Evaluation and prognostic value of $Cv\text{-}aCO_2/Da\text{-}vO_2$ in patients with septic shock receiving fluid resuscitation $Cv\text{-}aCO_2/Ca\text{-}vO_2$

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Abstract. The present study aimed to evaluate the prognostic value of venous-arterial CO_2 to arterial-venous O_2 ($Cv\text{-}aCO_2/Da\text{-}vO_2$) for patients with septic shock treated by fluid resuscitation. A total of 108 cases who received fluid resuscitation for septic shock at the Intensive Care Unit were retrospectively screened according to the 2012 surviving sepsis campaign guidelines. Patients were divided into 2 groups according to the $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio at 6 h after fluid resuscitation: Group A, $Cv\text{-}aCO_2/Da\text{-}vO_2 >1$; group B, $Cv\text{-}aCO_2/Da\text{-}vO_2 \leq 1$. The resuscitation target rate and transfused resuscitation volume at 6 h exhibited no significant difference between the 2 groups. The cardiac output at 6 and 24 h, as well as the ratio of patients who reached the target of resuscitation within 24 h, the 24-h lactic acid clearance rate and the number of cases with central venous oxygen saturation >70% were significantly decreased in group A compared with those in group B (all $P<0.05$). The Sequential Organ Failure Assessment score at day 3 in group A was higher compared with that in group B (7.94±1.6 vs. 6.82±1.9; $P=0.0013$). The mortality rate at day 7 and 35 was higher in group A compared with that in group B (29/52 vs. 6/56, $P<0.001$; 48/52 vs. 36/56; $P<0.001$). In conclusion, the $Cv\text{-}aCO_2/Da\text{-}vO_2$ was able to effectively evaluate the success rate of resuscitation and, regarding prognosis, it was able to identify patients at high risk of adverse outcomes.

Introduction

Septic shock is the most common acute critical disease encountered at the Intensive Care Unit (ICU). Septic shock is also the major cause of death at the ICU (1). The annual incidence of reported cases of septic shock is increasing year by year. Determination of the prognosis of patients with septic shock remains a difficult problem for clinicians. Disturbance of hemodynamics is the most prominent manifestation of septic shock (2). To maintain the stability of the cycle in the early stage of shock, resuscitation of a large amount of fluid is frequently required. After sufficient fluid resuscitation, certain patients exhibit obvious responses, including an increased amount of urine or blood pressure, while other patients exhibit a lesser reaction, leading to infusion of more fluids and gradually more tissue edema, but those patients remain in a state of hypotension with no increase in urine.

Once a patient's condition improves, a large amount of liquid returns to the blood vessels. If the function of the patient's heart, lung, liver and kidney are intact at this time, the excess liquid is eliminated by increasing the amount of urine, which is referred to as a negative balance of liquid in the clinic and the edema of the whole body fades away. Once this negative balance of fluid is present, fluid resuscitation may cause excessive load and aggravate the burden of the heart and lung. Indirect evaluation of prognosis through evaluating the success of fluid resuscitation has become the focus of clinical research (3). As a low-perfusion index for patients with septic shock, lactic acid has been used for numerous years (4). However, multiple non-perfusion factors may also cause an increase in lactic acid and consequently, the reliability of this index is limited. Therefore, the discovery of novel and more accurate indicators has become a hot spot of clinical research.

The Acute Physiology and Chronic Health Evaluation (APACHE II) score is used to evaluate the severity of septic shock, with a higher score indicating more serious septic shock, more extensive physiological dysfunction of the body and greater difficulty for patients to reach a negative fluid balance (5). The Sequential Organ Failure Assessment (SOFA) score numerically quantifies the number of organs with failure and the severity thereof (6). The two indexes are commonly used to evaluate the severity of septic shock in the clinic. Ospina-Tascón *et al* (7) indicated that the combination of arterial lactate levels and ratio of venous-arterial CO_2 to arterial-venous O_2 ($Cv\text{-}aCO_2/Da\text{-}vO_2$) exhibited an improved ability to identify high-risk.

