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The influence of high volume hemofiltration on extra vascular lung water and alveolar-arterial oxygen pressure difference in patients with severe sepsis

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Abstract. – OBJECTIVE: To explore the effects of high-volume hemofiltration (HVHF) on the plasma interleukin-6 (IL-6), pro-calcitonin (PCT), extra vascular lung water index (EVLWI) and alveolar-arterial oxygen exchange in patients with septic shock.

PATIENTS AND METHODS: 97 cases intensive patients with septic shock were enrolled from Department of Intensive Care Unit (ICU) of the Provincial Hospital affiliated to Shandong University between January 2011 and December 2014. According to the puting into practice of high-volume hemofiltration (HVHF) or not, all the patients were divided in two groups (NHVHF group, group A, n = 46 cases) and (HVHF group, group B, n = 51 cases). The plasma IL-6, PCT, intrathoracic blood volume index (ITBVI), extravascular lung water index (EVLWI) and pulmonary vascular permeability index(PVPI) was detected before treatment and after treatment 24h, 72h. The Alveolar- arterial oxygen pressure difference $P_{(A-a)}DO2$ was checked by arterial blood gas analysis (ABGA) at first and after treatment 24 hour, 72 hour, 7 day in two groups. The mortality at 28 day was compared between two groups.

RESULTS: After 72h treatment, the plasma IL-6, PCT in group B has a significant decrease. After 72h treatment, the level ITBVI, EVLWI and PVPI in group B had a significant improvement. The levels of $P_{(A-a)}DO2$ in HVHF group were reduced more significantly than N-HVHF group after 7 day. The EVLWI and $P_{(A-a)}DO2$ had a significant positive correlation (correlation ratio = 0.712, 95% confident interval [0.617, 0.773], $p = 0.001$). The mortality at 28 day had a significant decrease between groups (15.22% vs. 34.15%, $\chi^2 = 4.242$, $p = 0.038$).

CONCLUSIONS: HVHF could decrease plasma inflammatory factors and EVLWI so that it could improve the levels of alveolar-arterial-oxygen exchange in patients with septic shock, so it could improve the survival rate of patients.

Key Words:
High-volume hemofiltration (HVHF), Pulse indicator contour cardiac output (PICCO), Severe sepsis, Inflammatory factor, Extra vascular lung water index (EVLWI), Alveolar-arterial oxygen pressure difference.

Abbreviations

HVHF: high-volume hemofiltration; IL-6: interleukin-6; PCT: pro-calcitonin; EVLWI: extra vascular lung water index; ICU: Intensive Care Unit; ITBVI: intrathoracic blood volume index; PVPI: pulmonary vascular permeability index; $P_{(A-a)}DO2$: Alveolar- arterial oxygen pressure difference; ABGA: Arterial blood gas analysis; SIRS: Systemic inflammatory response syndrome; TNF-α: tumor necrosis factor-α; HMGB-1: high mobility group box-1; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; MODS: multiple organ dysfunction syndrome; CLS: capillary leak syndrome; CVC: central venous catheter; PiCCO: pulse indicator contour cardiac output; ELISA: enzyme-linked immunoassay; APTT: Activated partial thromboplastin time; CBP: Continuous blood purification; RRT: Renal replacement therapy; CRRT: continuous renal replacement therapy.

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Introduction

Systemic inflammatory response syndrome (SIRS) is a pro-inflammatory condition in the organism caused by infectious factors[1]. It is characterized by the rapid production and release of many pro-inflammatory mediators, represented by some early-phase inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), pro-calcitonin (PCT) and some late-phase inflammatory cytokines such as high mobility group box-1 (HMGB-1), etc[2-5]. These inflammatory mediators interact with each other leading to a chain reaction, namely "waterfall effect" causing an uncontrolled inflammatory reaction. Sepsis is a systemic inflammatory response syndrome induced by infection and also called severe sepsis if accompanied by organ dysfunction[6]. It is a severely acute disease and very common in the clinic and sometimes can evoke septic shock, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI). If severe sepsis and septic shock cannot be effectively controlled, the condition of the patient would promptly develop into multiple organ dysfunction syndrome (MODS) and finally resulting in death[7]. The morbidity of sepsis is quite high and increases with the speed of 2%-8% per year[8]. Besides, the mortality of septic shock is up to 20%-50%, threatening the life and prognosis of the septic patients. Therefore, how to treat severe sepsis early and efficiently has so far become an extremely difficult problem[9].

