

High-volume hemofiltration combined with early goal-directed therapy improves alveolar-arterial oxygen exchange in patients with refractory septic shock

H.-S. REN¹, M. LI², Y.-J. ZHANG³, L. WANG⁴, J.-J. JIANG¹, M. DING¹, C.-T. WANG¹

¹Department of Intensive Care Unit, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, P. R. China

²Department of Rheumatology and Clinical Immunology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, P. R. China

³Department of Gastroenterology in Health Care Building, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, P. R. China

⁴Department of Bone Surgery, Jinan Sixth People's Hospital, Jinan, P. R. China

Hongsheng Ren and Ming Li contributed equally to this work

Abstract. – OBJECTIVE: This study is to evaluate the effect of high-volume hemofiltration (HVHF) and early goal-directed therapy (EGDT) on alveolar-arterial oxygen exchange in patients with refractory septic shock.

PATIENTS AND METHODS: Patients were classified into two groups by a prospective cohort study: 86 received both HVHF and EGDT (the HVHF group), and 81 treated with EGDT only (the control group). Alveolar-arterial oxygen pressure was taken at baseline and at days 1, 3, and 7, and respiratory index (RI, ratio of P_{aO_2} alveolar-arterial oxygen pressure difference ($P_{A-a}DO_2$) to arterial oxygen pressure (P_{aO_2}) was calculated.

RESULTS: At day 7, the levels of central venous and arterial blood oxygen content were significantly higher in the HVHF vs. the control group (both with $p < 0.05$). The level of oxygen extraction ratio (O₂ER) was significantly higher in the HVHF than the control group ($p < 0.01$). The levels of $P_{A-a}DO_2$ and RI were significantly lower in the HVHF than the control group ($p < 0.05$ and $p < 0.01$, respectively). RI and the ratio of P_{aO_2} to the fraction of inspired oxygen were significantly higher in the HVHF than the control group ($p < 0.05$ and $p < 0.01$, respectively). The acute physiology and chronic health evaluation score and the sequential organ failure assessment score in the HVHF group were significantly lower compared to the control group ($p < 0.01$ and $p < 0.05$, respectively). At day 28, the mortality rate was lower in the HVHF vs. the control group ($p < 0.01$).

CONCLUSIONS: These findings demonstrated that HVHF, when used as an adjunctive therapy to the EGDP protocol, could improve alveo-

lar-arterial oxygen exchange, clinical outcome and survival in patients with refractory septic shock.

Key Words:

Sepsis, Oxygen extraction rate, Oxygen debt, Fluid resuscitation, Acute physiology, Chronic health evaluation.

Introduction

Sepsis can be defined as a systemic inflammatory response syndrome, which is secondary to an infection, either documented by microbiology cultures or other clinical evidence of infection. Septic shock, as defined by Bone¹ in earlier literature, is sepsis syndrome with hypotension that is responsive to fluid loading or pharmacotherapy. Bone¹ and Bone et al² also defined refractory septic shock as sepsis syndrome with hypotension that is not responsive to fluid loading or pharmacotherapy for a period longer than 1 h. Refractory septic shock patients are seriously ill and need rapid emergency admission to the hospital intensive care unit (ICU). Despite active treatment in the ICU, the reported death rate is over 50%³. Thus, there is an urgent need to examine its pathogenesis and explore effective therapies of refractory septic shock so as to reduce the mortality rate.

Refractory septic shock is characterized by inadequate tissue perfusion with an imbalance be-

tween tissue oxygen delivery (DO_2) and oxygen consumption (VO_2), and cumulative build-up of tissue hypoxia or oxygen debt. Sepsis causes severe plasma volume depletion, which acutely requires compensation by fluid resuscitation⁴. A hyperdynamic state is generally seen in septic shock patients and animal models with fluid resuscitation⁵⁻⁷. This state is characterized by elevated cardiac output, increased DO_2 , decreased systemic vascular resistance with or without decreases in mean arterial blood pressure (MAP), and increased tissue VO_2 . Impaired oxygen extraction capacity and lactic acidosis are also associated syndromes indicating microvascular injury and impaired microvascular control. Maldistribution of microvascular blood flow induces a tissue oxygen debt, and inefficient matching of microvascular oxygen supply to oxygen demand may in turn impair oxygen extraction. This is manifested by a pathologic oxygen supply dependency, whereby VO_2 is dependent on DO_2 , and a defected critical oxygen extraction ratio (O_2ER)⁸⁻¹¹.

