Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study*

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Objective: **There is no study that has compared, in a randomized manner, which vasopressor is most suitable in optimizing both systemic and regional hemodynamics in cardiogenic shock patients. Hence, the present study was designed to compare epinephrine and norepinephrine-dobutamine in dopamine-resistant cardiogenic shock.**

Design: **Open, randomized interventional human study.**

Setting: **Medical intensive care unit in a university hospital.**

Patients: **Thirty patients with a cardiac index of <2.2 L/min^{-1}/m^{-2} and a mean arterial pressure of <60 mm Hg resistant to combined dopamine-dobutamine treatment and signs of shock. Patients were not included in cases of cardiogenic shock secondary to acute ischemic events such as myocardial infarction. Noninclusion criteria also included immediate indication of mechanical assistance.**

Interventions: **Patients were randomized to receive an infusion of either norepinephrine-dobutamine or epinephrine titrated to obtain a mean arterial pressure of between 65 and 70 mm Hg with a stable or increased cardiac index.**

Main Results: **Both regimens increased cardiac index and oxygen-derived parameters in a similar manner. Patients in the norepinephrine-dobutamine group demonstrated heart rates lower ($p < .05$) than those in the epinephrine group. Epinephrine infusion was associated with new arrhythmias in three patients. When compared to baseline values, after 6 hrs, epinephrine infusion was associated with an increase in lactate level ($p < .01$), whereas this level decreased in the norepinephrine-dobutamine group. Tonometered PCO_2 gap, a surrogate for splanchnic perfusion adequacy, increased in the epinephrine-treated group ($p < .01$) while decreasing in the norepinephrine group ($p < .01$). Diuresis increased in both groups but significantly more so in the norepinephrine-dobutamine group, whereas plasma creatinine decreased in both groups.**

Conclusions: **When considering global hemodynamic effects, epinephrine is as effective as norepinephrine-dobutamine. Nevertheless, epinephrine is associated with a transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion. Thus, the combination norepinephrine-dobutamine appears to be a more reliable and safer strategy. (Crit Care Med 2011; 39:450–455)**

KEY WORDS: cardiogenic shock; epinephrine; norepinephrine; lactate; dobutamine

A clear recommendation for a specific catecholamine regimen in cardiogenic shock is currently lacking (1). Cardiogenic shock is defined as evidence of tissue hypoperfusion induced by heart failure after adequate correction of preload and major arrhythmia (2). Hypotension in this context of low cardiac output may further decrease organ perfusion, and especially renal and splanchnic perfusion, but can also dramatically decrease coronary perfusion pressure and thus increase the risk of myocardial ischemia. Numerous adverse effects of adrenergic agents on heart function have been reported. These range from tachycardia/tachyarrhythmia and myocardial stunning to necrosis and apoptosis. Adverse cardiac effects of catecholamines are frequently dose dependent and may counteract the re-establishment of normal heart function, leading to increased short- and long-term mortality (3).

The goal of the initial medical therapy of cardiogenic shock is to maintain arterial pressure adequate for tissue perfusion and to increase tissue perfusion. Dopamine, which was initially considered as the drug of choice, should be abandoned since it has recently been demonstrated to increase mortality in cardiogenic shock (4). Clinicians often use norepinephrine with low doses of dobutamine or epinephrine. These drugs increase heart rate (HR) and systemic vascular resistance and thus may increase myocardial oxygen demand, aggravate ischemia, and lead to cardiac arrhythmias. New evidence has emerged that has led to expansion of the cardiogenic shock paradigm. It is now well recognized that patients with severe heart failure/cardiogenic shock also exhibit a decrease in vascular resistances due to inflammation through the nitric oxide pathway or due to treatment such as angiotensin-converting enzyme inhibitors, and these patients may necessitate supplemental potent vasopressor therapy (5). Septic shock studies found no differences between epinephrine and norepinephrine-dobutamine in terms of efficiency or mortality (6). Both strategies enable the induction of vascular and cardiac effects, but the combination of norepinephrine and dobutamine has the theoretical advantage over epinephrine in allowing a precise modulation of these two types of effect. Furthermore, norepineph-

*See also p. 583.

