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Comparison of norepinephrine-dobutamine to dopamine alone for splanchnic perfusion in sheep with septic shock

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KEY WORDS septic shock; norepinephrine; dobutamine; dopamine; tonometry; splanchnic circulation; lactates; hemodynamics

ABSTRACT

AIM: To compare the effect of norepinephrine-dobutamine with dopamine alone on splanchnic perfusion in sheep with septic shock. **METHODS**: Twenty sheep with septic shock induced by lipopolysaccharides were divided into two groups. When systolic pressure decreased by 5.3 kPa, basic values of hemodynamic parameters and intestinal intramucosal pH (pH_i) were recorded. Each group was randomized to receive an intravenous infusion of norepinephrine-dobutamine or dopamine, and titrated to obtain mean arterial pressure (MAP) > 12 kPa with an optimal cardiac preload. Hemodynamic parameters and mucosal pH_i were repeated at 1, 2, 3, and 4 h after basic measurement. **RESULTS**: After norepinephrine-dobutamine or dopamine infusion, MAP, cardiac output, and oxygen delivery increased in all animals compared with basic values in both groups ($P < 0.05$). Compared with baseline values, lactate concentrations decreased at 3 h and 4 h [from (4 ± 2) mmol/L to (2 ± 1) mmol/L] in the norepinephrine-dobutamine group ($P < 0.05$). Arterial lactate concentrations had no change in dopamine group, but arterial pH decreased from 7.40 ± 0.05 to 7.26 ± 0.06 at 1 h ($P < 0.05$). No difference in pH_i was found in dopamine group, but in the norepinephrine-dobutamine group, compared with baseline, pH_i increased from 7.19 ± 0.04 to 7.36 ± 0.07 at 3 h ($P < 0.05$). **CONCLUSION**: Both norepinephrine-dobutamine and dopamine alone could improve systemic hemodynamics in sheep with septic shock, but norepinephrine-dobutamine was better than dopamine on splanchnic perfusion.

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INTRODUCTION

Septic shock still represented a major cause of death in patients with critical illness. After fluid resuscitation, prompt administration of catecholamines was usually necessary to increase oxygen delivery and maintain blood pressure. Nevertheless, both the gastrointestinal tract and liver might be perfused inadequately despite of the presence of normal systemic pressure. Low splanchnic perfusion was associated with multiple organ failure closely[1]. As catecholamines selected, more attention was paid to splanchnic perfusion after systemic hemodynamics were improved.

Previous studies showed dopamine increased systemic blood pressure and oxygen delivery and improved splanchnic perfusion[2,3], so dopamine was widely recommended for the treatment of septic shock. On the other hand, norepinephrine was considered to be deleterious[4], for fear of excessive vasoconstriction, many considered that this drug potentiating end-organ hypoperfusion, thereby contributing to increased mortality. However, in recent studies, dopamine failed to improve splanchnic perfusion[5], but norepinephrine and dobutamine had been found to be beneficial to increase splanchnic perfusion[6,7]. Dopamine and norepinephrine-dobutamine acted on both α and β receptors. Therefore, this prospective and randomized study was to compare the effect of norepinephrine-dobutamine with dopamine on systemic hemodynamics and splanchnic perfusion in sheep with septic shock.

MATERIALS AND METHODS

Animal preparation Twenty sheep (New Zealand Colliedle) weighing 22 - 27 kg each were purchased from Animal Center of Nanjing Agriculture University. Animals were fasted for 24 h before the experiments, with free access to water. Before the experi-

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ment, the sheep were anesthetized with ketamine hydrochloride (20 mg/kg, im) and placed in a supine position. A tracheotomy was performed, and the animals were mechanically ventilated with a volume controlled ventilation (Drager Evita 2dura, German). Ventilation was adjusted to keep arterial oxygen pressure (p_{a,O_2}) > 12 kPa and arterial carbon dioxide pressure between 4.7 - 6.0 kPa. During the study, animals were sedated with continuous infusion of γ-sodium hydroxybutyrate (5 mg/h, iv) to minimize changes in oxygen consumption.

