Original Article

Effects of high-volume hemofiltration on alveolar-arterial oxygen exchange in patients with refractory septic shock

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BACKGROUND: High-volume hemofiltration (HVHF) is technically possible in severe acute pancreatitis (SAP) patients complicated with multiple organ dysfunction syndrome (MODS). Continuous HVHF is expected to become a beneficial adjunct therapy for SAP complicated with MODS. In this study, we aimed to explore the effects of fluid resuscitation and HVHF on alveolar-arterial oxygen exchange, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in patients with refractory septic shock.

METHODS: A total of 89 refractory septic shock patients, who were admitted to ICU, the Provincial Hospital affiliated to Shandong University from August 2006 to December 2009, were enrolled in this retrospective study. The patients were randomly divided into two groups: fluid resuscitation (group A, $n=41$), and fluid resuscitation plus high-volume hemofiltration (group B, $n=48$). The levels of O_2 content of central venous blood ($C_{cv}O_2$), arterial oxygen content (C_aO_2), alveolar-arterial oxygen pressure difference $P_{(A-a)}DO_2$, ratio of arterial oxygen pressure/alveolar oxygen pressure (P_aO_2/P_AO_2), respiratory index (RI) and oxygenation index (OI) were determined. The oxygen exchange levels of the two groups were examined based on the arterial blood gas analysis at different times (0, 24, 72 hours and 7 days of treatment) in the two groups. The APACHE II score was calculated before and after 7-day treatment in the two groups.

RESULTS: The levels of $C_{cv}O_2$, C_aO_2 on day 7 in group A were significantly lower than those in group B ($C_{cv}O_2$: 0.60 ± 0.24 vs. 0.72 ± 0.28 , $P<0.05$; C_aO_2 : 0.84 ± 0.43 vs. 0.94 ± 0.46 , $P<0.05$). The level of oxygen extraction rate (O_2ER) in group A on the 7th day was significantly higher than that in group B (28.7 ± 2.4 vs. 21.7 ± 3.4 , $P<0.01$). The levels of $P_{(A-a)}DO_2$ and RI in group B on the 7th day were significantly lower than those in group A. The levels of P_aO_2/P_AO_2 and OI in group B on 7th day were significantly higher than those in group A ($P<0.05$ or $P<0.01$). The APACHE II score in the two groups reduced gradually after 7-day treatment, and the APACHE II score on the 7th day in group B was significantly lower than that in group A (8.2 ± 3.8 vs. 17.2 ± 6.8 , $P<0.01$).

CONCLUSION: HVHF combined with fluid resuscitation can improve alveolar-arterial-oxygen exchange, decrease the APACHE II score in patients with refractory septic shock, and thus it increases the survival rate of patients.

KEY WORDS: Fluid resuscitation; High-volume hemofiltration; Septic shock; Oxygen extraction rate; Alveolar-arterial oxygen exchange; P_aO_2/P_AO_2 ratio; Respiratory index; Oxygenation index; Acute Physiology and Chronic Health Evaluation II (APACHE II)

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INTRODUCTION

During systemic inflammatory response syndrome (SIRS), severe sepsis, or septic shock, the redistribution of blood volume and pulmonary edema may increase arterial lactatemia and cytokines, which later lead to multiple organ dysfunction syndrome (MODS).^[1] Early goal-directed therapy (EGDT) and fluid resuscitation at the early stage can't prevent such development.^[2] Clinically, refractory shock and irreversible shock refer to types of shock that present particularly difficult problems. The term refractory shock is applied when, in spite of apparently adequate therapy, the shock state continues. The shock which could not be rectified and sustained deterioration was named as refractory septic shock. Wang et al^[3,4] reported that high-volume hemofiltration (HVHF) as a method of continuous blood purification (CBP) is technically possible in severe acute pancreatitis (SAP) patients complicated with MODS. Continuous HVHF is expected to become a beneficial adjunct therapy for SAP patients complicated with MODS.

This study was undertaken to explore the effects of fluid resuscitation and HVHF on alveolar-arterial oxygen exchange, Acute Physiology and Chronic Health Evaluation II (APACHE II) score in patients with refractory septic shock.

