

Prognostic value of dobutamine stress test in patients with septic shock

QIU Hai-Bo¹, YANG Yi, ZHOU Shao-Xia, LIU Shao-Hua, ZHENG Rui-Qiang (Department of Critical Care Medicine, Zhong-Da Hospital, Southeast University, Nanjing 210009, China)

KEY WORDS septic shock; dobutamine; prognosis; oxygen consumption; human; randomized controlled trials

ABSTRACT

AIM: To evaluate the prognostic effect of dobutamine stress test in patients with septic shock. **METHODS:** Patients with septic shock received intravenous infusion of dobutamine at $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 1 h. Hemodynamics and oxygen metabolism was observed. A patient who was able to increase oxygen consumption index (V_{O_2}) by $>15\%$ was designated as a responder to the test. **RESULTS:** In 47 patients with septic shock, twenty one responders and twenty six nonresponders were identified, and mortality was 33.3% and 76.9% respectively. After the dobutamine infusion, the responders showed increases in cardiac index (18.1%), oxygen delivery index (12.7%), V_{O_2} (38.6%), and oxygen extraction ratio (18.0%), and reductions in systemic vascular resistance index (18.5%). The nonresponders demonstrated increases in cardiac index (11.5%), but no change in oxygen delivery, V_{O_2} , and oxygen extraction ratio. **CONCLUSION:** Dobutamine stress test might be a good predictor of outcome in patients with septic shock.

INTRODUCTION

A pathologic relationship between oxygen supply and demand exists in critically ill patients with septic shock and the relationship is associated with a severe tissue hypoxia and a poor outcome^[1,2]. However, Vallet and colleagues found that an increase in oxygen consumption of $>15\%$ after oxygen delivery increased by performing

a dobutamine stress test was a good predictor of a good outcome in septic patients^[3]. That is to say, the septic patients with oxygen supply dependency have better prognosis. Of course, these findings are contrary to previous work. There has been no study observing the effect of dobutamine stress on outcome of patients with septic shock. The current study was to investigate the relationship between an oxygen dependency and outcome in patients with septic shock by dobutamine stress test.

MATERIALS AND METHODS

Patients population Patients selected were critically ill with septic shock at intensive care unit (ICU) from January 1998 to December 1999. According to the criteria previously reported by the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM)^[4], septic shock was defined as sepsis with hypotension (systolic blood pressure <12.0 kPa or reduction of 5.3 kPa from baseline in the absence of other causes for hypertension). Blood pressure changes had persisted for more than one hour and had failed to respond to a fluid challenge (at least 500 mL). Patients were excluded from the study if they were not expected to survive for more than 12 h or if they were suffering from established cardiac disease.

Methods Data were recorded from each patient included demographic information (eg, sex, age), major diagnosis, infection sites, presence of preexisting chronic diseases, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores from the first 24 h on the ICU^[5]. The infection sites were divided into lung, abdomen, and others. Wound infection, cerebral infection, urinary tract infection, and the infection at unknown sites were considered as "others". Multiple organ failure determined by Fry was also recorded^[6].

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), pulmonary ar-

¹ Correspondence to Assoc Prof QIU Hai-Bo, MD, Ph D.

Phn 86-25-327-2200. Fax 86-25-331-3807.

E-mail HaiBoq@hotmail.com

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terial 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 $CI = CO/HR$. Systemic vascular resistance index (SVRI) was calculated as $SVRI (kPa \cdot s \cdot L^{-1}) = (MAP - CVP)/CI \times 8$. Pulmonary vascular resistance index (PVRI) was computed as $PVRI (kPa \cdot s \cdot L^{-1}) = (PAM - PAWP)/CI \times 8$.

