Changing Characteristics of Extravascular Lung Water After Fluid Resuscitation in Septic Shock Patients by Early PiCCO Monitoring

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Abstract: This study aims to explore the changing characteristics of extravascular lung water after fluid resuscitation in septic shock patients by early PiCCO monitoring. 42 patients who were admitted to the ICU in our hospital and diagnosed as septic shock were collected. The patients were divided into two groups: treatment group (PiCCO group) (n=21) and control group (CVP group) (n=21). They were given early fluid resuscitation using different monitoring methods on the basis of conventional treatment for septic shock to monitor the changes of hemodynamics, EVLWI, oxygenation index (PaO_2/FiO_2) and BNP level before and after resuscitation. The BNP and LAC levels of the treatment group were significantly lower than those of the control group within 72 h (P<0.05). The use time of vasoactive drug, duration of mechanical ventilation and length of stay in ICU were significantly shorter in the treatment group than those in the control group (P<0.05), but there were no significant differences in the incidence of MODS and mortality between the two groups (P>0.05). ITBVI and GEDVI immediately, 12 h and 24 h after the fluid resuscitation were increased in the two groups compared with those before, between which the difference was statistically significant (P<0.01). Compared with those before resuscitation, the differences in PaO_2/FiO_2 at each time point in the two groups were not statistically significant (P>0.05). Early fluid resuscitation under the guidance of PiCCO has significant effect, which can be used as one of indicators for hemodynamic monitoring.

Keywords: PiCCO, Septic Shock, Fluid Resuscitation, Pneumonedema

1. Introduction

Septic shock and its secondary multiple organ dysfunction syndrome (MODS) mainly lead to death in ICU wards, which bottleneck the development of critical care medical science at present. During septic shock, hemodynamic changes are mainly featured in abnormal distribution of blood flow, resulting in significant insufficiency of effective circulating blood volume. Therefore, organ tissue is in a hypoperfusion state, leading to tissue hypoxia, metabolic dysfunction and progression. How to provide patients with sufficient capacity to ensure adequate volume resuscitation while preventing pulmonary edema from aggravating is the difficulty of the hemodynamic management in critical care medicine [1, 2]. Therefore, for patients with septic shock, early fluid resuscitation is one of the important measures for circulatory support, and especially early goal directed therapy (EGDT) can maintain stable circulation, and improve organ tissue perfusion and tissue oxygen supply. However, clinically many patients with septic shock suffer from varying degrees of pulmonary edema and tissue edema due to increased capillary permeability. If fluid resuscitation is performed, there will be the risks of aggravated oxygen metabolism that deteriorates respiratory functions [3, 4].

For a long time, clinically central venous pressure (CVP) is mostly used in the hemodynamic monitoring of patients with septic shock. In recent years, a large number of studies have shown that the correlation between CVP and cardiac preload is not accurate enough for the impact of many factors. Continuous cardiac output monitoring (PiCCO) is a new minimally invasive hemodynamic monitoring technology, which can simultaneously monitor cardiac

output (CO), cardiac index (CI) and capacity indicators such as intra-thoracic blood volume index (ITBVI), global end-dilution volume index (GEDVI), extra-vascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI), and can also monitor vascular resistance changes. In addition, PiCCO, which can be operated in a convenient and simple way, can guide the clinical treatment of critically ill patients timely and effectively [5, 6].

This study aims to compare the effects of early fluid resuscitation under the guidance of PiCCO capacity monitoring and CVP monitoring on the levels of blood-brain natriuretic peptide (BNP), lactic acid (LAC), time of vasoactive drug application and prognosis.

2. Materials and Methods

The experiments were approved by the Clinical Ethics Committees of the First Teaching Hospital of Xinjiang Medical University.

2.1. General Information

42 hospitalized patients in ICU who were diagnosed as septic shock in our hospital from January 2019 to October 2019 were collected. The patients were divided into two groups: treatment group (PiCCO group) (n=21), in which there were 12 males and 9 females with the mean age of (44.6 ± 8.7) years old; control group (CVP group) (n=21), in which there were 11 males and 10 females with the age of (45.8 ± 9.2) years old on average.