Hence, one of the primary goals in refractory septic shock management is to ensure adequate oxygenation and oxygen delivery¹², which was firstly recommended by the jury of the 3rd European Consensus Conference in Intensive Care Medicine in 1995. It is now commonly accepted that a higher DO_2 is associated with increased survival and a lower occurrence of organ dysfunction¹³. DO_2 can be raised by adjusting the factors which usually involve increasing arterial blood oxygen content (C_aO_2) and/or cardiac output. Refractory septic shock patients who mostly have severe cardiorespiratory compromise may not be able to generate a high cardiac output and innately have a higher risk of death. In this case, C_aO_2 can be markedly affected by small increases or decreases in arterial oxygen pressure (P_aO_2). Therefore, maintaining P_aO_2 by improving gas exchange of lung is important in refractory septic shock¹⁴.

Some novel therapies have demonstrated a beneficial effect in improving the pulmonary function of experimental sepsis¹⁵, such as hemofiltration¹⁶. However, in hyperdynamic septic shock, there has been no clinical study on the effect of hemofiltration on pulmonary function. In this study, we applied high-volume hemofiltration (HVHF) as an adjunctive therapy linking to the early goal-directed therapy (EGDT) protocol that follows Surviving Sepsis Campaign bundle¹⁷. We hypothesized that HVHF improves he-

modynamics and oxygenation in patients with progressive refractory hypotension. The effects of HVHF on alveolar-arterial oxygen exchange were assessed. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scoring were performed to compare the outcome of EGDT-HVHF treatment to that of the EGDT treatment only. Sequential organ failure assessment (SOFA) includes respiratory, circulation, liver, kidney, blood and nerve organ. The main failure organ in our research is respiratory, circulation and kidney.

Patients and Methods

This study was approved by the hospital Ethical Committee (clinical trial registry number: Chinese Clinical Trial Registry (ChiCTR)-IPC-14005596). All patients or their relatives signed the informed consent for participating in the study.

Patients

This prospective cohort study was conducted in our ICU of Shandong Provincial Hospital Affiliated to Shandong University. 167 patients with refractory septic shock were enrolled between August 2009 and December 2012. Refractory septic shock was defined according to the standard criteria published by Bone et al². Exclusion criteria were less than 18 years or more than 75 years of age, death imminent within 6 h, and low APACHE II score (<15). Enrolled patients were divided into two groups according to being receipted successfully high volume hemofiltration (HVHF) within 24 hours when they entered ICU. The allocation criteria of the patients was that patients received HVHF in less than 24 hours will be divided into HVHF group, while patients who do not or were received HVHF in more than 24 hours will be allocated into control group. 86 patients in the hemofiltration group (47 males and 39 females with a mean age of 57.2 ± 16.4 years old) were treated with EGDT and HVHF. The control group consisted of 81 patients (45 males and 36 females, 55.7 ± 18.5 years old) received EGDT only. The baseline APACHE II scores in the control and the HVHF groups were similar (28.3 ± 9.3 and 27.5 ± 8.9 , respectively), so as the baseline SOFA scores in both groups (18.8 ± 6.3 and 17.6 ± 5.6 , respectively, $p > 0.05$). 6 patients in control group and 4 patients

Table I. Hemodynamic data in patients.

Group	n	C _{co} O ₂ (ml/L)				C _a O ₂ (ml/L)				O ₂ ER (%)			
		0d	1d	3d	7d	0d	1d	3d	7d	0d	1d	3d	7d
Control	81	0.47 ± 0.16	0.55 ± 0.24	0.59 ± 0.35	0.60 ± 0.24	0.72 ± 0.24	0.78 ± 0.28	0.82 ± 0.27	0.84 ± 0.43	32.5 ± 5.8	27.6 ± 3.7	28.6 ± 2.2	28.7 ± 2.4
Hemofiltration	86	0.46 ± 0.18	0.61 ± 0.28	0.66 ± 0.37	0.72 ± 0.28*	0.77 ± 0.29	0.82 ± 0.27	0.92 ± 0.33	0.94 ± 0.46*	34.5 ± 6.0	26.6 ± 3.7	25.6 ± 2.7	21.7 ± 3.4**

C_{co}O₂/O₂ content of central venous blood, C_aO₂: arterial oxygen content, O₂ER: oxygen extraction ratio. Vs. control group, * $p < 0.05$, ** $p < 0.01$.

Table II. Gas exchange data in patients.