METHODS

Patients

A total of 89 patients with refractory septic shock, who had been admitted to ICU of the Provincial Hospital Affiliated to Shandong University from August 2006 and December 2009, were enrolled in this retrospective study. Gastric carcinoma was found in 8 of the 89 patients, colon cancer in 18, lung cancer in 10, esophageal carcinoma in 3, thymoma in 1, liver cancer in 6, cancer of the pancreas in 2, history of neurosurgery in 9, rib fracture in 12, splenic rupture in 1, acute pregnancy fat liver in 6, postpartum hemorrhage in 1, peripartur cardiomyopathy in 2, severe acute pancreatitis in 6, and severe pneumonia in 4.

The 89 patients were randomly divided into two groups: fluid resuscitation (group A, $n=41$), and fluid resuscitation plus high-volume hemofiltration (group B, $n=48$). In group A, there were 23 males and 18 females, with age ranging from 22 to 74 (55.7 ± 18.5) years, and APACHE II score was 28.3 ± 9.3 . In group B, there were 26 males and 22 females, with age ranging from 25 to 78 (57.2 ± 16.4) years, and APACHE II score was 27.5 ± 8.9 . There were no significant differences in age, gender, and

disease severity between the two groups.

In group A, patients were treated with fluid resuscitation, drugs for vessel activity enhancement, anti-bacterial medication, and mechanical ventilation. The patients with refractory septic shock received six hours of early goal-directed therapy (EGDT), and the goal of the treatment was set for the following: preload (central venous pressure 8-12 mmHg), afterload ($65 \text{ mmHg} < \text{mean arterial pressure} < 90 \text{ mmHg}$), cardiac contractility (mixed venous oxygen saturation $> 70\%$), and urinary volume $> 0.5 \text{ mL/kg}$ per hour.^[5]

In group B, except for fluid resuscitation, the patients continued to receive high-volume hemofiltration (HV-CVVH) for at least 72 hours. Indwelling catheters (Prismaflex corporation, Switzerland) in the femoral vein were adopted for vascular access in these patients. The HVHF model was made with pre-displacement 70%-80% and filter replacement per 24 hours. Heparin was used for anti-coagulation at an initial dose of 15-25 U/kg. The displacement fluid velocity was 2000-3000 mL/h ($50\text{--}70 \text{ mL/kg}$ per hour), displacement volume was more than 60 L/d, and blood flow velocity was 150-200 mL/min.

Parameters of hemodynamics

The central venous oxygen content ($C_{cv}O_2$) and arterial oxygen content (C_aO_2) were detected through subclavian vein puncture and arteriopuncture, respectively. The oxygen extraction rate (O_2ER) was calculated with the following equation: $O_2ER = (C_aO_2 - C_{cv}O_2) / C_aO_2 \times 100\%$.

Indexes of oxygen exchange

The 0.5 mL blood was collected from the radial artery, and was anticoagulated with heparin. GEM Premier 3000 (GEM Premier Company, Germany) was used for the arterial blood gas analysis. The indexes of oxygen exchange included: 1) alveolar-arterial oxygen pressure difference: $P_{(A-a)}DO_2 = (P_a - P_{H_2O}) \times F_iO_2\% - P_aCO_2 - P_aO_2 = (760 - 47) \times F_iO_2\% - P_aCO_2 - P_aO_2 = 713 \times F_iO_2\% - P_aCO_2 - P_aO_2$; 2) $P_aO_2/P_{A-a}O_2$ ratio; 3) respiratory index (RI): $RI = P_{(A-a)}DO_2 / P_aO_2$; and 4) oxygenation index (OI): $OI = P_aO_2 / F_iO_2$. P_a : atmospheric pressure, 760 mmHg (standard state); P_{H_2O} : vapor pressure, 47 mmHg (standard state); $F_iO_2\%$: frequency in respiration oxygen; P_aO_2 : arterial oxygen pressure; $P_{A-a}O_2$: alveolar oxygen pressure; P_aCO_2 : pressure of carbon dioxide.