Arterial samples were withdrawn from the arterial catheter. Mixed venous 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 $D_{O_2} (L \cdot \min^{-1} \cdot m^{-2}) = CI \times C_{aO_2} \times 10$, where CI = cardiac index ($L \cdot \min^{-1} \cdot m^{-2}$), and arterial oxygen content (C_{aO_2}) = hemoglobin $\times 1.36 \times$ arterial oxygen saturation (S_{aO_2}) + $0.0031 \times$ arterial oxygen pressure (P_{aO_2}). Oxygen consumption index (V_{O_2}) was calculated as $V_{O_2} (L \cdot \min^{-1} \cdot m^{-2}) = CI \times (C_{aO_2} - C_{vO_2}) \times 10$, where C_{vO_2} (mixed venous oxygen content) = hemoglobin $\times 1.36 \times$ mixed venous saturation (S_{vO_2}) + $0.0031 \times$ mixed oxygen partial pressure (P_{vO_2}). Oxygen extraction ratio (O_2ext) was computed as $O_2ext = (C_{aO_2} - C_{vO_2})/C_{aO_2}$.

Before starting the dobutamine stress test, cardiac preload was optimized by using crystalloid fluid until there was no further increase in cardiac output and PAWP was maintained at 1.73 – 2.13 kPa. A dobutamine stress test was performed as described previously⁽³⁾. Baseline measurements of temperature, arterial and mixed venous blood gas, and hemodynamic data were recorded. An infusion of dobutamine at $10 \mu g \cdot kg^{-1} \cdot \min^{-1}$ was started via central venous catheter. During the infusion, fluid, sedative, and vasoactive drug administration were maintained constant, and ventilatory status also remained constant. If a patient's condition deteriorated during the test, the test was abandoned. After 1 h, the hemodynamic and blood gas measurements were repeated. The dobutamine infusion was then reduced or stopped.

Patients were designated as responders to the test if they were able to demonstrate a 15 % increase in oxygen consumption after the dobutamine infusion; they were designated as nonresponders if the oxygen consumption increased by < 15 %.

All results were reported as $x \pm s$ and analyzed by

two-tailed t test. A probability level less than 0.05 was considered significant.

RESULTS

Forty seven patients were enrolled into the study from January 1998 to December 1999. The average age for the population was (65 ± 12) a. All patients had septic shock. The source of infection was identified as lung infection in 26 patients, peritonitis in 20 patients, and a mixed infection in one. Forty-three patients needed ventilation support, thirty seven patients developed acute respiratory distress syndrome⁽⁷⁾, thirty four patients developed acute renal failure, twenty three patients developed acute gut failure, and 29 patients developed central nervous system failure. The ICU length of stay was (14 ± 16) d. The overall mortality was 57.4 % (Tab 1).

Before starting the dobutamine infusion, the population as a whole demonstrated a moderately hyperdynamic state; HR (102 ± 20) beats $\cdot \min^{-1}$, MAP (10.3 ± 1.2) kPa, PAP (3.4 ± 0.8) kPa, CI (3.1 ± 0.9) $L \cdot \min^{-1} \cdot m^{-2}$, SVRI (186 ± 75) $kPa \cdot s \cdot L^{-1}$, and PVRI (42 ± 32) $kPa \cdot s \cdot L^{-1}$. D_{O_2} and V_{O_2} were (0.43 ± 0.16) $L \cdot \min^{-1} \cdot m^{-2}$ and (0.13 ± 0.05) $L \cdot \min^{-1} \cdot m^{-2}$ respectively.

Twenty one responders and 26 nonresponders were identified. The difference between two groups was not significant (Tab 1). The mortality was 33.3 % in responders, which was markedly lower than that in nonresponders (76.9 %). After the dobutamine infusion, the responders showed significant increases in CI (18.1 %), P_{vCO_2} (9.3 %), D_{O_2} (12.7 %), V_{O_2} (38.6 %), and O_2ext (18.0 %). There were reductions in the SVRI (18.5 %) and S_{vO_2} (8.5 %). The nonresponders demonstrated increases in CI (11.5 %), and P_{vCO_2} (11.4 %) (Tab 2, 3, and 4). The responders differed from the nonresponders in that they had lower V_{O_2} at baseline, and higher O_2ext in response to dobutamine infusion. All of the responders were able to increase V_{O_2} when D_{O_2} was increased. The nonresponders had varied responses.

