Intensive Care Med (1999) 25: 942–948

ORIGINAL

B. Levy
L. Nace
P.-E. Bollaert
B. Dousset
J. P. Mallie
A. Larcan

Comparison of systemic and regional effects of dobutamine and dopexamine in norepinephrine-treated septic shock

Received: 26 October 1998
Final revision received: 11 April 1999
Accepted: 8 June 1999

This study was supported by a grant of Lilly France (Saint Cloud, France)

B. Levy (✉) · L. Nace · P.-E. Bollaert · A. Larcan
Polyvalent Intensive Care Unit,
Central Hospital, 29 Avenue du Marechal de Lattre de Tassigny, CO 34,
F-54035 Nancy Cedex, France
Fax: + 33-3-83 85 19 41
e-mail: b.levy@chu-nancy.fr

B. Dousset
Laboratoire de Biochimie,
Central Hospital, 29 Avenue du Marechal de Lattre de Tassigny, CO 34,
F-54035 Nancy Cedex, France

J.P. Mallie
Laboratoire d'Exploration Fonctionnelle Rénale, Faculté de Mèdecine,
F-54100 Vandoeuvre les Nancy, France

Abstract *Objectives*: To compare the effects of dobutamine and dopexamine on systemic hemodynamics, lactate metabolism, renal function and the intramucosal-arterial PCO_2 gap in norepinephrine-treated septic shock.
Design: A prospective, interventional, randomized clinical trial.
Setting: Adult medical/surgical intensive care unit in a university hospital.
Patients: After volume resuscitation, 24 patients were treated with norepinephrine alone titrated to obtain a mean arterial pressure of 75 mmHg and a cardiac index greater than 3.5 $l/min^{-1} \cdot m^{-2}$.
Interventions: Patients were randomized to receive an infusion of dobutamine ($n = 12$) (5 μg/kg per min) or dopexamine ($n = 12$) (1 μg/kg per min).
Measurements and main results: Baseline measurements included: hemodynamic parameters, renal parameters (diuresis, creatinine clearance and urinary sodium excretion), gastric mucosal-arterial PCO_2 gap, arterial and mixed venous gases and arterial lactate and pyruvate levels. These measurements were repeated after 1 (H_1), 4 (H_4) and 24 (H_{24}) h. No difference was found between dobutamine and dopexamine among H_0 and H_1, H_4 and H_{24} values for hemodynamics. Dobutamine and dopexamine at low doses had no significant effect on mean arterial pressure, heart rate, cardiac index, oxygen delivery, oxygen consumption and pulmonary artery occlusion pressure. No patients developed arrhythmia or electrocardiographic signs of myocardial ischemia. After 4 and 24 h lactate concentration decreased in the dobutamine group from 2.4 ± 1 mmol/l to 1.7 ± 0.7 mmol/l and 1.5 ± 0.4 mmol/l, respectively, while it increased in the dopexamine group from 2.3 ± 1 mmol/l to 2.7 ± 1 mmol/l after 4 h and returned to baseline values after 24 h (2.2 ± 0.6). After 24 h the lactate/pyruvate ratio decreased in the dobutamine group from 15 ± 5 to 12 ± 3 ($p < 0.05$) while it was unchanged in the dopexamine group (from 16 ± 6 to 17 ± 4). Arterial pH increased in the dobutamine group from 7.35 ± 0.05 to 7.38 ± 0.07 ($p < 0.05$) while it was unchanged in the dopexamine group (from 7.34 ± 0.01 to 7.35 ± 0.10). The PCO_2 gap decreased after 1 and 4 h in both the dobutamine and dopexamine groups ($p < 0.05$ with respect to baseline). When looking at individual responses, however, patients from both groups exhibited an increased gastric PCO_2 gap. No difference was found between dobutamine and dopexamine for renal parameters.
Conclusions: In norepinephrine-treated septic shock, low doses of neither dobutamine nor dopexamine caused significant effects on sys-

temic hemodynamics and renal function and both dobutamine and dopexamine inconsistently improved the PCO_2 gap. The present results support the need for individual measurement of the effects of catecholamine on the PCO_2 gap.