Outcome measures

In-hospital mortality (primary efficacy outcome),

Table 1. Values of C_{vO_2} , C_aO_2 , O_2ER (mena $\pm$ SD)

Groups	C_{vO_2}				C_aO_2				O_2ER			
	0 h	24 h	72 h	7 d	0 h	24 h	72 h	7 d	0 h	24 h	72 h	7 d
A (n=41)	0.47 $\pm$ 0.16	0.55 $\pm$ 0.24	0.59 $\pm$ 0.35	0.60 $\pm$ 0.24	0.72 $\pm$ 0.24	0.78 $\pm$ 0.28	0.82 $\pm$ 0.27	0.84 $\pm$ 0.43	32.5 $\pm$ 5.8	27.6 $\pm$ 3.7	28.6 $\pm$ 2.2	28.7 $\pm$ 2.4
B (n=48)	0.46 $\pm$ 0.18	0.61 $\pm$ 0.28	0.66 $\pm$ 0.37	0.72 $\pm$ 0.28*	0.77 $\pm$ 0.29	0.82 $\pm$ 0.27	0.92 $\pm$ 0.33	0.94 $\pm$ 0.46*	34.5 $\pm$ 6.0	26.6 $\pm$ 3.7	25.6 $\pm$ 2.7	21.7 $\pm$ 3.4**

Compared with group A, * P <0.05, ** P <0.01.

Table 2. Values of $P_{(A-a)}DO_2$, P_aO_2/P_AO_2 , respiratory index (RI) and oxygenation index (OI) (mena $\pm$ SD)

Groups	$P_{(A-a)}DO_2$				P_aO_2/P_AO_2				RI				OI			
	0 h	24 h	72 h	7 d	0 h	24 h	72 h	7 d	0 h	24 h	72 h	7 d	0 h	24 h	72 h	7 d
A (n=41)	311.81 $\pm$ 50.73	285.63 $\pm$ 48.32	280.83 $\pm$ 38.45	256.72 $\pm$ 25.73	0.62 $\pm$ 0.28	0.68 $\pm$ 0.25	0.69 $\pm$ 0.32	0.71 $\pm$ 0.37	6.37 $\pm$ 2.41	5.95 $\pm$ 2.10	5.87 $\pm$ 2.43	5.72 $\pm$ 1.95	128 $\pm$ 16	154 $\pm$ 21	179 $\pm$ 32	208 $\pm$ 36
B (n=48)	305.55 $\pm$ 51.32	278.6 $\pm$ 50.37	265.82 $\pm$ 30.41*	156.77 $\pm$ 22.73**	0.63 $\pm$ 0.21	0.79 $\pm$ 0.27	0.82 $\pm$ 0.36	0.91 $\pm$ 0.47*	6.87 $\pm$ 2.11	5.65 $\pm$ 2.17	5.17 $\pm$ 2.03	4.52 $\pm$ 1.55*	118 $\pm$ 15	164 $\pm$ 28	195 $\pm$ 38*	268 $\pm$ 42

Compared with group A, * P <0.05, ** P <0.01.

Table 3. APACHE II scores after HVHF between the two groups (mean $\pm$ SD)

Groups	n	APACHE II score	
		0 d	7 d
A	30	28.3 $\pm$ 9.3	17.2 $\pm$ 6.8
B	43	27.5 $\pm$ 8.9	8.2 $\pm$ 3.8*

Compared with group A, * P <0.01

end points with respect to hemodynamic parameters, oxygen exchange parameters, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were obtained serially for 7 days and compared between the study groups.^[6]

Statistical analysis

Data were expressed as mean $\pm$ standard deviation and the analysis of variance was performed with SPSS 12.0 software. The average value of the two groups was determined with Student's t test and the chi-square t test. A P value less than 0.05 or 0.01 was considered statistically significant.

RESULTS

Hemodynamics and oxygen exchange

The values of C_{vO_2} , C_aO_2 , O_2ER were compared between the two groups (Table 1). The values of $P_{(A-a)}DO_2$, P_aO_2/P_AO_2 , respiratory index (RI) and oxygenation index (OI) between the two groups are listed in Table 2.

APACHE II scores after HVHF

In group A, 11 patients died, with a mortality of 26.8% and in group B, 5 patients died, with a mortality of 10.4%. There was a significant difference in mortality between the two groups (P <0.05). The APACHE II score in group B was lower than that in group A (Table 3).

