



The Effects of High-volume Hemofiltration by Different Ultrasound Directing on Extra Vascular Lung Water Index in Patients with Septic Shock

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Abstract

Background: We explored the effects of high-volume hemofiltration(HVHF) by different ultrasound directing on the plasma N-terminal pro-B-type natriuretic peptide(NT-Pro-BNP), extra vascular lung water index (EVLWI), liquid net balance quantity and prognosis in patients with septic shock.

Methods: Overall, 107 intensive patients with septic shock were enrolled by retrospective analysis from Department of Intensive Care Unit (ICU) of the Shandong Provincial Hospital affiliated to Shandong University from 2014-2017. According to HVHF by different ultrasound directing, all the patients were divided into two groups ((ultrasonic cardiac output monitor (USCOM), group A, n=51cases)) and ((critical bedside ultrasound (CBU), group B, n=56cases)).

Results: The value of CI in group A had a significant positive correlation with the value of PCCI by the PiCCO₂ monitoring ($P<0.05$). The lung ultrasound water B lines in group B also had a significant positive correlation with the value of EVLWI by the PiCCO₂ monitoring. The cumulative liquid net balance quantity in group B had a more significant elevation than group A after treatment 7th d. The level of EVLWI after treatment 48 h and 72 h, the level of plasma NT-Pro-BNP, the levels of P(A-a)DO₂,OI and blood lactic after treatment 72 h, and the APACHE II scores and SOFA scores after treatment 7thd were reduced more significantly in group B than group A ($P<0.001$). The mortality at 28th day had a more significant decrease in group B than group A.

Conclusion: It could decrease the level of NT-Pro-BNP, EVLWI, P(A-a)DO₂,which then improves pulmonary oxygenation. Consequently, it decreased the APACHE II and SOFA scores and improved the 28th survival rate of patients.

Keywords: Critical bedside ultrasound, Septic shock, High-volume hemofiltration

Introduction

The early goal-directed therapy is hardly to prevent the progress of septic shock. Its death rate is staying at high level. Serious pyohemia and infec-

tion shock guideline (2012) showed mortality in septic shock was 20%-40% (1). Even though fluid resuscitation is one of the main methods to

treat septic shock, fluid overload and pneumoedema caused by inappropriate fluid resuscitation can influence the prognosis of patients (2). It is difficult to recognize fluid overload in the early time. The symptoms, physical signs and laboratory detections which used to judge fluid overload is atypical and belate. The sensitivities that had used beside x-ray chest judge pneumoedema is very low. Now pulse indicator contour cardiac output (PiCCO2) and extra vascular lung water index (EVLWI) is the common objective assessments of pulmonary edema (3). But it is costly, invasive and more complications. It also cannot be with continuous use.

There are no effective and non-invasive monitoring methods for pneumoedema. Beside ultrasound starts to be used in severe patients (4). During the progress of our retrospective analysis which compared different lung ultrasound and PiCCO2 monitoring, guided the amount of liquid recover under the high volume hemo-filtration (HVHF), developed appropriate liquid management strategies via the changes of acute physiology and chronic health evaluation-II (APACHE-II), sepsis-related organ failure assessment (SOFA). Our aim was to reduce the fatality rate of septic shock.

Material and Methods

Patients' data

We retrospectively analysed 107 patients who admitted to our hospital's Department of Critical Care Medicine (ICU) from 2014-2017. The patients were diagnosed as septic shock, took capacity recovery, PiCCO2 monitoring and high-volume hemofiltration (HVHF). HVHF was implemented at least 72 h.

Inclusion criteria: Diagnose of all patients according with the diagnostic criteria of septic shock (5), age ≥ 18 yr old, age ≤ 80 yr old. According to its implement ultrasonic cardiac output monitoring (USCOM) and critical bedside ultrasound (CBU) monitor, all of patients were divide into two groups. Group USCOM (group A), n=51 cases, male 28, female 23, age 22-78 yr old, average

(52.7 \pm 15.6) yr old; Group CBU (group B) n=56 cases, male 32, female 24, age 24-79 yr old, average (54.3 \pm 16.2) yr old. There was no significant difference between the two groups in age gender disease severity according to APACHE II and SOFA scores.

