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Glenn Hernandez
Alejandro Bruhn
Cecilia Luengo
Tomas Regueira
Eduardo Kattan
Andrea Fuentealba
Jorge Florez
Ricardo Castro
Andres Aquevedo
Ronald Pairumani
Paul McNab
Can Ince

Effects of dobutamine on systemic, regional and microcirculatory perfusion parameters in septic shock: a randomized, placebo-controlled, double-blind, crossover study

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G. Hernandez (✉) · A. Bruhn · T. Regueira · E. Kattan · A. Fuentealba · J. Florez · R. Castro · A. Aquevedo · R. Pairumani
Departamento de Medicina Intensiva, Pontificia Universidad Católica de Chile, Marcoleta 367, 8320000 Santiago, Chile
e-mail: glennguru@gmail.com

G. Hernandez · C. Ince
Department of Translational Physiology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

C. Luengo
Unidad de Pacientes Críticos, Hospital Clínico Universidad de Chile, Santos Dumont 999 Independencia, Santiago, Chile

P. McNab
Departamento de Enfermedades Cardiovasculares, Pontificia Universidad Católica de Chile, Marcoleta 367, Santiago, Chile

Abstract *Purpose:* The role of dobutamine during septic shock resuscitation is still controversial since most clinical studies have been uncontrolled and no physiological study has unequivocally demonstrated a beneficial effect on tissue perfusion. Our objective was to determine the potential benefits of dobutamine on hemodynamic, metabolic, peripheral, hepatosplanchnic and microcirculatory perfusion parameters during early septic shock resuscitation. *Methods:* We designed a randomized, controlled, double-blind, crossover study comparing the effects of 2.5-h infusion of dobutamine (5 mcg/kg/min fixed-dose) or placebo in 20 septic shock patients with cardiac index $\geq$2.5 l/min/m^2 and hyperlactatemia. Primary outcome was sublingual perfused microvascular density. *Results:* Despite an increasing cardiac index, heart rate and left ventricular ejection fraction, dobutamine had no effect on sublingual perfused vessel density [9.0 (7.9–10.1) vs. 9.1 n/mm (7.9–9.9); $p = 0.24$] or microvascular flow index [2.1 (1.8–2.5) vs. 2.1 (1.9–2.5); $p = 0.73$] compared to placebo. No differences between dobutamine and placebo were found for the lactate levels, mixed venous-arterial pCO_2 gradient, thenar muscle oxygen saturation, capillary refill time or gastric-to-arterial pCO_2 gradient. The indocyanine green plasma disappearance rate [14.4 (9.5–25.6) vs. 18.8 %/min (11.7–24.6); $p = 0.03$] and the recovery slope of thenar muscle oxygen saturation after a vascular occlusion test [2.1 (1.1–3.1) vs. 2.5 %/s (1.2–3.4); $p = 0.01$] were worse with dobutamine compared to placebo. *Conclusions:* Dobutamine failed to improve sublingual microcirculatory, metabolic, hepatosplanchnic or peripheral perfusion parameters despite inducing a significant increase in systemic hemodynamic variables in septic shock patients without low cardiac output but with persistent hypoperfusion.

Keywords Septic shock · Lactate · Dobutamine · Perfusion · Microcirculation

Introduction

Current septic shock resuscitation strategies include fluid administration to optimize the preload followed by vasopressors to restore blood pressure as initial steps toward improving tissue perfusion [1–3]. Nevertheless, a number of patients evolve with persistent global or tissue hypoperfusion despite this initial resuscitation. In this setting, dobutamine, a drug with inotropic and vasodilatory properties, may be added to increase oxygen delivery (DO_2) or to directly improve tissue perfusion [1–3]. Over the last decades, some experimental and clinical studies have shown potential benefits of dobutamine, such as increasing cardiac output [4], central ($ScvO_2$) [3] or mixed venous oxygen saturations (SvO_2) [5], and eventually hepatosplanchnic perfusion [6]. In a more recent clinical study, a marked improvement in microcirculatory derangements was observed after 2 h of dobutamine infusion [7]. Based on these data, current guidelines recommend dobutamine for septic shock in patients with low cardiac output or with persistent hypoperfusion after initial resuscitation [1, 8].