Swan-Ganz catheter was inserted through 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 femoral artery catheter. Cardiac index (CI) was calculated as CI = CO/HR.

Arterial blood samples were withdrawn from the arterial catheter. Mixed venous blood samples were collected from the distal port of the pulmonary artery catheter. All blood gas measurements were performed on a blood gas analyzer (Nova, USA). Oxygen delivery index (D_{O_2}) was computed as $D_{O_2}(L \cdot min^{-1} \cdot m^{-2}) = CI \times C_{a,O_2} \times 10$, and arterial oxygen content (C_{a,O_2}) = hemoglobin × 1.36 × S_{a,O_2} (arterial oxygen saturation) + 0.0031 × p_{a,O_2}. Oxygen consumption index (V_{O_2}) was calculated as $V_{O_2}(L \cdot min^{-1} \cdot m^{-2}) = CI \times (C_{a,O_2} - C_{v,O_2}) \times 10$, where C_{v,O_2} (mixed venous oxygen content) = hemoglobin × 1.36 × S_{v,O_2} (mixed venous saturation) + 0.0031 × p_{v,O_2} (mixed oxygen partial pressure).

After the abdomen was opened with a midline incision, the superior mesenteric artery was gently dissected, and electromagnetic flow probes in adequate size was attached to the vessel. Blood flow was monitored continuously using electromagnetic flow instrument (NIHON KOHDEN, Japan). The tonometer was inserted into jejunum by purse-string. The tonometer balloon was filled with 2.5 mL 0.9 % saline and sufficient time (1 h) was allowed for the partial pressure of carbon dioxide (p_{CO_2}) of intestinal mucosa to equilibrate with the saline. Intestinal mucosal pH_i was calculated with a tonometric technique using the following modification of the Henderson-Hasselbalch equation: $pH_i = 6.1 + \lg C_{a,HCO_3^-} / (F \times 0.03 \times p_{tonometric\ saline,\ CO_2})$, where F was a time-dependent factor for partially equilibrated samples and supplied by the tonometer manufacturer. The animals were stabilized for 30 min after the abdomen was closed.

Experimental protocol Animals were infused intravenously with LPS (*E coli* O127: B8, Sigma) 3 μg/kg for 30 min, then 40 $ng \cdot min^{-1} \cdot kg^{-1}$ continuously. When systolic pressure decreased by 5.3 kPa, basic data of hemodynamic, oxygen metabolism, and pH_i were recorded.

Study animals were randomly divided into two groups. The first group ($n = 10$) received dopamine, another group ($n = 10$) received norepinephrine-dobutamine. Dopamine infusion was started at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, norepinephrine was started at 2 $\mu g \cdot min^{-1}$, and dobutamine was infused at a fixed dose of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$[8]. The therapeutic goal was to achieve MAP > 12 kPa by administration of the drugs. Hemodynamic, metabolic parameters, and mucosal pH_i were recorded at 1 h, 2 h, 3 h, and 4 h after basic measurement. During the study, PAWP was always kept at the optimal level by fluid resuscitation.

At the end of experiment, all animals were killed by a bolus injection of saturated potassium chloride solution.

Statistical analysis All results were reported as $\bar{x} \pm s$ and analyzed by two-tailed t-test. A probability level less than 0.05 was considered significant.

RESULTS

Hemodynamics The basic measurements of MAP in dopamine group and in norepinephrine-dobutamine group were (8.6 ± 1.5) and (8.6 ± 1.6) kPa, CI were (5 ± 2) and (6 ± 2) $L \cdot min^{-1} \cdot m^{-2}$, respectively. One hour after basic measurement, all animals fulfilled the therapeutic goals (MAP about 12 kPa). Compared with basic value, MAP and CI were increased in both groups at 1 h, 2 h, 3 h, and 4 h ($P < 0.05$). No statistical difference in systemic hemodynamic measurements was found between dopamine and norepinephrine-dobutamine (Tab 1).