Key words Septic shock · Catecholamines · Intramucosal pH · Dobutamine · Dopexamine · Gastric tonometry

Introduction

Septic shock is typically characterized by decreased arterial pressure, normal or increased systemic blood flow and decreased oxygen extraction. Nevertheless, despite a systemic elevated blood flow, regional hypoperfusion and tissue hypoxia may be present. Systemic parameters monitored during resuscitation may not reflect regional blood flow abnormalities. Both the gastrointestinal tract and liver may be inadequately perfused despite seemingly normal systemic measurements of tissue oxygenation. Evidence is increasing that gastrointestinal function, particularly splanchnic perfusion as well as the integrity of gut mucosa, contributes in perpetuating or initiating multiorgan failure [1]. A logical approach focuses on assessing regional oxygenation. Gastric tonometry is a non-invasive monitoring technique that measures gastric mucosal PCO_2, from which the PCO_2 gap (gastric mucosal PCO_2-$PaCO_2$) is derived.

Three different mechanisms have been proposed to explain an increase in the PCO_2 gap: (a) a decrease in mucosal blood flow (CO_2 stagnation), (b) an increase in anaerobic tissue CO_2 production due to intracellular buffering of hydrogen ions generated by anaerobic glycolysis and (c) an alteration in the intermediary metabolism unrelated to changes in blood flow or tissue oxygenation but rather associated with an excessive increase in production protons [2]. The first step in the treatment of septic shock is to increase mean arterial pressure (MAP). Norepinephrine is commonly used in the treatment of septic shock. With its strong alpha-adrenergic mediator and vasopressor effects, norepinephrine may threaten hepatosplanchnic perfusion. It would seem logical to add a sympathomimetic agent with vasodilatory properties (possibly in the splanchnic region), like dobutamine or dopexamine, to the administered norepinephrine. Indeed. recent studies suggest that beta-agonists such as dobutamine or dopexamine improve splanchnic perfusion or gastric mucosal blood flow in critically ill patients [3, 4, 5, 6, 7].

The maintenance of renal perfusion and renal function is also an important goal in septic shock therapy. Data concerning the combined effects of catecholamine association on renal function and the PCO_2 gap are scarce. The aim of the present study was to compare the effects of dobutamine and dopexamine on systemic hemodynamics, lactate metabolism, renal function and PCO2 gap in norepinephrine-treated septic shock.

Methods

Study design and patient population

The study received the approval of the local ethics committee and written informed consent was obtained from the closest relative. Twenty-four patients with hyperdynamic septic shock were included. Patients were eligible for the study if they had septic shock defined by the following criteria: (a) MAP lower than 60 mmHg after optimal volume resuscitation, (b) oliguria with a urine output less than 20 ml/h, and hyperlactatemia with an arterial lactate concentration greater than 2.2 mmol/l in the presence of a definable source of infection and/or positive blood culture. Volume resuscitation was considered optimal when, at a given level, additional fluid infusion was no longer accompanied by an increase in cardiac index (CI).

Hemodynamic and metabolic parameters

Heart rate (HR) was monitored continuously. Routine clinical monitoring of the patients included a thermodilution pulmonary artery catheter with fiberoptic continuous monitoring of mixed venous oxygen saturation (Oximetrix, Abbott, Chicago, USA) and a radial or femoral artery catheter. The zero reference level for supine position was the midchest 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 undertaken. Cardiac output was measured in triplicate by injecting 10 ml of 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_21) and oxygen consumption index (VO_21) were calculated using a standard formula.

Tonometric measurements

Gastric intramucosal PCO_2 was measured with a tonometer. The tonometer (NGS Catheter, Tonometrics Division, Instrumentarium, Helsinki, Finland) was inserted nasogastrically or orogastrically and its position in the stomach confirmed radiologically. The tonometer balloon was filled with 2.5 ml of a phosphate-buffered (1,610 g/l Na_2HPO_4; 6,072 g/l NaH_2PO_4) solution and enough time (1 h) was allowed for the PCO_2 of the gastric mucosa to equilibrate with this solution. Recent works demonstrate that the accuracy and reliability of gastric tonometry measurements are improved when a phosphate-buffered solution is used and that the same correcting factors evaluated for saline may be used to correct PCO_2 in buffered solutions [8]. Simultaneous anaerobic samples of the measured phosphate-buffered solution and arterial blood were obtained and immediately analyzed for phosphate-buffered PCO_2 and arterial blood bicarbonate. The specimens measured by tonometry were collected in a luer-lok syringe (5 ml B-D, Plastipak, Becton Dickinson, USA). All patients received histamine-re-