Group	n	P _(A-a) DO ₂ (mmHg)				PaO ₂ /PAO ₂				RI				PaO ₂ /FiO ₂ (mmHg)			
		0d	1d	3d	7d	0d	1d	3d	7d	0d	1d	3d	7d	0d	1d	3d	7d
Control	81	311.81 ± 50.73	285.63 ± 48.32	280.83 ± 38.45	256.72 ± 25.73	0.62 ± 0.28	0.68 ± 0.25	0.69 ± 0.32	0.71 ± 0.37	6.37 ± 2.41	5.95 ± 2.10	5.87 ± 2.43	5.72 ± 1.95	128 ± 16	154 ± 21	179 ± 32	208 ± 36
Hemofiltration	86	305.55 ± 51.32	278.6 ± 50.37	265.82 ± 30.41*	156.77 ± 22.73**	0.63 ± 0.21	0.79 ± 0.27	0.82 ± 0.36	0.91 ± 0.47*	6.87 ± 2.11	5.65 ± 2.17	5.17 ± 2.03	4.52 ± 1.55*	118 ± 15	164 ± 28	195 ± 38*	268 ± 42**

P_(A-a)DO₂: alveolar-arterial oxygen pressure difference, P_aO₂: arterial oxygen pressure, P_aO₂/PAO₂: alveolar oxygen pressure, RI: Respiratory index, FiO₂: fraction of inspired oxygen. Vs. control group, * $p < 0.05$, ** $p < 0.01$.

in HVHF groups died within 6 h, mainly after hemodynamic disturbances, but the difference was non-significant ($p > 0.05$).

In our study, the causes of refractory septic shock for the patients included the abdominal infection (58 cases, accounts for 35%), pulmonary infection (50 cases, 30%), urinary tract infection (25 cases, 15%), and the thoracic cavity infection (14 cases, 8%), the pelvic cavity infection (12 cases, 7%), and the blood stream infection (8 cases, 5%) (Figure 1).

Management Algorithm

To manage our patients more efficiently, we employed a multi-interventional approach, which incorporates fluid resuscitation, vaso-pressor agents, antibiotic, steroids and mechanical ventilation, and various interventions according to EGDT. It aims at maintaining the central venous pressure (CVP) higher than 8-12 mmHg, MAP higher than 65-90 mmHg, central venous oxygen saturation (ScvO₂) greater than 70% and urine volume greater than 0.5 ml·kg⁻¹·h⁻¹ within 6 h¹⁶. Patients in the HVHF group received HVHF treatment at the same time. All patients were assessed by the APACHE II and SOFA scoring during the procedure as previously described¹⁸.

The HVHF Technique

A double-lumen 12F catheter (Vas-cath, Bard, Inc., Salt Lake City, UT, USA) was inserted percutaneously in the femoral or internal jugular vein. High-volume continuous venovenous hemofiltration (HV-CVVH) was performed with a polysulfone hemofilter, 1.4 m² surface area, 220 μm pore size, and priming volume of 90 ml (Aquaplast, Minntech, San Clemente, CA, USA) for 72 h. The hemofiltration monitor was set to deliver 200 ml min⁻¹ blood flow and an ultrafiltration rate of 50-70 ml·kg⁻¹·h⁻¹ (Diapact System, B. Braun, Melsungen, Germany). Ultrafiltration rate was increased gradually over 60-120 min according to hemodynamic tolerance to reach the target rate. A neutral fluid balance was programmed. Blood ultra filtrate was replaced using a bicarbonate-based solution with the following composition: sodium 140 mEq l⁻¹, potassium 2.0 mEq l⁻¹, calcium 1.5 mEq l⁻¹, magnesium 0.5 mEq l⁻¹, chloride 111 mEq l⁻¹, bicarbonate 35 mEq l⁻¹, glucose 1 g l⁻¹, and osmolality 296 mOsm kg⁻¹ (B. Braun). Body temperature was kept over 35°C using a heating device supplied with the monitor. Heparin was used for anticoag-

ulation. Bloodlines were flushed every 30 min with 150 ml of a 0.9% NaCl solution to check for permeability.

