± 5.0	14 ± 5.8	14 ± 5.0	15 ± 5.8	14 ± 5.8
$PaCO_2$ (mmHg)	Ep	39 ± 2	42 ± 2	41 ± 3	39 ± 2	43 ± 2
	Nor-Dob	38 ± 2	40 ± 2	42 ± 3	42 ± 2	44 ± 2
$PgCO_2$ (mmHg)	Ep	49 ± 3	54 ± 5*	55 ± 4*	50 ± 4	46 ± 4†
	Nor-Dob	48 ± 3	48 ± 3	45 ± 4	45 ± 4	46 ± 3

* $p < 0.01$ versus baseline;
† $p < 0.01$ difference between Ep and Nor-Dob

sion and high doses of dopamine. In patients treated with norepinephrine-dobutamine, CI and DO_2 increased, a pattern which differs from previous studies with norepinephrine alone [2–4]. This difference probably results from the combination of norepinephrine with doubtamine suggesting a cardiac effect (beta 1) of dobutamine or a peripheral vascular effect (beta 2 effect) counterbalancing the alpha effect of norepinephrine. When compared on systemic hemodynamic parameters, epinephrine and norepinephrine-dobutamine induced similar effects.

Epinephrine was associated with a marked but transient lactic acidosis. In volunteers, epinephrine increases blood glucose, glycerol, lactate, and VO_2 [13, 16] through an increase in glycolysis. Recently, in patients with severe sepsis without shock, Day et al. [17] reported an increase in lactate level without an increase in calculated VO_2. In septic shock, Bollaert et al. [1] and Wilson et al. [18] observed similar changes in lactate levels during epinephrine infusion. An increase in lactate levels does not always result from tissue hypoxia. Hypoxic-anaerobic metabolic production of lactate may be global (shock) or focal (e.g., bowel ischemia). A nonhypoxic increase in lactate level may result from impaired clearance of lactate (liver dysfunction), dysfunction of pyruvate dehydrogenase that has been proved to occur during sepsis [19], increased protein degradation causing amino acid conversion to pyruvate, and accelerated aerobic glycolysis [20]. In these nonhypoxic circumstances, hyperlactatemia occurs with a normal lactate/pyruvate (L/P) ratio < 10, whereas L/P ratios higher than 10 indicate tissue hypoxia. Because lactate and pyruvate measurements on peripheral venous blood and any delay in the denaturation of blood may induce high L/P ratios [21], the value of the L/P ratio in clinical practice has been questioned. However, using the same technique for blood sampling in the control group without shock, we observed a normal L/P ratio. We therefore feel that the increase in the L/P ratio during epinephrine treatment can be interpreted as a marker of anaerobic metabolism.

Gastric tonometry is a noninvasive monitoring technique that measures gastric intramucosal PCO_2. Gastric pHi may be indirectly calculated by substituting in the Henderson-Hasselbalch equation the steady-state adjusted PCO_2 and the arterial blood bicarbonate concentration, assuming that gastric mucosal and blood HCO_3 are equivalent. The puta-

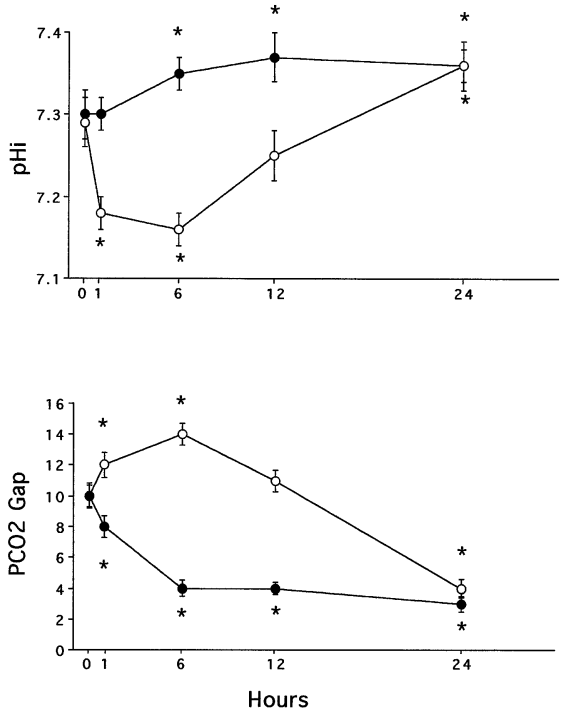

Fig. 1 Evolution of gastric pHi *top* and PCO_2 gap (tonometer PCO_2– arterial PCO_2) *bottom* during infusion of epinephrine *open circles* or norepinephrine-dobutamine *closed circles.* * $p < 0.01$ versus baseline