The desired effect of the dobutamine stress test was to be able to predict patients who were going to have a poor outcome from septic shock. The study identified that the test had high sensitivity (70.0 %) and specificity (74.1 %) (Tab 5, Fig 1). The overall hospital mortality rate was lower in the responders than in the

Tab 1. Demographic data.

	Population	Responders	Nonresponders	P
Age	65 ± 12	65 ± 14	65 ± 11	0.9167
Sex (male)	40.4 (19/47)	38.1 (8/21)	42.3 (11/26)	0.7698
APACHE II score/%	24 ± 11	25 ± 10	24 ± 12	0.5395
APACHE II mortality prediction/%	44 ± 29	45 ± 28	44 ± 30	0.8399
Site of infection				
Pulmonary	26	14	12	
Abdomen	20	7	13	0.2938
Other	1	0	1	
Ventilation required/%	91.5 (43/47)	100.0 (21/21)	84.6 (22/26)	0.0602
Duration of ventilation/d	7 ± 6	7 ± 8	6 ± 4	0.4513
Acute respiratory distress syndrome/%	78.7 (37/47)	80.7 (17/21)	76.9 (20/26)	0.7372
Acute renal failure/%	72.3 (34/47)	76.2 (16/21)	69.2 (18/26)	0.5959
Acute gut failure/%	48.9 (23/47)	33.3 (7/21)	61.5 (16/26)	0.0545
Central nervous system failure/%	61.7 (29/47)	52.4 (11/21)	69.2 (18/26)	0.2374
ICU length of stay/d	14 ± 16	16 ± 19	12 ± 13	0.2693
Hospital mortality/%	57.4 (27/47)	33.3 (7/21)	76.9 (20/26)	0.5959

Tab 2. Hemodynamic data for responders (n = 21) and non-responders (n = 26) before and after dobutamine stress test. $\bar{x} \pm s$.

	HR/bpm	MAP/kPa	PAP/kPa	PAWP/kPa	CVP/kPa	CI/ L·min ⁻¹ ·m ⁻²	SVRI/ kPa·s·L ⁻¹	PVRI/ kPa·s·L ⁻¹
Responders								
Baseline	102 ± 17	10 ± 1	3.5 ± 0.9	1.6 ± 0.7	1.4 ± 0.4	3.0 ± 0.7	189 ± 62	42 ± 19
With dobutamine	100 ± 22	10 ± 2	3.7 ± 1.1	1.6 ± 0.6	1.7 ± 0.6	3.5 ± 1.0	154 ± 54	40 ± 20
P	0.478	0.947	0.207	1.000	0.047	<0.001	<0.001	0.384
t value	0.720	0.067	1.293	0	2.077	4.140	4.144	0.884
Nonresponders								
Baseline	102 ± 23	10 ± 1	3 ± 4	1.7 ± 0.7	1.6 ± 0.5	3.1 ± 1.1	184 ± 86	43 ± 40
With dobutamine	105 ± 21	11 ± 2	3.4 ± 0.8	1.7 ± 0.7	1.6 ± 0.6	3.5 ± 1.3	1748 ± 71	36 ± 14
P	0.433	0.519	0.084	0.467	1.000	0.026	0.600	0.316
t value	0.797	0.655	1.805	0.739	0	2.379	0.631	1.024

HR: heart rate; MAP: mean systemic arterial pressure; PAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CVP: right atrial pressure; CI: cardiac index; SVRI: systemic vascular resistance index; PVRI: pulmonary vascular resistance index.