Measurements

All patients were mechanically ventilated and their fraction of inspired oxygen (F_iO_2) was kept constant throughout the procedure. Patients were continuously monitored with a thermodilution subclavian vein catheter and a radial-artery catheter. The arterial and central venous blood gases were measured with blood gas electrodes (GEM Premier 3000, GEM Premier Company, Munich, Germany). Central venous blood oxygen content ($C_{cv}O_2$), C_aO_2 , O_2ER , and $P_{A-a}DO_2$ were calculated according to the standard formulae. Ratio of P_aO_2 to alveolar oxygen pressure (P_AO_2) and ratio of P_aO_2 to F_iO_2 were also calculated. The ratio of $P_{A-a}DO_2$ to P_aO_2 was used as respiratory index (RI). Measurements were taken at baseline and at days 1, 3, and 7 during the procedure.

Statistical Analysis

Statistical analysis was performed using the SPSS software application (version 18.0 for Microsoft Windows: SPSS Inc., Chicago, IL, USA). Variables having a Gaussian distribution were shown as means $\pm$ standard deviation. Comparison between groups was assessed using the Student *t*-test. Data with a Skewed distribution were presented as medians and interquartile ranges, and the Mann-Whitney *U*-test was used to detect

the difference between groups. For qualitative variables, the chi-square or Fisher exact test was used. Significance was set at $p < 0.05$.

Results

Hemodynamic Changes in Patients

Our results showed that $C_{cv}O_2$ and C_aO_2 increased over time during the entire observational period in both the HVHF and the control groups. At day 7, patients from the HVHF group had a significant decrease in O_2ER (21.7 ± 3.4 vs. 34.5 ± 6.0 , $p < 0.05$), while this change was not found in the control group (28.7 ± 2.4 vs. 32.5 ± 5.8 , $p > 0.05$) (Table I). At day 7, $C_{cv}O_2$ and C_aO_2 were significantly higher in the HVHF group as compared to the control group ($C_{cv}O_2$: 0.72 ± 0.28 vs. 0.60 ± 0.24 ; C_aO_2 : 0.94 ± 0.46 vs. 0.84 ± 0.43 , $p < 0.05$); consequently, a significantly lower O_2ER was found in the HVHF versus the control groups (21.7 ± 3.4 vs. 28.7 ± 2.4 , $p < 0.01$) (Table I).

Gas Exchange Changes in Patients

Both groups showed an increase in the ratio of P_aO_2 to P_AO_2 and the ratio of P_aO_2 to F_iO_2 and a decrease in $P_{(A-a)}DO_2$ and RI during the therapy (Table II). At day 3, $P_{(A-a)}DO_2$ was significantly lower in the HVHF group as compared to the control group ($p < 0.05$), while the ratio of P_aO_2 to F_iO_2 was significantly higher in the HVHF vs. the control groups ($p < 0.05$). At day 7, statistically

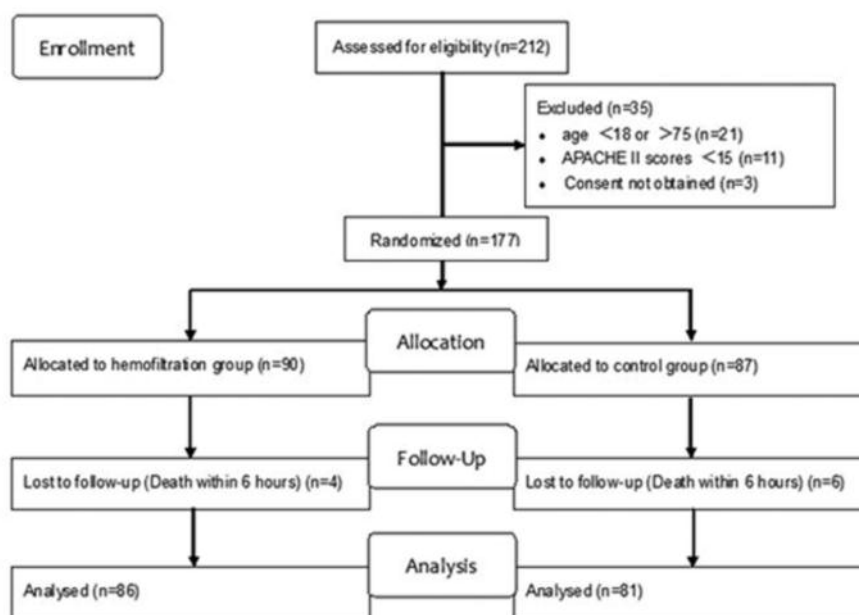
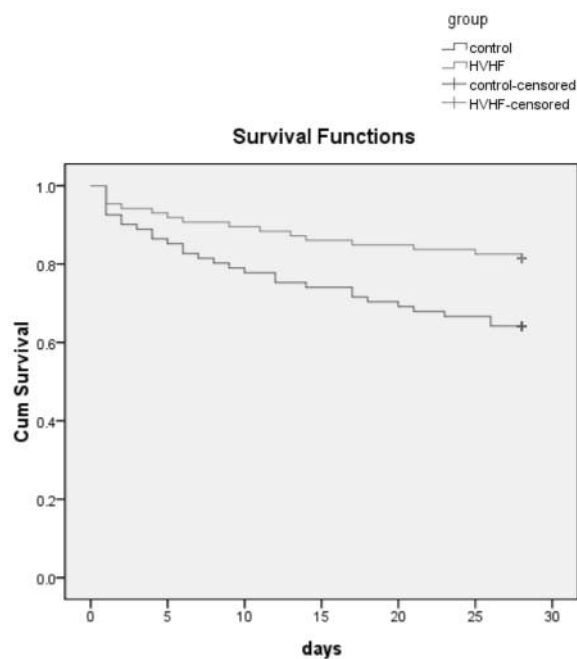