However, other studies have yielded conflicting data concerning the effects of dobutamine on hepatosplanchnic and microcirculatory perfusion [9–14], and it remains unclear whether it can improve lactate clearance or peripheral perfusion. In addition, dobutamine has been associated with serious adverse events [4, 15].

Despite the strong recommendations for dobutamine use to improve tissue perfusion in septic shock, the supporting evidence is quite weak. Thus, further studies are required to determine the contribution of dobutamine for this specific purpose. Therefore, we designed a prospective placebo-controlled double-blind crossover study to comprehensively assess the effects of dobutamine on hemodynamic, metabolic, peripheral, hepatosplanchnic, and microcirculatory perfusion parameters during early septic shock resuscitation.

Methods

This was a prospective, randomized, double-blind, placebo-controlled, crossover study, conducted from February 2011 to August 2012 in a mixed 16-bed intensive care unit (ICU) at a university hospital. The Institutional Review Board of the university approved the study, and all patients or surrogates signed an informed consent form before enrollment.

Study population

All consecutive adult patients admitted to the ICU within 24 h of septic shock onset diagnosed according to the 2001 Consensus Definition [16] with a basal arterial lactate >2.4 mmol/l and mechanically ventilated were considered eligible for this protocol.

We excluded patients with pregnancy, refractory hypotension, acute coronary syndrome within the last 3 months, previous use of dobutamine during the last 72 h, cardiac index <2.5 l/min/m^2, non-sinus rhythm, heart rate >140 bpm, anticipated surgery or dialysis during the study period, Child B or C liver cirrhosis, or a do-not-resuscitate status.

Study design

Eligible patients were randomized into two groups: the first group primarily received dobutamine at a fixed dose of 5 mcg/kg/min for 2.5 h, followed by a 5 % dextrose solution as placebo for another 2.5 h, without a washout-period; the second group was subjected to the same interventions in the inverse sequence (Fig. 1). Randomization to the treatment sequence was performed through sealed opaque envelopes in two blocks of ten at a one-to-one proportion.

Dobutamine and placebo infusions were prepared at the ICU satellite pharmacy by an unblinded research nurse and labeled as infusion 1 or 2 following the allocation contained in the randomization envelope. Attending physicians, investigators, nurses and relatives were blinded to the specific drug.

In order to start the study period, patients should have a pulmonary artery catheter in place, hemoglobin >8 g/dl and temperature <39 °C and should have maintained a pulse pressure variation <10 % for at least 1 h without fluid challenges. A continuous infusion of normal saline was administered during the study period to maintain pulse pressure variation below 10 %. Norepinephrine infusion was adjusted to keep the mean arterial pressure ≥65 mmHg. Before and during the protocol, all patients were sedated to maintain a Sedation-Agitation Scale score [17] of 1–2 and mechanically ventilated in volume-controlled mode with ventilatory settings adjusted according to current recommendations [1]. No new vasopressors or inotropes were administered after starting the study protocol. As a safeguard, in case of cardiovascular instability, such as life-threatening hypotension, tachycardia >150 bpm, acute atrial fibrillation or ST changes in the cardiac monitor, the study had to be stopped and randomization disclosed.

Data collection and outcomes

Biochemical and clinical variables were collected at baseline. Study assessments comprised systemic hemodynamics, transthoracic echocardiography, peripheral perfusion, thenar muscle oxygen saturation (StO_2)

