

## Effects of norepinephrine, epinephrine, and norepinephrine-dobutamine on systemic and gastric mucosal oxygenation in septic shock

ZHOU Shao-Xia, QIU Hai-Bo<sup>1</sup>, HUANG Ying-Zi, YANG Yi, ZHENG Rui-Qiang (Department of Critical Care Medicine, Zhong-Da Hospital and School of Clinical Medicine, Southeast University, Nanjing 210009, China)

**KEY WORDS** septic shock; dopamine; norepinephrine; epinephrine; dobutamine; hemodynamics

### ABSTRACT

**AIM:** To compare the effects of dopamine, norepinephrine, epinephrine, and the combination of norepinephrine and dobutamine on systemic and gastric mucosal oxygen metabolism in patients with septic shock.

**METHODS:** Sixteen patients with septic shock were enrolled in the present study. Each patient received dopamine firstly, then in a random succession epinephrine, norepinephrine, or norepinephrine-dobutamine, a mean systemic arterial pressure adjusted to  $>9.31$  kPa. After 120 min of each treatment, hemodynamic, oxygen metabolic, and gastric mucosal parameters were obtained.

**RESULTS:** Epinephrine induced a significant increase in heart rate compared with other three groups ( $P < 0.05$ ), and a significant higher cardiac index compared with norepinephrine alone and norepinephrine-dobutamine ( $P < 0.05$ ). Oxygen extraction ratio values were lower with epinephrine infusion as compared with other three groups ( $P < 0.05$ ). Arterial lactate concentrations decreased significantly with norepinephrine-dobutamine as compared with dopamine and epinephrine infusions ( $P < 0.05$ ). As compared with epinephrine infusion, the gastric intramucosal pH values were higher with norepinephrine-dobutamine infusion ( $7.25 \pm 0.09$  vs  $7.14 \pm 0.07$ ,  $P < 0.05$ ). **CONCLUSION:** Dopamine, norepinephrine, epinephrine, or norepinephrine-dobutamine improved blood pressure. Epinephrine and dopamine had deleterious effect on oxygen metabolism, while norepinephrine plus low dose of dobutamine improved gastric mucosal perfusion and tissue oxygen utilization.

### INTRODUCTION

Administration of vasoactive agents to elevate systemic perfusion pressure is a widely accepted treatment of septic shock. Although these agents, such as dopamine, norepinephrine, and epinephrine, have been shown to improve systemic hemodynamics, their effects on regional perfusion are not well defined. Patients with septic shock often died of multiple organ failure despite having achieved normal systemic hemodynamics by fluid resuscitation and vasoactive agents. Tissue hypoxia, especially in the splanchnic area, is still considered to be an important cofactor in the pathogenesis of multiple organ failure. Lavi *et al* reported that gastric intramucosal acidosis developed and persisted for at least 48 h in patients resuscitated from septic shock to conventional resuscitative end points<sup>(1)</sup>. So it is necessary to further explore the effects of different vasoactive agents on the splanchnic perfusion in septic shock patients.

Conventionally, dopamine is considered to be the vasoactive agent of choice to improve systemic perfusion pressure. Previous studies showed dopamine increased systemic blood pressure and oxygen delivery and improved splanchnic perfusion<sup>(2,3)</sup>, so dopamine was widely recommended for the treatment of septic shock. On the other hand, for fear of excessive vasoconstriction, norepinephrine was considered to be deleterious<sup>(4)</sup> to end-organ perfusion, thereby contributing to increased mortality. However, our study in sheep with septic shock demonstrated that both norepinephrine-dobutamine and dopamine could improve systemic hemodynamics, but norepinephrine-dobutamine was better than dopamine on splanchnic perfusion<sup>(5)</sup>. This current prospective, randomized clinical study was to observe the effects of dopamine, norepinephrine, epinephrine, and the combination of norepinephrine and dobutamine on hemodynamic profile and systemic and splanchnic oxygen metabolism in septic shock patients.

<sup>1</sup> Correspondence to Prof QIU Hai-Bo, MD, PhD. Pbn 86-25-327-2200. Fax 86-25-327-2010. E-mail HaiBoq@hotmail.com  
Received 2001-10-27 Accepted 2002-03-12

## MATERIALS AND METHODS

**Study population** The study protocol was approved by our hospital ethical committee. Sixteen patients with septic shock in Department of Critical Care Medicine (ICU) of Zhong-Da Hospital, Southeast University were studied after informed consent was received from each patient or close relatives. And the study was conducted in accordance with the Helsinki Declaration. Patients ranged in age between 25 and 64 a; their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II at admission to ICU were averaged 22. All of the patients were the Han nation.