Exclusion criteria: HIV infected cases, advanced cancer patients, end-of-life patients, patients with cardiogenic shock, pregnant woman with obstructive shock, patients with leukemia or who refused to participate.

Removed criteria: the patients who failed to complete the 28-day survival rate of follow-up, gave up treatment halfway, or went to other hospital for treatment.

This study met medical ethical standards with the approving of the Hospital Ethics Committees of Shandong provincial. Written informed consents were obtained from all subjects.

Methods

All patients were monitored immediately and at 24 h, 48 h, 72 h after treatment. We extracted the patient's blood, and then tested the patient's blood routine, coagulation, liver and kidney function. We took 1.8 ml of venous blood to 1.09 mol/L sodium citrate at rate 9:1 anticoagulation, 3000 r/min 15minutes centrifuge, serum -20 °C preservation. The immunochromatographic method was used to determinate PCT goal by standard diagnostic kit (BRAHMS Company, Germany). RocheElecys 2010 electrochemiluminescence immunoassay analyser was used to determinate NT-proBNP by NT-pro BNP kits (Roche Company, Switzerland). All operations were inferred strictly accordance with the instruction.

We recorded the difference between the amount of input and output of 24 h and calculated net balance of accumulated fluid for seven days (6).

From the patient right internal jugular vein or right subclavian vein, we inserted into the central venous catcher, connected PiCCO2 temperature probe. From patients' arteria femoral, we inserted into PiCCO2 catheter (PV2015L20, PULSION

Company, Germany). We connected to the monitor which had PiCCO2 module. We monitored patient's PCCI, EVLWI continuously. We rapidly injected 15 ml of ice saline from the temperature probe which was connected with the intravenous or subclavian venous catheters. All surveys were measured at least three times in a row. We took the average of three valid measurements as each monitoring data (7).

We had done consciously beside high-flow venous hemofiltration at least 72 h. We used femoral vein indwelling catheter, high-volume continuous, pre-replacement method 70% or completely after the replacement, changed the filter each 24 h, the anticoagulation was heparin or sodium citrate. The amount of replacement liquid was 3000-4000 ml/h (50-70 ml·kg⁻¹·h⁻¹), the amount of replacement was beyond 60 L/d, the blood flow was 150~200 ml/min (8). According to patient's different dates under the guidance of ultraphonic, we adjusted ultrafiltration volume.

USCOM monitor

We used the continuous ultrasound noninvasive cardiac output detector of USCOM (company, Australia) (9) to get the best blood flow chart and data. We asked the patient to lie in the supine position, put the probe on the suprasternal fossa and increased the pressure appropriately until a triangular systolic flow signal spectrogram appeared. All surveys were measured three times and we took the average.

CBU monitor

We used the portable ultrasound machine for monitoring, phased array (1-5 MHz) probe. The radical bundle extending from pleural line to route and decaying with the breathing changes was B line. According to pulmonary ultrasound guide recommendation, we selected eight sections of the front chest wall to observe lung water. If more than three lines appeared in an intercostal space section, then we believed the B line was positive (10).

Condition score

At the beginning, 72 h, 7 d after treatment, we conducted APACHE-II and SOFA scores (11,12) and counted the survival and deaths of patients of 28 d followed-up.

Statistical method

All the measurement data were expressed as mean \pm standard deviation, *t*-test between two groups, the incidence with χ^2 test, correlation analysis using Person correlation. All the data were processed by SPSS 17.0 computer software (Chicago, IL, USA). If the *P* value was <0.05 , we regarded the difference was statistical significance.

Results

Correlation analysis

The cardiac output index (CI) in group A was significant positively correlated with the continuous cardiac output index (PCCI) monitored by PiCCO2 (correlation coefficient $R=0.689$, 95% confidence interval (0.607,0.769), $0.01 < P < 0.05$). There was also a significant positive correlation between the number of pulmonary ultrasound B in group B and the extravascular lung water index (EVLWI) monitored by PiCCO2 (correlation coefficient $R = 0.705$, 95% confidence interval (0.657, 0.815), $0.01 < P < 0.05$).

