British Journal of Anaesthesia **100 (4):** 494–503 (2008)
doi:10.1093/bja/aen017 Advance Access publication February 27, 2008

BJA

CRITICAL CARE

Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study†

A. Morelli[1]*, C. Ertmer[2], M. Lange[2], M. Dünser[3], S. Rehberg[2], H. Van Aken[2], P. Pietropaoli[1] and M. Westphal[2]

[1]Department of Anesthesiology and Intensive Care, University of Rome 'La Sapienza', Viale del Policlinico 155, 00161 Rome, Italy. [2]Department of Anesthesiology and Intensive Care, University Hospital of Muenster, Albert-Schweitzer-Str. 33, 48149 Muenster, Germany. [3]Department of Intensive Care Medicine, University of Bern, 3010 Bern, Switzerland

**Corresponding author. E-mail: andrea.morelli@uniroma1.it*

Background. Terlipressin bolus infusion may reduce cardiac output and global oxygen supply. The present study was designed to determine whether dobutamine may counterbalance the terlipressin-induced depression in mixed-venous oxygen saturation (Sv_{O_2}) in patients with catecholamine-dependent septic shock.

Methods. Prospective, randomized, controlled study performed in a university hospital intensive care unit. Septic shock patients requiring a continuous infusion of norepinephrine (0.9 μg kg^{-1} min^{-1}) to maintain mean arterial pressure (MAP) at 70 (SD 5) mm Hg were randomly allocated to be treated either with (i) sole norepinephrine infusion (control, n=20), (ii) a single dose of terlipressin 1 mg (n=19), or (iii) a single dose of terlipressin 1 mg followed by dobutamine infusion titrated to reverse the anticipated reduction in Sv_{O_2} (n=20). Systemic, pulmonary, and regional haemodynamic variables were obtained at baseline and after 2 and 4 h. Laboratory surrogate markers of organ (dys)function were tested at baseline and after 12 and 24 h.

Results. Terlipressin (with and without dobutamine) infusion preserved MAP at 70 (5) mm Hg, while allowing to reduce norepinephrine requirements to 0.17 (0.2) and 0.2 (0.2) μg kg^{-1} min^{-1}, respectively [*vs*1.4 (0.3) μg kg^{-1} min^{-1} in controls at 4 h; each $P<0.001$]. The terlipressin-linked decrease in Sv_{O_2} was reversed by dobutamine at a mean dose of 20 (8) μg kg^{-1} min^{-1} [Sv_{O_2} at 4 h: 59 (11)% *vs* 69 (12)%, P=0.028].

Conclusions. In human catecholamine-dependent septic shock, terlipressin (with and without concomitant dobutamine infusion) increases MAP and markedly reduces norepinephrine requirements. Although no adverse events were noticed in the present study, potential benefits of increasing Sv_{O_2} after terlipressin bolus infusion need to be weighted against the risk of cardiovascular complications resulting from high-dose dobutamine.

Br J Anaesth 2008; **100**: 494–503

Keywords: arterial pressure, drug effects; complications, vasoconstriction; intensive care; oxygen, transport

Accepted for publication: January 10, 2008

Aggressive fluid challenge and administration of catecholamines play a pivotal role in the current treatment regimen of patients with septic shock. Owing to adrenergic and post-receptor abnormalities in sepsis, however, the efficacy of catecholamines often gradually decreases over time,[1 2] necessitating incremental doses to counteract arterial hypotension. Excessive catecholamine concentrations, in turn, may contribute to major side-effects (e.g.

†This study was performed in the Intensive Care Unit of the Department of Anesthesiology and Intensive Care of the University of Rome, 'La Sapienza'.

tachyarrhythmias or pulmonary hypertension), thereby further impairing cardio-circulatory functions.[3]

During the last years, arginine vasopressin and terlipressin have been identified as useful adjunct vasopressors in the treatment of catecholamine-dependent septic shock.[4–11] Since terlipressin is a pro-drug with a long effective half-life of approximately 6 h, it is usually given as intermittent bolus injection.[8] This approach, however, may contribute to an overshooting increase in systemic vascular resistance and a marked reduction in cardiac index (CI),[12 13] thereby compromising oxygen delivery index (DO_2I) and mixed-venous oxygen saturation (Sv_{O_2}).

We hypothesized that dobutamine, a synthetic catecholamine with predominantly β_1-adrenergic properties, may reverse the terlipressin-associated depression in global oxygen supply in patients with catecholamine-dependent septic shock. Therefore, the primary endpoint of this prospective, randomized, controlled, open-labelled, clinical pilot study was to determine, whether dobutamine is a useful inotropic agent to reverse the reduction in Sv_{O_2} resulting from terlipressin bolus infusion. Secondary endpoints included differences in norepinephrine requirements, systemic and regional haemodynamics, and organ function between the groups.

Methods

Patients

The study was performed in an 18-bed multidisciplinary intensive care unit. It was approved by the local institutional ethics committee, and informed consent was obtained from the patients' next of kin. We enrolled patients who fulfilled the criteria of catecholamine-dependent septic shock.[14] Enrolment of the patients started in November 2005 and ended in October 2006. All patients eligible for the study were included when the norepinephrine dose required to maintain mean arterial pressure (MAP) between 70 (5) mm Hg reached 0.9 μg kg^{-1} min^{-1}, despite adequate volume resuscitation [pulmonary artery occlusion pressure (PAOP)=12–15 mm Hg and central venous pressure (CVP)=8–12 mm Hg]. Exclusion criteria were age <18 yr, pronounced cardiac dysfunction (i.e. CI≤2.2 litre min^{-1} m^{-2} in the presence of PAOP>18 mm Hg, significant valvular heart disease, present or suspected coronary artery disease), pregnancy, present or suspected acute mesenteric ischaemia or vasospastic diathesis (e.g. Raynaud's syndrome or related diseases).