Diagnostic criteria for septic shock: 1) clinically definite infection; 2) existence of SIRS; 3) systolic blood pressure less than 90mmHg or more than 40 mmHg lower than the original baseline value for at least 1 h or blood pressure maintained by infusion or drugs; 4) poor adverse tissue perfusion such as oliguria (<30 ml/h) for over 1 h or acute consciousness disorder. The shock time of onset of patients enrolled was less than 24 h, and all patients were given mechanical ventilation auxiliary support [7].

Exclusion criteria: 1) patients above 70 years old (elderly patients had poor functional reserve of basis organs with uncertain therapeutic effect); 2) patients with large area of myocardial infarction, acute coronary syndrome and history of cardiac insufficiency; 3) patients with acute severe craniocerebral injury (severe cerebral trauma, massive cerebral hemorrhage, massive cerebral infarction and severe brain-stem injury), GCS score <5; 4) patients with severe underlying diseases beyond cure: active massive hemorrhage than cannot be stopped; severe abdominal infection beyond effectively drainage; advanced cancer; in dying state difficult to be cured [8].

2.2. General Treatment

Broad-spectrum antibiotics that could cover possible pathogens as much as possible were given to protect organ functions, monitor clotting function, kidney function, liver function, blood lactate (LAC) level, blood gas analysis changes and altered mental status, and vasoactive drugs were discontinued after the blood pressure was restored to normal after active treatment.

2.3. Early Fluid Resuscitation

The two groups of patients were performed early fluid resuscitation by different monitoring methods on the basis of the conventional treatment of septic shock.

2.4. Monitor Indices

The changes in hemodynamics, and levels of EVLWI, oxygenation index (PaO_2/FiO_2) and BNP before and after fluid resuscitation were monitored.

2.5. Fluid Supplement of the Treatment Group Under PiCCO Monitoring

PiCCO thermosensitive catheter and central venous catheter were connected with PiCCO monitoring module respectively after being connected with the temperature probe to record the monitoring data of patients, including CI, ITBI, GEDI, EVLWI and SVV. The data reached the following levels within 12 h: 1) GEDI>700 ml/m^2 or ITBI>850 ml/m^2; 2) mean arterial pressure $\geq$ 70 mmHg, urine output$\geq$0.2 ml/kg/h; 3) central venous oxygen saturation $\geq$ 75%. Method of fluid resuscitation: the patients with CI<3.0 L/min/m^2, if EVLWI<10 ml/kg, vasoactive drug was added to adjust CI to higher than 3.0 L/min/m^2 and maintain EVLWI <10ml/kg and SVV <10%. When CI>3.0 L/min/m^2 and EVLWI>10 ml/kg, the amount of fluid was limited and diuresis was performed appropriately.

2.6. Fluid Supplement of the Control Group by CVP Measurements

The data reached within 12 h: CVP 9-11 mmHg; mean arterial pressure $\geq$ 70mmHg; urine output $\geq$ 0.5ml/kg/h; central venous oxygen saturation $\geq$ 75%. Method of fluid resuscitation: if CVP$\leq$8 mmHg, fluid infusion was applied, and if CVP $\geq$ 12mmHg, the amount of fluid was limited.

2.7. Hemodynamic Indices

Single indicator thermodilution was used: central venous catheter was catheterized into the right internal jugular vein for continuous monitoring of CVP, and then connected with the temperature probe and PiCCO monitor (PULSION Medical Systems AG, Germany). Femoral artery was placed into PiCCO catheter (PULSION Medical Systems AG, Germany). PiCCO monitor was opened to connect with pressure transducer for continuous monitoring of invasive arterial pressure after zero setting. 30 mL of normal saline at 4°C~10°C was injected via central venous catheter to measure EVLWI, ITBVI, GEDVI, CI and SI, and pulmonary capillary permeability index (PVPI) was tested using the method of single indicator thermodilution.

2.8. Blood Gas Analysis

Arterial blood pH value, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial oxygen saturation (SaO_2) were measured, and the PaO_2/FiO_2 ratio was calculated.