Tab 3. Data of blood gas for responders (n = 21) and non-responders (n = 26) before and after dobutamine stress test. $\bar{x} \pm s$.

	pHa	P _{aO₂} /kPa	P _{aCO₂} /kPa	S _{aO₂} %	pHv	P _{vO₂} /kPa	P _{vCO₂} /kPa	S _{vO₂} %
Responders								
Baseline	7.4 ± 0.1	20 ± 11	4.9 ± 1.4	98 ± 3	7.4 ± 0.1	5.0 ± 1.5	5.6 ± 1.3	67 ± 11
With dobutamine	7.4 ± 0.1	17 ± 9	5.1 ± 1.2	97 ± 2	7.4 ± 0.1	4.6 ± 0.9	6.1 ± 1.4	61 ± 11
P	0.190	0.480	0.407	0.649	0.200	0.099	0.022	0.002
t value	1.344	1.376	0.842	0.460	1.312	1.709	2.440	3.446
Nonresponders								
Baseline	7.4 ± 0.1	14 ± 7	4.9 ± 1.6	96 ± 3	7.4 ± 0.1	4.8 ± 0.8	5.4 ± 1.6	64 ± 10
With dobutamine	7.4 ± 0.1	14 ± 7	5.1 ± 1.8	94 ± 9	7.3 ± 0.1	5.1 ± 1.0	6.0 ± 2.2	66 ± 12
P	0.307	0.719	0.521	0.144	0.317	0.090	0.048	0.325
t value	1.043	0.364	0.652	1.510	1.022	1.768	2.087	1.005

P_{aO₂}: arterial oxygen pressure; P_{aCO₂}: arterial carbon dioxide pressure; S_{aO₂}: arterial oxygen saturation; P_{vO₂}: mixed oxygen partial pressure; S_{vO₂}: mixed venous saturation.

Tab 4. Data of oxygen metabolism for responders (n = 21) and non-responders (n = 26) before and after dobutamine stress test. $\bar{x} \pm s$. ^bP < 0.05 vs responders.

	$D_{O_2}/L \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	$V_{O_2}/L \cdot \text{min}^{-1} \cdot \text{m}^{-2}$	$O_2\text{ext}/\%$	Temperature/ $^{\circ}\text{C}$	Lactate/ $\text{mmol} \cdot \text{L}^{-1}$
Responders					
Baseline	0.39 ± 0.14	0.11 ± 0.04	32 ± 11	37.1 ± 1.5	4.9 ± 3.6
With dobutamine	0.44 ± 0.14	0.16 ± 0.05	37 ± 12	37.2 ± 1.2	4.6 ± 4.1
P	0.015	< 0.001	0.001	0.452	0.594
t value	2.594	> 100	3.732	0.762	0.540
Non-responders					
Baseline	0.46 ± 0.18	0.15 ± 0.05^b	36 ± 16	37.3 ± 1.5	4.1 ± 2.4
With dobutamine	0.48 ± 0.17	0.13 ± 0.04	30 ± 10^b	37.4 ± 1.5	3.4 ± 3.1
P	0.417	0.059	0.052	0.609	0.185
t value	0.826	1.979	2.042	0.518	1.365

D_{O_2} : oxygen delivery index; V_{O_2} : oxygen consumption index; $O_2\text{ext}$: oxygen extraction ratio.

Tab 5. Prognostic value of the dobutamine test.

	Survivor	Nonsurvivor	Total
Responders	14	7	21
Non-responders	6	20	26
Total	20	27	47

$\chi^2 = 9.0295$, $P = 0.0026$, $RR = 6.667$, sensitivity = 70.0 %, specificity = 74.1 %.

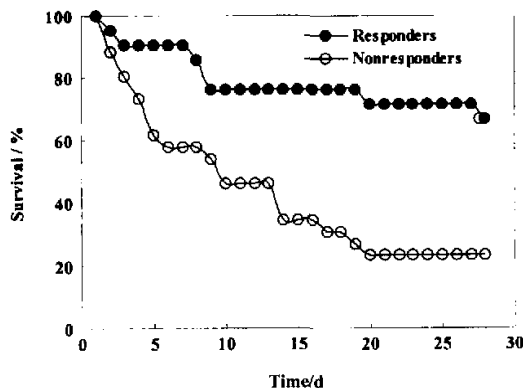


Fig 1. Survival curves for responders and nonresponders.

nonresponders. But the mortality predictions from the APACHE II scoring system had no difference between the responders and nonresponders (Tab 1).