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rine is less thermogenic than epinephrine and may have a more desirable effect on myocardial oxygen consumption but also on splanchnic oxygenation (7). To our knowledge, there is no study that compared, in a randomized manner, which vasopressor is most suitable in optimizing both systemic and regional hemodynamics in cardiogenic shock patients. Hence, the present pilot, prospective, randomized study was designed to compare systemic hemodynamic as well as metabolic and splanchnic effects of epinephrine and norepinephrine-dobutamine in dopamine-resistant nonischemic cardiogenic shock.

METHODS

Study Design and Patient Population

The study received the approval of our local ethics committee and written informed consent was obtained from the closest relative. The present study included 30 consecutive patients with cardiogenic shock. In order to be included in the study, patients had to present the following:

1) Acute or chronic heart failure with an ejection fraction of <30% and a cardiac index (CI) of <2.2 L/min^{-1}/m^{-2}.
2) Absence of hypovolemia (pulmonary artery occlusion pressure of >15 mm Hg and, in ventilated patients, pulse pressure variations of <13% and/or when additional fluid infusion was no longer accompanied by an increase in CI).
3) Systolic arterial pressure of <90 mm Hg or mean arterial pressure (MAP) of <60 mm Hg, or a drop in MAP of >30 mm Hg despite dopamine up to 20 μg/kg/min. In case of dopamine intolerance (rapid atrial fibrillation of >160 beats per min or ventricular tachycardia), the patient was considered as dopamine resistant.
4) Urine output of <0.5 ml/kg/h resistant to diuretics.
5) Lactate level of >2 mmol/L.
6) Signs of hypoperfusion: cold and/or clammy skin, liver dysfunction, or impaired mentation.
7) No signs of acute cardiac ischemia or two negative troponin measurements at 6-hr intervals in case of left bundle branch block.

Patients were not included in cases of cardiogenic shock secondary to acute ischemic events, such as myocardial infarction, acute and sustained atrial and ventricular arrhythmias, septic shock, poisoning, and pulmonary embolism. Pure right ventricular failure was also excluded. Noninclusion criteria also included an immediate indication of a ventricular assist device.

Hemodynamic and Metabolic Parameters

HR was monitored continuously. Routine clinical monitoring of the patients included a thermodilution pulmonary-artery catheter with a fiber optic continuous monitoring of mixed venous oxygen saturation (Oximetrix, Abbott, Chicago, IL) and a radial or a femoral artery catheter. The zero reference level for 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 (central venous pressure), mean pulmonary artery pressure, and pulmonary artery occlusion pressure were undertaken. Each point was the average of the 10 min preceding the measurement. 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, and oxygen consumption index were calculated using standard formulae. There was no additional volume loading or change in ventilator parameters or catecholamine dose during the first hour of the study. Blood gases were measured with a blood gas analyzer standardized to saline measurements (Ciba Corning, Halsted, Essex, UK).

Tonometric Measurements

Gastric mucosal PCO_2 was measured by tonometry. The tonometer (Tonometrics, Hopkinton, MA) was inserted either naso- or orogastrically and its position in the stomach was confirmed radiologically. The tonometer was connected to an automated gas analyzer (Tonocap, Datex, Helsinki, Finland). Once the tonometer balloon was filled with air and allowed to equilibrate for 30 mins, the gas was automatically sampled and measured by infrared spectroscopy. Simultaneous arterial blood was obtained and immediately analyzed for PCO_2 and arterial blood bicarbonate determination. All patients received histamine receptor (H_2) blocking agents by a bolus of 50 mg ranitidine followed by continuous infusion (6.25 mg/h). During the study, the nasogastric tube was not on continuous aspiration and intravenous sodium bicarbonate was not given. Enteral feedings were not given during the first 24 hrs.