Change of cumulative liquid net balance quantity

There was no significant difference in the net balance of liquid between the two groups at 24 h, 48 h, 72 h after treatment. After 7th d, the net balance of accumulated liquid in group B was significant different from that in group A (1276 ± 248 vs 537 ± 39 , $t = 21.04$, $P = 0.001$).

Before treatment, after treatment 24 h, 48 h, 72 h, there was no significant difference in plasma PCT level between group B and group A. Before treatment, after treatment 24 h, 48 h, the level of plasma of NT-Pro BNP had no significant change, but after treatment of 72 h, the level of plasma NT-Pro BNP decreased, and it was statistically significant (Table 1).

Table 1: Comparison of inflammatory cytokines and cardiac function parameter in serum level between groups as mean ± standard deviation

Group	Number	PCT (ug/L)				NT-Pro BNP (ug/L)			
		0h	24h	48h	72h	0h	24h	48h	72h
Group A	51	49.3	31.7	18.2	8.3	2975.8	1868.5	1265.2	804.9
		±15.2	±12.3	±8.1	±3.2	±198.4	±138.5	±90.7	±56.2
Group B	56	47.2	32.4	17.3	7.1	2909.4	1825.4	1237.5	721.8
		±12.5	±11.2	±8.2	±2.9	±188.3	±145.9	±86.7	±43.9 *
		<i>t</i> =0.776	<i>t</i> =0.321	<i>t</i> =571	<i>t</i> =1.616	<i>t</i> =1.866	<i>t</i> =1.567	<i>t</i> =1.611	<i>t</i> =8.466
		<i>P</i> =0.415	<i>P</i> =0.625	<i>P</i> =0.509	<i>P</i> =0.125	<i>P</i> =0.065	<i>P</i> =0.142	<i>P</i> =0.135	<i>P</i> =0.001

Before treatment, after treatment 24 h, 48 h, 72 h, thoracic blood volume index (ITBVI) and global end-diastolic volume index (GEDVI) had no significant difference in two groups. There was no significant difference between the two groups in PVPI and EVLWI before treatment, 24 h, 48 h after treatment, but the pulmonary vascular permeability in group B was significantly

higher than that in group A (PVPI) and extravascular lung water index (EVLWI) decreased, they were statistically significant (Table 2).

The difference between the alveolar oxygen pressure and the partial pressure of arterial oxygen (P(A-a)DO₂), oxygenation index (OI) and arterial lactate (Lac) in the two groups were not significant before and 24 h and 48 h after treatment.

Table 2: Comparison of hemodynamic parameters level between groups (mean ± standard deviation)

Group	Number	ITBVI (ml/m ²)				GEDVI (ml/m ²)			
		0h	24h	48h	72h	0h	24h	48h	72h
Group A	51	1304.2	1163.4±368.0	1079.4±295.5	967.8	1259.7	1258.2	1263.3	1079.4
		±373.5			±242.9	±415.2	±372.3	±351.0	±285.2
Group B	56	1265.6	1244.5±327.4	1141.6	901.2	1391.6	1175.4	1164.2	995.9
		±363.7		±269.3	±204.5	±404.6	±302.3	±295.8	±294.3
		<i>t</i> =1.229	<i>t</i> =1.199	<i>t</i> =1.134	<i>t</i> =1.528	<i>t</i> =1.662	<i>t</i> =1.255	<i>t</i> =1.571	<i>t</i> =1.489
		<i>P</i> =0.239	<i>P</i> =0.182	<i>P</i> =0.263	<i>P</i> =0.137	<i>P</i> =0.092	<i>P</i> =0.252	<i>P</i> =0.145	<i>P</i> =0.163
Group	Number	PVPI				EVLWI (ml/kg)			
		0h	24h	48h	72h	0h	24h	48h	72h
Group A	51	13.4	12.3	11.4	10.8	19.5	17.2	13.8	11.5
		±4.5	±3.5	±3.2	±3.5	±6.3	±5.2	±4.7	±3.3
Group B	56	12.9	11.9	9.8	6.1	18.9	15.4	11.7±	7.3
		±3.5	±2.9	±3.4*	±2.7**	±5.6	±5.0	4.2*	±3.1**
		<i>t</i> =0.637	<i>t</i> =0.641	<i>t</i> =2.507	<i>t</i> =7.723	<i>t</i> =0.519	<i>t</i> =1.821	<i>t</i> =2.428	<i>t</i> =6.768
		<i>P</i> =0.699	<i>P</i> =0.629	<i>P</i> =0.029	<i>P</i> =0.001	<i>P</i> =0.742	<i>P</i> =0.082	<i>P</i> =0.035	<i>P</i> =0.001