The aim of the present study was to investigate whether $Cv\text{-}aCO_2/Da\text{-}vO_2$ may serve as an independent predictor of the success rate of resuscitation and the prognosis of patients with septic shock. Also the present study aimed to further clarify the specific value of $Cv\text{-}aCO_2/Da\text{-}vO_2$ as a high-risk indicator.

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Patients and methods

Patients. The clinical data of patients (n=108; male, 74; female, 34) with septic shock treated at the ICU, The First Hospital of Shijiazhuang (Shijiazhuang, China), from March 2012 to December 2017, were retrospectively reviewed. The patient characteristics are listed in Table I. The inclusion criteria were as follows: i) Patients with septic shock who received resuscitation at the ICU; ii) the septic shock was diagnosed in accordance with the diagnostic criteria of septic shock of International Sepsis Definitions Conference in 2001 (8): Systolic blood pressure <90 mmHg, or <40 mmHg than the base value, patient is not able to recover or requires maintenance by vasoactive drugs after 1 h of fluid resuscitation, patients with low perfusion of organ tissue and patients with lactic acid poisoning, oliguria or changes in state of acute consciousness. Patients were excluded if the following applied: Age of <18 years, pregnancy, chronic renal failure, acute cerebrovascular disease, severe arrhythmia, valvular heart disease, untreated tumors, expected death within 48 h and excessive volume load as judged by the clinicians, or patients with heart function intolerance of dilatant. The present study was approved by the Ethics Committee of First Hospital of Shijiazhuang and written informed consent was obtained from each subject or their immediate family members.

Resuscitation. A dual-lumen vein catheter was inserted through the internal jugular vein or subclavian vein after patients were admitted to the ICU. Standardized treatment was performed following the China guidelines for sepsis from 2014, as early as possible (9). This included fluid resuscitation as soon as possible, vasoactive drug application, complete recording of etiological information within 1 h, antibiotic application and oxygen therapy. The resuscitation target in the first 6 h was as follows: Central venous pressure (CVP) 8-12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, urine volume ≥0.5 ml/kg/h, central venous oxygen saturation ($SCVO_2$) ≥70% or SvO_2 ≥65% and a superior vena cava oxygen saturation of >70%.

Demographic data and parameters. Demographic data, including the patients' gender and age, as well as basic vital signs, including body temperature, heart rate, blood pressure were obtained. Routine examination indexes, including arterial blood gas analysis, upper vena cava blood gas analysis, routine hematuria, liver and kidney function, electrolytes, myocardial enzymes and myocardial markers were determined, and chest, thoracic and abdominal computed tomography was performed. The following parameters were evaluated with a GEM Premier 4000 blood gas analyzer (GE Healthcare) and recorded: $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio at 6-h of resuscitation, resuscitation rate at 6 h, incidence of multiple organ dysfunction and mortality rate at day 7 and 35. The $Cv\text{-}aCO_2/Da\text{-}vO_2$ was calculated according to Ospina-Tascón *et al* (7) with assistance by Werfen.

Statistical analysis. Statistical analysis was performed with SPSS 19 software (IBM Corp.). The measured data were expressed as the mean ± standard deviation. Continuous variables between the 2 groups were compared using the t-test and count data were compared with a Chi-squared test. Kaplan-Meier analysis with the log-rank (Mantel-Cox) test was performed to compare survival in the 2 groups with follow up to 35 days. P<0.05 was considered to indicate a statistically significant difference.

Table I. Baseline data of the 2 groups.

Variable	Group A	Group B	P-value
Case (N)	52	56	-
Sex (male, N)	36	38	0.878
Age (yrs.)	59 (51-71)	60 (47-69)	
APACHE II Score	17.9±2.0	18.5±2.2	0.123
SOFA score at day 1	8.86±1.7	8.72±1.8	0.679

SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation. Age was shown as median (Interquartile Range, IQR).