PCO_2 gap is defined by the difference between gastric mucosal PCO_2 and arterial PCO_2 and is used as a reliable index of gastric mucosa hypoperfusion (8).

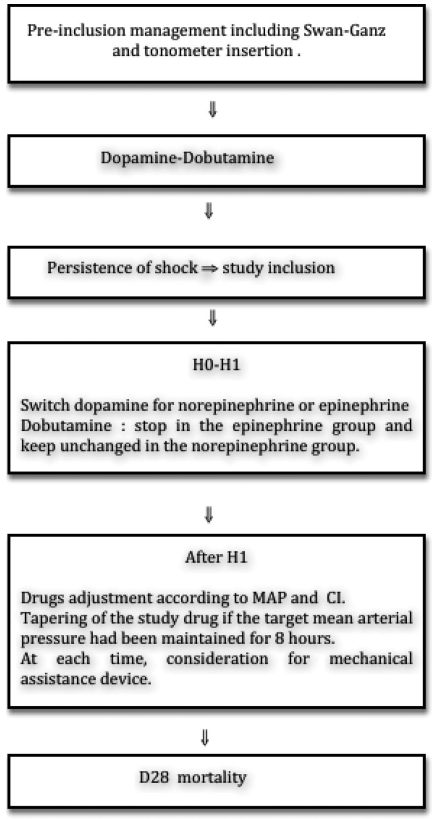

Figure 1. Study synopsis. *MAP*, mean arterial pressure; *CI*, cardiac index.

Metabolic Measurements

Lactate Determination. Arterial blood samples were collected in fluoride-oxalate–containing tubes. Lactate was measured by enzymatic-colorimetric method adapted to an automatic Wako analyzer (Biochem Systems, Meudon, France). The normal value range is <2 mmol/L.

Pyruvate. Arterial blood samples were immediately deproteinized by the addition of iced perchloric acid (1 mol/L) and immediately analyzed. Pyruvate was measured by enzymatic-ultraviolet method. The normal value range is 40–68 μmol/L for pyruvate. The analytical range for lactate is 0–10,000 μmol/L and that for pyruvate is 0–300 μmol/L. Run-to-run precision expressed as coefficient of variation is 1.5% for lactate and 5.9% for pyruvate (9).

Therapeutic Protocol

Patients were previously treated according to the recommendations endorsed by the European Society of Cardiology (10). The therapeutic protocol is shown in Figure 1. In cases of hypotension associated with low cardiac output and signs of hypoperfusion or congestion, dobutamine was first administered. In cases of persistent hypotension after dobutamine, up to 10 μg/kg/min dopamine was used at a dose ranging from 2 to 20 μg/kg/min. The infusion rate was increased by 5 μg/kg/min every 10 mins. Hence,

Table 1. Characteristics of the study groups (mean ± SD)

Clinical Characteristics	Epinephrine (n = 15)	Norepinephrine-Dobutamine[a] (n = 15)
Age, years	66 ± 12	64 ± 10
Sex, M:F	10:5	11:4
Simplified Acute Physiology II score	52 ± 5	50 ± 5
Sequential Organ Failure Assessment score	8 ± 3	9 ± 2
Left ventricular ejection fraction	24 ± 5	24 ± 5
Cardiovascular history		
History of heart failure	13	14
Ischemic cardiomyopathy	8	10
Dilated cardiomyopathy	5	3
Valvular disease	2	2
Atrial fibrillation/flutter	6	7
Previous intubation	2	2
Chronic treatment		
Diuretics	15	15
Angiotensin converting enzyme inhibitors or angiotensin receptor blockers	12	13
Aldosterone antagonists	1	1
β-blockers	0	0
Mechanical ventilation		
Invasive	12	13
Noninvasive	3	2

[a]No significant differences between groups.

the time needed to reach the highest dose of 20 μg/kg/min was 30 mins. In case of failure, patients were eligible for the study.