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

However, at 72 h after treatment, the difference between alveolar oxygen pressure and arterial oxygen pressure (P(A-a)DO₂), oxygenation index (OI) and arterial lactate (Lac) had decreased significantly, it was statistically significant (Table 3). There was no significant difference in APACHE-II score and SOFA score between the two groups before treatment and at 72 h, however,

APACHE-II scores and SOFA scores in group B were significantly lower than those in group A at 7th day after treatment, both of which had a statistically significant meaning (Table 4).

After 28 d of following-up, there were 17 dead patients in group A and 9 dead patients in group B, it had significant differences in mortality rates (33.33% vs 16.07%, X² = 4.324, *P* < 0.05).

Table 3: Comparison of Alveolar- arterial oxygen pressure difference P(A-a) DO₂, oxygenation index (OI) and artery atrial blood lactic between two groups (mean \pm standard deviation)

Group	N	P(A-a) DO ₂ (mmHg)				Oxygenation index OI				LAC (mmol/l)			
		0	24h	48h	72h	0	24h	48h	72h	0	24h	48h	72h
Group A	51	315.7 ± 47.7	290.5 ± 46.5	250.2 ± 38.7	221.2 ± 29.3	112.4 ± 34.2	127.7 ± 41.5	131.8 ± 37.3	158.2 ± 33.4	6.3 ± 2.4	4.6 ± 2.0	3.6 ± 2.3	3.1 ± 1.7
Group B	56	305.4 ± 52.6	276.2 ± 48.3	236.7 ± 39.5	181.9 $\pm 21.8^{**}$	124.5 ± 36.6	138.3 ± 30.7	140.4 ± 31.2	198.7 $\pm 41.5^{**}$	6.7 ± 2.1	3.8 ± 2.1	2.9 ± 1.3	1.8 $\pm 0.7^{**}$
		<i>t</i> =1.062 <i>P</i> =0.323	<i>t</i> =1.559 <i>P</i> =0.184	<i>t</i> =1.785 <i>P</i> =0.078	<i>t</i> =7.780 <i>P</i> =0.001	<i>t</i> =1.768 <i>P</i> =0.082	<i>t</i> =1.491 <i>P</i> =0.139	<i>t</i> =1.287 <i>P</i> =0.235	<i>t</i> =5.583 <i>P</i> =0.001	<i>t</i> =0.914 <i>P</i> =0.394	<i>t</i> =1.766 <i>P</i> =0.089	<i>t</i> =913 <i>P</i> =0.073	<i>t</i> =5.082 <i>P</i> =0.001

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

Table 4: Comparison of acute physiology and chronic health evaluation II (APACHE II), sepsis-related organ failure assessment (SOFA) after high-volume hemofiltration (HVHF) between groups (mean \pm standard deviation)

Group	Number	APACHE II			SOFA		
		0	3d	7d	0	3d	7d
Group A	51	24.5 \pm 8.3	19.4 \pm 8.2	14.3 \pm 6.5	15.9 \pm 6.1	13.9 \pm 4.8	12.8 \pm 3.8
Group B	56	25.1 \pm 7.4	17.3 \pm 7.1	8.2 \pm 3.3**	16.5 \pm 5.7	12.6 \pm 3.3	8.2 \pm 3.1**
		<i>t</i> =0.393 <i>P</i> =0.637	<i>t</i> =1.409 <i>P</i> =0.178	<i>t</i> =7.175 <i>P</i> =0.001	<i>t</i> =0.524 <i>P</i> =0.495	<i>t</i> =617 <i>P</i> =0.132	<i>t</i> =6.822 <i>P</i> =0.001