From 180 screened septic patients, 70 consecutive patients met the inclusion criteria. Among these, 10 patients were excluded before randomization because of low CI (i.e. ≤2.2 litre min^{-1} m^{-2} in the presence of PAOP>18 mm Hg). The remaining 60 patients were enrolled in the present study.

All patients received mechanical ventilation using a volume-controlled mode. The ventilatory settings remained unchanged throughout the study. All patients were sedated with sufentanil and midazolam.

Measurements

Systemic haemodynamic monitoring of the patients included a pulmonary artery catheter (7.5 F, Edwards Lifesciences, Irvine, CA, USA) and a radial artery catheter. MAP, right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), and PAOP were measured at end-expiration. HR was analysed from a continuous recording of ECG with ST segments monitored. CI was measured using the continuous thermodilution technique (Vigilance II®, Edwards Lifesciences). Arterial and mixed venous blood samples were taken to determine oxygen tensions and saturations, carbon dioxide tensions, standard bicarbonate, and base excess (BE). Sv_{O_2} was measured discontinuously by intermittent mixed-venous blood gas analyses. Systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), left-ventricular stroke work index (LVSWI), right-ventricular stroke work index (RVSWI), DO_2I, oxygen consumption index (VO_2I), and oxygen extraction ratio (O_2-ER) were calculated using standard formulae.

Regional haemodynamic monitoring of the patients was performed using a 4 F oximetry thermo-dye dilution catheter (PV2024L, Pulsion Medical System AG, Munich, Germany) inserted through the femoral artery for the determinations of plasma disappearance rate of indocyanine green (PDR) and blood clearance of indocyanine green related to body surface area (CBI). PDR and CBI were determined with the Cold Z-021 system (Pulsion Medical System AG) using an established protocol.[15 16] In addition, an air-tonometer (Tonocap, Datex-Ohmeda, Helsinki, Finland) was inserted via the naso-gastric route for gastric mucosal carbon dioxide tension measurement and for the calculation of the gradient between gastric mucosal and arterial P_{CO_2} ($Pg\text{-}a_{CO_2}$).

Arterial blood samples were drawn and analysed for pH, arterial lactate, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total bilirubin (BILT), international normalized ratio (INR), activated partial thromboplastin time ratio (aPTTr), and cardiac troponin I (cTnI). Urine samples were collected to assess urinary output.

Study design

Sixty septic shock patients requiring norepinephrine doses of 0.9 μg kg^{-1} min^{-1} to maintain MAP at 70 (5) mm Hg, despite adequate volume resuscitation, were randomized to one of the three study groups (n=20 each) using a computer-based procedure. In the 'control group' (Group 1), norepinephrine infusion was titrated to maintain the defined threshold MAP of 70 (5) mm Hg. Whereas patients

allocated to the 'terlipressin group' (Group 2) received a single bolus dose of terlipressin 1 mg, the 'terlipressin-dobutamine group' (Group 3) was treated with a combination therapy consisting of a single bolus dose of terlipressin 1 mg and a titrated infusion of dobutamine. In the latter group, dobutamine infusion was started immediately after terlipressin administration at a rate of 3 μg kg^{-1} min^{-1} and was progressively increased (in steps of 1–3 μg kg^{-1} min^{-1}) to reverse the anticipated, terlipressin-associated depression in Sv_{O_2}, and thus to maintain Sv_{O_2} at baseline (Fig. 1). Dobutamine in doses up to 20 μg kg^{-1} min^{-1} was allowed to increase Sv_{O_2}.

Fluid challenge (hydroxyethyl starch 6% 130/0.4) was performed to maintain PAOP and CVP at baseline ±3 mm Hg during the 4 h study period. Packed red blood cells were transfused when Hb concentrations decreased below 8 g dl^{-1}. In all patients treated with terlipressin, norepinephrine was titrated to maintain MAP at 70 (5) mm Hg. All other medications were held constant.

Systemic, pulmonary, and regional haemodynamic measurements, and blood gases, were determined at baseline, and 2 and 4 h after randomization.

Surrogate variables of organ (dys)function and injury (ASAT, ALAT, BILT, INR, aPTTr, and cTnI) were analysed at baseline, and 12 and 24 h after randomization. Likewise, arterial lactate concentrations and urinary output were determined at baseline, and 2 and 4 h after randomization.

In patients surviving the 4 h intervention period, norepinephrine was titrated to maintain MAP at 70 (5) mm Hg. Dobutamine infusion was adjusted to keep Sv_{O_2} at baseline. None of the patients received further terlipressin infusions.

Statistical analysis

Sigma Stat 3.10 software (SPSS, Chicago, IL, USA) was used for statistical analysis. On the basis of a power analysis (expected standard deviation of residuals=15%, desired power=80%, and an alpha error=5%), we determined that a sample size of n=20 per group would be sufficient to detect a 15% decrease in Sv_{O_2} in the TP group. After testing for normal distribution (Kolmogorov–Smirnov test), differences within and between the groups were analysed using a two-way analysis of variance for repeated measurements. After confirming significant group differences over time, appropriate *post hoc* comparisons (Student–Newman–Keuls) were performed. The number of patients requiring norepinephrine infusion in each study group was compared using Fisher's exact test. For all statistical tests, a P-value of <0.05 was regarded as statistically significant. Data are expressed as means (SD), if not otherwise indicated.