Septic shock was defined as sepsis with hypotension (systolic arterial pressure < 11.97 kPa or a fall more than 5.32 kPa from the baseline), persisting despite adequate fluid resuscitation and requiring the administration of vasopressor agents<sup>[6]</sup>. The excluding criteria were: (1) patients were not expected to survive for more than 24 h; (2) patients were suffering from established cardiac diseases.

**Hemodynamic and systemic oxygen metabolism monitoring** A pulmonary artery catheter (7 Fr, Arrow International, USA) was inserted through right internal jugular vein. Cardiac output (CO) was measured by thermodilution method. Right atrial pressure (CVP), mean pulmonary arterial pressure (PAP), and pulmonary arterial wedge pressure (PAWP) were monitored using calibrated pressure transducer. Mean systemic arterial pressure (MAP) was continuously monitored via an indwelling radial artery catheter. Cardiac index (CI) was calculated as  $CI = CO/HR$  (heart rate). Systemic vascular resistance index (SVRI) was calculated as  $SVRI = (MAP - CVP)/CI \times 80$ . Pulmonary vascular resistance index (PVRI) was calculated as  $PVRI = (PAP - PAWP)/CI \times 80$ .

Arterial samples and mixed venous samples were withdrawn from the arterial catheter and the distal port of the pulmonary artery catheter, respectively. All blood gas measurements and arterial lactate concentrations were performed on a blood gas analyzer (Nova M, USA).

Oxygen delivery index ( $D_{O_2}$ ) was computed as  $D_{O_2}$  ( $L \cdot \min^{-1} \cdot m^{-2}$ ) =  $CI \times C_{a,O_2} \times 10$ , where arterial oxygen content ( $C_{a,O_2}$ ) = hemoglobin concentration (Hb)  $\times 1.36 \times$  arterial oxygen saturation ( $S_{a,O_2}$ ) +  $0.0031 \times$  arterial oxygen partial pressure ( $p_{a,O_2}$ ).

Oxygen consumption index ( $V_{O_2}$ ) was calculated as  $V_{O_2}$  ( $L \cdot \min^{-1} \cdot m^{-2}$ ) =  $CI \times (C_{a,O_2} - C_{v,O_2}) \pm 10$ , where  $C_{v,O_2}$  (mixed venous oxygen content) = Hb  $\times 1.36 \times$  mixed venous saturation ( $S_{v,O_2}$ ) +  $0.0031 \times$  mixed oxygen partial pressure ( $p_{v,O_2}$ ). Oxygen extraction ratio (OER) was calculated as  $OER = V_{O_2}/D_{O_2}$ .

**Assessment of gastric intramucosal pH (pH<sub>i</sub>)** pH<sub>i</sub> was assessed with the method described by Fiddian-Green, using a gastric tonometer (TRIP NGS, Tonometrics, Finland) inserted via the nasal route. The correct gastric position of the tonometer was verified radiologically.

The tonometer balloon was filled with 2.5 mL of 0.9 % saline. Tonometric saline solution was assayed for  $pCO_2$  following an equilibration period of 120 min with a blood gas analyzer (Nova M, Nova, USA). pH<sub>i</sub> was then calculated using a modified Henderson-Hasselbalch equation:  $pH_i = 6.1 + \lg(\text{arterial } HCO_3^-)/(F \times 0.03 \times \text{tonometric saline } pCO_2)$ , where  $F$  is a time-dependent correction factor provided by the manufacturer. Enteral nutrition was discontinued during the period of tonometric monitoring.

**Experimental protocol** Each patient received dopamine firstly, then in a random succession epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine. Dosages of these agents were adjusted to maintain a MAP > 9.31 kPa. The switch from one treatment to another was performed by a progressive overlap of both treatments, during which doses of both therapies were adjusted to maintain a constant MAP. A continuous intravenous fluid infusion was performed to maintain a constant PAWP during the protocol. After 120 min of stability for each treatment, measurements of hemodynamic, oxygen metabolic, and gastric mucosal parameters were obtained.