Inflammatory mediators could damage the lung capillary endothelium, leading to the increase of pulmonary vascular permeability index (PVPI), which is named capillary leak syndrome (CLS)[10]. A large amount of the serum protein and water permeates into the tissue space and increases the extra vascular lung water index (EVLWI) and finally causes pulmonary edema[11]. Lung oxygenation and alveolar-arterial oxygen pressure difference ($P_{(A-a)}DO_{2)}$ are reduced in this syndrome[12]. On the other hand, hypovolemia and hypoproteinemia can occur, resulting in decreased circulating blood volume, tissue perfusion disorder, and multiple organ dysfunction.

Extra vascular lung water is the fluid in extra vascular lung tissue, including intracellular, interstitial, and alveolar fluid. Excess interstitial fluid and alveolar fluid could cause lung edema. The normal content of extra vascular lung water in an adult is 3-7 ml/kg[13]. The cause of increased lung water can be pathophysiologically divided into high hydrostatic pulmonary edema, high capillary permeable pulmonary edema, and mixed pulmonary edema[14]. High hydrostatic pulmonary edema is also called cardiogenic pulmonary edema, which is results from increased resistance of pulmonary circulation from cardiac function decline. The amount of lung water is determined by the hydrostatic pressure difference between pulmonary capillary and interstitial tissue of the lung. High capillary permeable pulmonary edema includes pulmonary endogenous factors such as pulmonary infection, and pulmonary exogenous factors such as allergy, drugs and toxins.

Patients with severe sepsis commonly have hypovolemia[15]. Extensive vasodilation and increased capillary permeability caused by systemic uncontrolled inflammation could lead to severe abnormal volume distribution; which reduces effective circulating blood volume, ventricular preload, diastole pressure and cardiac output, resulting in the decreased oxygen delivery unable to meet the metabolic need.

For those patients with severe sepsis, especially accompanied with ALI and AKI, finding an approach to reduce extra vascular lung water with intensive volume resuscitation and prevent pulmonary oxygenation disorder is the focus of this study.

The mortality rate of patients with severe sepsis and septic shock is up to 20-40%, in which the main cause of death is multiple organ dysfunction syndrome (MODS) induced by the systemic inflammatory response[16,17]. High volume hemofiltration (HVHF) could partly remove inflammatory mediators and cytokines in plasma. However, whether HVHF could reduce the mortality rate of patients with severe sepsis and septic shock is still controversial. The purpose of this study is to explore the effects of HVHF on the plasma inflammatory mediators, extra vascular lung water index (EVLWI), alveolar-arterial oxygen exchange and prognosis in patients with severe sepsis.

Patients and Methods

Patients

Data were obtained from patients with septic shock in intensive care unit (ICU) of the Shandong Provincial Hospital in China from January 2011 to December 2014. The inclusion criteria: patients are aged ≥ 18 with severe sepsis[16]. The exclusion criteria: patients with advanced stage

of malignant tumor, terminal stage, pregnancy. Patients who have abandoned treatment or were not able to complete 28 days follow-up were also excluded. This study was approved by the Ethics Committee of the Shandong Provincial Hospital (registration number 2010-008). The purposes and procedures of the study were explained to the participants or their relatives and written informed consents were obtained.