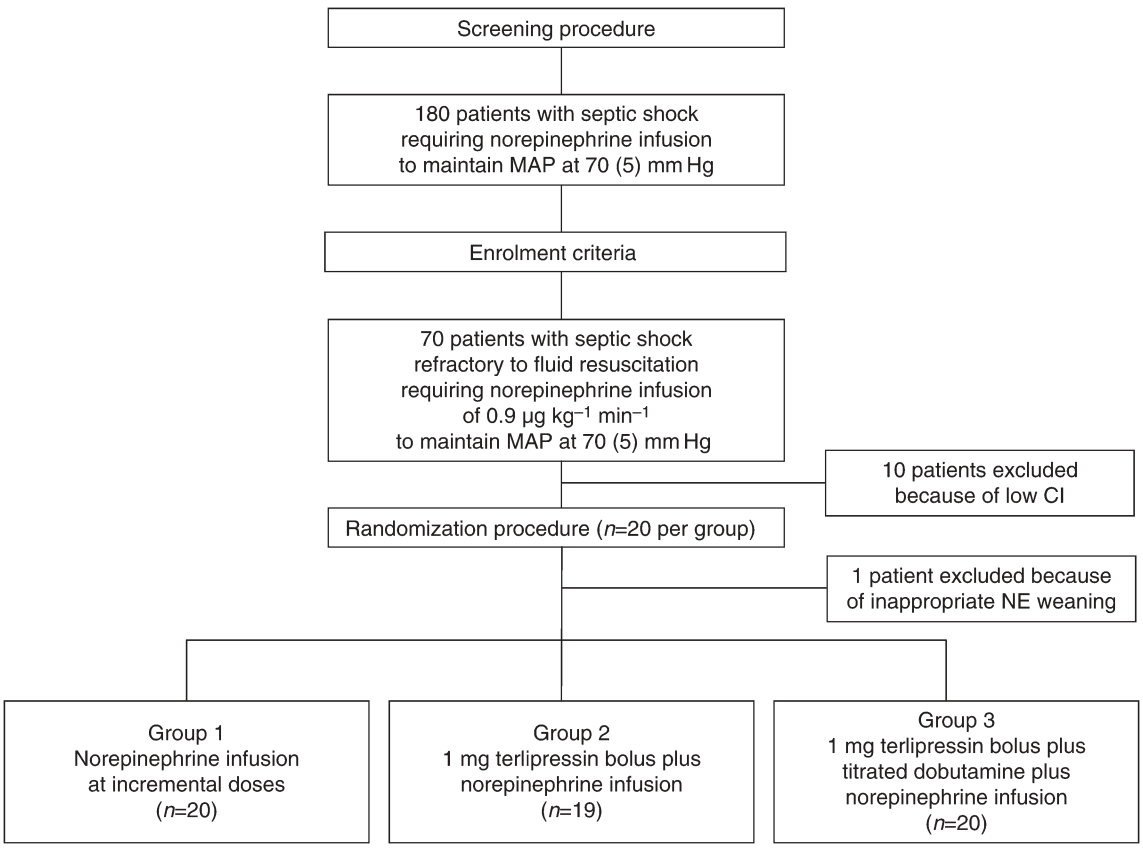

Fig 1 Study design. MAP, mean arterial pressure; CI, cardiac index.

Results

Each of the 60 patients enrolled into the present study completed the entire study period. One patient randomized to Group 2, however, had to be excluded from data analysis due to inappropriate weaning from norepinephrine (i.e. norepinephrine infusion rate had not been adequately reduced, although MAP levels exceeded goal values).

Demographic data

Baseline characteristics and causes of septic shock of the 59 patients analysed in the present study are summarized in Tables 1 and 2, respectively. There were no differences in age, sex, body weight, Simplified Acute Physiology Score II (SAPS II), or time of norepinephrine infusion between the groups before randomization. All patients received i.v. hydrocortisone (200 mg day^{-1} continuously administered via an infusion pump). Five patients in Group 1, and four patients in Groups 2 and 3 received activated protein C during the study period. All patients included in the study survived the 4 h (haemodynamic) and 24 h (laboratory) study period. Overall mortality was not significantly different between the three study groups.

Table 1 Baseline and outcome characteristics of study patients. Data are presented as mean (range), or mean (SD), if not indicated otherwise. SAPS II, Simplified Acute Physiology Score II; NE, norepinephrine; ICU, intensive care unit; Group 1, control group; Group 2, terlipressin group; Group 3, terlipressin–dobutamine group

	Group 1 (n=20)	**Group 2 (n=19)**	**Group 3 (n=20)**
Age (yr)	67 (29–83)	66 (28–84)	66 (37–82)
Sex (male/female)	14/6	13/6	16/4
Body weight (kg)	75 (14)	77 (17)	77 (15)
SAPS II	59 (10)	60 (12)	61 (12)
NE infusion before randomization (h)	40 (15)	40 (14)	39 (23)
ICU mortality (%)	70	63	70
ICU stay (days)	14 (10)	16 (10)	15 (10)
ICU stay of survivors (days)	23 (11)	24 (6)	19 (9)

Table 2 Causes of septic shock of study patients. Data are presented as number (n). Group 1, control group; Group 2, terlipressin group; Group 3, terlipressin–dobutamine group

Diagnoses	**Group 1 (n=20)**	**Group 2 (n=19)**	**Group 3 (n=20)**
Peritonitis	9	9	11
Pneumonia	5	6	5
Pancreatitis	2	2	0
Meningitis	0	1	2
Pulmonary abscess	0	1	0
Necrotizing fascitis	0	0	2
Endocarditis	2	0	0
Mediastinitis	2	0	0

Systemic haemodynamic variables

There were no differences in haemodynamic variables and norepinephrine doses between the groups at baseline. When compared with Groups 1 and 3, CI was significantly lower in Group 2 at 2 h (P=0.031 and P=0.002, respectively; Fig. 2). Whereas the highest MAP was noticed in Group 3 ($P \leq 0.001$ between Group 1 and Group 2), the highest SVRI was recorded in patients allocated to Group 2 ($P \leq 0.001$ between Group 1 and Group 3; Fig. 2). In addition, LVSWI was higher in Group 3 than in the two other study groups (P=0.006 between Group 1 and P=0.013 *vs* Group 2; Fig. 2). In patients allocated to Group 2, RVSWI significantly decreased ($P<0.001$ compared with baseline at 2 h; Table 3). Despite a time-dependent decrease in HR in Group 2, HR was similar between the groups. Besides a significantly higher PVRI in Group 3 when compared with Group 2 (P=0.047), MPAP, PAOP, and RAP remained unchanged during the intervention period (each $P>0.05$; Table 3).