Figure 1.

Table III. APACHE II and SOFA changes in patients.

Group	n	APACHE II score		SOFA score	
		0d	7d	0d	7d
Control	81	28.3 ± 9.3	17.2 ± 6.8	18.8 ± 6.3	12.8 ± 3.9
Hemofiltration	86	27.5 ± 8.9	8.2 ± 3.8**	17.6 ± 5.8	7.6 ± 3.3*

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; Vs. control group, * $p < 0.05$, ** $p < 0.01$.


Figure 2.

significant changes were found in $P_{(A-a)}DO_2$, RI, the ratio of P_aO_2 to P_{aO_2} , and the ratio of P_aO_2 to F_iO_2 between two groups (256.72 ± 25.73 vs. 156.77 ± 22.73 , 5.72 ± 1.95 vs. 4.52 ± 1.55 , 0.71 ± 0.37 vs. 0.91 ± 0.47 , 208 ± 36 vs. 268 ± 42 , $p < 0.05$). Detailed allocation for the two groups is listed in Table II.

APACHE II and SOFA Changes in Patients

Comparison of the APACHE II (Acute Physiology And Chronic Health Evaluation II) and the SOFA (Sequential Organ Failure Assessment) scores between two groups were showed in Table III. At day 7, the APACHE II score and the SOFA score were lower in the HVHF group than that in the control group (APACHE II score: 17.2 ± 6.8 vs. 8.2 ± 3.8 , SOFA score: 12.8 ± 3.9 vs.

7.6 ± 3.3 ($p < 0.01$, $p < 0.05$). By day 28, 15 patients in the HVHF group died whereas the number of death doubled in the control group. The difference in the mortality rate between two groups was statistically significant (37.04% vs. 17.44%, $\chi^2 = 8.1363$, $p < 0.01$).

Survival of the Patients with Kaplan Meier Survival Plot

As shown in Figure 2 and Table IV, after Log Rank test, $X^2 = 6.245$, $p = 0.012$. According to the standard of $\alpha = 0.05$, the difference between the two groups was statistically significant.

Discussion

To the best of our knowledge, this is the first clinical study assessing the effect of HVHF as an adjunctive therapy on gas exchange of refractory septic shock patients. Our findings confirmed that HVHF not only improved gas exchange in refractory septic shock patients, but also significantly stabilized hemodynamics and decreased mortality rate in this setting as previously reported¹⁹.

In the medical literature, the protocol for HVHF is not well defined for now. Honore et al¹⁶ hold the idea that HVHF includes continuous high-volume hemofiltration (CHVH) of $50-70 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ 24 h a day and intermittent IHVH with brief, very high-volume treatment at $100-120 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ for a short period of 4-8 h, followed by conventional CVVH. This latter strat-

Table IV. Comparison of survival time distribution in the two groups.

Chi-Square	df	Sig
Log Rank (Mantel-Cox)	1	0.012

Test of equality of survival distribution for the different levels of group.

egy initially developed by Ronco et al²⁰ is also called “pulse HVHF”. This definition is consistent with what was defined at the 2001 Critical Care Nephrology Conference²¹, where HVHF was defined as ultrafiltration flow rates greater than 50 ml·kg⁻¹·h⁻¹ and very HVHF for ultrafiltration flow rates greater than 100 ml·kg⁻¹·h⁻¹. In clinical practice, no superior renal replacement therapy has been identified. A recent guideline²² recommended that elevates that equivalency of CVVH or intermittent hemodialysis should be elevated to a Grade 2B recommendation. However, CVVH technique provides a smooth and continuous control of the volume status while avoiding the cardiovascular instability associated with intermittent hemodialysis²³. Taken all these into consideration, we opted to use CHVH in our study.