Table 1 Characteristics of study group (mean ± SD)

	Dobutamine (n = 12)	Dopexamine (n = 12)
Age, year	54 ± 10	56 ± 9
Sex, M : F	8 : 4	9 : 3
APACHE II score	23 ± 5	24 ± 5
Primary illness	M: n = 8 S: n = 4	M: n = 8 S: n = 4
Norepinephrine μg/kg/min [range]	0.53 [0.2–1.9]	0.60 [0.18–1.7]
Source of infection	Pulmonary: 6 Abdominal: 4 Urinary: 2	Pulmonary: 7 Abdominal: 4 Meningitis: 1

Definition of abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; OSF: number of organ system failure; M: medical patients; S: surgical patients

ceptor (H_2) blocking agents (50 mg bolus of ranitidine followed by a continuous infusion of 10 mg/h) which was started at least 12 h before the study. During the study, the nasogastric tube was not on continuous aspiration and intravenous sodium bicarbonate and enteral feedings were not given.

Metabolic measurement

Lactate determination. Arterial blood samples were collected in tubes containing fluoride-oxalate, and placed on ice. Lactate was immediately measured by an enzymatic-colorimetric method adapted for automatic analysis (Wako, Biochem Systems, France); the higher limit of a normal value was 2 mmol/l.

Pyruvate determination. Arterial blood samples were immediately deproteinized by the addition of 2 ml of perchloric acid (1 mol/l) to 2 ml of whole blood and placed on ice. Pyruvate was immediately measured by an enzymatic ultra violet method.

The analytical range is 0–10000 μmol/l for lactate, 0–300 μmol/l for pyruvate. Run-to-run precision, expressed as a coefficient of variation, was 1.5 % for lactate, 5.9 % for pyruvate.

Renal function

Two-hour diuresis was measured before a baseline measurement. Serum creatinine and urine samples were collected for urine volume, urinary sodium excretion and creatinine clearance. Creatinine measurements were performed using the modified Jaffé method and clearance values were calculated using the standard formula. The bladder was emptied with 200 ml of air used to flush residual urine from the bladder at the start and at the end of each urine collection. These measurements were repeated after 24 h (H_{24}).

Therapeutic protocol

After volume resuscitation, patients were treated with norepinephrine alone titrated to obtain a MAP greater than 75 mmHg. Patients were included in the study if CI was greater than 3.5 $l \cdot min^{-1} \cdot m^{-1}$ without modification in norepinephrine titration during 2 h. After meeting the inclusion criteria, each patient received either dobutamine (5 μg/kg per min) or dopexamine (1 μg/kg per min) through a dedicated central venous line according to the randomization code using sealed envelopes. Baseline parameters were determined at a 1-h interval to ensure the stability of the PCO_2 gap (H_{0A} and H_0). Baseline measurements included: hemodynamic parameters, tonometric parameters after 60 min of time equilibration, arterial and mixed venous gases and arterial lactate and pyruvate levels. These measurements were repeated after 1 (H_1), 4 (H_4) and 24 (H_{24}) h. There was no additional volume loading, no change in ventilator parameters and norepinephrine titration from H_0 to H_4. Blood gases and specimens assessed by tonometry were measured with a blood gas analyser (Ciba Corning, Halsted, Essex, UK).

Statistical analysis

Data are reported as the mean ± SD. Baseline values were compared using an unpaired, two-tailed *t*-test. Differences between the dobutamine and dopexamine groups were established 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 an *F* value was statistically significant, a paired *t*-test with the Bonferroni correction was used. A *p* value of less than 0.05 was considered significant.

Results

The clinical characteristics of the study groups are summarized in Table 1. At the time of inclusion, no difference was observed between the two groups regarding the severity scores, hemodynamic parameters, lactate and pyruvate levels or PCO_2 gap. No difference was found for hemodynamics and the PCO_2 gap between H_{0A} and H_0.

Hemodynamic measurements

No difference was found between dobutamine and dopexamine among H_0 and H_1, H_4 and H_{24} values (Table 2). Dobutamine and dopexamine at low doses had no significant effect on MAP, HR, CI, oxygen delivery and oxygen consumption in norepinephrine-treated septic shock. No patients developed arrhythmia or electrocardiographic signs of myocardial ischemia.