Oxygen transport, gas exchange, and acid–base balance

There were no differences in oxygen transport variables and acid–base balance between the groups at BL (Fig. 3; Table 4). Whereas single terlipressin infusion reduced DO_2I (P=0.031 between Group 1 and P=0.009 *vs* Group 3 at 2 h; Fig. 3) and increased O_2-ER (P=0.004 between Group 1 and P=0.003 *vs* Group 3 at 2 h; Fig. 3), VO_2I remained unchanged (Table 4). When compared with Groups 1 and 3, Sv_{O_2} was significantly reduced in patients treated with sole terlipressin infusion (P=0.034 between Group 1 and P=0.039 *vs* Group 3 at 2 h after randomization; Fig. 3). There were no differences in pH, Pa_{CO_2}, Pa_{O_2}, Sa_{O_2}, BE, and Hb concentrations between the groups (each $P>0.05$; Table 4).

Regional haemodynamic variables and organ function

All investigated surrogate markers of organ (dys)function were similar between the groups at BL. During the intervention period, there was no difference in mucosal and regional blood flow variables ($Pg\text{-}a_{CO_2}$, PDR, and CBI). In addition, surrogate parameters of hepatic function and injury (BILT, ASAT, and ALAT), coagulation system (INR and aPTTr), and myocardial injury (cTnI) were similar between the groups (Table 5). However, terlipressin (with and without additional dobutamine infusion) increased urinary output when compared with baseline values ($P<0.001$ in Group 2 and P=0.028 in Group 3 at 4 h; Table 5). Arterial lactate significantly increased over time in the control group (P=0.008) and tended to increase when compared with the terlipressin group (P=0.084 at 4 h after randomization; Fig. 3).

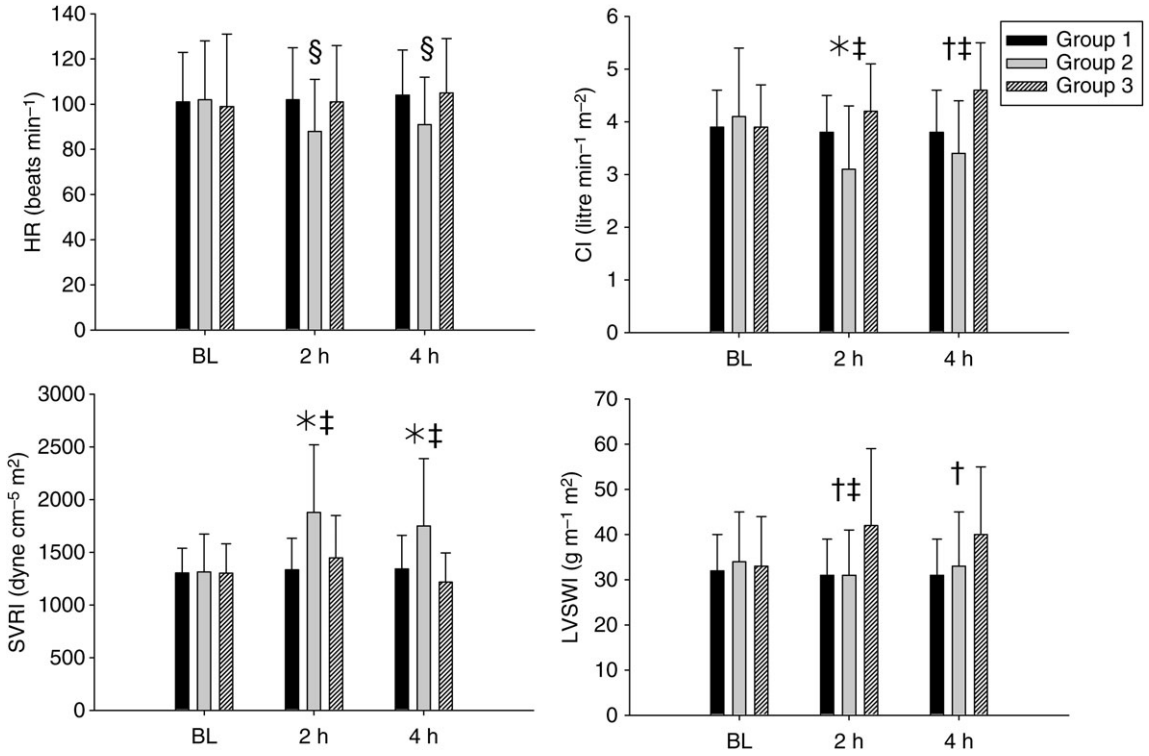

Fig 2 Systemic haemodynamics of study patients. Data are presented as mean values (SD). BL, baseline; HR, heart rate; CI, cardiac index; SVRI, systemic vascular resistance index; LVSWI, left-ventricular stroke work index; *$P<0.05$ Group 1 *vs* Group 2; $^{\dagger}P<0.05$ Group 1 *vs* Group 3; $^{\ddagger}P<0.05$ Group 2 *vs* Group 3; $^{\S}P<0.05$ *vs* BL (in all groups). Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}.

Norepinephrine and dobutamine requirements

Whereas norepinephrine requirements increased over time in the control group, norepinephrine doses significantly decreased in Groups 2 and 3 (each $P<0.001$; Fig. 4). In eight patients in Group 2 and nine patients in Group 3, respectively, norepinephrine was discontinued after terlipressin administration (Table 6). Apart from temporary changes in skin colour (i.e. pallor) related to cutaneous vasoconstriction after terlipressin injection, we did not notice any skin lesions in the study population.