The ratio of P_aO₂ to F_iO₂ is a widely used index for evaluating oxygen exchange. It's getting more and more important because it forms part of the definitions of ARDS and acute lung injury (ALI) established by the *American-European Consensus Conference*²⁴, and of the Lung Injury Score²⁵. P_{A-a}DO₂ is another index for evaluating gas exchange function of the lungs²⁶. A lower P_aO₂/F_iO₂ and a higher P_{A-a}DO₂ are essential characteristics of the septic patients²⁷. In our study, the calculated P_aO₂/P_AO₂ and RI were used to assess shunt and ventilation-perfusion imbalance. In sepsis, P_aO₂ was significantly lower. However, after ventilatory and ultrafiltration, F_iO₂, P_aCO₂, and P_AO₂ remained unchanged but P_aO₂ increased significantly. Thus, an increase in P_aO₂/P_AO₂ and P_aO₂/F_iO₂ was observed. In contrast, reduction in P_{A-a}DO₂ resulted in a decrease in RI in the HVHF group. At day 7, patients' P_(A-a)DO₂ and RI of the HVHF Group were lower than those of the control group ($p < 0.05$). P_aO₂/P_AO₂ and P_aO₂/F_iO₂ of HVHF Group were higher than those of the control group. This demonstrated that HVHF can improve pulmonary function in patients with refractory septic shock. With the increase in CaO₂, DO₂ increased in refractory septic shock patients receiving both the HVHF and early goal-directed therapy (EGDT) therapies. We also found a more rapid increase in CcvO₂. This may lead to a reduction in O₂ER and VO₂ after treatment, say, at day 7. It was believed that raising DO₂ to higher than 600 ml·min⁻¹·m⁻² and keeping ScvO₂ higher than 70% in critically ill patients may correct oxygen debt and improve outcome²⁸.

Our research showed that the APACHE II and SOFA scores in the HVHF group were lower than those in the control group at day 7, and the mortality rate was significant different between two groups at day 28. The organ function of respiratory, circulation, kidney is improved by high volume hemofiltration (HVHF) and general therapy. These results disagree with some previous reports^{29,30}. In fact, there have been insufficient clinical data to support the use of HVHF in critically patients with severe sepsis and/or septic shock. Evaluation of the efficacy of hemofiltration in sepsis remains complicated because of the heterogeneity of the study populations and the hemofiltration strategies. Ultrafiltration dose appears to be an important factor. “Renal dose” is insufficient for the removal of inflammatory mediators (medium molecules) and, therefore, contributes little to the cardiovascular stabilization in patients with septic shock. In this setting, a higher dose of ultrafiltration (>50 ml·kg⁻¹·h⁻¹) or “septic dose” may be needed³¹. Timing is probably another important issue. In most experimental studies, hemofiltration started before or shortly after the microbial challenge. In clinical practice, however, hemofiltration is not initiated until shock and organ failure are already established. Honore and Matson³² reported an association between a better survival and an earlier start of hemofiltration in patients with severe septic shock. Our study suggested that patients with refractory septic shock may benefit from HVHF if a higher dose of ultrafiltration (50 or 70 ml·kg⁻¹·h⁻¹) was administered at an early stage.

Our study contributes significantly to the knowledge of hemofiltration support in refractory septic shock. Firstly, it introduced HVHF as an adjunctive therapy into a hemodynamic management algorithm according to the “bundle” theory³³. Secondly, it demonstrated a positive effect in a not well-studied setting of refractory septic shock. Thirdly, precise hemodynamic and oxygen metabolic goals were set for the effects of HVHF therapy. If these goals are achieved at the end of the HVHF procedure, the probability of survival might be improved. The effect is possibly due to remove pro- and anti-inflammatory mediators^{34,35}.

Our results suggested that refractory septic shock patients may benefit from HVHF if a higher dose of ultrafiltration (50 or 70 ml·kg⁻¹·h⁻¹) was early used in Chinese people. However, data did not justify the use of HVHF in patients with severe sepsis or septic shock. Moreover, HVHF

may correct oxygen debt and improve pulmonary function by removing pro- and anti-inflammatory mediators of lung, but the mechanism remains speculative and further research is needed.