After meeting inclusion criteria, each patient received either epinephrine or norepinephrine according to the randomization code. Epinephrine and norepinephrine were initiated at 0.1 μg/kg/min. The infusion rate of epinephrine and norepinephrine was titrated on MAP at 5-min intervals to obtain a MAP of between 65 and 70 mm Hg with a stable or increased CI. Concomitantly, dopamine was stopped. Dobutamine was stopped in the epinephrine group and continued at the same regimen in the norepinephrine-dobutamine group. Between baseline and the first hour, ventilator settings were kept constant. Continuous insulin infusion was used to maintain glycemia under 1.5 g/L.

Baseline measurements included the following: hemodynamic parameters, tonometric parameters, arterial and mixed venous gases, lactate, and pyruvate blood levels. These measurements were repeated after 1 hr (H_1), 6 hr (H_6), 12 hr (H_{12}), and 24 hrs (H_{24}).

Troponin, creatinine, creatinine clearance, diuresis, and liver enzymes were measured at H_0 and H_{24}.

For safety assessment, a 12-lead electrocardiograph was performed at H_0, H_1, H_6, and H_{24}.

Statistical Analysis

Data are reported as mean ± SD. Baseline values were compared using an unpaired, two-tailed *t* test. The difference between epinephrine and norepinephrine-dobutamine groups 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 $<.05$ was considered significant.

RESULTS

During the 26-month study, 85 patients were admitted in our intensive care unit for cardiogenic shock. Thirty-five patients were excluded because they had acute myocardial infarction and 20 were excluded for sustained arrhythmia (four), associated septic shock (four), poisoning (three), pure right ventricular failure (three), and immediate indication of mechanical assist device (six). 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 with regard to severity scores, hemodynamic measurements, as well as tonometric and metabolic parameters (baseline values) (Tables 1, 2, and 3). At the time of inclusion, all patients were treated with a combination of dopamine (10 ± 2 μg/kg/min) and dobutamine (8 ± 2 μg/kg/min). A further increase in dopamine was not tolerated in 10 of 15 patients. Before introducing epinephrine or norepinephrine, no patients were treated with aortic counterpulsation.

Considering all measured parameters after 24 hrs, there were no differences between the two groups.

Hemodynamic Measurements. At H_1, all patients fulfilled the therapeutic goals (Table 2, Fig. 2). MAP and CI increased in all patients ($p < .01$). Both drugs increased CI and oxygen-derived parameters similarly. HR increased transiently in the epinephrine group ($p < .05$) but subsequently returned to baseline levels or below. Throughout the period of observation, HR was significantly higher ($p < .05$) in the epinephrine group than in the norepinephrine-dobutamine group. Epinephrine was associated with new supraventricular arrhythmia in two patients (13%) and with sustained ventricular tachycardia in one patient. These new arrhythmias were successfully treated with amiodaron. The double product (HR × systolic arterial pressure) measured at H_1, H_6, and H_{12} did not change in the norepinephrine group but increased in the epinephrine group ($p < .05$).

Oliguria was reversed in 10 patients in the epinephrine group and in 13 patients in the norepinephrine-dobutamine group ($p = .05$).

Patients were treated for 5 ± 2 days in both groups.

Metabolic and Tonometric Measurements. Metabolic and tonometric measurements are shown in Table 3 and Figure 3. Compared to baseline values, arterial lactate concentrations at H_6 increased in the epinephrine-treated group ($p < .01$) while decreasing in the norepinephrine-treated group ($p < .01$). During the first 12 hrs, both lactate level and lactate/pyruvate ratio were higher in the epinephrine group when compared to the norepinephrine-dobutamine group ($p < .05$). Lactic acidosis in the epinephrine-treated group was transient since it recovered within 12 hrs. The lactate/pyruvate ratio also increased transiently in the epinephrine-treated group ($p < .01$), whereas it decreased over time in the norepinephrine-dobutamine-treated group. Insulin needs increased during the first 12 hrs in the epinephrine group and decreased in the norepinephrine group.