Patients allocated to Group 3 required a mean dobutamine dose of 20 (8) μg kg^{-1} min^{-1} to reverse the terlipressin-linked depression in $S\text{v}_{\text{O}_2}$. However, no obvious clinical adverse effects related to infusion of high dobutamine doses were noticed.

Since we originally determined the maximum dose of dobutamine as 20 μg kg^{-1} min^{-1}, we additionally performed a per-protocol analysis excluding patients who received more than the predetermined maximum dose. Within this per-protocol analysis, seven patients were excluded from Group 3. The mean dobutamine dose of the remaining 13 patients was 15 (5) μg kg^{-1} min^{-1} and the terlipressin-linked decrease in $S\text{v}_{\text{O}_2}$ was significantly reversed [$S\text{v}_{\text{O}_2}$ at 4 h: 59 (11)% *vs* 69 (11)%, Group 2 *vs* Group 3; $P=0.046$]. The major results of both analyses were thus the same.

Discussion

The major findings of the present study are (i) that terlipressin with and without additional dobutamine infusion markedly increased MAP and reduced norepinephrine requirements and (ii) that high dobutamine doses were needed to reverse the terlipressin-associated depression in $S\text{v}_{\text{O}_2}$.

In accordance with previous clinical studies,[8–11] terlipressin was effective in increasing MAP and allowed significant weaning from norepinephrine. Since we administered a relatively high bolus dose of terlipressin (1 mg), MAP exceeded goal values of 70 (5) mm Hg in some patients, despite discontinuation of norepinephrine infusion. In this regard, it is important to underline that in eight patients in Group 2 and in nine patients in Group 3, norepinephrine was completely discontinued after terlipressin administration (Table 6).

Compared with the control group, however, terlipressin bolus infusion was linked to significant reductions in CI, DO_2I, and $S\text{v}_{\text{O}_2}$. The depression in CI is a typical characteristic of terlipressin bolus infusion[8–11 17] and may be explained by baroreceptor activation and an increase in left ventricular afterload.[18] Alternatively, the terlipressin-associated reductions in CI and DO_2I may also be explained by a reduction of global oxygen demand or myocardial dysfunction in response to an increased afterload.

Table 3 Haemodynamics and catecholamine requirements of study patients. Data are presented as mean values (SD). Group 1, control group; Group 2, terlipressin group; Group 3, terlipressin–dobutamine group. BL, baseline; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary arterial occlusion pressure; RAP, right atrial pressure; PVRI, pulmonary vascular resistance index; RVSWI, right-ventricular stroke work index. *$P<0.05$ Group 2 *vs* Group 1; †$P<0.05$ *vs* BL (in all groups); ‡$P<0.05$ Group 3 *vs* Group 1; §$P<0.05$ Group 3 *vs* Group 2. Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}

Variable	BL	2 h	4 h
MAP (mm Hg)			
Group 1 (n=20)	73 (4)	73 (3)	74 (3)
Group 2 (n=19)	74 (2)	78 (7)*,†	78 (7)*,†
Group 3 (n=20)	72 (3)	85 (16)†,‡,§	80 (12)†,‡
MPAP (mm Hg)			
Group 1 (n=20)	26 (5)	26 (5)	26 (5)
Group 2 (n=19)	26 (5)	25 (5)	27 (5)
Group 3 (n=20)	27 (5)	28 (5)	28 (5)
PAOP (mm Hg)			
Group 1 (n=20)	14 (2)	14 (2)	14 (2)
Group 2 (n=19)	14 (2)	15 (2)	15 (2)
Group 3 (n=20)	15 (2)	16 (2)	16 (2)
RAP (mm Hg)			
Group 1 (n=20)	12 (4)	12 (3)	12 (3)
Group 2 (n=19)	12 (2)	12 (2)	11 (3)
Group 3 (n=20)	11 (3)	12 (3)	12 (3)
PVRI (dyne s cm^{-5} m^2)			
Group 1 (n=20)	255 (79)	251 (92)	261 (102)
Group 2 (n=19)	259 (160)	302 (188)†,§	322 (155)
Group 3 (n=20)	261 (111)	239 (112)	223 (123)
RVSWI (g m^{-2} beat^{-1})			
Group 1 (n=20)	8 (3)	7 (3)	7 (3)
Group 2 (n=19)	8 (4)	6 (3)†	8 (4)
Group 3 (n=20)	9 (3)	10 (4)	10 (3)
Dobutamine requirements (μg kg^{-1} min^{-1})			
Group 1 (n=20)	0	0	0
Group 2 (n=19)	0	0	0
Group 3 (n=20)	0	20 (8)	20 (8)

Recently, Broking and colleagues[19] reported that dobutamine is a useful agent to reverse the terlipressin-associated suppressions in CI and global oxygen transport in ovine endotoxaemia. However, the efficacy and safety of a combination therapy with terlipressin and dobutamine have not yet been determined in human septic shock.

Dobutamine is a synthetic catecholamine with β_1- and β_2-adrenergic properties. As a result of its positive inotropic and chronotropic effects, dobutamine increases HR and CI. In the present study, the combination of terlipressin and dobutamine maintained MAP at threshold values and reduced norepinephrine requirements. Notably, dobutamine increased CI, DO_2I, and Sv_{O_2} without increasing HR. Since maintenance of adequate CI and Sv_{O_2} appears to be beneficial in septic shock,[20] the addition of dobutamine may be rational if terlipressin infusion alone leads to a reduction in Sv_{O_2}. However, it is still debated whether or not an increase in CI and DO_2I represents a therapeutically useful goal.[20 21]

The strong vasoconstrictive response after terlipressin bolus infusion necessitated high incremental dobutamine doses to reverse the depression in global oxygen transport. Importantly, although we envisaged 20 μg kg^{-1} min^{-1} of dobutamine as the maximal dose, seven patients (35%) required higher doses [28 (6) μg kg^{-1} min^{-1} at 4 h] to maintain Sv_{O_2} at baseline. In this context, it is noteworthy that high doses of dobutamine may result in adverse effects, such as increased myocardial oxygen demand, tachyarrhythmias, or, in the presence of hypovolaemia, a decrease in MAP.