Oxygen metabolism and splanchnic perfusion After basic measurement, D_{O_2} was increased in all animals at 1 h, 2 h, 3 h, and 4 h ($P < 0.05$). Compared with baseline values, arterial lactate concentrations were decreased at 3 h and 4 h [from (4 ± 2) mmol/L to (2 ± 1) mmol/L] in the norepinephrine-dobutamine

group ($P<0.05$). Arterial lactate concentrations had no difference in the dopamine group, but arterial pH decreased from (7.40 ± 0.05) to (7.26 ± 0.06) at 1 h ($P<0.05$). No difference in pH_i was found in the dopamine group, but in the norepinephrine-dobutamine group, compared with baseline, pH_i increased from (7.19 ± 0.04) to (7.36 ± 0.07) at 3 h ($P<0.05$) (Tab 2).

DISCUSSION

The first aim of vasoactive drugs in septic shock was to maitain blood pressure and improve systemic oxygen delivery. Our present study showed that both dopamine and norepinephrine-dobutamine could raise arterial pressure and oxygen delivery in sheep with septic shock. In sheep treated with norepinephrine-dobutamine, CI and D_{O_2} increased, while both of which did not increase with norepinephrine alone[6]. As a strong alpha receptors agonist and slight cardiac beta receptors activator, norepinephrine can reverse refractory hypotention of septic shock, but had no significant effect on CI. So the combination of norepinephrine and dobutamine might improve CI and D_{O_2} more effectively. Dopamine acted on the alpha and beta-receptors meanwhile, which could improve CI and D_{O_2} markedly. Thus, dopamine and norepinephrine-dobutamine had similar effects on systemic hemodynamics and oxygen delivery.

Compared with baseline values, arterial lactate concentration had no statistical difference in the dopamine group, but decreased at 3 h and 4 h in the norepinephrine-dobutamine group. Lactate was one of the

Tab 1. Effect of norepinephrine-dobutamine (Dobu-NE) or dopamine (Dopa) alone on hemodynamic parameters. $n=10$. $\bar{x}\pm s$. $^bP<0.05$ *vs* baseline.

	Group	Pre-LPS	Baseline	Time after baseline/h 1	2	3	4
MAP/kPa	Dopa	15.0 ± 1.6^b	8.6 ± 1.5	12.3 ± 2.0^b	11.3 ± 1.1^b	12.4 ± 0.9^b	11.9 ± 1.5^b
	Dobu-NE	13.4 ± 1.9^b	8.6 ± 1.6	11.7 ± 2.4^b	11.7 ± 2.0^b	12.1 ± 1.2^b	12.0 ± 0.7^b
HR/min^{-1}	Dopa	148 ± 23	149 ± 17	140 ± 28	129 ± 24	139 ± 20	133 ± 29
	Dobu-NE	137 ± 14	150 ± 28	170 ± 22	170 ± 25	170 ± 16	178 ± 17
PAP/kPa	Dopa	1.9 ± 0.8	2.4 ± 0.6	2.7 ± 0.3	2.6 ± 0.6	2.8 ± 0.8	2.6 ± 0.7
	Dobu+NE	2.4 ± 0.2	2.4 ± 0.4	2.7 ± 0.6	2.3 ± 0.4	2.8 ± 0.6	2.7 ± 0.4
PAWP/kPa	Dopa	1.2 ± 0.1	1.2 ± 0.3	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	1.2 ± 0.2
	Dobu-NE	1.3 ± 0.1	1.2 ± 0.3	1.6 ± 0.3	1.2 ± 0.2	1.2 ± 0.3	1.2 ± 0.2
CI L·min^{-1}·m^{-2}	Dopa	6 ± 1	5 ± 2	9 ± 2^b	9 ± 1^b	10 ± 3^b	10 ± 1^b
	Dobu-NE	7 ± 1	6 ± 2	9 ± 2^b	8 ± 1^b	9 ± 2^b	8 ± 2
Mesenteric artery	Dopa	0.35 ± 0.15	0.27 ± 0.17	0.37 ± 0.18	0.40 ± 0.19	0.25 ± 0.05	0.24 ± 0.06
flow/L·min^{-1}·m^{-2}	Dobu-NE	0.47 ± 0.15	0.6 ± 0.4	0.45 ± 0.12	0.37 ± 0.16	0.48 ± 0.09	0.52 ± 0.08