2.9. Statistical Analysis

All the data were analyzed by SPSS 13.0. The measurement data were expressed as (x±s). The groups were compared by the t test. The numeration data were subjected to the X^2 test.

$P < 0.05$ was considered statistically significant.

3. Results

3.1. General Information

There were no statistically significant differences in the gender, age, admission APACHE II score and basic infection focus distribution between the two groups (P>0.05) (Table 1).

Table 1. General information.

Group	Gender (M/F)	Age	APACHE II	LAC (mmol/L)	Infection resource (n)		
					Lung	Abdominal cavity	Others
Treatment	12±9	44.6±8.7	21.5±4.7	6.3±2.9	16	4	1
Control	11±10	45.8±9.2	20.6±5.3	6.23±3.1	15	5	1

3.2. BNP and LAC Levels Within 72 h

The BNP level in the treatment group showed an overall downward trend within 72h of early resuscitation. Except the first 12h, the BNP levels at each time point in the treatment group were significantly lower than those in the control group (P <0.05) (Table 2).

Table 2. BNP levels within 72 h.

Group	12 h	24 h	48 h	72 h
Treatment	629.4±83.6	673.8±96.8*	485.1±83.8*	317.3±69.2*
Control	536.5±74.5	836.7±104.5	738.6±93.5	638.7±83.5

*P<0.05 vs the control group.

Compared with the control group, the blood LAC level of the treatment group gradually decreased. The LAC level of the treatment group was significantly lower than that of the

control group (P <0.05), and the differences within 24 h and 48 h were highly significant (Table 3).

Table 3. LAC levels within 72 h.

Group	12 h	24 h	48 h	72 h
Treatment	7.2±3.5	5.1±2.7*	2.8±1.2*	2.2±1.3
Control	7.8±3.6	9.8±3.4	5.7±3.1	3.1±1.4

*P<0.05 vs the control group.

3.3. Indices Before Resuscitation

Before resuscitation, the CI and SVI levels of the control group were higher than those of the treatment group, between which the differences were statistically significant (P<0.05), but no significant difference was found in other indices (P>0.05) (Table 4).

Table 4. Hemodynamic indices before resuscitation.

Group	ITBVI (ml/m²)	CEDVI (ml/m²)	CI (L/min·m²)	SVI (ml/m²)	CVP (mmHg)	PaO₂/FiO₂ (mmHg)
Treatment	686.7±99.8	538.9±75.9	2.5±1.5*	24.7±8.9*	11.7±3.6	185.8±48.1
Control	679.3±96.3	536.8±73.8	4.1±1.4	36.8±9.5	11.3±3.4	198.6±46.8

*P<0.05 vs the control group.

3.4. Hemodynamic Data Before and After Fluid Resuscitation

Shock symptoms and signs changed evidently after fluid resuscitation. The results show that ITBVI and GEDVI immediately, 12 h and 24 h after fluid resuscitation were increased in the two groups compared with those before, between which the differences were statistically significant (P<0.01). Compared with that before resuscitation, the differences of PaO_2/FiO_2 at each time point in the two groups were not statistically significant (P>0.05). The CI and SVI levels at each time point in the control group did not significantly differ from those before resuscitation (P>0.05).

Nevertheless, the CI levels immediately and 2 h after fluid resuscitation were higher than those before resuscitation (P<0.01), and the SVI levels 12 h and 24 h after fluid resuscitation were increased compared with that before resuscitation (P<0.01). Compared with that before resuscitation, CVP in the control group was increased only in 24 h (P<0.01), while those in the treatment group 12 h and 24 h after resuscitation were elevated (P<0.01). Compared with that before resuscitation, EVLWI of the two groups instantly, 12 h and 24 h after resuscitation were increased (P<0.05) (Table 5).

Table 5. Hemodynamic data before and after fluid resuscitation.