Nevertheless, it has to be taken into consideration that whereas dobutamine at 5 μg kg^{-1} min^{-1} is usually efficacious in normal subjects or in patients with non-septic heart failure,[22 23] it may be of poor efficacy in patients with severe septic shock because of impaired signal transduction and down-regulation of β-adrenergic receptors.[24 25] However, it is worth mentioning that despite the high dobutamine doses infused in the present study, no adverse events were noticed, even in those patients who required dobutamine dosages exceeding 20 μg kg^{-1} min^{-1}. In this regard, it may be especially important that there was no increase in HR in patients treated with high dobutamine doses and that troponin I concentrations were comparable between the groups (Table 7). Although dobutamine infusion was adjusted to maintain Sv_{O_2} at baseline, Sv_{O_2} values were higher at the end of the intervention period. This may be explained by discontinuous measurements of this variable and the short intervention period that made it difficult to exactly adjust the dobutamine dose to re-establish baseline Sv_{O_2} values.

Previous studies using vasopressin receptor agonists in patients with septic shock after adequate fluid resuscitation showed less or no unwanted side-effects in the splanchnic circulation.[6 9 26 27] In harmony with these findings, terlipressin did not increase the $Pg\text{-}a_{CO_2}$ gap in the present study. Whereas dobutamine prevented the terlipressin-associated impairments in CI and DO_2I, we did not notice differences between the three study groups in terms of $Pg\text{-}a_{CO_2}$ gap. The absence of detrimental splanchnic haemodynamic effects is also confirmed by the lack of differences between the groups in PDR and CBI. On the contrary, the absence of significant increases in arterial lactate concentrations (when compared with the control group) suggests a positive effect on oxygen balance and tissue oxygenation in both terlipressin-treated groups. However, since lactate generation during septic shock may be fostered by catecholamines,[28] the difference between the terlipressin-treated groups and the control group may have also been related to decreased norepinephrine requirements.

Our results are in accordance with the recent study of Asfar and colleagues.[27] The latter authors reported that although terlipressin decreased both cardiac output and portal venous blood flow, it increased hepatic arterial blood flow, thereby leading to an unaffected splanchnic oxygen delivery and $Pg\text{-}a_{CO_2}$ gradient. In harmony with the results of the liver perfusion measurements (i.e. PDR and CBI), we did not find differences in terms of liver

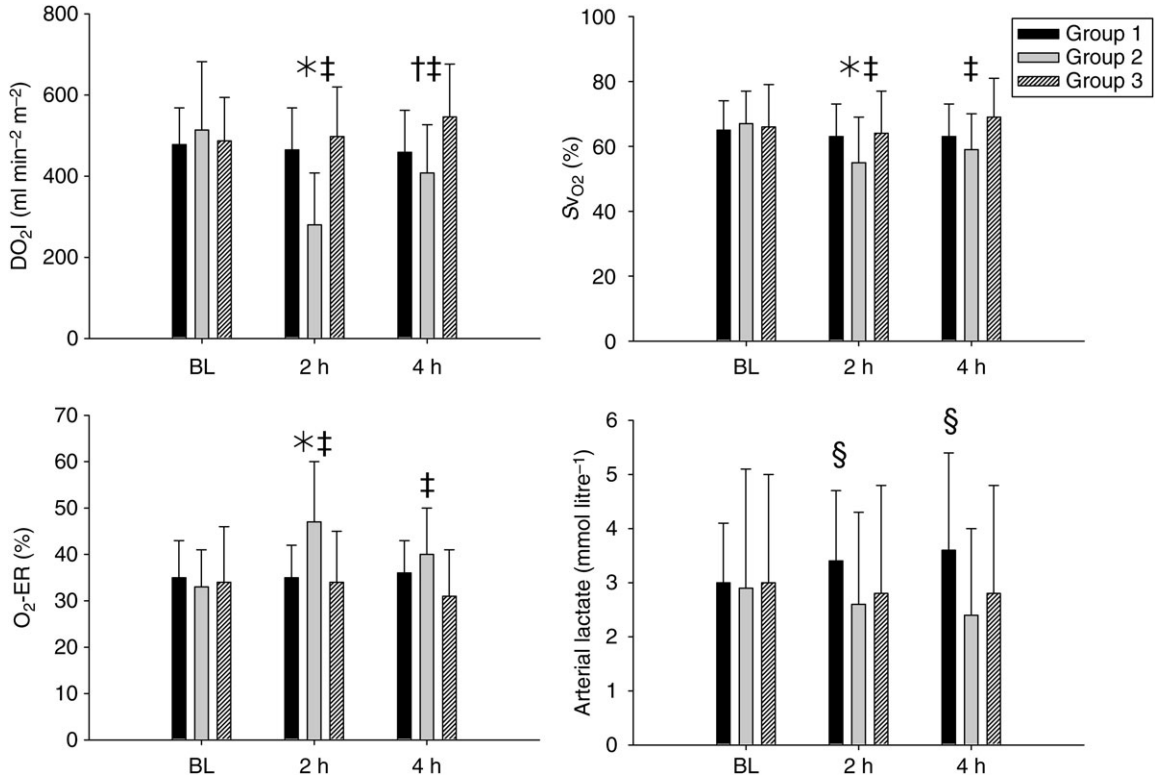

Fig 3 Systemic oxygen delivery, oxygen extraction, and mixed-venous oxygen saturation of study patients. Data are presented as mean values (SD). BL, baseline; DO_2I, systemic oxygen delivery index; O_2-ER, oxygen extraction rate; Sv_{O_2}, mixed-venous oxygen saturation; *$P<0.05$ Group 1 *vs* Group 2; $^{\dagger}P<0.05$ Group 1 *vs* Group 3; $^{\ddagger}P<0.05$ Group 2 *vs* Group 3; $^{\S}P<0.05$ *vs* BL (in all groups). Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}.

enzymes and BILT 24 h after terlipressin administration, suggesting a lack of drug-related acute hypoxic liver injury.