tive consequences of intramucosal acidosis and associated mucosal injury include increased gut permeability, bacterial translocation, sepsis, and multiple organ system failure [8]. Although the pronostic value of a persistently low pHi is well demonstrated, the mechanisms responsible for the development of gut mucosal acidosis in sepsis remain to be elucidated. Three different causes have been proposed, including a decrease in mucosal blood flow (CO_2 stagnation), an increase in anaerobic tissue CO_2 production due to intracellular buffering of hydrogen ions generated by anaerobic glycolysis, and an alteration in intermediary metabolism unrelated to changes in blood flow or tissue oxygenation but associated with excess production of protons [22–25]. A major problem arises in interpreting a low intramucosal pHi accompanied by a low arterial pH. Given these potential difficulties, the use of the PCO_2 gap, which is independent of the systemic acid-base status, is gaining popularity [26, 27].

With regard to achieving adequate splanchnic perfusion in septic shock, despite a similar increase in arterial pressure and oxygen delivery in both groups, the PCO_2 gap increased in epinephrine-treated patients (Fig. 1). That finding suggests that epinephrine increased splanchnic oxygen utilization and CO_2 production through a thermogenic effect especially if gastric blood flow did not increase to the same extent, inducing a mismatch between splanchnic DO_2 and splanchnic VO_2. An another hypothesis is that epinephrine decreased mucosal blood flow with a decrease in CO_2 efflux, the net result being an increase in the PCO_2 gap. These results confirm the preliminary results of Meier-Hellmann and Reinhart [28] in three patients with septic shock. Changing the combination of norepinephrine and dobutamine to epinephrine alone induced a decrease in splanchnic perfusion in the presence of an unchanged arterial pressure and cardiac output, an increase in lactate level, and a decrease in pHi.

Such a transient effect on the PCO_2 gap was not observed in the norepinephrine-dobutamine group (Fig. 1). In experimental septic conditions, norepinephrine did not decrease splanchnic blood flow [29, 30]. Ruokonen et al. [31], in human septic shock, found that the effects of norepinephrine on global splanchnic blood flow and VO_2 were nonuniform and unpredictable. Marik and Mohedin [32] demonstrated that norepinephrine compared to high doses of dopamine increased, but did not correct, pHi in septic shock. We hypothesized that the association with a β_2-adrenergic agonist like dobutamine, which favors mucosal blood flow at the expense of flow to the gut wall muscle [33], might counteract detrimental splanchnic effects of norepinephrine. Our results are consistent with those of Meier-Hellmann et al. [28] in 10 patients in septic shock. In their study, changing the combination of dobutamine and norepinephrine to norepinephrine alone induced a decrease in splanchnic perfusion and cardiac output with an increase in hepatic venous O_2 extraction. Gutierrez et al. [11], studying patients with sepsis syndrome, found that low-dose dobutamine (5 μg/kg per min) increased pHi and decreased the PCO_2 gap, despite a stable CI and DO_2. Whether dobutamine increased splanchnic perfusion in sepsis through an increase in cardiac output or whether it redistributed the blood flow to the mucosa is unclear. The last hypothesis is supported by Neviere and Vallet [34], who assessed the effects of 5 μg/kg per min dobutamine on pHi, PCO_2 gap, and mucosal perfusion by a laser Doppler flowmeter probe in septic patients. Dobutamine at a rate of 5 μg/kg per min increased systemic DO_2 and was associated with a significant increase in gastric pHi and a decrease in the PCO_2 gap. At the same time, gastric mucosal blood flow increased out of proportion to the systemic DO_2.

Despite a marked but transient decrease in epinephrine-treated patients, pHi increased in both groups from 7.30 (which is below the "normal" value defined by Maynard et al. [35]) to 7.36 (which is above this normal value) after 24 h. Nevertheless, improvement was much faster in patients treated by the combination of norepinephrine and dobutamine and obtained at H_6. It is unclear why the deleterious effects of epinephrine on gastric pHi were transient. Many hypotheses may be suggested, including a metabolic counterregulatory mechanism, spontaneous evolution, desensitization [36], or a dose effect.

In summary, we found that considering the effects on global hemodynamics, epinephrine is as effective as norepinephrine-dobutamine. Gastric mucosal acidosis and global metabolic changes observed in epinephrine-treated patients are consistent with a markedly inadequate though transient, splanchnic oxygen utilization. Nevertheless, if these episodes of intramucosal acidosis are severe enough and/or long enough, they might be followed by clinical evidence of ischemic injury. The exact mechanisms and the clinical relevance of these transient changes remain to be elucidated. Furthermore, it is unknown whether the choice of a

specific catecholamine in septic shock influences the patient's outcome. Nevertheless, in hyperdynamic, dopamine-resistant septic shock, the metabolic and splanchnic effects of norepinephrine-dobutamine appeared to be more predictable and more appropriate to the current goals of septic shock therapy than the effects of epinephrine alone.

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