Group	Index	Before	After Immediately	12 h	24 h
Treatment	ITBVI (ml/m^2)	716.8±116.7	796.8±104.6*	937.5±137.6*	824.6±121.8*
Control		714.9±109.4	884.9±126.4*	901.6±108.9*	881.5±132.5*
Treatment	GEDVI (ml/m^2)	594.6±73.8	701.5±84.5*	731.5±115.5*	653.5±112.5*
Control		596.4±74.5	676.8±85.5*	716.1±105.6*	694.5±106.5*
Treatment	CI [L/(min·m^2)]	2.9±1.1	3.7±1.3*	3.8±1.2*	3.2±1.1
Control		3.8±1.1	3.9±1.2	3.5±1.1	3.6±1.1
Treatment	SVI (ml/m^2)	26.1±8.7	27.9±8.9	31.5±10.5*	31.7±9.7*
Control		36.6±9.4	38.4±10.6	37.5±11.6	38.9±11.9
Treatment	CVP (mmHg)	9.6±3.1	9.8±3.4	12.4±3.8*	12.9±4.1*
Control		11.1±2.8	11.6±2.4	11.4±2.6	14.2±3.8*
Treatment	PaO$_2$/FiO$_2$ (mmHg)	192.6±34.5	179.3±36.1	191.3±39.1	197.3±41.0
Control		218.6±43.6	224.6±46.5	227.6±50.4	221.7±48.4
Treatment	EVLWI (ml/kg)	11.5±3.0	13.5±3.4*	15.6±4.3*	12.9±4.1#
Control		6.7±1.2	8.4±1.8#	8.6±1.6#	10.6±2.4*
Treatment	MAP (mmHg)	48.1±12.6	49.2±11.6	52.4±12.7	58.1±13.8#
Control		52.3±16.4	52.9±17.1	67.2±16.2	59.7±17.4#
Treatment	Heart rate (bpm)	117.6±31.5	117.0±29.8	108.4±28.4*	104.6±29.8*
Control		124.5±34.5	123.7±32.1	106.2±24.9*	103.8±22.9*
Treatment	UV (ml/h)	19.6±8.2	20.6±8.4	28.1±9.7#	35.7±9.9*
Control		24.6±9.4	24.7±8.9	35.1±8.1#	39.2±9.2*

Compared with the results before administration, #P<0.05, *P<0.01.

3.5. Follow Up

The patients were followed up for 30 d. The use time of vasoactive drug, duration of mechanical ventilation and length of stay in ICU were significantly shorter in the treatment group than those in the control group (P<0.05), but there were no significant differences in the incidence of MODS and mortality between the two groups (P>0.05) (Table 6).

Table 6. Follow-up results.

Group	Discontinued time of vasoactive drug (h)	Mechanical ventilation duration (h)	ICU stay length (d)	MODS [n(%)]	Morality [n(%)]
Treatment	52.6±14.7*	163.7±37.2*	17.9±5.8*	4 (19.05%)	2 (9.52%)
Control	60.1±13.8	228.4±47.9	26.9±6.9	5 (23.81%)	1 (4.76%)

*P<0.05 vs the control group.

4. Discussion

The pathophysiologic characteristics of severe septic shock are manifested as follows. The decline of systemic vascular resistance accompanied by normal or increased cardiac output is often referred to as high-velocity type hemodynamic status. The basis of hemodynamic change is systolic and diastolic dysfunction of peripheral vessel so as to cause abnormal blood flow distribution, inadequate tissue perfusion, pathological dependence of oxygen supply and consumption, increased capacity of vascular bed, leading to relative capacity insufficiency, and meanwhile capillary permeability increases, intravascular fluid leaks to tissue and the third space, and cardiac function is inhibited. Therefore, about 50% of severe sepsis patients will appear different forms of left ventricular dysfunction with or without right ventricular hypofunction [9, 10]. B-type natriuretic peptide (BNP), which can be significantly increased during left heart failure, is an independent risk factor for the diagnosis of left heart failure and prognosis evaluation. In recent years, it has been reported that pulmonary arterial hypertension and right ventricular dilatation can also lead to increased plasma BNP. Chung et al. found that plasma BNP level was positively correlated to mean pulmonary artery pressure (r = 0.73), and was related to the severity of right ventricular dysfunction [11].