In line with previous clinical trials,[9–11] urinary output increased over time in both terlipressin-treated groups, despite its potential antidiuretic effect. In this context, it is noteworthy that vasopressin analogues may increase glomerular filtration rate by increasing resistance of efferent glomerular arterioles without constricting afferent arterioles.[29] In addition, terlipressin is less likely to produce antidiuretic effects when compared with arginine vasopressin due to the higher V_1 receptor selectivity of terlipressin.

In the light of our results, we would like to emphasize that potential benefits of increasing Sv_{O_2} after terlipressin infusion need to be weighted against the potential risk of cardiovascular complications resulting from high dose dobutamine infusion. Future large-scale studies are needed to clarify whether the combination of terlipressin and dobutamine is superior to standard therapy with norepinephrine. It also remains to be determined whether the reductions in CI and Sv_{O_2} after terlipressin infusion have to be regarded as detrimental effects, or as a surrogate of reduced metabolic demands.

The present study has some limitations that need to be acknowledged. First, direct measurements of regional and local splanchnic blood flow in septic shock patients would be invasive, require special skills and instruments that are not readily available at the bedside. Thus, in the present study, hepatosplanchnic perfusion was assessed using PDR and CBI; mucosal blood flow was evaluated by gastric tonometry. Secondly, terlipressin was administered at a fixed dose without adaptation for body weight. However, body weight of the enrolled patients was similarly distributed within the three study groups. In addition, terlipressin was administered as a relatively high dose bolus infusion, which resulted in decreases in CI, DO_2I, and Sv_{O_2}. A continuous, low-dose infusion of terlipressin may prevent these unwanted side-effects[30 31] and thus may reduce dobutamine requirements. Thirdly, since the effects of the combination therapy of terlipressin and dobutamine were not exactly predictable, for safety reasons the present trial was designed as a short-term haemodynamic pilot study. Therefore, we investigated only a small number of septic shock patients treated with a single dose of terlipressin to evaluate the effects of a titrated dobutamine infusion on cardiopulmonary haemodynamics and global oxygen transport over a brief period. Hence, we cannot rule out the possibility of adverse metabolic alterations or side-effects in response to repeated administration of terlipressin alone or in combination with dobutamine for a prolonged

Table 4 Gas exchanges, oxygen consumption, acid–base variables, and haemoglobin concentrations of study patients. Data are presented as mean values (SD). TP, Group 2, terlipressin; Group 3, terlipressin and dobutamine; BL, baseline; Pa_{O_2}, arterial oxygen partial pressure; Sa_{O_2}, arterial oxygen saturation; Pa_{CO_2}, arterial carbon dioxide partial pressure; BE, arterial base excess. VO_2I, systemic oxygen consumption index; Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}

Variable	BL	2 h	4 h
pH [$-\log_{10}$ c(H^+)]			
Group 1 (n=20)	7.35 (0.07)	7.35 (0.09)	7.35 (0.1)
Group 2 (n=19)	7.37 (0.06)	7.38 (0.07)	7.39 (0.06)
Group 3 (n=20)	7.36 (0.1)	7.36 (0.08)	7.35 (0.09)
Pa_{O_2} (mm Hg)			
Group 1 (n=20)	131 (48)	129 (44)	131 (43)
Group 2 (n=19)	147 (59)	140 (57)	128 (51)
Group 3 (n=20)	134 (49)	109 (42)	135 (48)
Sa_{O_2} (%)			
Group 1 (n=20)	98 (2)	97 (5)	97 (5)
Group 2 (n=19)	98 (4)	98 (4)	97 (5)
Group 3 (n=20)	97 (3)	95 (6)	97 (5)
Pa_{CO_2} (mm Hg)			
Group 1 (n=20)	43 (6)	44 (8)	44 (9)
Group 2 (n=19)	42 (5)	43 (7)	43 (6)
Group 3 (n=20)	46 (9)	46 (9)	47 (10)
BE (mmol $litre^{-1}$)			
Group 1 (n=20)	−1.7 (5)	−1.8 (6)	−1.7 (6)
Group 2 (n=19)	0.2 (4)	−0.1 (4)	0.1 (4)
Group 3 (n=20)	0.4 (6)	−0.2 (5)	−0.5 (5)
VO_2I (ml min^{-1} m^{-2})			
Group 1 (n=20)	166 (38)	163 (43)	163 (41)
Group 2 (n=19)	163 (42)	158 (31)	155 (30)
Group 3 (n=20)	155 (43)	163 (45)	160 (43)
Haemoglobin (g $litre^{-1}$)			
Group 1 (n=20)	89 (10)	89 (10)	88 (12)
Group 2 (n=19)	91 (16)	89 (15)	89 (15)
Group 3 (n=20)	91 (10)	87 (10)	86 (10)

Table 5 Regional haemodynamic variables of study patients. Data are presented as mean values (SD). TP, Group 2, terlipressin; Group 3, terlipressin and dobutamine; BL, baseline; $Pg\text{-}a_{CO_2}$, difference between gastric mucosal and arterial carbon dioxide partial pressure; CBI, blood clearance of indocyanine green; PDR, plasma disappearance rate of indocyanine green. $^{\dagger}P<0.05$ *vs* BL (in all groups). Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}