DISCUSSION

Infective or noninfective injury stimulates the immune system to produce inflammatory cytokines, such as TNF- α , IL-1, IL-6, IL-10, prostaglandin, leukotriene, platelet activating factor, and nitric oxide, which may cause the damage of vascular endothelial cell function in the lung, increase the capillary permeability, and finally result in pulmonary edema and oxygenation dysfunction. Sepsis is a potentially deadly medical condition that is characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and the presence of a known or suspected infection.^[7,8] The body may develop this inflammatory response by the immune system to microbes in blood, urine, lungs, skin, or other tissues, and then MODS may develop. Severe sepsis is accompanied by single or multiple organ dysfunction or failure, eventually leading to death.^[9] Although our understanding of the complex pathophysiological alterations that occur in severe sepsis and septic shock has increased greatly as a result of recent clinical and preclinical studies, mortality associated with the disorder remains unacceptably high, ranging from 30% to 50%.^[10-13]

The rapid diagnosis and effective management of sepsis is critical to successful treatment.^[14] The Surviving Sepsis Campaign, an initiative of the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine, was developed to improve the management, diagnosis, and treatment of sepsis. The agreement among the three societies and funding for the campaign came to a conclusion on December 31, 2008.^[15]

HVHF refers to displacement liquid velocity>45 mL/kg per hour or ultrafiltration volume>60 L/d.^[16] Compared with CVVHF, HVHF can clear not only solutes with small molecular weight (water, serum creatinine, urea

nitrogen, and electrolysis), but also solutes with large molecular weight (inflammatory factors, and toxic substance), which may interrupt waterfall-like chain reaction of inflammatory factors, and alleviate organ injury. HVHF can increase P_aO_2 and oxygenation index, decrease P_aCO_2 , improve heart and lung function, remove toxin, and ameliorate blood electrolyte disturbances and acid-base imbalance. HVHF therapy was safe and effective for MODS.^[17,18]

ARDS often occurs after major operation, especially thoracic operation or abdominal operation. The manifestations of ARDS mainly present as respiratory distress and hypoxemia, and the mechanism may be connected with the increased capillary permeability and pulmonary edema after SIRS induced by trauma. Though $C_{v}O_2$, C_aO_2 , and P_aO_2 can be easily detected, they are easy to be affected by F_iO_2 . The respiratory index (RI) and oxygenation index (OI) are parameters of mechanical ventilation, and OI can truly reflect the degree of lung injury. Because P_aO_2 doesn't change obviously during the early stage of ARDS, OI can't timely reflect the lung injury during ARDS. $P_{(A-a)}DO_2$ can reflect pulmonary shunt, ventilation/perfusion ratio imbalance, but it is affected by F_iO_2 . RI is the ratio of $P_{A-a}O_2$ and P_aO_2 , and without the effect of F_iO_2 , it can reflect pulmonary gas exchange and oxygenation changes earlier than $P_{(A-a)}DO_2$. $P_{(A-a)}DO_2$, $P_aO_2/P_{A-a}O_2$, RI and OI should be considered for the assessing lung oxygenation during early phase. In this study, we found $P_{(A-a)}DO_2$, $P_aO_2/P_{A-a}O_2$, RI and OI were improved after HVHF. This indicated that the combination of fluid resuscitation and HVHF could effectively improve pulmonary edema and pulmonary oxygenation.

HVHF has beneficial effects on severe sepsis, improving hemodynamics and unselectively removing proinflammatory and anti-inflammatory mediators.^[19-23] Animal experiments showed that early HVHF can remove excess inflammatory mediators in the circulation, stabilize neutrophils, improve immune function, and prevent MODS. In this study, the mortality was significantly higher in group A than in group B (26.8% vs. 10.4%, $P < 0.05$) at the 7th day between the two groups, and the APACHE II score at the 7th day was also significantly higher in group A than in group B (17.2 ± 6.8 vs. 8.2 ± 3.8 , $P < 0.01$).

In summary, compared with fluid resuscitation, HVHF combined with fluid resuscitation can improve alveolar-arterial-oxygen exchange, decrease the APACHE II score in patients with refractory septic shock, and thus increase the survival rate of these

patients.

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Contributors: Ren HS proposed the study and wrote the first draft. All authors contributed to design and interpretation of the study and to further drafts. Wang CT is the guarantor.

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