Metabolic measurements

After 4 h, lactate concentration decreased in the dobutamine group from 2.4 ± 1 mmol/l to 1.7 ± 0.7 mmol/l, while it increased in the dopexamine group from 2.3 ± 1 mmol/l to 2.7 ± 1 mmol/l ($p < 0.01$). The lactate/pyruvate ratio decreased in the dobutamine group from 15 ± 5 to 12 ± 3 ($p < 0.05$), while it was unchanged in the dopexamine group (from 16 ± 6 to 17 ± 4). Arterial pH increased in the dobutamine group from 7.35 ± 0.05 to 7.38 ± 0.07 ($p < 0.05$), while it was unchanged in the dopexamine group (from 7.34 ± 0.01 to 7.35 ± 0.10).

Table 2 Evolution of hemodynamic, metabolic and tonometric values (mean ± SD)

		H0	H1	H4	H24	Dobutamine vs dopexamine
MAP [mm Hg]	Dobutamine	84 ± 6	81 ± 5	80 ± 5	82 ± 4	NS
	Dopexamine	83 ± 6	85 ± 9	83 ± 6	79 ± 5	
HR [beats/min]	Dobutamine	100 ± 7	109 ± 8	111 ± 8*	105 ± 7	NS
	Dopexamine	106 ± 11	110 ± 10	116 ± 11*	107 ± 9	
CI [l/min · m^{-2}]	Dobutamine	5.0 ± 0.7	5.4 ± 0.7	5.3 ± 1.3	5.2 ± 1	NS
	Dopexamine	5.4 ± 1.0	5.8 ± 0.8	5.7 ± 1.0	5.3 ± 1	
DO_2I	Dobutamine	630 ± 120	665 ± 110	660 ± 100	640 ± 90	NS
ml · min^{-1} · m^{-2}	Dopexamine	650 ± 90	680 ± 100	670 ± 110	660 ± 100	
VO_2I	Dobutamine	160 ± 40	158 ± 45	160 ± 30	150 ± 40	NS
ml · min^{-1} · m^{-2}	Dopexamine	165 ± 45	155 ± 40	150 ± 50	150 ± 60	
PAOP [mm Hg]	Dobutamine	15 ± 2	14 ± 3	15 ± 2	16 ± 3	NS
	Dopexamine	14 ± 2	15 ± 2	13 ± 2	15 ± 2	
Lactate [mmol/l]	Dobutamine	2.4 ± 1	1.9 ± 0.7	1.7 ± 0.7*	1.5 ± 0.4	$p < 0.05$
	Dopexamine	2.3 ± 1	2.3 ± 1.0	2.7 ± 1.0*	2.2 ± 0.6	
Lactate/pyruvate	Dobutamine	15 ± 5	13 ± 3	12 ± 3*	10 ± 2*	$p < 0.05$
	Dopexamine	16 ± 6	14 ± 2	17 ± 4	14 ± 3	
$PaCO_2$	Dobutamine	37 ± 3	36 ± 2	36 ± 3	35 ± 3	NS
	Dopexamine	35 ± 2	36 ± 3	34 ± 2	34 ± 2	
Arterial pH	Dobutamine	7.35 ± 0.05	7.38 ± 0.06*	7.38 ± 0.07*	7.38 ± 0.07*	$p < 0.05$
	Dopexamine	7.34 ± 0.01	7.32 ± 0.10	7.31 ± 0.10*	7.34 ± 0.10	
PCO_2 gap [mm Hg]	Dobutamine	12 ± 5	9 ± 3*	9 ± 4	NA	NS
	Dopexamine	11 ± 5	8 ± 4*	8 ± 3		

Definition of abbreviations; MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; DO_2I = oxygen delivery index; VO_2I = oxygen consumption index; PAOP = pulmonary artery occlusion pressure.
* $p < 0.05$ versus H0

Tonometric measurements

The PCO_2 gap decreased after 1 and 4 h in both the dobutamine and dopexamine groups ($p < 0.05$ with respect to baseline). No difference was found between dobutamine and dopexamine treatment.