The PCO_2 gap increased in the epinephrine-treated group ($p < .01$) but decreased in the norepinephrine group ($p < .01$). The increase in PCO_2 gap in the epinephrine-treated group was transient and subsequently returned to normal values within 24 hrs (Fig. 2). Nevertheless,

Table 2. Hemodynamic parameters

Parameter	Group	Baseline	H_1	H_6	H_{12}	H_{24}
Vasopressor titration, μg/kg/min	Ep	0	0.21 ± 0.09	0.25 ± 0.07	0.18 ± 0.08	0.15 ± 0.08
	Nor	0	0.23 ± 0.08	0.19 ± 0.08	0.17 ± 0.07	0.13 ± 0.07
Mean arterial pressure, mm Hg	Ep	55 ± 9	68 ± 9[a]	69 ± 11[a]	65 ± 10[a]	64 ± 9[a]
	Nor-Dob	54 ± 8	67 ± 10[a]	68 ± 12[a]	66 ± 8[a]	65 ± 11[a]
Cardiac index, $L/min^{-1}/m^{-2}$	Ep	1.6 ± 0.4	2.5 ± 0.4[a]	2.7 ± 0.5[a]	2.4 ± 1	2.9 ± 0.5
	Nor-Dob	1.6 ± 0.4	2.4 ± 0.3[a]	2.5 ± 0.5[a]	2.4 ± 0.4[a]	2.8 ± 0.4[a]
Heart rate, beats/min	Ep	121 ± 19	128 ± 15[a,b]	118 ± 11[a,b]	115 ± 15[a,b]	108 ± 19[a,b]
	Nor-Dob	125 ± 15	100 ± 19[a]	98 ± 15[a]	100 ± 19[a]	95 ± 15[a]
Mean pulmonary artery pressure, mm Hg	Ep	45 ± 7	43 ± 8	41 ± 7	42 ± 8	40 ± 8
	Nor-Dob	44 ± 7	42 ± 7	42 ± 8	41 ± 7	40 ± 7
Pulmonary artery occlusion pressure, mm Hg	Ep	20 ± 7	19 ± 4	18 ± 7	18 ± 7	18 ± 7
	Nor-Dob	21 ± 4	19 ± 4	18 ± 7	18 ± 7	18 ± 7
Right atrial pressure, mm Hg	Ep	15 ± 2	15 ± 2	14 ± 5	15 ± 2	14 ± 2
	Nor-Dob	16 ± 2	16 ± 2	14 ± 3	14 ± 3	15 ± 2
Mixed venous oxygen saturation, %	Ep	48 ± 4	60 ± 4[a]	63 ± 7[a]	63 ± 7[a]	67 ± 5[a]
	Nor-Dob	49 ± 6	64 ± 8[a]	64 ± 6[a]	62 ± 5[a]	72 ± 8[a]
Oxygen delivery index, $mL \cdot min^{-1} \cdot m^{-2}$	Ep	192 ± 40	350 ± 62[a]	378 ± 47[a]	345 ± 80[a]	406 ± 70[a]
	Nor-Dob	185 ± 35	345 ± 60[a]	350 ± 56[a]	340 ± 90[a]	395 ± 65[a]
Oxygen consumption index, $mL \cdot min^{-1} \cdot m^{-2}$	Ep	118 ± 35	134 ± 42[a]	140 ± 50[a]	142 ± 35[a]	141 ± 31[a]
	Nor-Dob	120 ± 31	129 ± 42[a]	132 ± 4[a]	135 ± 31[a]	135 ± 27[a]

Ep, epinephrine; Nor-Dob, norepinephrine-dobutamine.
[a]$p < .05$ vs. baseline; [b]$p < .05$ epinephrine versus norepinephrine-dobutamine.