HR: heart rate; MAP: mean systemic arterial pressure; PAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CI: cardiac index.

Tab 2. Effect of norepinephrine-dobutamine (Dobu-NE) or dopamine (Dopa) alone on metabolic parameters. $n=10$. $\bar{x}\pm s$. $^bP<0.05$ *vs* baseline.

	Group	Pre-LPS	Baseline	Time after baseline/h 1	2	3	4
D_{O_2}/L·min^{-1}·m^{-2}	Dopa	0.54 ± 0.29	0.47 ± 0.20	0.82 ± 0.17^b	0.80 ± 0.07^b	0.90 ± 0.25^b	0.86 ± 0.10^b
	Dobu-NE	0.57 ± 0.24	0.54 ± 0.12	0.74 ± 0.11^b	0.71 ± 0.10^b	0.75 ± 0.08^b	0.70 ± 0.12
V_{O_2}/L·min^{-1}·m^{-2}	Dopa	0.08 ± 0.02	0.07 ± 0.02	0.08 ± 0.06	0.07 ± 0.03	0.10 ± 0.06	0.13 ± 0.05
	Dobu-NE	0.05 ± 0.03	0.07 ± 0.03	0.07 ± 0.03	0.07 ± 0.04	0.09 ± 0.04	0.06 ± 0.03
Arterial pH	Dopa	7.48 ± 0.03	7.40 ± 0.05	7.26 ± 0.06^b	7.33 ± 0.09	7.30 ± 0.07	7.36 ± 0.04
	Dobu-NE	7.41 ± 0.04	7.35 ± 0.07	7.35 ± 0.07	7.36 ± 0.04	7.35 ± 0.04	7.38 ± 0.05
Lactate mmol·L^{-1}	Dopa	2 ± 1	3 ± 2	2 ± 1	2 ± 1	2 ± 1	3 ± 2
	Dobu-NE	2 ± 1^b	4 ± 2	4 ± 2	3 ± 1	2 ± 1^b	2 ± 1^b
pH_i	Dopa	7.36 ± 0.07	7.26 ± 0.06	7.25 ± 0.07	7.24 ± 0.07	7.31 ± 0.08	7.30 ± 0.09
	Dobu-NE	7.31 ± 0.07	7.19 ± 0.04	7.23 ± 0.11	7.28 ± 0.07	7.36 ± 0.07^b	7.34 ± 0.06

D_{O_2}: oxygen delivery index; V_{O_2}: oxygen consumption index; pH_i: intramucosal pH.

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metabolic byproducts of anaerobic metabolism, measurement of lactate had been used to assess the adequacy of tissue oxygenation in the critical illness. Increase in serum lactate concentration had been observed in patients with anaerobic metabolism[9]. Moreover, increased lactate concentration was associated with high mortality rates in septic shock patients. Our results suggested norepinephrine-dobutamine might improve tissue oxygenation.