Results

Baseline data. After screening, 108 cases treated between January 2012 and December 2017 were selected. Of these, 59 cases were male and 49 were female, and their average age was 55.4±13.4 (range 34-71) years. The patients were divided into 2 groups according to the calculated $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio at 6 h after fluid resuscitation: Group A, $Cv\text{-}aCO_2/Da\text{-}vO_2$ >1 (n=52); group B, $Cv\text{-}aCO_2/Da\text{-}vO_2$ <1 (n=56). The average age was 63.2±5.2 years in group A and 61.9±3.2 years in group B. The baseline data of the 2 groups are listed in Table I. Comparison indicated that the age and gender distribution were not significantly different between the 2 groups, while group A had a lower APACHE II score and higher SOFA score at day 1; however, the differences were not significant.

Resuscitation within 24 h. Table II provides a comparison of resuscitation data between the two groups. The ratio of subjects who reached the target of resuscitation at 6 h was not significantly different between groups A and B (40/52 vs. 43/56; P=0.987), while the ratio of subjects who reached the target of resuscitation was significantly decreased in group A compared with that in group B at 24 h (42/52 vs. 53/56; P=0.027). In addition, the 24-h lactate clearance rate in group A was significantly lower than that in group B (0.21±0.14 vs. 0.47±0.15; P<0.0001). The number of cases with $SCVO_2$ >70% in group A was also lower than that group B (30 vs. 44; P=0.038) and the 24-h cardiac output (CO) in group A was significantly decreased compared with in group B (4.47±0.34 vs. 5.03±0.41; P<0.0001).

SOFA score and mortality. At day 1, the SOFA score in group A was similar to that in group B and the SOFA score had decreased in the two groups after resuscitation. At day 3, the SOFA score was significantly decreased in group B compared with in group A (6.82±1.92 vs. 7.94±1.62; P=0.0013; Fig. 1). In addition, the mortality rate at day 7 and 35 was significantly higher in group A when compared with that group B (29/52 vs. 6/56; P<0.001; 37/52 vs. 21/56; P<0.001), which was shown in Table II.

Table II. Comparison of 2 groups with 24-h of resuscitation.

Variable	Group A	Group B	P-value
Case (N)	52	56	-
Mechanical ventilation (case, N)	49	54	0.587
Adrenaline user (case, N)	52	56	-
Resuscitation volume at 6-h (ml)	3,029±320	2,992±288	0.529
Reached targeted resuscitation case at 6-h (N)	40	43	0.987
Lactate clearance rate at 6-h (%)	16.5±10.2	23.5±15.2	0.0063
CO at 6-h (l/min)	4.45±0.38	4.85±0.49	<0.0001
Reached targeted resuscitation case at 24-h (N)	42	53	0.0268
Lactate clearance rate at 24-h (%)	21.1±13.9	47.4±15.6	<0.0001
Case of $SCVO_2$ at 24-h >70% (N)	30	44	0.038
CO at 24-h (l/min)	4.47±0.34	5.03±0.41	<0.0001
Mortality at day 7 (N, dead/survival)	29/23	6/50	<0.001
Mortality at day 35 (N, dead/survival)	37/15	21/35	<0.001

CO, Cardiac output. Continuous variables between the 2 groups were compared using the t-test and count data were compared with a Chi-squared test.

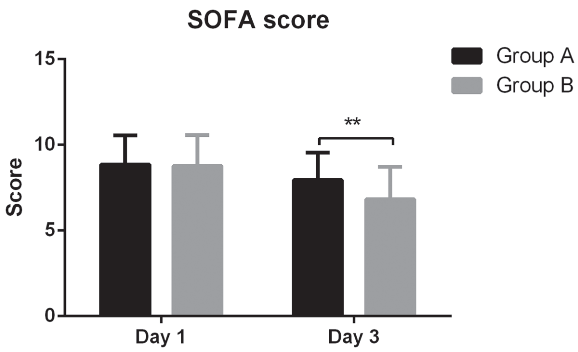

Figure 1. SOFA score in the two groups. The SOFA score in group B at day 3 was lower compared with that in group A. Groups: A, $Cv\text{-}aCO_2/Da\text{-}vO_2 > 1$; B, $Cv\text{-}aCO_2/Da\text{-}vO_2 \leq 1$. **P<0.01 with comparisons indicated by lines. SOFA, Sequential Organ Failure Assessment; $Cv\text{-}aCO_2/Da\text{-}vO_2$, venous-arterial CO_2 to arterial-venous O_2.