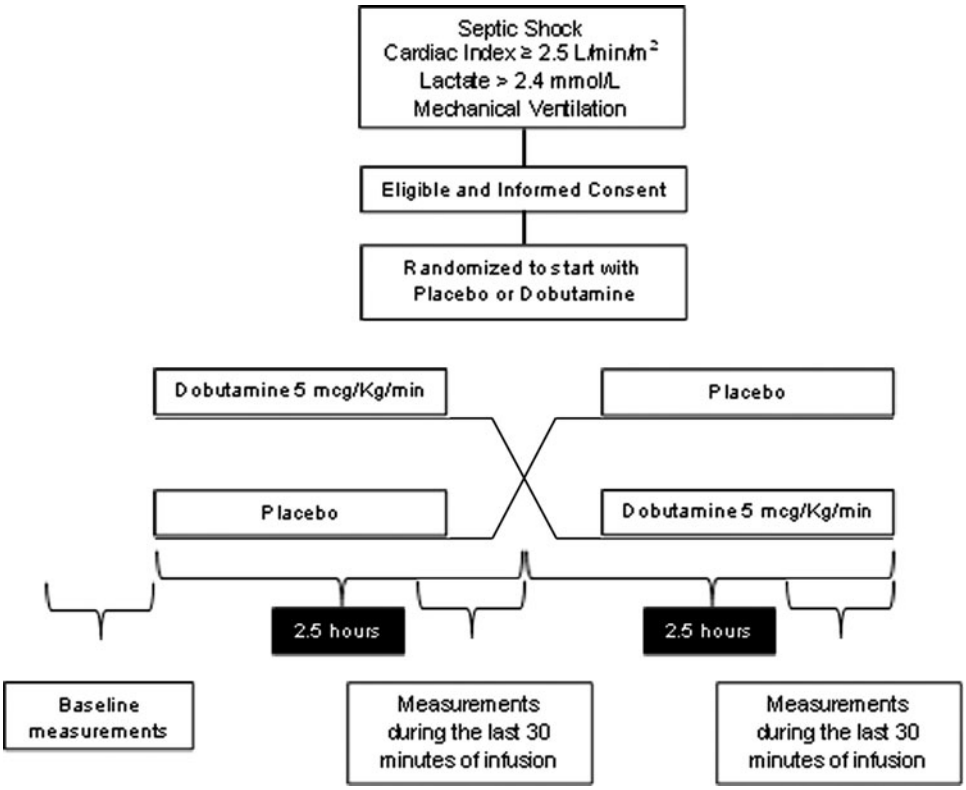

Fig. 1 Diagram of the study design

(InSpectra Model 650, Hutchinson Technology, Hutchinson, MN), StO_2 changes during a vascular occlusion test, arterial lactate levels, gastric tonometry (Tonocap, Datex Ohmeda, Helsinki, Finland), indocyanine green (ICG)-plasma dissapareance rate (LiMon Pulsion Medical Systems, Germany) and sublingual microcirculatory perfusion (Microscan®, Microvision Medical, Amsterdam, The Netherlands). They were assessed at baseline (within 30 min before starting the first drug infusion) and repeated within the last 30 min of each drug infusion period.

Primary outcome was sublingual perfused small vessel density, while secondary outcomes were the microvascular flow index, proportion of perfused vessels, cardiac index, left ventricle ejection fraction, capillary refill time, central-to-toe temperature gradient, baseline StO_2 and its recovery slope after a vascular occlusion test, arterial lactate, gastric-to-arterial pCO_2 gradient and (ICG)-plasma disappearance rate. Perfused small vessel density was calculated semiquantitatively by counting the vessels <20 um crossing a 3 × 3 gridline [18]. Further details of measurements and analysis are presented in file E1 (online data supplement ESM).

Statistical analysis

Based on a previous study [7], we estimated that a sample size of 20 patients would yield a statistical power of 80 % to detect an increase in perfused small vessel density of 0.6 vessels/mm during infusion of dobutamine compared to placebo.

To compare effects of dobutamine versus placebo, we followed recommendations for crossover trials [19]. As dobutamine has such a rapid elimination (half-life of 4.5 min), we estimated a priori that a washout period between treatments was not necessary. However, we performed a test for carryover effects, which consisted of comparing the sum of the results obtained in both periods for the two sequences with the Mann-Whitney *U* test. Differences between dobutamine and placebo were analyzed by comparing the period differences for the two sequences with the Mann-Whitney *U* test. All comparisons between dobutamine and placebo were analyzed with this method. Accordingly, obtained *p* values corresponded to the treatment effect adjusted by period in the whole study group.

The Kolmogorov-Smirnov test was used to verify data distribution normality. Since the majority of data exhibited a non-normal distribution, we reported data as the median (interquartile range) with non-parametric statistics for analysis including a Mann-Whitney *U* test for continuous data and Fisher's exact test for categorical data. *p* values <0.05 were considered statistically significant. Reported *p* values are two-sided. SPSS software version 17.0 (Chicago, IL, USA) was used for calculations.