**Statistical analysis** Data were analyzed on SPSS 10.0 software (SPSS Inc, 1999, USA). All data were expressed as  $\bar{x} \pm s$ . Statistical comparison was carried out using one way ANOVA, and if analysis of variance was significant, least significant difference was used. A  $P$  value < 0.05 was considered statistically significant.

## RESULTS

**Hemodynamics** As shown in Tab 1, no statistical differences were found for CVP, PAWP, PAP,

**Tab 1. Effects of dopamine, norepinephrine, epinephrine, and norepinephrine-dobutamine on hemodynamics.  $n = 16$ .  $\bar{x} \pm s$ . <sup>a</sup> $P < 0.05$  vs Ep. <sup>b</sup> $P < 0.05$  vs Dopa.**

	HR /beat·min <sup>-1</sup>	MAP/kPa	PAP/kPa	CVP/kPa	PAWP/kPa	CI /L·min <sup>-1</sup> ·m <sup>-2</sup>	SVRI /kPa·s·L <sup>-1</sup>	PVRI /kPa·s·L <sup>-1</sup>
Dopa	93 ± 10 <sup>b</sup>	12.1 ± 1.5	3.9 ± 0.7	1.7 ± 0.7	1.6 ± 0.5	4.9 ± 1.0	131 ± 23	30 ± 9
Nor	93 ± 10 <sup>b</sup>	12.5 ± 1.3	4.1 ± 0.7	1.7 ± 0.5	1.7 ± 0.5	4.4 ± 1.1 <sup>b</sup>	157 ± 48 <sup>b</sup>	36 ± 15
Ep	110 ± 14	11.6 ± 0.8	4.3 ± 0.8	1.7 ± 0.5	1.7 ± 0.5	5.2 ± 1.1	118 ± 33	31 ± 13
Nor + Dobu	87 ± 9 <sup>b</sup>	12.0 ± 1.3	4.0 ± 0.4	1.6 ± 0.4	1.7 ± 0.5	4.1 ± 1.0 <sup>bc</sup>	163 ± 60 <sup>b</sup>	35 ± 16

HR: heart rate; MAP; mean systemic arterial pressure; PAP; mean pulmonary arterial pressure; PAWP; pulmonary arterial wedge pressure; CI; cardiac index; SVRI; systemic vascular resistance index; PVRI; pulmonary vascular resistance index; Dopa; dopamine; Nor; norepinephrine; Ep; epinephrine; Nor + Dobu; norepinephrine-dobutamine.

and MAP during dopamine, norepinephrine, epinephrine and norepinephrine-dobutamine infusions. Epinephrine induced a significant increase in heart rate compared with other three groups ( $P < 0.05$ ), and a significant higher CI compared with norepinephrine alone and norepinephrine-dobutamine ( $P < 0.05$ ).

**Systemic oxygen metabolism** There was no statistical difference among each group for  $D_{O_2}$ . However, OER values were lower with epinephrine infusion as compared with other three groups ( $P < 0.05$ ). Arterial lactate concentrations dropped significantly with norepinephrine-dobutamine as compared with dopamine and epinephrine infusions ( $P < 0.05$ , Tab 2).

**Gastric mucosal oxygenation** As compared with epinephrine infusion, the  $pH_i$  values were higher with norepinephrine-dobutamine infusion ( $P < 0.05$ , Tab 2). Although the differences were not statistically significant between each treatment, the difference between gastric and arterial  $p_{CO_2}$  ( $p_{g-a,CO_2}$ ) with norepinephrine-dobutamine tended to be the lower compared with those obtained with dopamine, epinephrine, or norepinephrine alone.

## DISCUSSION

With regard to systemic hemodynamics, the present study demonstrated that dopamine, norepinephrine, epinephrine, or the combination of norepinephrine and dobutamine could restore and maintain stable perfusion pressure and oxygen delivery in patients with septic shock. But none of the four therapies could reverse the decreased  $pH_i$  completely, which is a surrogate marker of tissue oxygenation and a good prognostic predictor<sup>[7]</sup>. Gastric intramucosal acidosis persisted despite normalized systemic hemodynamics and oxygen delivery. Fourteen out of 16 patients were died of multiple organ failure. Thus, as the resuscitation end point of septic shock, normalization of systemic hemodynamics and elevation of oxygen delivery are far less enough. It is fundamental to improve tissue hypoxia to prevent multiple organ failure.