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

Discussion

When the body is in systemic inflammatory response syndrome (SIRS), severe sepsis, or septic shock, the plasma inflammatory mediators will increase damage capillary endothelial cells then increase pulmonary vascular permeability (PVP), cause extra-vascular lung water index (EVLW). These changes will decrease Alveolar-arterial oxygen exchange capacity and lead to tissue hypoxia-arterial blood lactate increase, as result, the patients would develop a multiple organ dysfunction syndrome (13).

Research showed that normal human PCT concentration is 0.033 ug/L. As a biomarker, serum PTC level has a high degree of specificity and sensitivity which can be used to monitor bacterial infections. This can reflect the severity of the disease and evaluate the patient's prognosis (14, 15). Ventricular myocytes produce NT-proBNP by the increased stimulation of left ventricular walls pressure. NT-proBNP is the predictors of left ventricular preload and cardiac function. According to reports (16), NT-proBNP can be used as the marker to recognize sepsis-induced heart

failure. NT-pro BNP reflects the preload of heart which is positively correlated with global end-diastolic volume index (GEDVI) and intrathoracic blood volume index (ITBVI).

PiCCO₂ has become the clinical gold standard for hemodynamic monitoring of patients and been used to guide the treatment shock. Research confirmed the accuracy of PiCCO₂. Using the technology of PiCCO₂ to measure PCCI which can reflect heart pumping blood fraction, EVLWI which can reflect the severity of pulmonary directly. All of this are closely related to the prognosis of critically ill patients (17). It had showed that noninvasive and repeatable cardiac output monitoring cardiac index (CI) such as USCOM, which reflected the change of heart pumping blood (9). Slight lung hydrostatic pressure increase can cause B line. Ultrasonic lung water monitoring can reflect the dynamic change of body capacity which can help guide the more individual and accurate capacity management. As an index, pulmonary ultrasound B line can be used to reflect the condition of pneumonodema, it had been proved by a research (18-20). The total number of ultrasound B-lines and EVLW

has a good correlation for lung oxygenation function and acute respiratory distress syndrome (ARDS) patients (21). Our research showed that there had a significant positive correlation between the CI and the PCCI monitored by PiCCO2 in group A. (Correlation coefficient $R = 0.689$). There was also a significant positive correlation between the number of pulmonary ultrasound B line and EVLWI monitored by PiCCO2 (Correlation coefficient $R = 0.705$).

Early use of PiCCO2 hemodynamic monitoring was related to non-invasive use USCOM monitor cardiac output index. There are good correlations between pulmonary ultrasound B line and PiCCO2. The USCOM and the CBU have the advantages of non-invasive and can be repeated. More importantly, it is that pulmonary ultrasound can play the advantages of non-invasive, simple and economical, glide to capacity management better. Our research showed that two groups of 24, 48, 72 h after treatment, there was no significant difference of liquid between the two groups. There was significant different of accumulate liquid net balance between the two groups amount when 7 d after treatment.

NT-proBNP is caused by excessive pulling off ventricular cells when the capacity is too heavy. At that time, there is already a serious overload or even with heart failure. For critical ill patients, NT-proBNP can not predict the increase of cycle capacity and heart failure. As a monitoring indicator GEDVI and ITBVI, that can reflect the preload of heart and heart failure. They can reflect the information of capacity accurately which more sensitive than NT-proBNP. EVLWI reflect directly pulmonary edema and its severity, provide evidence for finding pulmonary edema timely and accurately. It is more responsive than GEDVI and ITBVI, in reflecting early capacity overload and heart failure (19). Monitoring PVPI, EVLWI can evaluate capillary permeability capacity load, heart failure and high EVLWI patients have poor prognosis, they need longer mechanical ventilation. Our research showed that PCT had no significant difference before treatment, after treatment 24, 48, 72 h between two groups. But the plasma NT-proBNP concentrations in

group B were lower than those in group after treatment 72 h. The difference was statically significant. There was no difference between this two groups in ITBVI, GEDVI, PVPI, EVLWI before treatment and after treatment 24 h, 48 h. There was significant difference between two groups in EVLWI after treatment 72 h.