Conclusions

Our results demonstrated that of hemodynamic treatment incorporating HVHF as an adjunctive therapy for patients with refractory septic shock improved hemodynamic and oxygenation changes, as well as patient survival.

Acknowledgements

The authors thank Ms. Juan Zeng and Mr. Peng Wang for their valuable help to collect the data in patients. The study was supported by grants from the Natural Science Foundation of Shandong Province (Nos. ZR2013HM062 and Y2006C77), Shandong province excellent middle-aged and young scientists encouragement research foundation (No. BS2009YY025), and Shandong province science and technology development plan of medical and health (Nos. 2013WS0110 and 2009QZ020).

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

- 1) BONE RC. Sepsis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. *Ann Intern Med* 1991; 114: 332-333.
- 2) BONE RC, BALK RA, CERRA FB, DELLINGER RP, FEIN AM, KNAUS WA, SCHEIN RM, SIBBALD WJ. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101: 1644-1655.
- 3) JONES AE, TROYER JL, KLINE JA. Cost-effectiveness of an emergency department-based early sepsis resuscitation protocol. *Crit Care Med* 2011; 39: 1306-1312.
- 4) GREENFIELD N, BALK RA. Evaluating the adequacy of fluid resuscitation in patients with septic shock: controversies and future directions. *Hosp Pract* 2012; 40: 147-157.
- 5) HILTON AK, BELLOMO R. A critique of fluid bolus resuscitation in severe sepsis. *Crit Care* 2012; 16: 302.
- 6) HOGUE B, CHAGNON F, LESUR O. Resuscitation fluids and endotoxin-induced myocardial dysfunction: is selection a load-independent differential issue? *Shock* 2012; 38: 307-313.
- 7) ROMERO-BERMEJO FJ, RUIZ-BAILEN M, GIL-CEBRAN J, HUERTOS-RANCHAL MJ. Sepsis-induced cardiomyopathy. *Curr Cardiol Rev* 2011; 7: 163-183.
- 8) ALDERS DJ, GROENEVELD AB, BINSI TW, DE KANTER FJ, VAN BEEK JH. Endotoxemia decreases matching of regional blood flow and O₂ delivery to O₂ uptake in the porcine left ventricle. *Am J Physiol Heart Circ Physiol* 2011; 300: 1459-1466.
- 9) GOLDMAN D, BATEMAN RM, ELLIS CG. Effect of sepsis on skeletal muscle oxygen consumption and tissue oxygenation: interpreting capillary oxygen transport data using a mathematical model. *Am J Physiol Heart Circ Physiol* 2004; 287: 2535-2544.
- 10) MANTHOU CA. Sepsis, lactate, and oxygen supply dependence. *Chest* 2012; 141: 1361-1364.
- 11) BARBEE RW, REYNOLDS PS, WARD KR. Assessing shock resuscitation strategies by oxygen debt repayment. *Shock* 2010; 33: 113-122.
- 12) BALK RA. Severe sepsis and septic shock: definitions, epidemiology, and clinical manifestations. *Crit Care Clin* 2000; 16: 179-192.
- 13) RICHARD C. Tissue hypoxia. How to detect, how to correct, how to prevent? *Intensive Care Med* 1996; 22: 1250-1257.
- 14) VINCENT JL, DE BACKER D. Oxygen transport – the oxygen delivery controversy. *Intensive Care Med* 2004; 30: 1990-1996.
- 15) MAYBAUER MO, MAYBAUER DM, FRASER JF, WESTPHAL M, SZABÓ C, COX RA, HAWKINS HK, TRABER LD, TRABER DL. Combined recombinant human activated protein C and ceftazidime prevent the onset of acute respiratory distress syndrome in severe sepsis. *Shock* 2012; 37: 170-176.
- 16) HONORE PM, JOANNES-BOYAU O, BOER W, COLLIN V. High-volume hemofiltration in sepsis and SIRS: current concepts and future prospects. *Blood Purif* 2009; 28: 1-11.
- 17) NEE PA, RIVERS EP. The end of the line for the Surviving Sepsis Campaign, but not for early goal-directed therapy. *Emerg Med J* 2011; 28: 3-4.
- 18) NGUYEN HB, BANTA JE, CHO TW, VAN GINKEL C, BURROUGHS K, WITTLAKE WA, CORBETT SW. Mortality predictions using current physiologic scoring systems in patients meeting criteria for early goal-directed therapy and the severe sepsis resuscitation bundle. *Shock* 2008; 30: 23-28.
- 19) HONORE PM, JAMEZ J, WAUTHIER M, LEE PA, DUGERNIER T, PIRENNE B, HANIQUE G, MATSON JR. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med* 2000; 28: 3581-3587.
- 20) BRENDOLAN A, D'INTINI V, RICCI Z, BONELLO M, RATANARAT R, SALVATORI G, BORDONI V, DE CAL M, ANDRIKOS E, RONCO C. Pulse high volume hemofiltration. *Int J Artif Organs* 2004; 27: 398-403.
- 21) WANG S, ZHOU J, CAI JF. Traditional coronary artery bypass graft versus totally endoscopic coronary