Methods

Measurements of Inflammatory Cytokines

Blood samples were obtained from all subjects when were newly diagnosed as septic shock, 24h and 48h after treatments. Blood routine examination, live and renal function test were performed. 1.8 ml of blood sample were withdrawn by venipuncture and after centrifugation at 4°C for 15 minutes, plasma were stored at −80°C. Interleukin-6 (IL-6) was tested by commercial enzyme-linked immunoassay (ELISA) kit (Shenzhen Company, China). Pro-calcitonin (PCT) was determined by luminescence immunoassay kit (Brahms Inc, Hennigsdorf, Germany).

Placements of Central Venous Catheter (CVC) and Pulse Indicator Contour Cardiac Output (PiCCO) Catheter

CVC was inserted from a right internal jugular vein or right subclavian vein (Arrow Electronics, Inc., Centennial, CO, USA) and connected with PiCCO temperature probe. We inserted PiCCO catheter from femoral artery and connected it with a PiCCO monitor[18]. Intrathoracic blood volume index (ITBVI), extra vascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI) were measured. When EVLWI and PVPI were tested, 15 ml of ice-cold saline was rapidly injected within 5 seconds from PiCCO temperature probe. The measurements were repeated three times and the average was considered as the monitoring data for each test.

Oxygen Exchange Index Monitoring

A quantity of 0.5 ml of blood samples were obtained from radial artery and arterial blood gas analysis (GEM Premier 3000, Hamburg, Germany) were performed after anti-coagulation by heparin. Alveolar-arterial oxygen tension difference:

$$[P_{(A\text{-}a)}DO2] = [(Pa\text{-}PH_2O) \times FiO_2\%\text{-}PaCO_2\text{-}PaO_2] = [(760\text{-}47) \times FiO_2\%\text{-}PaCO_2\text{-}PaO_2] = [713 \times FiO_2\%\text{-}PaCO_2\text{-}PaO_2]$$

P_a: atmospheric pressure, the standard state is 760 mmHg; PH_2O: saturated water vapor pressure, the standard state is 47 mmHg; $F_iO_2\%$: Fraction of inspiration O_2; P_aO_2: arterial partial pressure of oxygen; P_AO_2: alveolar oxygen partial pressure; P_aCO_2: partial pressure of carbon dioxide in arterial blood.

Depending on Treatment with HVHF, all Subjects Recruited in our Study were Divided Into a non-HVHF Group (Group A) and HVHF Group (Group B)

In accordance with International Guidelines for Management of Severe Sepsis and Septic Shock in 2008, 2012[19,20], volume resuscitation was introduced to all subjects under monitoring of PiCCO. Patients in group B received HVFV treatment at least 72 hours. The HVHF was performed via vascular access established by indwelling formal vein catheter. The blood flow was 180-240 ml/min, and ultrafiltration rate was 35-50 ml/kg/h during HVHF. The substitute fluid was infused with pre-dilution. Heparin was used for anti-coagulation, whose initial dose was 15-25 U/kg, and maintenance dose was 5-15 U/kg/h. Activated partial thromboplastin time (APTT) in post-filter peripheral blood was checked every 4 hours, keeping it in a range of 70-100 seconds. The survival status of all of the subjects were followed up at 28 days after being diagnosed as severe sepsis.

Statistical Analysis

All values were expressed as mean±SD. We compared parameters between the two groups with a *t*-test. Incident rates were defined by χ^2-test and relativities were determined by Person correlation analysis. Statistical analyses were performed using SPSS software (18.0 for Windows, SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

Results

1. Patients characteristics. Ninety-seven subjects with severe sepsis were randomly divided into two groups. Group A consisted of 46 patients, 26 men and 20 women with the age ranging 22-77 years old (mean 53.6 ± 16.9). Group B consisted of 51 patients, 28 men, and

23 women age 24-78 years old (mean 55.8 ± 17.6). No significant differences were found in age, gender and disease severity (APACHE II and SOFA score).