DISCUSSION

In healthy volunteers, dobutamine is a powerful in-

otrope with the ability to increase D_{O_2} by up to 100 %, which explains its action on α_1 , α_2 , β_1 , and β_2 receptors^[8,9]. Through its action on the β receptors, there is a thermogenic effect that causes an increase in V_{O_2} ^[9]. Therefore, the normal response to the infusion of dobutamine is to increase both D_{O_2} to the tissue and whole body V_{O_2} . However, many studies demonstrated that oxygen supply dependency with dobutamine infusion was predictive of poor outcome in patients with sepsis^[2].

Compared to previous studies^[2], the present study had different results. Our results showed that the ability to increase oxygen consumption by the dobutamine infusion was associated with good outcome. It suggests that patients whose cells are functioning in a normal manner do well and patients whose cells are no longer able to function normally have a poor outcome.

In our study, the effect of dobutamine on hemodynamics was markedly different between responders and nonresponders. In responders, CI and D_{O_2} increased, which might be related to dobutamine's cardiac effect (β_1 effect). P_{vCO_2} and V_{O_2} increased, which were induced by dobutamine's thermogenic effect (β_1 effect), and SVRI decreased, which was associated with a peripheral vascular effect (β_2 effect). $O_2\text{ext}$ increased and S_{vO_2} decreased, which might be associated with increase in the tissue oxygen consumption by the whole body. The results suggest that cells or tissues can use more oxygen when oxygen supply is increased.

The nonresponders demonstrated increases in CI and P_{vCO_2} . But there was no effect on V_{O_2} , S_{O_2} , and SVRI. It suggests that effect of dobutamine decreased,

which may be associated with decreased activity of β receptor in nonresponders.

The study showed that the most sensitive and specific marker for poor outcome in these patients was the ability to increase oxygen consumption by < 15 % in dobutamine stress test. The result was different from the study of Vallet and colleagues^[3]. Vallet used inclusion criteria for sepsis and excluded any patient with shock. All of our patients fulfilled criteria of ACCP/SCCM for septic shock. It indicates that oxygen supply dependency as a predictor of outcome may be useful in patients with septic shock.

Our results also showed that the APACHE II scoring system was able to predict mortality for the group as a whole with reasonable accuracy. But the system was unable to give an accurate mortality prediction for the responders and nonresponders. The APACHE II scoring system, which was used to evaluate prognosis of patient at admission to ICU, fails to take into account the effects of time bias before admission to ICU^[10], but the dobutamine stress test might predict the outcome of patient at anytime, thus dobutamine stress test was better able to provide dynamic method to identify patient with poor prognosis.

The work demonstrates that the ability of patients with septic shock to increase both oxygen delivery to the tissue and whole body oxygen consumption in dobutamine stress test is strongly predictive of good outcome.

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多巴酚丁胺应激试验对感染性休克患者的预后评价

邱海波¹, 杨毅, 周韶霞, 刘少华, 郑瑞强
(东南大学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; 多巴酚丁胺; 预后; 氧消耗; 人类; 随机对照试验

目的: 观察多巴酚丁胺应激试验对感染性休克患者的预后价值. **方法:** 感染性休克患者静脉持续滴注多巴酚丁胺 $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ 1 h, 观察患者全身血流动力学和氧代谢的改变, 氧耗量 (V_{O_2}) 增加 15 % 以上者为试验阳性. **结果:** 47 例感染性休克患者中, 21 例应激试验阳性, 26 例阴性. 阳性组应用多巴酚丁胺后心指数 (CI) 增加 18.1 %, 氧输送增加 12.7 %, V_{O_2} 增加 38.6 %, 氧摄取率增加 18.0 %, 体血管阻力指数降低 18.5 %. 阴性组 CI 增加 11.5 %, 氧输送、 V_{O_2} 和氧摄取率均无明显改变. 阴性组患者病死率 76.9 %, 阳性组为 33.3 % ($P < 0.05$). **结论:** 多巴酚丁胺应激试验可作为感染性休克患者预后评估的动态指标.

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