- artery bypass graft or robot-assisted coronary artery bypass graft – meta-analysis of 16 studies. *Eur Rev Med Pharmacol Sci* 2014; 18: 790-797.
- 22) DELLINGER RP, LEVY MM, RHODES A, ANNANE D, GERLACH H, OPAL SM, SEVRANSKY JE, SPRUNG CL, DOUGLAS IS, JAESCHKE R, OSBORN TM, NUNNALLY ME, TOWNSEND SR, REINHART K, KLEINPELL RM, ANGUS DC, DEUTSCHMAN CS, MACHADO FR, RUBENFELD GD, WEBB S, BEALE RJ, VINCENT JL, MORENO R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup: surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; 39: 165-228.
- 23) VANHOLDER R, VAN BIESEN W, HOSTE E, LAMEIRE N. Pro/con debate: continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish? *Crit Care* 2011; 15: 204.
- 24) BERNARD GR, ARTIGAS A, BRIGHAM KL, CARLET J, FALKE K, HUDSON L, LAMY M, LE GALL JR, MORRIS A, SPRAGG R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818-824.
- 25) MURRAY JF, MATTHAY MA, LUCE JM, FLICK MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988; 138: 720-723.
- 26) BENGTSSON J, BAKE B, JOHANSSON A, BENGTSON JP. End-tidal to arterial oxygen tension difference as an oxygenation index. *Acta Anaesthesiol Scand* 2001; 45: 357-363.
- 27) SÁNCHEZ CASADO M, QUINTANA DÍAZ M, PALACIOS D, HORTIGÜELA V, MARCO SCHULKE C, GARCÍA J, CANABAL A, PÉREZ PEDRERO MJ, VELASCO RAMOS A, ARRESE MA. Relationship between the alveolar-arterial oxygen gradient and PaO₂/FiO₂-introducing PEEP into the model. *Med Intensiva* 2012; 36: 329-334.
- 28) TÁNCZOS K, MOLNÁR Z. The oxygen supply-demand balance: a monitoring challenge. *Best Pract Res Clin Anaesthesiol* 2013; 27: 201-207.
- 29) SINANGIL A, KO Y, UNSAL A, BASTURK T, SAKACI T, AHBAP E, BUDAK SK, DONER B, M. Sevinc. Effects of infectious complications on patients' survival in peritoneal dialysis. *Eur Rev Med Pharmacol Sci* 2013; 17: 1064-1072.
- 30) RONCO C, BELLOMO R, HOMEL P, BRENDOLAN A, DAN M, PICCINNI P, LA GRECA G. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; 356: 26-30.
- 31) ROMERO CM, DOWNEY P, HERNÁNDEZ G. High volume hemofiltration in septic shock. *Med Intensiva* 2010; 34: 345-352.
- 32) HONORE PM, MATSON JR. Short-term high-volume hemofiltration in sepsis: perhaps the right way is to start with. *Crit Care Med* 2002; 30: 1673-1674.
- 33) KANG MJ, SHIN TG, JO U, JEON K, SUH GY, SIM MS, LIM SY, SONG KJ, JEONG YK. Factors influencing compliance with early resuscitation bundle in the management of severe sepsis and septic shock. *Shock* 2012; 38: 474-479.
- 34) HONORE PM, JOANNES-BOYAU O, GRESSENS B. Blood and plasma treatments: high-volume hemofiltration: a global view. *Contrib Nephrol* 2007; 156: 371-386.
- 35) JEONG SJ, SONG YG, KIM CO, KIM HW, KU NS, HAN SH, CHOI JY, KIM JM. Measurement of plasma sTREM-1 in patients with severe sepsis receiving early goal-directed therapy and evaluation of its usefulness. *Shock* 2012; 37: 574-578.