Results

Enrolled patients had a median age of 67 years (57–73), APACHE II score of 23.5 (19.3–25) and basal SOFA score of 10 (8.3–14.5). Sepsis sources were abdominal in 11, respiratory in 3 and others in 6. Patients fulfilled septic shock criteria for 6.2 h (2.3–12.3) before being recruited for the study and exhibited a hospital mortality of 15 %. There were no significant differences in any variable at baseline between the two study groups. Baseline characteristics of the whole population and of subgroups starting with dobutamine or placebo are shown in Tables 1 and E1 (Table E1 in the online data supplement ESM).

Hemodynamic and echocardiographic parameters

Fluid administration (normal saline solution) was comparable between groups during dobutamine and placebo periods [318 ml (230–372) vs. 330 ml (204–423); $p = 0.83$]. Dobutamine significantly increased the heart rate, cardiac index and left ventricular ejection fraction compared to placebo (Table 2). These effects were not associated to changes in norepinephrine requirements, pulse pressure variation, central venous pressure or pulmonary artery occlusion pressure (Table 2). No differences in diastolic function (E/e′) or other echocardiographic variables were observed.

Peripheral perfusion parameters

No significant effect of dobutamine on capillary refill time, temperature gradients or StO_2 was observed (Table 2). However, the recovery slope of StO_2 after the vascular occlusion test worsened with dobutamine compared to placebo.

Metabolic-related perfusion parameters

Dobutamine induced a significant increase in DO_2 and SvO_2. Nonetheless, this was not associated with differences in VO_2, mixed venous-arterial pCO_2 gradient or lactate levels compared to placebo (Table 2).

Hepatosplanchnic perfusion parameters

Dobutamine induced no significant beneficial effect on gastric tonometry. Nevertheless, the indocyanine green

Table 1 Baseline parameters of the whole population and subgroups randomized to start with dobutamine or placebo

	All patients ($n = 20$)	Dobutamine–placebo ($n = 10$)	Placebo–dobutamine ($n = 10$)	p value
Hemodynamic and echocardiographic parameters				
Heart rate (bpm)	95 (84–100)	95 (83–101)	93 (83–105)	0.96
Mean arterial pressure (mmHg)	73 (70–84)	73 (67–86)	76 (72–83)	0.52
Central venous pressure (mmHg)	13 (11–16)	14 (11–19)	12 (10–15)	0.37
Pulmonary artery occlusion pressure (mmHg)	15 (11–19)	15 (11–19)	14 (10–19)	0.74
Cardiac index (l/min/m^2)	3.2 (2.9–3.9)	3.1 (2.9–3.4)	3.7 (2.8–4.3)	0.38
Left ventricular ejection fraction (%)	62 (51–70)	57 (47–69)	63 (57–71)	0.44
Norepinephrine dose (mcg/kg/min)	0.18 (0.08–0.29)	0.13 (0.07–0.33)	0.21 (0.07–0.25)	0.71
Pulse pressure variation (%)	6 (4–8)	6 (5–8)	7 (4–9)	0.77
Peripheral perfusion parameters				
Capillary refill time (s)	3 (2–6)	3 (2–7)	3 (2–5)	0.67
Central to peripheral temperature difference (°C)	8.7 (7–11)	9.1 (8–11)	8.4 (5–11)	0.31
Thenar muscle O_2 saturation (%)	78 (73–85)	74 (72–80)	84 (76–88)	0.07
StO_2 recovery slope after VOT (%/s)	1.9 (1.1–3.1)	2.9 (1.6–2.7)	1.7 (0.4–3.6)	0.42
Metabolic-related perfusion parameters				
Mixed venous oxygen saturation (%)	76 (70–79)	76 (68–78)	77 (75–83)	0.34
Mixed venous-arterial pCO_2 gradient (mmHg)	4.9 (2.2–6.5)	4.4 (1.5–7.5)	5.4 (2.5–6.1)	0.86
Arterial lactate (mmol/l)	3.3 (2.6–4.8)	3.6 (2.5–4.8)	3.3 (2.7–4.9)	0.96
Hepatosplanchnic parameters				
Intraabdominal pressure (mmHg)	10 (8–15)	10 (8–14)	10 (7–17)	0.98
ICG plasma disappearance rate (%/min)	19 (11.9–22.7)	19 (12.2–23.7)	19 (10.1–24)	0.73
Gastric-arterial pCO_2 gradient (mmHg)	8.2 (5.5–15.8)	8.1 (4.7–15)	8.3 (5.7–25.5)	0.75
Sublingual microcirculatory parameters				
Perfused vessel density (n/mm)	8.2 (7.5–9.3)	8.4 (7.3–9.3)	8.2 (7.3–10.1)	0.79
Percent of perfused vessels (%)	74 (67–81)	73 (63–80)	75 (69–82)	0.42
Microvascular flow index	2.0 (1.3–2.2)	1.7 (1.2–2.2)	2.2 (1.3–2.3)	0.59