Lactic acid is produced mainly through anaerobic glycolysis, metabolized and cleared in the liver and kidney, whose elevation reflects the increase of anaerobic metabolism in the case of low perfusion. Early fluid resuscitation aims to maintain venous blood capacity, increase cardiac output and tissue oxygen supply in patients with septic shock, correct hypoperfusion, and the monitoring on lactate dynamic changes, as an indicator that can clearly reflect tissue hypoperfusion LAC quickly and accurately. In this study, the lactate level of the treatment group was significantly lower than that of the control group, and showed a gradual downward trend, which confirms again that early fluid resuscitation under the guidance of PiCCO capacity monitoring can accurately grasp the fluid infusion volume and speed to maintain venous blood capacity and effectively improve tissue and organ perfusion, so as to speed up the discharge of metabolic acidic products, reduce the side effects caused by the accumulation of acidic metabolites as soon as possible, playing an active role in maintaining environmental stability in patients with septic shock, and its direct consequences can lead to the dosage reduction and disuse of

vasoactive drugs, shorter duration of mechanical ventilation and decreased length of stay in ICU [12, 13].

In case of septic shock, due to the abnormal distribution of systemic blood flow, patients may suffer from varying degrees of relative or absolute lack of effective circulating volume. Therefore, fluid resuscitation is one of the important means of circulatory support in patients with septic shock, which can effectively improve tissue perfusion. Studies have shown that the application of colloidal liquid on septic shock patients for fluid resuscitation can significantly improve the levels of ITBVI and ITBVI of patients with different degrees of pulmonary edema and significantly improve the CI and SI levels of patients with relatively high lung water [14, 15]. Although septic shock patients may experience increased EVLWI and CVP to varying degrees in the fluid resuscitation process, especially for those whose lung water level has been already high, the temporary increase of lung water cannot affect oxygenation and respiratory function. EVLWI, as a quantitative indicator for pulmonary edema, can provide the pathological process of its occurrence, development and evolution in an early, sensitive, intuitive way, helping guide its treatment and prognosis [16, 17]. The EVLWI has a significant correlation with duration of mechanical ventilation, length of stay and mortality of patients with severe infection and septic shock. Extravascular lung water monitoring experiences the development process from qualitative to quantitative analysis, from invasion to non-invasion, from experiment to the clinic and then to the bedside. There are many methods for EVLW measurement, such as X-ray chest radiograph, indirect method of measurement, dry weight method, double-tracer dilution method and PiCCO; but EVLWI measured by PiCCO to reflect the severity of pulmonary edema is most convenient and reliable.

Increased capillary permeability in septic shock patients may result in the loss of albumin, tissue edema and pulmonary edema. Although there is no generally-accepted recommendation for the selection of fluid for resuscitation with the best effect, it is found that more total crystalloid solution is needed than colloid solution for fluid resuscitation. In this process, whether crystalloid solution has an impact on oxygenation or not needs to be confirmed by further research [18, 19]. Therefore, the blood volumes of patients in early resuscitation in this study were markedly increased and maintained more than 12 h. In the early stage of resuscitation, even patients with increased lung water may have no obvious deterioration of oxygenation after resuscitation. In addition, to increase colloid osmotic pressure cannot effectively reduce lung water. Therefore, non-high-capacity fluid resuscitation may be also applied to patients with pulmonary edema. Currently, septic shock is a difficult problem in the work of ICU. Its mortality increases with the severity of the disease which needs to be able to quickly raise blood pressure, improve blood perfusion of the heart and increase the perfusion of vital organs so as to improve tissue ischemia, hypoxia and to prevent the occurrence of multiple organ failure [20].

5. Conclusion

In summary, by monitoring the changes of CI, EVLW I, ITBVI and GEDVI, PiCCO monitoring technology can show the volume status of patients with septic shock in a dynamic, accurate and intuitive way. The early fluid resuscitation under the guidance of PiCCO has significant effect, and meanwhile the PiCCO monitoring is simple, minimally invasive and safe, which can substitute for CVP to be one of hemodynamic monitoring indicators for EGDT.

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