2. **Changes of inflammatory cytokine levels before and after HVHF treatment**. The levels of IL-6 and PCT in plasma before HVFV treatment showed no significant differences between two groups. However, both at 24 and 72 hours after HVFV treatment, IL-6, and PCT levels were markedly reduced in group B compared with group A (Table I).
3. **Comparison of hemodynamic parameters between groups.** After 24 and 72 hours of HVHF treatment, ITBVI, EVLWI and PVPI in group B were decreased than that in group A. On the other hand, the hemodynamic parameters above showed no such change before HVHF treatment (Table II).
4. **As shown in Table III, HVFV treatment also reduced [$P_{(A-a)}DO_2$] in group B ($p < 0.05$-0.01).**
5. **Correlation analysis showed that [$P_{(A-a)}DO_2$] was positively correlated with EVLWI (R = 0.712, $p = 0.001$), and 95% confidence interval is [0.629, 0.782].**

This result indicates that alveolar-arterial oxygen exchange ability was improved more obviously as extra vascular lung water was reduced.

Comparison of Survival Rate

17 patients were dead in group A and eight patients were dead in group B after 28 days of HVHF treatment. The mortality rate was significantly different between the two groups (36.96% *vs.* 15.69%, $\chi^2 = 4.452$, $p = 0.032$).

Discussion

The IL-6 levels were markedly increased in the plasma of the patients with sepsis, and the elevation degree was closely associated with the septic severity and prognosis. Continuous elevated IL-6 levels could enhance the occurrence and mortality of multiple organ dysfunction syndromes (MODS)[21]. Besides, it was demonstrated that PCT concentration was extremely low in healthy people (0.033 ug/L) and was not increased or only slightly increased in local infection or non-specific infection, such as virus and fungus[22]. However, the levels of PCT were rapidly increased within 2-4 hours in patients with severe systemic bacterial infection[23]. The PCT concentrations were reduced to 50% in averages 2-4 days in patients recovering from sepsis but in patients who had died of sepsis, the continuous PCT elevation time was up to 27 days[24]. This study indicated that continuous PCT increase in serum suggested the presence of sepsis. The serum PCT, as an effective biomarker in monitoring infection, exhibited a high specificity and sensitivity, which played an important role in the early diagnosis of sepsis[25,26]. Our research demonstrated that the IL-6 and PCT levels were significantly decreased in group B compared with group A 72 hours after HVHF, indicating HVHF could remove inflammatory cytokines in serum.

It was shown that real-time monitoring the changes of extravascular lung water and lung vascular permeability by pulse induced contour cardiac output ($PICCO_2$) could predict the fluid response of patients with sepsis shock, which was disturbed by spontaneous breath[27]. Liquid treatment could be adjusted according to the dynamic quantitative change of extra vascular lung water and lung vascular permeability via PICCO, which provides new methods of liquid therapy for patients with septic shock. $PICCO_2$ capacity indicators such as ITBVI and EVLWI could accurately monitor the change of cardiac preload and provide a reliable basis for clinical diagnosis, treatment, and research.

Table I. Comparison of inflammatory cytokines in plasma level between groups ($\bar{x}$ ± S).

Group	Case N	IL-6 (μg/L)			PCT (μg/L)		
		0h	24h	72h	0h	24h	72h
A	46	80.2 ± 29.6	71.2 ± 26.5	62.7 ± 18.6	32.5 ± 10.2	16.9 ± 7.4	15.1 ± 7.2
B	51	86.4 ± 31.8	64.6 ± 21.6	32.4 ± 15.1**	34.6 ± 11.4	14.9 ± 8.8	7.1 ± 3.2**
		$t = 0.209$	$t = 1.473$	$t = 6.952$	$t = 0.314$	$t = 1.644$	$t = 6.942$
		$p = 0.778$	$p = 0.149$	$p = 0.001$	$p = 0.729$	$p = 0.109$	$p = 0.001$

Compare group A, *$p < 0.05$, *$p < 0.01$.

Table II. Comparison of hemodynamic parameters level between groups ($\bar{x} \pm S$).