One of the main findings in present study was the significant increase in  $pH_i$  when norepinephrine was used in combination with dobutamine. After norepinephrine-dobutamine infusion, cardiac index was significant lower than that after epinephrine and dopamine infusion, thus this effect was not associated with an increase in cardiac

**Tab 2. Effects of dopamine, norepinephrine, epinephrine, and norepinephrine-dobutamine on oxygen metabolism.  $n = 16$ .  $\bar{x} \pm s$ . <sup>a</sup> $P < 0.05$  vs Dopa. <sup>b</sup> $P < 0.05$  vs EP. <sup>c</sup> $P < 0.05$  vs Nor + Dobu.**

	$D_{O_2}$ / L·min <sup>-1</sup> ·m <sup>-2</sup>	$V_{O_2}$ / L·min <sup>-1</sup> ·m <sup>-2</sup>	OER/%	Lactate/mmol·L <sup>-1</sup>	$pH_i$	$p_{g-a,CO_2}$ / kPa
Dopa	636 ± 282	168 ± 32	29 ± 8 <sup>c</sup>	2.6 ± 2.2 <sup>b</sup>	7.21 ± 0.10	3.6 ± 2.0
Nor	511 ± 165	159 ± 31	33 ± 6 <sup>c</sup>	1.6 ± 1.2	7.18 ± 0.14	4 ± 3
Ep	592 ± 173	137 ± 40 <sup>b</sup>	24 ± 6	2.3 ± 1.6 <sup>b</sup>	7.14 ± 0.07 <sup>b</sup>	4.1 ± 0.8
Nor + Dobu	486 ± 175	134 ± 36 <sup>b</sup>	30 ± 8 <sup>c</sup>	1.1 ± 0.7	7.25 ± 0.09	3.1 ± 1.7

$D_{O_2}$ : oxygen delivery index;  $V_{O_2}$ : oxygen consumption index; OER; oxygen extraction ratio;  $pH_i$ ; gastric mucosal pH;  $p_{g-a,CO_2}$ : gastric-arterial  $p_{CO_2}$  difference; Dopa; dopamine; Nor; norepinephrine; Ep; epinephrine; Nor + Dobu; norepinephrine-dobutamine.

index. It may be related to a blood flow redistribution effect of dobutamine toward gastric mucosa. Dobutamine-induced redistributive effect may be due to either an increase of the fraction of cardiac output that was distributed to the global hepatosplanchnic blood flow and/or to a redistribution of blood flow within gastric wall layers toward mucosa<sup>[8-10]</sup>. Thus, the increase in  $pH_i$  after norepinephrine-dobutamine infusion could be the effect of  $\beta_2$ -adrenergic effects of dobutamine.

To the contrary, although cardiac index was much higher than other three therapies, oxygen extraction ratio was the lowest after epinephrine infusion. The net effects of epinephrine infusion on systemic and splanchnic region oxygen metabolism were manifested as the lowest  $pH_i$  value and the higher lactate concentration, showing an apparent systemic and tissue ischemia. This may be related to increased shunt flow and decreased tissue oxygen uptake<sup>[10,11]</sup>. As epinephrine has the most strong thermogenic effect, it may increase oxygen demand of tissues when used in patients with septic shock.

Dopamine could increase oxygen delivery and oxygen consumption, but redistributive blood flow away from the gut mucosa<sup>[12]</sup>. In the present study, although dopamine did not show evident deleterious effect on gastric perfusion in the present study compared with norepinephrine, epinephrine, and norepinephrine-dobutamine, the lactate level after dopamine infusion was much higher than other three therapies. That is to say, dopamine is detrimental to oxygen metabolism for septic shock patients.

In conclusion, for the same level of MAP as the therapeutic goal in patients with septic shock, present study showed that administration of dopamine, norepinephrine, epinephrine, or norepinephrine-dobutamine improved systemic hemodynamics effectively. However, epinephrine and dopamine had deleterious effect on oxygen metabolism, while norepinephrine plus low dose of dobutamine improved gastric mucosal perfusion and tissue oxygen utilization.