Values are expressed as median (interquartile range); $p < 0.05$ considered as significant
StO_2 thenar muscle oxygen saturation, *VOT* vascular occlusion test, *ICG* indocyanine green

Table 2 Comparison of hemodynamic, echocardiographic, peripheral and metabolic-related perfusion parameters with placebo or dobutamine

Parameter	Placebo	Dobutamine	*p* value
Hemodynamic and echocardiographic parameters			
Heart rate (bpm)	93 (84–108)	108 (97–122)	<0.01
Mean arterial pressure (mmHg)	71 (68–80)	69 (65–75)	0.52
Central venous pressure (mmHg)	13 (11–16)	11 (9–14)	0.13
Pulmonary artery occlusion pressure (mmHg)	13 (10–15)	12 (10–15)	0.15
Cardiac index (l/min/m^2)	3.7 (3.2–4.1)	4.2 (3.5–5.0)	<0.01
Left ventricular ejection fraction (%)	63 (58–72)	74 (64–78)	0.02
Left ventricular shortening fraction (%)	32 (28–44)	38 (31–43)	0.16
Norepinephrine dose (mcg/kg/min)	0.15 (0.07–0.33)	0.16 (0.06–0.42)	0.65
Pulse pressure variation (%)	6 (2–8)	6 (3–8)	0.16
Urine output (ml)	90 (51–119)	53 (25–220)	0.39
Peripheral perfusion parameters			
Capillary refill time (s)	3 (2–4)	3 (2–5)	0.67
Central-to-toe temperature gradient (°C)	6.8 (4.9–10.5)	6.9 (5.3–10.0)	0.54
Thenar muscle oxygen saturation (%)	82 (74–88)	84 (75–88)	0.1
StO_2 recovery slope after VOT (%/s)	2.5 (1.2–3.4)	2.1 (1.1–3.1)	0.01
Metabolic-related perfusion parameters			
Mixed venous oxygen saturation (%)	77 (72–81)	78 (75–81)	0.05
Mixed venous-arterial pCO_2 gradient (mmHg)	3.3 (1.5–3.8)	3.6 (0.4–4.6)	0.45
Arterial lactate (mmol/l)	2.8 (2.4–3.9)	2.8 (2.4–4.0)	0.20
Oxygen delivery (ml/min/m^2)	566 (374–722)	717 (419–771)	0.02
Oxygen consumption (ml/min/m^2)	129 (100–156)	140 (106–167)	0.35

Values are expressed as median (interquartile range); $p < 0.05$ considered as significant
StO_2 thenar muscle oxygen saturation, *VOT* vascular occlusion test

plasma disappearance rate was lower with dobutamine compared to placebo (Table 3).

Sublingual microcirculatory parameters

We found no significant effect of dobutamine on perfused microvascular density or in any of the other assessed microcirculatory variables, (Table 3; Figs. 2, 3).

Adverse events

No serious adverse events such as cardiac arrhythmia, myocardial ischemia or sudden hypotension were registered; thus, the study could be completed in all patients. However, the heart rate increased over 130 bpm in three patients during dobutamine infusion.

Complete results are additionally provided in the online data supplement ESM.