Group	Case N	ITBVI (ml/m²)			EVLWI (ml/kg)			PVPI		
		0h	24h	72h	0h	24h	72h	0h	24h	72h
A	46	967.3 ± 314.6	1246.8 ± 324.1	970.2 ± 312.4	21.4 ± 6.7	14.9 ± 6.4	12.6 ± 3.9	7.6 ± 2.5	5.1 ± 2.8	4.3 ± 2.1
B	51	971.5 ± 304.8	1169.9 ± 312.8	625.6 ± 134.1**	22.6 ± 7.3	11.7 ± 4.8	7.4 ± 2.3**	7.4 ± 3.3	4.6 ± 2.9	2.1 ± 1.1**
		$t = 0.159$	$t = 1.614$	$t = 6.223$	$t = 1.233$	$t = 1.782$	$t = 6.453$	$t = 0.313$	$t = 1.194$	$t = 5.713$
		$p = 0.746$	$p = 0.113$	$p = 0.001$	$p = 0.265$	$p = 0.085$	$p = 0.001$	$p = 0.674$	$p = 0.264$	$p = 0.001$

Compare group A, *$p < 0.05$, *$p < 0.01$.

The EVLWI is related to the fluid volume and can be used to predict the occurrence of pulmonary edema. It is also significantly correlated with the survival rate. It was shown that EVLWI and PVPI of patients with septic shock were obviously increased at three days after they were admitted to the hospital. Therefore, EVLWI might be an indicator of the severity and prognosis of acute lung injury induced by sepsis[28]. The evidence demonstrated that if patients with septic shock showed a negative balance in the intake and output and clearly decreased the EVLWI, their prognosis would be better[29].

A lot of inflammatory cytokines is released in MODS, leading to increased permeability in pulmonary capillary. Therefore, we need keep monitoring whether cardiac preload is over-high or pulmonary edema occurs[30,31]. In severe infection and during septic shock treatment, improvement of effective tissue perfusion in organs is critical, but capillary leakage often occurs in this period, thus, it is difficult to avoid completely the occurrence of pulmonary edema[32]. Severe pulmonary edema could lead to acute respiratory failure, and acute left ventricular failure, which would induce MODS. EVLWI could reflect the presence and severity of pulmonary edema, and the predictive valve of maximum EVLWI is better than initial EVLWI[33]. Besides, ITBVI is a sensitive index in evaluating cardiac preload, which could reflect volume load accurately[34]. Our findings showed that, ITBVI, EVLWI and PVPI in group B were decreased compared to that in group A after 72 hours of HVHF treatment. These results indicated that HVHF could prevent extra vascular lung water production via modulating blood volume and could reduce the occurrence of pulmonary edema by decreasing inflammatory cytokines and permeability in pulmonary capillary.

As the volume overloads, the body shows a series of changes that affect oxygen diffusion and causes tissue hypoxia, leading to aggravated condition and increased mortality. Continuous high EVLW often suggests that the treatment is ineffective and prognosis is bad[35]. Keeping the negative fluid balance and reducing the EVLWI can improve the edema in interstitial tissue of the lung. Therefore, diffusion distance of the alveolar oxygen from the alveoli to the pulmonary capillary is decreased, and oxygen pressure and oxygenation are improved. On the other hand, recovery of the alveolar elasticity and increased alveolar ventilation could also improve oxygenation. Decreased $P_{(A\text{-}a)}DO_2$ indicates improved pulmonary ventilation[36].

Table III. Comparison of alveolar- arterial oxygen pressure difference $P_{(A-a)}DO2$ between two groups ($\bar{x} \pm S$).

Group	Case N	$P_{(A-a)}DO2$ (mmHg)			
		0	24h	72h	7d
A	43	326.7 ± 49.3	290.5 ± 45.7	273.1 ± 36.2	225.2 ± 29.5
B	48	319.4 ± 51.4	273.4 ± 47.2	251.5 ± 28.4*	171.3 ± 21.5**
		$t = 0.535$	$t = 1.913$	$t = 2.322$	$t = 6.554$
		$p = 0.583$	$p = 0.064$	$p = 0.028$	$p = 0.001$

Compare group A, *$p < 0.05$, *$p < 0.01$.