Variable	BL	2 h	4 h
$Pg\text{-}a_{CO_2}$ (mm Hg)			
Group 1 (n=20)	14 (7)	17 (9)	15 (7)
Group 2 (n=19)	14 (5)	17 (5)	14 (4)
Group 3 (n=20)	14 (7)	17 (8)	14 (8)
CBI (ml min^{-1} m^{-2})			
Group 1 (n=20)	416 (192)	418 (192)	401 (155)
Group 2 (n=19)	428 (182)	399 (150)	401 (141)
Group 3 (n=20)	365 (167)	429 (181)	465 (209)
PDR (%)			
Group 1 (n=20)	15 (5)	15 (5)	15 (5)
Group 2 (n=19)	16 (6)	16 (6)	15 (5)
Group 3 (n=20)	15 (6)	17 (7)	17 (7)
Urinary output (ml h^{-1})			
Group 1 (n=20)	103 (45)	103 (72)	96 (48)
Group 2 (n=19)	100 (64)	160 (128)†	147 (119)†
Group 3 (n=20)	103 (56)	134 (69)†	130 (76)†

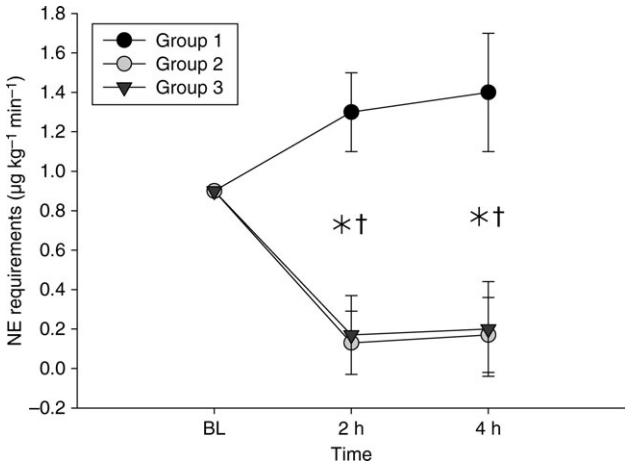

Fig 4 Norepinephrine requirements. Data are presented as mean values (SD). BL, baseline; NE, norepinephrine; $^{*}P<0.05$ Group 1 *vs* Group 2; $^{\dagger}P<0.05$ Group 1 *vs* Group 3. Baseline data were obtained at the fixed norepinephrine dose of 0.9 μg kg^{-1} min^{-1}.

period. Fourthly, although Luckner and colleagues[3] reported a positive correlation between high norepinephrine doses and mortality, it is still unclear whether the reduction of norepinephrine dosages *per se* represents a therapeutic target.

In conclusion, this is the first prospective, randomized clinical study showing that terlipressin bolus administration (with and without concomitant dobutamine infusion) significantly reduces norepinephrine requirements in septic shock patients and that high doses of dobutamine are needed to reverse the terlipressin-linked depression in Sv_{O_2}. In this context, it is noteworthy that dobutamine infusion in the present study was not associated with any clinically obvious cardiovascular side-effects. However, large-scale studies are needed to clarify whether combined terlipressin and dobutamine infusion improves the overall outcome when compared with norepinephrine infusion. In addition, future trials are warranted to investigate whether continuous low-dose terlipressin infusion, or intermittent infusion of low-dose terlipressin boli, may omit decreases in CI and Sv_{O_2},[30] and thereby reduce inotropic requirements.

Table 6 Norepinephrine requirements of study patients. Data show the absolute number and percentage of patients requiring norepinephrine infusion in each group at each time point. BL, baseline; $^{*}P<0.005$ Group 1 *vs* Group 2; $^{\dagger}P<0.005$ Group 1 *vs* Group 3

Time point	Group 1 (n=20)	Group 2 (n=19)	Group 3 (n=20)
BL	20 (100%)	19 (100%)	20 (100%)
2 h	20 (100%)	11 (58%)*	11 (55%)†
4 h	20 (100%)	12 (63%)*	10 (50%)†

Table 7 Organ function of study patients. Data are presented as mean values (SD). Group 2, terlipressin; Group 3, terlipressin and dobutamine; BL, baseline; BILT, total bilirubin; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; INR, international normalized ratio; aPTTr, activated partial thromboplastin time ratio. Baseline data were obtained at the fixed NE dose of 0.9 $\mu g\ kg^{-1}\ min^{-1}$

Variable	BL	12 h	24 h
BILT (mg dl^{-1})			
Group 1 (n=20)	1.5 (1)	1.6 (1)	1.6 (1)
Group 2 (n=19)	1.5 (1)	1.5 (2)	1.6 (1)
Group 3 (n=20)	1.5 (1)	1.5 (1)	1.6 (2)
ASAT (U $litre^{-1}$)			
Group 1 (n=20)	64 (52)	60 (33)	61 (30)
Group 2 (n=19)	68 (66)	82 (99)	64 (41)
Group 3 (n=20)	65 (70)	67 (70)	69 (71)
ALAT (U $litre^{-1}$)			
Group 1 (n=20)	52 (47)	46 (31)	55 (41)
Group 2 (n=19)	46 (25)	55 (42)	53 (32)
Group 3 (n=20)	56 (65)	60 (71)	61 (77)
INR			
Group 1 (n=20)	1.28 (0.3)	1.27 (0.3)	1.27 (0.3)
Group 2 (n=19)	1.37 (0.3)	1.38 (0.3)	1.32 (0.2)
Group 3 (n=20)	1.42 (0.3)	1.35 (0.2)	1.37 (0.3)
aPTTr			
Group 1 (n=20)	1.29 (0.4)	1.19 (0.5)	1.22 (0.3)
Group 2 (n=19)	1.27 (0.3)	1.22 (0.2)	1.30 (0.3)
Group 3 (n=20)	1.37 (0.4)	1.31 (0.3)	1.27 (0.3)
Troponine I (ng ml^{-1})			
Group 1 (n=20)	0.8 (2)	1.0 (2)	1.3 (2)
Group 2 (n=19)	0.8 (2)	2.4 (8)	1.7 (6)
Group 3 (n=20)	0.8 (2)	1.4 (4)	1.3 (4)

Funding

This study was funded by an independent research grant from the Department of Anesthesiology and Intensive Care of the University of Rome, 'La Sapienza'.

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