## REFERENCES

- 1 Oud L, Haupt MT. Persistent gastric intramucosal ischemia in patients with sepsis following resuscitation from shock. *Chest* 1999; 115: 1390-6.
- 2 Townsend MC, Schirmer WJ, Schirmer JM, Davis K, Fry DE. Low dose dopamine improves effective hepatic blood flow in murine peritonitis. *Circ Shock* 1987; 21: 149-53.
- 3 Angehm W, Schmid E, Althaus F, Niedermann k, Rothlin

M. Effect of dopamine on hepatosplanchnic blood flow. *J Cardiovasc Pharmacol* 1980; 2: 257-65.

- 4 Shepherd AP, Pawlik W, Mailman D, Burks TF, Jacobson ED. Effects of vasoconstrictors on intestinal vascular resistance and oxygen extraction. *Am J Physiol* 1976; 230: 298-305.
- 5 Yang Y, Qiu HB, Zhou SX, Tan Y, Li SQ. Comparison effect of norepinephrine-dobutamine to dopamine on splanchnic perfusion in sheep with septic shock. *Acta Pharmacol Sin* 2002; 23: 133-7.
- 6 American college of chest physician/society of critical care medicine consensus conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864-74.
- 7 Marik PE. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; 104: 225-59.
- 8 Joly LM, Monchi M, Cariou A, Chiche JD, Bellenfant F, Brunet F, et al. Effects of dobutamine on gastric mucosal perfusion and hepatic metabolism in patients with septic shock. *Am J Respir Crit Care Med* 1999; 160: 1983-6.
- 9 Neviere R, Mathieu D, Chagnon JL, Lebleu N, Wattel F. The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med* 1996; 154: 1684-8.
- 10 Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, et al. Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. *Crit Care Med* 1999; 27: 893-900.
- 11 Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock; a prospective, randomized study. *Intensive Care Med* 1997; 23: 282-7.
- 12 Giraud GD, MacCannell KL. Decreased nutrient blood flow during dopamine- and epinephrine-induced intestinal vasodilation. *J Pharmacol Exp Ther* 1984; 30: 214-30.

去甲肾上腺素、肾上腺素及去甲肾上腺素-多巴酚丁胺对感染性休克病人全身及胃粘膜氧代谢的影响

R96 A

周韶霞, 邱海波<sup>1</sup>, 黄英姿, 杨毅, 郑瑞强

(东南大学医学院附属中大医院危重病医学科, 南京 210009, 中国)

关键词 感染性休克; 多巴胺; 去甲肾上腺素; 肾上腺素; 多巴酚丁胺; 血液动力学

目的: 比较多巴胺、去甲肾上腺素、肾上腺素及去甲肾上腺素-多巴酚丁胺对感染性休克患者全身及胃

粘膜氧代谢的影响。方法：首先用多巴胺，然后随机应用肾上腺素、去甲肾上腺素，或去甲肾上腺素-多巴酚丁胺，调整剂量维持平均动脉压  $> 9.31$  kPa。药物注射后 120 min，记录血流动力学、氧代谢及胃粘膜 pH 参数。结果：与其它三组比较，肾上腺素使心率明显增加 ( $P < 0.05$ )，心排指数明显高于去甲肾上腺素组或去甲肾上腺素-多巴酚丁胺组 ( $P < 0.05$ )，氧摄取率明显低于其它三组 ( $P < 0.05$ )。与多巴胺、肾上腺素比较，去甲肾上腺素-多巴酚丁胺合用时动脉血乳酸值明显降低 ( $P < 0.05$ )。与肾上

腺素比较，去甲肾上腺素-多巴酚丁胺合用时胃粘膜 pH 值明显增加 ( $7.25 \pm 0.09$  vs  $7.14 \pm 0.07$ ,  $P < 0.05$ )。结论：多巴胺、去甲肾上腺素、肾上腺素及去甲肾上腺素-多巴酚丁胺均能升高血压。但是肾上腺素和多巴胺使氧代谢恶化，而去甲肾上腺素与小剂量多巴酚丁胺合用可改善胃粘膜灌注和组织氧利用。

(责任编辑 吕 静)

---

## The 8th Annual Conference and Exhibition of the Society for Biomolecular Screening

2002, Sep 22 - 26

The Hague, The NETHERLANDS

Info: The Society for Biomolecular Screening  
36 Tamarack Avenue, # 348  
Department of Pharmacology  
Danbury, CT 06811, USA  
Phn +1 203-743-1336  
Fax +1 203-748-7557  
E-mail [tnackid@sbsonline.org](mailto:tnackid@sbsonline.org)  
Website: [www.sbsonline.org](http://www.sbsonline.org)