Discussion

In this randomized, double-blind, crossover study in septic shock patients with persistent hypoperfusion after initial resuscitation, dobutamine failed to improve sublingual microcirculatory, hepatosplanchnic, peripheral perfusion parameters or lactate levels, despite inducing

Table 3 Comparison of hepatosplanchnic and sublingual microcirculatory perfusion parameters with placebo or dobutamine

Parameter	Placebo	Dobutamine	*p* value
Hepatosplanchnic parameters			
Intraabdominal pressure (mmHg)	12 (8–16)	12 (9–17)	0.39
ICG plasma disappearance rate (%/min)	18.8 (11.7–24.6)	14.4 (9.5–25.6)	0.03
ICG retention rate at 15 min (%)	6.0 (2.8–17.4)	11.5 (2.3–24.3)	0.06
Gastric-arterial pCO_2 gradient (mmHg)	13 (7–18)	13 (7–29)	0.52
Sublingual microcirculatory parameters			
Total microvascular density (n/mm)	11.8 (10.2–12.5)	11.9 (9.7–12.5)	0.91
Perfused vessel density (n/mm)	9.1 (7.9–9.9)	9.1 (7.9–10.1)	0.24
Proportion of perfused microvessels (%)	75 (69–79)	79 (72–84)	0.09
Microvascular flow index	2.1 (1.9–2.5)	2.1 (1.8–2.5)	0.73
Het Index MFI	0.58 (0.46–0.73)	0.47 (0.40–0.86)	0.52

Values are expressed as median (interquartile range); $p < 0.05$ considered as significant
ICG indocyanine green, *Het Index MFI* heterogeneity of microvacular flow index

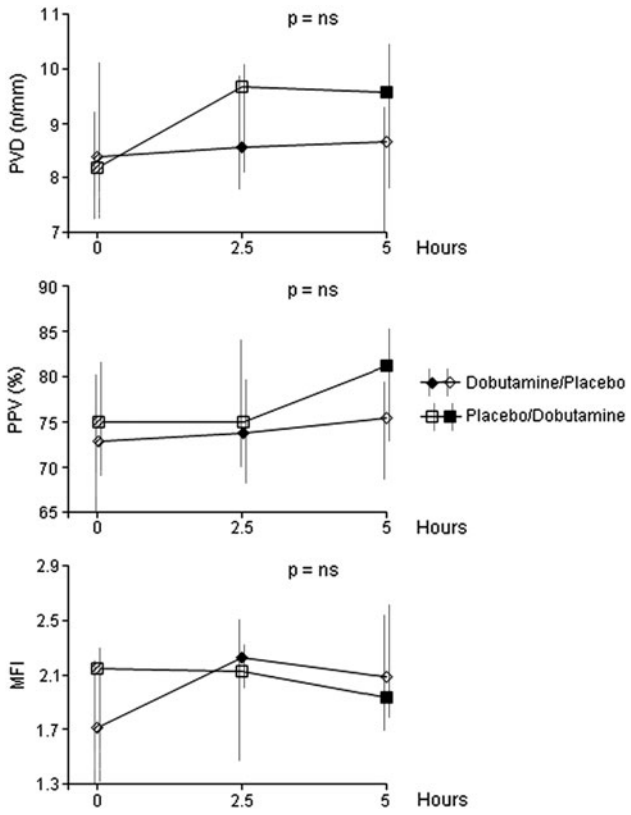

Fig. 2 Changes in sublingual perfused vessel density (*PVD*), proportion of perfused vessels (*PPV*) and microvascular flow index (*MFI*) in patients randomized to the sequence dobutamine/placebo (*diamonds*) or to the sequence placebo/dobutamine (*squares*). Data at time zero correspond to baseline values, while values taken at 2.5 or 5 h correspond to dobutamine (*black*) or placebo (*white*). *p* values were calculated by comparing the period differences (5–2.5 h) between both sequence groups by Mann-Whitney *U* test and therefore correspond to the treatment effect of dobutamine versus placebo, adjusted by period

a significant increase in systemic hemodynamic variables.