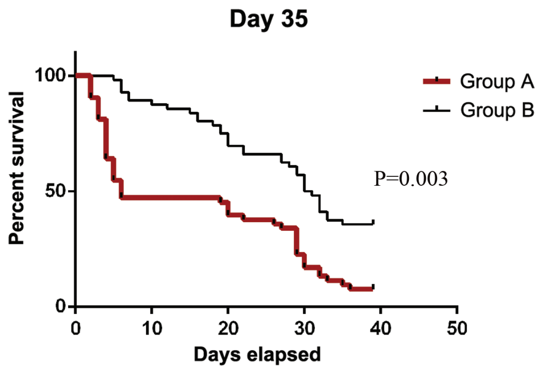

Figure 2. Kaplan-Meier analysis for comparison of survival between the two groups during the 35-day follow up period. During this time, the survival was significantly different between the two groups [P=0.0012; log-rank (Mantel-Cox) test]. Groups: A, $Cv\text{-}aCO_2/Da\text{-}vO_2 > 1$; B, $Cv\text{-}aCO_2/Da\text{-}vO_2 \leq 1$. $Cv\text{-}aCO_2/Da\text{-}vO_2$, venous-arterial CO_2 to arterial-venous O_2.

Survival analysis. Kaplan-Meier analysis with the log-rank (Mantel-Cox) test was performed to compare survival in the 2 groups with follow up to 35 days. The results suggested that survival in group A was significantly lower than that in group B (P=0.003; Fig. 2). The median survival time in group A during 35-day period was 6 days, while the median survival time in group B was 17 days.

Discussion

The treatment of sepsis represents a severe healthcare challenge worldwide. The reported incidence of sepsis in the past 10 years in developed countries is 4.37/100,000 per year, with a mortality rate of 17.1%. The incidence of severe sepsis is 2.72/100,000 per year, with a mortality rate of 26.4% (10). A Chinese study determined that the number of hospitalized sepsis patients accounts for >50% of the total number of ICU patients (11). For developing countries, no relevant data are available, but the rate is expected to be even higher.

Since Rivers *et al* (1) proposed the concept of early goal-directed therapy in 2001, early fluid resuscitation therapy for septic shock has received widespread clinical attention. A series of guidelines published in recent years have affirmed that early fluid resuscitation, early diagnosis and early hemodynamic support are important means of septic shock treatment (12-14). Rivers *et al* (1) also proposed to achieve the goal of resuscitation within 6 h after the onset of septic shock and strive to correct early hemodynamic abnormalities and systemic tissue hypoxia in the early stage of shock in order to prevent the occurrence of more serious inflammation and multiple organ failure. Fitch and Gossage (15) determined that if the MAP was raised to 65-75 mmHg within 1 h after fluid resuscitation, the hemodynamic status of septic shock patients was significantly improved in the early stage. Early fluid resuscitation in septic shock can improve hemodynamic stability, improve tissue and organ perfusion, reduce the incidence of multiple organ failure and reduce mortality.

These benefits stem from the increased emphasis on monitorable and assessable goal-directed therapy in early fluid resuscitation. Fluid resuscitation remains a challenge in daily practice due to the potential hazards of insufficient vascular content and overload. Various methods have been developed to set targets for fluid resuscitation. Simple evaluation of the vital signs, CVP and urine volume as indicators has certain limitations. $SCVO_2$ may reflect the balance of oxygen supply and demand in the entire body. When $SCVO_2$ is >70%, oxygen supply and demand reach a balance. $SCVO_2$ may be used as an evaluation index of fluid resuscitation in the early stage of septic shock (16).