Table 3. Metabolic, splanchnic, and renal parameters

Parameter	Group	Baseline	H_1	H_6	H_{12}	H_{24}
Arterial pH	Ep	7.32 ± 0.07	7.26 ± 0.07[a,b]	7.26 ± 0.11[a,b]	7.32 ± 0.07[b]	7.38 ± 0.11[a]
	Nor-Dob	7.31 ± 0.11	7.33 ± 0.07	7.38 ± 0.07	7.40 ± 0.07[a]	7.38 ± 0.11[a]
Lactate, mmol/L	Ep	4.1 ± 1.5	4.8 ± 1.5[a,b]	4.9 ± 1.0[a,b]	3.2 ± 1.0[b]	2.3 ± 1.0[a]
	Nor-Dob	4.0 ± 1.5	3.7 ± 1.0	2.7 ± 1.0[a]	2.4 ± 0.9[a]	2.1 ± 0.7[a]
Lactate/pyruvate ratio	Ep	30 ± 5	35 ± 7[a,b]	30 ± 6[b]	25 ± 5.0[a,b]	15 ± 6[a]
	Nor-Dob	28 ± 5	25 ± 5	20 ± 5.0[a]	16 ± 5.8[a]	14 ± 5[a]
Insulin, UI/h	Ep	2 ± 0.2	12 ± 4[a,b]	8 ± 2[a,b]	6 ± 1[a,b]	1 ± 0.2
	Nor-Dob	2 ± 0.3	2.5 ± 2	2.0 ± 0.2	1.3 ± 0.2[a]	1 ± 0.2[a]
PCO_2 gap, mm Hg	Ep	17 ± 5	25 ± 8[a,b]	24 ± 7[a,b]	17 ± 6[b]	12 ± 4[a]
	Nor-Dob	18 ± 6	14 ± 5	13 ± 5[a]	10 ± 4[a]	9 ± 3[a]
Diuresis, mL/h	Ep	20 ± 5				90 ± 20[a,b]
	Nor-Dob	17 ± 3				130 ± 30[a]
Creatinine, μmol/L	Ep	220 ± 40				150 ± 36[a]
	Nor-Dob	240 ± 35				130 ± 32[a]

Ep, epinephrine; Nor-Dob, norepinephrine-dobutamine; PCO_2 gap, tonometer PCO_2-arterial PCO_2.
[a]$p < .05$ vs. baseline; [b]$p < .05$ epinephrine vs. norepinephrine-dobutamine.

we did not observe any sign of clinical gut ischemia.

We did not observe any significant changes in electrocardiogram or troponin levels during the study.

Outcome. Ten patients survived in the epinephrine group and 11 in the norepinephrine-dobutamine group.

DISCUSSION

Effects of Epinephrine and Norepinephrine-Dobutamine on Systemic Hemodynamics and Lactate Metabolism. The present study demonstrates that both epinephrine and norepinephrine-dobutamine improved arterial pressure, oxygen delivery, and renal perfusion in patients with cardiogenic shock after failure of dopamine. Vasopressors in cardiogenic shock because may have side effects such as the following: 1) excessive increase in left ventricular afterload with a subsequent decrease in cardiac output; 2) increase in myocardial oxygen consumption with a risk of cardiac ischemia, especially if coronary circulation is impaired; or 3) arrhythmias due to an excessive intracellular calcium load (11). The only difference observed in the present study between the two catecholamine regimens was a transient increased HR in epinephrine-treated patients associated with new supraventricular arrhythmia in two patients (13%) and in one patient with sustained ventricular tachycardia, effectively treated with magnesium and amiodarone. Conversely, the norepinephrine-dobutamine group demonstrated a reduced HR, resulting in a sustained and significant difference in HR between the two groups. Whether this bradycardic effect was the result of the infusion or simply a time effect is unknown. Furthermore, during epinephrine infusion, the double product, which reflects myocardial work and is proportional to myocardial oxygen consumption, increased under epinephrine while remaining unchanged in the norepinephrine-dobutamine group (12, 13).