Concerning the effects of dobutamine on macrohemodynamic parameters, we found an increase of 15 % in the cardiac index, 12 % in the heart rate and 16 % in the left ventricle ejection fraction, which is in concordance with previous data [15, 20]. Dobutamine has been used in several previous studies as part of hemodynamic management algorithms aimed at increasing DO_2 as a tool to improve tissue perfusion [2–5]. Hayes et al. [4] performed a randomized controlled study of DO_2 maximization in 100 critically ill patients using dobutamine at median doses of 25 mcg/kg/min (range 2.5–200) in the treatment group. Despite increasing DO_2, dobutamine failed to improve oxygen consumption and was associated with a 20 % higher absolute mortality risk. Two more recent trials of perfusion-oriented strategies included dobutamine as part of the protocol. Although both trials showed an improvement in outcome, the specific contributing role of dobutamine was not addressed, and <50 % of patients received the drug overall [2, 3].

In the present study, we included a cohort of 20 septic shock patients with evidence of persistent hypoperfusion. All patients had hyperlactatemia and moderate to severe sublingual microcirculatory abnormalities, and almost half of them had hepatosplanchnic or peripheral hypoperfusion. As expected, the increase in cardiac output obtained with dobutamine resulted in increased DO_2 and SvO_2. However, there was no beneficial effect of dobutamine on any of the assessed tissue perfusion parameters. Moreover, despite the low doses used in this trial, dobutamine led to a significant rise in heart rate that might potentially increase myocardial oxygen consumption.

Both favorable and neutral effects of dobutamine on sublingual microcirculatory parameters have been reported [7, 14, 15]. De Backer et al. [7] showed in 22 septic shock patients that a fixed dose of dobutamine at 5 mcg/kg/min applied for 2 h markedly increased the proportion of perfused microvessels from 48 to 67 %. Based on this study, dobutamine has been suggested as a potential tool to improve microvascular flow [21]. However, an important limitation of this study is the lack of a control arm. In a more recent clinical trial, dobutamine was infused at increasing doses up to 10 mcg/kg/min for 20-min periods in septic shock patients. Dobutamine failed to induce any significant change in sublingual microcirculatory variables when considering the whole study group [15]. Morelli et al. [14] compared the sublingual microcirculatory effects of levosimendan versus

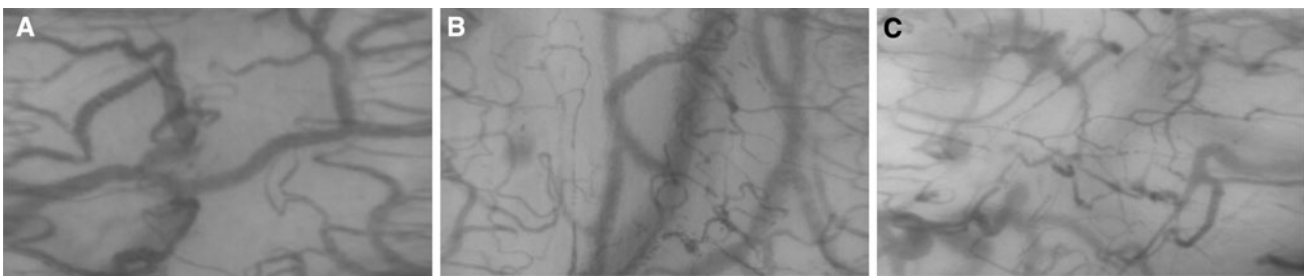

Fig. 3 Images of sublingual microcirculation of patient no. 8 at baseline **a**, after placebo **b** and after dobutamine, **c**. Corresponding perfused vessel density values were 7.9, 8.7 and 8.3 n/mm, respectively

dobutamine in septic shock patients. Dobutamine in doses of 5 mcg/kg/min had no significant beneficial effects in any microcirculatory variables. In the present study, when comparing dobutamine to placebo in a double-blind design, we found no differences on sublingual microcirculatory variables, despite the increase in cardiac output and DO_2. We observed whether there was any relation between the severity of sublingual microvascular alterations at baseline and the specific response to dobutamine, but we found no indication in that direction. According to our results, dobutamine should not be recommended to treat microvascular dysfunction in sepsis [21].