Evolution of PCO_2 gap in individuals. (Fig. 1) Dobutamine group: PCO_2 gap > 8 mmHg ($n = 7$) – decrease in six patients and increase in one; PCO_2 gap < 8 mmHg ($n = 5$) – increase in one patient. Dopexamine group: PCO_2 gap > 8 mmHg ($n = 7$) – decrease in six patients and increase in one; PCO_2 gap < 8 mmHg ($n = 5$) – increase in two patients.

Renal function

No difference was found between dobutamine and dopexamine for renal parameters (Table 3). Diuresis increased in the dobutamine group (from 85 ± 33 to 100 ± 51 ml/h; $p = 0.05$), while it did not change in the dopexamine group (65 ± 93 to 55 ± 38 ml/h). Creatinine clearance did not change in either group. Urinary sodium increased in the dopexamine group (from 34 ± 16 meq/l to 64 ± 25 meq/l; $p < 0.05$) and did not change in the dobutamine group.

Discussion

Concerning the evolution of systemic hemodynamic and oxygenation parameters, low doses of dobutamine or dopexamine slighty increased CI and oxygen delivery. As our patients were hyperkinetic and reached high values of oxygen delivery, it was not our aim to increase this parameter to super-physiologic values. Similar observations have been made in severe sepsis and norepinephrine or epinephrine-treated septic shock when dobutamine or dopexamine were added. The dobutamine and dopexamine doses were therefore adjusted in the light of previous studies demonstrating the efficacy of dobutamine and dopexamine in improving pHi or the PCO_2 gap without marked variations in systemic hemodynamics [9, 10]. A change in tonometric parameters could therefore not be attributed to an increase in systemic oxygen delivery.

With regards to the effects of dobutamine and dopexamine on lactate/pyruvate ratio, before introducing dobutamine or dopexamine patients had a moderate in-

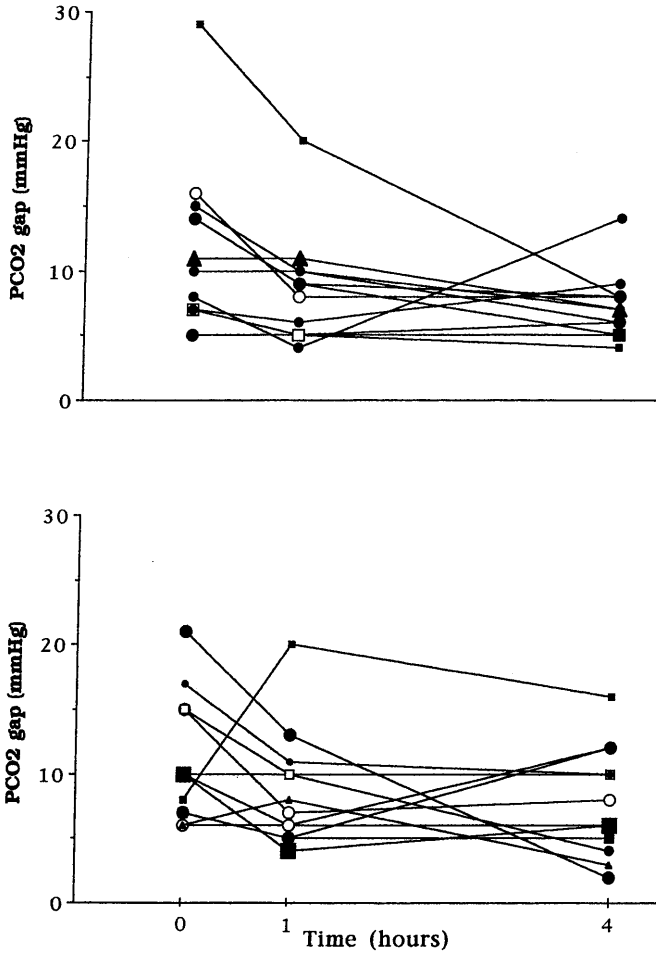

Fig. 1 PCO_2 gap before and during the administration of dobutamine (*top*) and dopexamine group (*bottom*). Each line represents an individual patient