As previously demonstrated in septic shock (6), epinephrine transiently increased insulin requirement and lactate level with an elevated lactate/pyruvate ra-

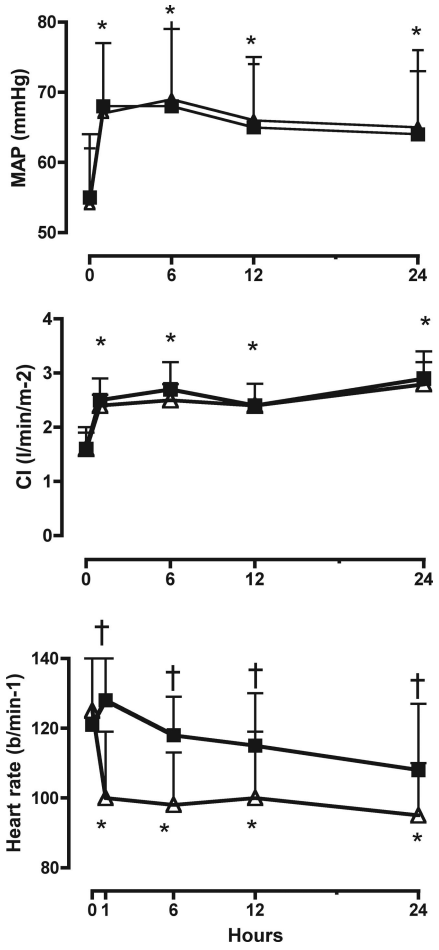

Figure 2. Evolution of mean arterial pressure (*MAP*) (*top*), cardiac index (*CI*) (*middle*), and heart rate (*HR*) (*bottom*). *Squares*, epinephrine-treated patients; *triangles*, norepinephrine-dobutamine-treated patients. *$p < .05$ vs. H_0; †$p < .05$ vs. H_0 and $p < .05$ epinephrine vs. norepinephrine-dobutamine.

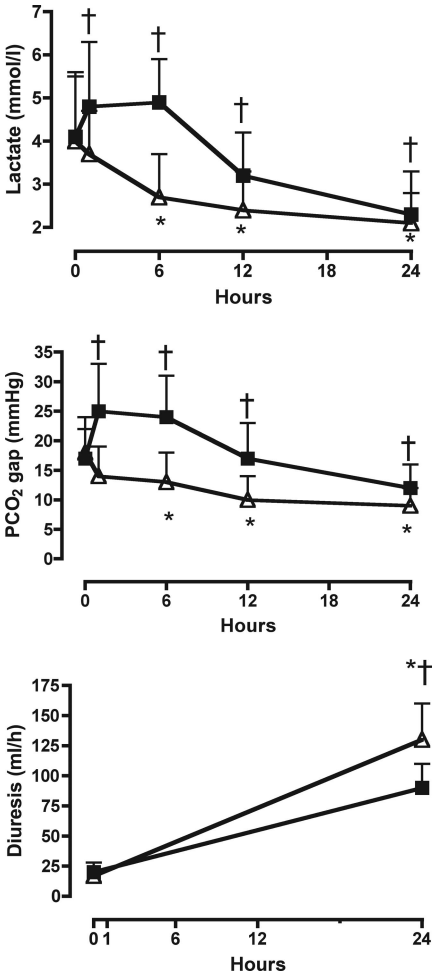

Figure 3. Evolution of lactate (*top*), PCO_2 gap (*middle*), and diuresis (*bottom*). *Squares*, epinephrine-treated patients; *triangles*, norepinephrine-dobutamine-treated patients. †$p < .05$ vs. H_0 and *$p < .05$ epinephrine vs. norepinephrine-dobutamine.

tio (14). During sepsis, but also in shock of various etiologies including cardiogenic shock, this mechanism has been attributed in part to an increase in so-called aerobic glycolysis due to the activation of the Na-K-ATPase pump under epinephrine-associated beta-2 stimulation (15). The clinical impact of this transient hyperlactatemia is not established. Nevertheless, during shock, the therapeutic use of epinephrine may decrease the usefulness of lactate as a marker of the efficiency of initiated therapy.