During the process of fluid resuscitation of septic shock, pulmonary capillary leak syndrome is the most common complication. It can lead to reduced ARDS. It is crucial to recognize ARDS. We should considerate (P(A-a)DO₂), OI, Lac which can evaluate early lung oxygenation function(21). Our research showed that there was no significant difference between the two groups in (P(A-a)DO₂), OI, Lac before treatment and after treatment 24, 48 h. It was statistically significant after treatment 72 h.

Research confirmed that pulmonary ultrasound B-line monitoring was more accurate and sensitive to judge the increase and elimination of the pulmonary water in patients with advanced disease sensitively and accurately. Pulmonary ultrasound B line is more sensitive and accurate than NT-proBNP. Our research showed that B line which was displayed by ultrasound can guide high-volume filtration (HVHF) to decrease better EVLWI. It can effectively prevent the occurrence of extravascular lung water, reduce inflammatory mediators and pulmonary capillary permeability.

The patients in insufficient effective circulation need full and timely recovery of capacity to maintain a stable cycle. Early goal-directed therapy (EGDT) can effectively improve patient survival rate, but excess fluid load can make the patient's prognosis worse (22). Cordemans propose a concept of Late Goal Directed after Fluid Resuscitation (LGDFR) (23). Malbrain propose a precept of ROSE (24). However, there are no specific research data to tell when the LGDFR begins, finish and the amount of grasped dehydration.

Open fluid recovery and liquid overload can lead increasing of inducing the needs of organ support, mechanical ventilation time and complication, even increases fatality rate. New England Journal of Medicine published the outcome PROCESS, it leads larger clinical controversy (25).

Compared with the general treatment EGDT, it does not reduce fatality rates, hospitalization time, the time of living in ICU better. It also does not reduce organ support time (26).

Circulatory capacity overload seriously affects the outcome of patients. It is necessary to strengthen supervision and do goal-oriented dehydration therapy because the fight against patients is relatively hidden. We should have aggressive volume recovery early to correcting low perfusion. We can achieve the best condition through titration capacity management (27). When the condition of patient improves gradually, reduce the support and dehydration to reduce excess circulation capacity. Effective clearance capacity after resuscitation volume overload is beneficial to patient prognosis. Gordmans found that it could reduce extravascular lung water and improve patient's prognosis by PEEP and using albumin furosemide for dehydration (28). Our research accurately adjusted the capacity by using high-volume hemofiltration (HVHF), achieved refinement of capacity recovery and management strategy by critical ultrasound directing.

Ensuring organ perfusion and avoiding fluid overload is the essential to the treatment of septic shock. Therefore, objective, effective, especially non-invasive monitoring methods are necessary. After early full capacity of recovery, we should properly limit lipid intake properly and timely, then get into the late dehydration. For patients with poor cardiac function, we should pay more attention to capacity overload, closely monitor and implement late capacity management. Pulmonary ultrasound B line can reflect the capacity of critically ill patients accurately and sensitively. Our research show that: after treatment 7 d, the scores of APACHE- II, SOFA in group B were significantly lower than A group. The difference was statistically significant. After 28 d of following, the mortality rate had significant difference between the two groups.

Conclusion

For patients with septic shock, it is more effective depending on lung water B line monitored by pulmonary ultrasound than on heart output mon-

itored by USCOM. The former can better guide HVHF to control liquid negative balance, decrease the level of plasma NT-proBNP, reduce extravascular lung water index and the difference in alveolar-arterial oxygen exchange. It can also better improve oxygenation, lower the APACHE- II's rating and SOFA's rating, improve patient's outcomes after 28 d. However, this research was a retrospective study so that we should use prospective randomized study in the further studying.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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