crease in lactate and lactate/pyruvate ratio. During dobutamine infusion the lactate level and the lactate/pyruvate ratio decreased, confirming previously published results [9]. On the other hand, dopexamine infusion was associated with a slight increase in lactate level without modifying the lactate/pyruvate ratio. The explanation for this is unclear. A non-hypoxic increase in lactate concentration may result from impaired clearance of lactate, that would suggest a decrease in hepatic metabolic performance with dopexamine [11], although Reinelt et al. [12] described a similar decrease in lactate level with dobutamine and dopexamine related to improved hepatic clearance in one patient. Moreover, Tighe et al. [13] reported, in porcine septic shock, that dopexamine maintained the hepatic ultrastructure while dobutamine worsened the shock induced in morphology. It is therefore unlikely that dopexamine decreased hepatic metabolic performance. Geisser et al. [14] have demonstrated in volunteers that a low dose of dopexamine (0.75 μg/kg/min) decreased lactate level whereas higher doses increased it. The increased level measured at higher doses was attributed to a beta-2 adrenergic receptor-mediated effect. Nevertheless, these effects have also been described with dobutamine, although it was demonstrated that the thermogenic effect of dobutamine was attenuated by metabolic stress [15].

Recently, Reinelt et al. [16] demonstrated in human septic shock that, when norepinephrine was replaced by phenylephrine, the splanchnic blood flow and splanchnic lactate uptake rate were reduced without any change in splanchnic volume of oxygen (VO_2). It was hypothetized that beta-adrenergic receptor stimulation may determine hepatosplanchnic perfusion and oxygen availability, but not oxygen utilization. Thus, modifying the degree of exogenous beta-adrenergic receptor stimulation may change splanchnic metabolism. Stress states with increased plasma concentrations of catecholamines, glucagon and cortisol attenuate the response to dobutamine. Furthermore, the different relative beta-adrenergic receptor potencies of dobutamine and dopexamine together with impaired beta-adrenergic responsiveness and altered calorigenic response to dobutamine may explain the difference between dobutamine and dopexamine. The effects of prior administration of norepinephrine that could interact with the specific effects of dobutamine and dopexamine on receptors should also be taken into account. Finally, although statistically significant, the variation of lactate and lactate/pyruvate ratio are modest and might not be clinically relevant.

Concerning the effects of dobutamine and dopexamine on renal function, both dobutamine and dopexamine have proven their capacities to improve renal function and/or increase diuresis in ICU patients [17, 18]. It has been maintained that norepinephrine decreases renal blood flow and that low-dose (2 μg/kg per min) dopamine added to norepinephrine normalizes it in volunteers [19]. Dopaminergic stimulation can produce renal vasodilatation and causes increases in renal blood flow and glomerular filtration rate, inducing an increase in diuresis and natriuresis [20]. The possible effects of dobutamine on renal function are mediated through an increase in CI since dobutamine does not act on dopaminergic receptors. Moreover, it is possible that, by virtue of its beta-2 agonist-mediated effect, dobutamine limits norepinephrine-induced decreases in renal blood flow. Beneficial effects of norepinephrine have been described in septic shock patients, especially when the latter were hypotensive [21]. These effects were probably mediated through an increase in renal perfusion pressure. Data concerning the effects of dopaminergic agents in septic states demonstrate that diuresis might increase, though renal function does not improve. In catecholamine-treated septic shock, Lherm at al. [22] demonstrated that 2 μg/kg per min of dopamine had no renal

Table 3 Evolution of renal parameters (mean ± SD)

		H0	H24	Dobutamine vs Dopexamine
Urine volume [ml/h]	Dobutamine	85 ± 33	100 ± 51*	p = 0.05
	Dopexamine	60 ± 23	55 ± 38	
Creatinine clearance [ml/min]	Dobutamine	51 ± 27	54 ± 22	NS
	Dopexamine	56 ± 29	54 ± 26	
Urinary Na+[meq/l]	Dobutamine	33 ± 15	47 ± 26	NS
	Dopexamine	34 ± 16	64 ± 25*	

* $p < 0.05$ versus H0

effects. These results are confirmed here. Neither dopexamine nor dobutamine had any impact on renal function. Clearly, in hyperkinetic septic shock, when the MAP is within the normal range after volume resuscitation and vasopressor, there is no justification for adding dobutamine or dopexamine to improve renal function.