In summary, both regimens improved systemic hemodynamics with a more favorable profile regarding cardiac energetics and metabolism with the norepinephrine-dobutamine combination.

Effects of Epinephrine on Tonometric Parameters and Renal Function. Despite similar increases in arterial pressure and oxygen delivery/consumption in both groups, the PCO_2 gap increased in epinephrine-treated patients (Fig. 3). This finding could suggest 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 oxygen delivery and splanchnic oxygen consumption. Another hypothesis is that epinephrine may have decreased mucosal blood flow along with a decrease in CO_2 efflux, the net result being an increase in the PCO_2 gap. Since gastric mucosal blood flow was not measured in the present study, it is difficult to interpret this measurement. Nevertheless, during cardiogenic shock, splanchnic blood flow is directly correlated with cardiac output (16). Thus, in our patients in whom cardiac output markedly increased, the increase in the PCO_2 gap under epinephrine is likely related to the thermogenic effects of epinephrine. Furthermore, despite a marked increase in epinephrine-treated patients, the PCO_2 gap after 24 hrs of treatment was no longer different when compared to norepinephrine-dobutamine patients. This time-response profile, identical to lactate kinetics, is highly evocative of a metabolic effect.

In regard to renal function, both regimens improved diuresis in these oliguric patients, although the effects of norepinephrine-dobutamine were greater. Creatinine levels also improved without any differences between regimens.

Altogether, norepinephrine-dobutamine improves both the adequacy of gastric mucosa perfusion, used as a surrogate for splanchnic perfusion, and indices of renal function. By contrast, epinephrine appears to be associated with potential deleterious effects on the adequacy of splanchnic perfusion (17). Nevertheless, the clinical impact of this transient gastric hypoperfusion is not established.

Limitations of the Study. The main limitation is the small number of patients enrolled in the study that may limit the conclusions concerning the outcome. Nevertheless, the data obtained will be useful to plan an outcome-based prospective randomized study. We chose to restrict our study population to nonischemic cardiogenic shock, since hemodynamics in cardiogenic shock associated with myocardial infarction is highly dependent on the success rate and the timing of myocardial reperfusion (18). Based on these results, we are conducting a prospective randomized double-blind study in cardiogenic shock secondary to acute myocardial infarction to address this question. We observed more arrhythmia in the epinephrine group. While this side effect is well correlated with the physiology, the present observation may not provide sufficient basis to definitively conclude that epinephrine causes a higher rate of tachyarrhythmias given the small number of patients in the two groups, with three patients exhibiting tachyarrhythmias in the epinephrine group vs. none in the norepinephrine group.

CONCLUSIONS

Perhaps the most challenging aspect to the care of a patient with severe heart failure/cardiogenic shock is to decide at which level of arterial blood pressure

does chronic therapeutic lowering of afterload become pathologic. Thus, in association with an absolute level of arterial pressure, we also used indices of organ hypoperfusion such as diuresis, lactate level, and/or hypoperfused extremities (10). We found that the correction of hypotension correlated with the improvement in cardiac output was associated with the reversal of organ hypoperfusion such as acute renal failure, likely indicating an improvement in global tissue perfusion. Nevertheless, priority should be given to the correction of decreased blood flow and, therefore, catecholamines should be discontinued as soon as possible to the profit of chronic treatment of heart failure.

To conclude, we compared epinephrine and norepinephrine-dobutamine in cardiogenic shock without acute coronary syndrome and found that in terms of global hemodynamic effects, epinephrine is as effective as norepinephrine-dobutamine. Nevertheless, epinephrine is associated with a transient lactic acidosis, elevated HR, likely more arrhythmia, and inadequacy of gastric mucosa perfusion. Thus, the combination norepinephrine-dobutamine appears to be a more reliable and safe strategy in this particular setting.

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