Permeability in pulmonary capillary is increased in patients with severe sepsis, shock, trauma, burn, severe acute pancreatitis and after chest and abdominal surgery, often leading to enhanced extra vascular lung water and reduced lung oxygenation[37]. The common complication is acute respiratory distress syndrome (ARDS). $P_{(A-a)}DO_2$ is usually used as an index in evaluating the early lung oxygenation. In this research, we found $P_{(A-a)}DO_2$ were improved in group B after HVHF treatment, indicating that HVHF treatment could ameliorate pulmonary edema and improve lung oxygenation. Linear correlation analysis showed that $P_{(A-a)}DO_2$ was positively correlated with EVLWI (R = 0.712). After 72 hours of HVHF treatment, EVLWI and $P_{(A-a)}DO_2$ were significantly decreased in group B, indicating that HVHF treatment could ameliorate pulmonary edema and improve alveolar-arterial oxygen exchange ability.

With the development of continuous blood purification, (CBP), its function has far exceeded renal replacement therapy, (RRT), especially in inflammatory mediator removal, immune function improvement, internal environment regulation and hemodynamic stability[38]. High volume hemofiltration (HVHF) is a blood purification technique developed on the basis of continuous renal replacement therapy (CRRT)[39]. The principle of HVHF to treat septic shock is enhancing the clearance of large and medium molecules via increasing substitution fluid volume or ultrafiltration rate. As an efficient blood purification method, HVHF could preferably remove inflammatory mediators, improve hemodynamically and enhance the survival rate of patients with severe sepsis and septic shock compared with traditional continuous renal replacement therapy.

HVHF treatment could remove inflammatory cytokines, regulate fluid and acid-base balance, improve hemodynamics, reconstruct immune balance and treat patients with MODS tendency effectively[40,41]. Seventeen patients in group A and eight patients in group B were dead at 28 days after HVHF treatment. The mortality rate was significant lower in group B (36.96% *vs.* 15.69%, $\chi^2 = 4.452$, $p = 0.032$). This study exhibited that HVHF could enhance the survival rate of the patients.

Conclusions

The HVHF could decrease plasma inflammatory factors and EVLWI so that it could improve the levels of alveolar- arterial oxygen exchange in patients with severe sepsis so that it could improve the survival rate of patients.

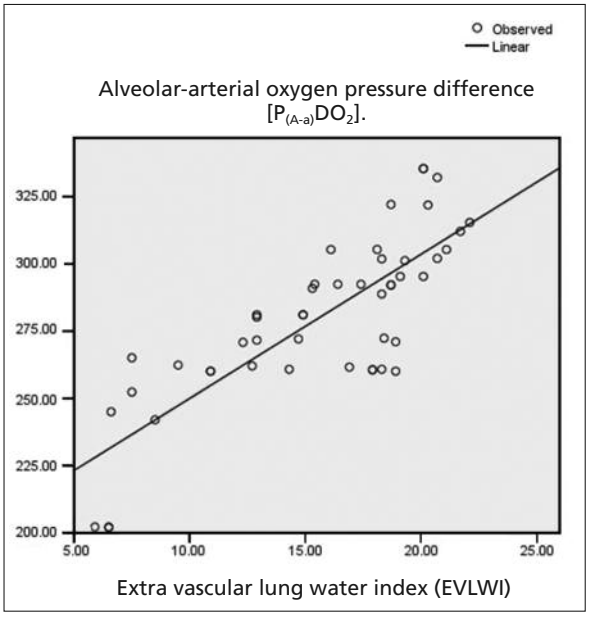

Figure 1. The liner correlation of extra vascular lung water index (EVLWI) and Alveolar-arterial oxygen pressure difference $[P_{(A-a)}DO_2]$.

A limitation of this study is that the case number was still small large. Thus, we will perform a prospective study about the precise effect of HVHF on extra vascular lung and alveolar-arterial oxygen exchange in further study.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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