With regards to the effects of dobutamine and dopexamine on tonometric parameters in norepinephrine-treated septic shock, most of the available literature on gastric tonometry has been reported in terms of gastric mucosal pH (pHi). The clinical value of the PCO_2 gap in managing the patient and/or predicting outcome requires elucidation. We fixed a cutoff level at 8 mmHg [9], corresponding to patients without systemic acid-base disturbances ($PaCO_2$ = 40 mmHg and HCO_3- = 24 mmol/l) for a pHi of 7.32, that is generally considered as the lower limit in the majority of studies [23]. We considered 10 mmHg as the lowest difference between a normal PCO_2 gap (1 ± 1 mmHg) and an elevated PCO_2 gap. In septic shock patients the PCO_2 gap is generally slightly elevated (from 12 to 20 mmHg) [9, 24, 25, 26, 27] yet still lower than the 25 mmHg which Schlichtig et al. fix as the highest value of the PCO_2 gap compatible with aerobic metabolism [28]. It is therefore difficult to correlate an increase in the PCO_2 gap and ischemic gastric mucosa.

Recently Elizalde et al. [29], using laser-Doppler flowmetry and reflectance spectrophotometry, demonstrated the relationship between a decrease in pHi and a decrease in gastric mucosa perfusion (r = 0.53). Temmesfeld-Wollbrück et al. [10] demonstrated that for vasopressor-treated septic shock patients a decreased value of oxygenated hemoglobin ($HbiO_2$) (reflecting both gastric mucosal perfusion and gastric mucosal oxygenation) was associated with a decreased pHi or an increased PCO_2 gap. Nevertheless, during a 2 μg/kg per min dopexamine infusion, $HbiO_2$ increased and the PCO_2 gap did not change. Thus, during catecholamine therapy, it is difficult to interpret an absence of modification in PCO_2 gap, since an improvement in perfusion or metabolism might be counterbalanced by an increase in oxygen consumption. Both dobutamine and dopexamine significantly decreased the PCO_2 gap. When looking at individual responses, however, patients from both groups exhibited an increased gastric PCO_2 gap (Fig. 1). That inconsistency underlines the difficulty in estimating the adequacy of the PCO_2 gap, and emphasizes the need to assess it individually with tonometry. Nevertheless, before using regional capnometry to titrate catecholamines in clinical practice, it should be demonstrated that: (a) the PCO_2 gap is a marker for mortality in ICU patients and (b) a decrease in the PCO_2 gap with catecholamine treatment is associated with an improved pronosis.

For stable, norepinephrine-treated patients, this study has shown that: (a) some patients present decreased gastric mucosal perfusion, as estimated by regional capnometry, (b) low doses of neither dobutamine nor dopexamine caused significant effects on systemic hemodynamics and renal function, (c) dobutamine infusion was associated with a slight decrease in lactate level while dopexamine was not and (d) both dobutamine and dopexamine inconsistently improved the PCO_2 gap. When clinicians have to manipulate the PCO_2 gap with catecholamines, our results support the need for individual measurement with gastric tonometry [30, 31, 32].

References

1. Fiddian-Green RG (1993) Associations between intramucosal acidosis in the gut and organ failure. Crit Care Med 21: S103–S107
2. Russell JA (1997) Gastric tonometry: does it work? Intensive Care Med 23: 3–6
3. Silverman HJ, Tuma P (1992) Effects of dobutamine infusions and packed red blood cell transfusions. Chest 102: 184–188
4. Gutierrez G, Clark C, Brown SD, Ortiz V, Nelson C (1994) Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. Am J Respir Crit Care Med 150: 324–329
5. Maynard ND, Bihari DJ, Dalton RN, Smithies MN, Mason RC (1995) Increasing splanchnic blood flow in the critically ill. Chest 108: 1648–1654
6. Smithies MN, Yee TH, Jackson L, Beale R, Bihari D (1994) Protecting the gut and the liver in the critically ill: effects of dopexamine. Crit Care Med 22: 789–795