A recent study confirmed that the $SCVO_2$ value is frequently reported to be normal or near normal on admission to the ICU (17). In addition, normal hemodynamic and oxygen metabolism indices do not ensure adequate tissue perfusion and do not prevent progression and organ dysfunction leading to death or complete organ failure (18). Lactic acid has also been proposed as a target for resuscitation (19). In fact, not only the basic level of lactate, but the direction of lactate level changes after treatment intervention is also associated with clinical prognosis (20). However, the effects that have been reported when using the lactate-oriented resuscitation cluster strategy are not consistent among studies (21). Therefore, more indicators reflecting tissue hypoperfusion should be explored, particularly when $SCVO_2$ is close to normal.

Recently, the partial pressure of carbon dioxide ($Pv\text{-}aCO_2$) has been recommended as an alternative indicator of hypoperfusion (22). Derived from oxygen parameters, persistently elevated $Pv\text{-}aCO_2$ is an independent predictor of poor prognosis and may predict changes of lactate levels (22). However, high cardiac conduction to high flow prevents the accumulation of intravenous carbon dioxide in septic shock (23). $Pv\text{-}aCO_2$ may be normal even in the presence of severe tissue hypoperfusion; similarly, due to the Haldane effect, $Pv\text{-}aCO_2$ increases in certain patients even without tissue hypoperfusion (22). Therefore, the change of CO_2 must be evaluated through the change in O_2. Under aerobic metabolism conditions, the production of CO_2 should not exceed the utilization of O_2. Thus, the ratio of $Pv\text{-}aCO_2/Da\text{-}vO_2$ may replace the ratio of VCO_2/VO_2 (i.e. respiratory quotient) and identify patients at risk of anaerobic metabolism.

Using this principle, Mekontso-Dessap *et al* (24) demonstrated that $Pv\text{-}aCO_2/Da\text{-}vO_2$ >1.4 was significantly superior to $Pv\text{-}aCO_2$, SvO_2 and $Da\text{-}vO_2$ in predicting hyperlactatemia in critically ill patients. Importantly, changes in $Pv\text{-}aCO_2/Da\text{-}vO_2$ are more sensitive than lactic acid, making it an attractive monitoring indicator. Therefore, when $SCVO_2$ or SvO_2 is relatively low, the change of $Cv\text{-}aCO_2/Da\text{-}vO_2$ may better reflect the change of oxygen consumption than that of $Pv\text{-}aCO_2/Da\text{-}vO_2$. This is due to $Cv\text{-}aCO_2/Da\text{-}vO_2$ reflecting persistent anaerobic metabolism.

Ospina-Tascón *et al* (7) suggested that $Cv\text{-}aCO_2/Da\text{-}vO_2$ is a reliable indicator for resuscitation, while the present clearly indicated that 1 is a suitable threshold. In the present study, it was demonstrated that the CO at 6 and 24 h, ratio of patients who reached the target of resuscitation at 24 h, lactic acid clearance rate at 24 h and number of cases with $SCVO_2$ >70% were decreased in patients with $Cv\text{-}aCO_2/Da\text{-}vO_2$ >1. In addition, the mortality rate at day 7 and 35 was increased in patients with $Cv\text{-}aCO_2/Da\text{-}vO_2$ >1 and the survival rate was different at day 35, which demonstrated that $Cv\text{-}aCO_2/Da\text{-}vO_2$ may be used to effectively evaluate the success rate of resuscitation and identify patients at high risk of adverse outcomes. It may be suggested that if the $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio is >1, early intervention may improve the prognosis of such patients.

If patients present with a $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio of <1, it provides a measure of the extent of anaerobic metabolism. In this case, the present study recommends the following actions: Increase the dose of fluid resuscitation, increase CO, improve total hypoxia levels and improve the respiratory function of patients. If the $Cv\text{-}aCO_2/Da\text{-}vO_2$ ratio increases, indicating improved prognosis, intensive fluid resuscitation can then be reduced.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ was in charge of manuscript writing and data analysis. XS and SW were in charge of clinical data recording. ZH and HC were in charge of design of the experiments, analysis and interpretation of the data, and also provided funding support. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of First Hospital of Shijiazhuang and written informed consent was obtained from each subject or their immediate family members.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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