This study showed pH_i increased markedly at 3 h in the norepinephrine-dobutamine group, but did not change in dopamine group. This finding was not associated with an increase in CI and D_{O_2}, it might be related to the blood flow redistribution induced by dobutamine toward intestinal mucosa. The measurement of tissue pH provided a metabolic index of adequacy of tissue oxygenation. pH_i was an important signal of intestinal perfusion, low pH_i indicated inadequate intestinal perfusion and hypoxia. The putative consequences of intramucosal acidosis and associated mocosal injury include increased gut permeability, bacterial translocation, sepsis, and multiple organ failure. Therefore the gut had been regarded as the motor of multiple organ dysfunction syndrome(MODS). A normal tissue pH could be used as an end point to the goal of shock resuscitation[10].

Traditional study showed dopamine increased splanchnic perfusion, and norepinephrine could decrease gut blood flow through its strong agonization of alpha receptor effect. In Meier-Hellmanni's study, norepinephrine alone induced a decrease in splanchnic perfusing in septic shock patients[11]. Dobutamine could increased systemic D_{O_2} and was associated with a significant increase in gastric pH_i in septic patients[7]. But dobutamine often failed to increase systemic pressure alone in septic shock. Therefore, norepinephrine combinated with dobutamine might increase the splanchnic perfusion in septic shock. Recent studies showed combined norepinephrine with dobutamine increased pH_i and decreased arterial lactate concentration[12,13]. In our study, intestinal blood flow did not change markedly, and pH_i was increased in norepinephrine-dobutamine group, but not in dopamine group, which suggested norepinephrine-dobutamine appeared to be predictable and more appropriate to the goals of septic shock therapy.

Our results also showed systemic hemodynamic and oxygen metabolism data did not truly reflect tissue perfusion. This present study demonstrated arterial lactate concentration and pH_i were almost abnormal in dopamine group, even blood pressure and systemic hemodynamics had been improved after dopamine used. It suggested that it was not enough to improve systemic hemodynamics only in septic shock, improving tissue perfusion, especially intestinal perfusion might be more important.

In summary, this work demonstrated both norepinephrine-dobutamine and dopamine could improve hemodynamic state of sheep with septic shock, but on splanchnic perfusion, norepinephrine-dobutamine was better than dopamine. Norepinephrine and dobutamine might be a good combination in septic shock therapy, and dopamine was not routinely recommended to improve intestinal perfusion.

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去甲肾上腺素和多巴酚丁胺联用与多巴胺单用对感染性休克绵羊内脏灌流的比较

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关键词 感染性休克; 去甲肾上腺素; 多巴酚丁胺; 多巴胺; 压力测量法; 内脏循环; 乳酸盐类; 血液动力学

目的: 观察多巴酚丁胺加去甲肾上腺素和单用多巴胺对感染性休克绵羊内脏灌注的影响. **方法**: 利用内毒素(LPS)复制感染性休克模型, 当收缩压下降至5.3 kPa时记录血流动力学及肠粘膜 pH(pH_i)的基础值. 20只绵羊随机分为两组, 分别静脉注入多巴酚丁胺加去甲肾上腺素及多巴胺, 调整药物剂量, 使平均动脉压升高到12 kPa, 观察用药前(基础值)及用药后1, 2, 3, 4 h的血流动力学和内脏灌注指标 pH_i. **结果**: 两组动物在用药后血压、心排指数及氧输送较用药前明显升高. 多巴胺组动脉乳酸浓度及 pH_i 无明显改变, 但动脉 pH 值在用药后1 h从 7.40±0.05 降至 7.26±0.06 ($P<0.05$). 应用多巴酚丁胺加去甲肾上腺素后3 h和1 h, 动脉乳酸浓度从 (4±2) mmol/L 降至 (2±1) mmol/L 和 (2±1) mmol/L ($P<0.05$), 用药后3 h, pH_i 从 7.19±0.04明显升高到 7.36±0.07 ($P<0.05$). **结论**: 多巴酚丁胺加去甲肾上腺素和单用多巴胺均能改善感染性休克绵羊全身血流动力学状态, 但在改善内脏灌注上, 多巴酚丁胺与去甲肾上腺素联用明显优于多巴胺单用.

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