7. Neviere R, Mathieu D, Chagnon JL, Lebleu N, Wattel F (1996) The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. Am J Respir Crit Care Med 154: 1684–1688
8. Temmesfeld-Wollbrück B, Szalay A, Olchewski H, Grimminger F, Seeger W (1997) Advantage of buffered solutions or automated capnometry in air-filled balloons for use in gastric tonometry. Intensive Care Med 23 :423–427
9. Levy B, Bollaert PE, Lucchelli JP, Sadoune LO, Nace L, Larcan A (1997) Dobutamine improves the adequacy of gastric mucosal perfusion in epinephrine-treated septic patients. Crit Care Med 25: 1649–1654
10. Temmesfeld-Wollbrück B, Szalay A, Mayer K, Olschewski H, Seeger W, Grimminger F (1998) Abnormalities of gastric mucosal oxygenation in septic shock. Partial responsiveness to dopexamine. Am J Respir Crit Care Med 157: 1586–1592
11. Levraut J, Ciebiera JP, Chave S, et al. (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157: 1021–1026
12. Reinelt H, Radermacher P, Fischer G, Trunk E, Wiedeck H, Mezödy M, Georgieff M, Vogt J (1997) Dobutamine and dopexamine and the splanchnic metabolic response in septic shock. Clin Intensive Care 8: 38–41
13. Tighe D, Moss R, Heywood G, Al-Saady N, Bennett D (1995) Goal-directed therapy with dopexamine, dobutamine, and volume expansion: effects of systemic oxygen transport on hepatic ultrastructure in porcine sepsis. Crit Care Med 23: 1997–2007
14. Geisser W, Träger K, Hähn A, Georgieff M, Ensinger H (1997) Metabolic and calorigenic effects of dopexamine in healthy volunteers. Crit Care Med 25: 1332–1337
15. Uusaro A, Hartikainen J, Parviainen M, Takala J (1995) Metabolic stress modifies the thermogenic effect of dobutamine in man. Crit Care Med 23: 674–680
16. Reinelt P, Radermacher P, Kiefer P, Fischer G, Wachter U, Vogt J, Georgieff M (1999) Impact of exogenous β-adrenergic receptor stimulation on hepatosplanchnic oxygen kinetics and metabolic activity in septic shock. Crit Care Med 27: 325–331
17. Duke GJ, Briedis JH, Weaver RA (1994) Renal support in critically ill patients: low-dose dopamine or low-dose dobutamine. Crit Care Med 22: 1919–1925
18. Juste RN, Panikkar K, Soni N (1998) The effects of low-dose dopamine on haemodynamic and renal parameters in patients with septic shock requiring treatment with noradrenaline. Intensive Care Med 24: 564–568
19. Richer M, Robert S, Lebel M (1996) Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Crit Care Med 24: 1150–1156
20. Schwartz LB, Gewertz BIL (1988) The renal response to low dose dopamine. J Surg Res 45: 564–588
21. Martin C, Eon B, Saux P, Aknin P, Gouin F (1990) Renal effects of norepinephrine used to treat septic shock patients. Crit Care Med 18: 282–285
22. Lherm T, Troche G, Rossignol M, Bordes P, Zazzo JF (1996) Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines. Intensive Care Med 22: 213–219
23. Fiddian-Green RG (1995) Gastric intramucosal pH, tissue oxygenation and acid-base balance. Br J Anaesth 74: 591–606
24. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer Ph, Nabet P, Larcan A (1997) Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock. A prospective, randomized study. Intensive Care Med 23: 282–287
25. Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, Samii K (1999) Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med 27: (in press)
26. Radermacher P, Buhl R, Santak B, Klein M, Kniemeyer HW, Becker H, Tarnow J (1995) The effects of prostacyclin on gastric intramucosal pH in patients with septic shock. Intensive Care Med 21: 414–421
27. Eichelbrönner O, Reinelt H, Wiedeck H, Mezödy M, Rossaint R, Georgieff M, Radermacher P (1996) Aerosolized prostacyclin and inhaled nitric oxide in septic shock – different effects on splanchnic oxygenation. Intensive Care Med 22: 880–887
28. Schlichtig R, Bowles SA (1994) Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. J Appl Physiol 76: 2443–2451
29. Elizade I, Hernandez C, Llach J, Monton C, Bordas JM, Pique JM, Torres A (1998) Gastric intramucosal acidosis in mechanically ventilated patients: role of mucosal blood flow. Crit Care Med 26: 827–832
30. Brinkmann A, Caizia E, Träger K, Radermacher P (1998) Monitoring the hepato-splanchnic region in the critically ill patient. Measurement techniques and clinical relevance. Intensive Care Med 24: 542–555
31. Vincent JL, Creteur J (1998) Gastric mucosal pH is definitely obsolete – please tell us more about gastric mucosal PCO_2. Crit Care Med 26: 1479–1481
32. Silva E, DeBacker D, Creteur J, Vincent JL (1998) Effects of vasoactive drugs on gastric intramucosal pH. Crit Care Med 26: 1749–1758