Septic shock may compromise splanchnic perfusion, which may lead to mucosal ischemia, increased permeability and a predisposition to bacterial or endotoxin translocation [22, 23]. Various inotropes, including dobutamine, have been studied with the aim of restoring splanchnic perfusion in septic shock [24, 25]. Experimental and clinical studies have shown conflicting and contradictory results [26–32].

Some clinical non-controlled studies have associated dobutamine use with improvements in gastric mucosal perfusion, assessed by gastric tonometry [9, 12, 24]. However, two randomized controlled studies in septic patients could not confirm these observations [11, 13]. In addition, a few studies have addressed potential effects of dobutamine on hepatic perfusion using indocyanine green clearance, again with conflicting findings [9, 10, 33]. Unfortunately, none of these studies included a placebo control or a clear description of preload optimization and co-interventions.

In the present study, we evaluated hepatosplanchnic perfusion with gastric tonometry and indocyanine green clearance. The latter is influenced by liver function and perfusion, but acute changes are explained mainly by variations in liver perfusion [33]. At baseline, gastric tonometry was normal in most patients, and hepatosplanchnic perfusion was moderately impaired. We found no improvement with dobutamine in these two parameters. Surprisingly, dobutamine even decreased indocyanine green clearance. We do not have a clear explanation for this finding, but it could be related to observations from a previous study where dobutamine was found to decrease fractional liver blood flow [10].

Correction of peripheral hypoperfusion during resuscitation is usually considered a favorable sign [34–36]. There are no data about the effects of dobutamine on peripheral perfusion in septic shock. In patients with congestive heart failure, dobutamine has been shown to increase peripheral blood flow as well as reactive hyperemia after a vascular occlusion test [37, 38]. However, in this series of septic shock patients we observed no effect of dobutamine on peripheral perfusion markers. Moreover, dobutamine decreased the post-ischemic thenar StO_2 recovery rate, which is in sharp contrast with results described for patients with congestive heart failure. These discrepant findings may be related to differences in endothelial function between both disease states.

Lactate is routinely measured in septic shock patients and has been proposed as a target to guide resuscitation [2]. Persistent hyperlactatemia after initial resuscitation is usually advocated as an argument to further increase DO_2. However, its interpretation may be largely more complex [34]. Although tissue hypoperfusion has been traditionally considered the most common cause of hyperlactatemia, there is increasing evidence for concomitant non-hypoxic and thus non-flow-responsive mechanisms such as epinephrine-driven aerobic muscle lactate production [34]. Eventually adrenergic agonists could have antagonistic effects on lactate production, either decreasing hypoxic-related generation or, on the contrary, increasing skeletal muscle aerobic production [34, 39]. This subject clearly requires more research. In our study, despite the increase in cardiac output obtained with dobutamine, there was no impact on lactate levels when compared to placebo.

We acknowledge several limitations of our study. First, the sample size was rather small. Although it fit our sample size calculation, we can't exclude that the statistical power was insufficient to detect smaller differences in some variables. However, it is unlikely that we missed clinically relevant effects because of this reason. Second, because most clinicians feel compelled to use inotropes in patients with low cardiac output, we excluded them from this trial. Third, we did not include a washout period. This decision was made considering the very short half-life of dobutamine (<4 min) and the need to shorten the study period to decrease the impact of ongoing resuscitation and co-interventions on results. Nevertheless, and as recommended by experts in crossover trials, we adjusted the results to the potential bias introduced by period and sequence, and this analysis discarded a carryover effect of the drug. Fourth, we used a fixed dobutamine dose without titrating the drug against sublingual microcirculatory findings. Fifth, we assessed sublingual microcirculatory images with a semiquantitative method performed manually instead of using a software-based quantitative approach, which could be more precise and reproducible. However, the semiquantitative method has been validated by experts [18].

In conclusion, dobutamine failed to improve sublingual microcirculatory, metabolic, hepatosplanchnic or peripheral perfusion parameters despite inducing a significant increase in systemic hemodynamic variables in septic shock patients without low cardiac output but with persistent hypoperfusion. Thus, our study challenges current septic shock guidelines recommending dobutamine to improve tissue hypoperfusion after initial resuscitation.

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Conflicts of interest The authors declare that they have no conflict of interest.

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