Evaluation and prognostic value of Cv-aCO₂/Da-vO₂ in patients with septic shock receiving fluid resuscitation Cv-aCO₂/Ca-vO₂

HUILING ZANG, XIAOHUI SHEN, SHENGCHI WANG, ZHIHONG HE and HUI CHENG

Department of Intensive Care Unit, The First Hospital of Shijiazhuang, Shijiazhuang, Hebei 050000, P.R. China

Received October 23, 2018; Accepted July 16, 2019

DOI: 10.3892/etm.2019.7956

Abstract. The present study aimed to evaluate the prognostic value of venous-arterial CO₂ to arterial-venous O₂ (Cv-aCO₂/Da-vO₂) 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-aCO₂/Da-vO₂ ratio at 6 h after fluid resuscitation: Group A, Cv-aCO₂/Da-vO₂ >1; group B, Cv-aCO₂/Da-vO₂ ≤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 lactate 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; 48/56 vs. 36/56; P<0.001). In conclusion, the Cv-aCO₂/Da-vO₂ 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. Osypina-Tascón et al (7) indicated that the combination of arterial lactate levels and ratio of venous-arterial CO₂ to arterial-venous O₂ (Cv-aCO₂/Da-vO₂) exhibited an improved ability to identify high-risk.

The aim of the present study was to investigate whether Cv-aCO₂/Da-vO₂ 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-aCO₂/Da-vO₂ as a high-risk indicator.

Correspondence to: Dr Zhilihong He or Dr Hui Cheng, Department of Intensive Care Unit, The First Hospital of Shijiazhuang, 36 Fanxi Road, Changnan, Shijiazhuang, Hebei 050000, P.R. China
E-mail: 537728379@qq.com
E-mail: hcheng6699@163.com

Key words: Cv-aCO₂/Da-vO₂, septic shock, curative effect, prognosis
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 (SCVO2) ≥70% or SvO2 ≥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-aCO2/\(v\)-O2 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-aCO2/\(v\)-O2 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.

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-aCO2/\(v\)-O2 ratio at 6 h after fluid resuscitation: Group A, Cv-aCO2/\(v\)-O2 >1 (n=52); group B, Cv-aCO2/\(v\)-O2 ≤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. The measured data were expressed as the mean ± standard deviation. Continuous variables 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.

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 SCVO2 >70% in group A was also lower than that in 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.

| 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).
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 the 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.

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 SCVO₂ 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.

**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 the 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. SCVO₂ may reflect the balance of oxygen supply and demand in the entire body. When SCVO₂ is >70%, oxygen supply and demand reach a balance. SCVO₂ may be used as an evaluation index of fluid resuscitation in the early stage of septic shock (16).

A recent study confirmed that the SCVO₂ 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 SCVO₂ is close to normal.

Recently, the partial pressure of carbon dioxide (Pv-aCO₂) has been recommended as an alternative indicator of hypoperfusion (22). Derived from oxygen parameters, persistently elevated Pv-aCO₂ 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-aCO₂ may be normal even in the presence of severe tissue hypoperfusion; similarly, due to the Haldane effect, Pv-aCO₂ increases in certain patients even without tissue hypoperfusion (22). Therefore, the change of CO₂ must be evaluated through the change in O₂. Under aerobic metabolism conditions, the production of CO₂ should not exceed the utilization of O₂. Thus, the ratio of Pv-aCO₂/Da-VO₂ may replace the ratio of VCO₂/VO₂ (i.e. respiratory quotient) and identify patients at risk of anaerobic metabolism.

Using this principle, Mekontso-Dessap et al (24) demonstrated that Pv-aCO₂/Da-VO₂ >1.4 was significantly superior to Pv-aCO₂, SvO₂, and Da-VO₂ in predicting hyperlactatemia in critically ill patients. Importantly, changes in Pv-aCO₂/Da-VO₂ are more sensitive than lactic acid, making it an attractive monitoring indicator. Therefore, when SCVO₂ or SvO₂ is relatively low, the change of Cv-aCO₂/Da-VO₂ may better reflect the change of oxygen consumption than that of Pv-aCO₂/Da-VO₂. This is due to Cv-aCO₂/Da-VO₂ reflecting persistent anaerobic metabolism.

Ospina-Tascón et al (7) suggested that Cv-aCO₂/Da-VO₂ >70% were decreased in patients with Cv-aCO₂/Da-VO₂ >1. In addition, the mortality rate at day 7 and 35 was increased in patients with Cv-aCO₂/Da-VO₂ >1 and the survival rate was different at day 35, which demonstrated that Cv-aCO₂/Da-VO₂ 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-aCO₂/Da-VO₂ ratio is >1, early intervention may improve the prognosis of such patients.

If patients present with a Cv-aCO₂/Da-VO₂ 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-aCO₂/Da-VO₂ ratio increases, indicating improved prognosis, intensive fluid resuscitation can then be reduced.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Science and Technology Support Plan of Shijiazhuang Science and Technology Bureau (grant no. 151460623).

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.

References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E and Tomlanovich M: Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368-1377, 2001.
The hemodynamics of septic shock: A historical perspective. Curr Vasc Pharmacol 11: 133-138, 2013.

Feihl F, Waerber B and Llaudet L.

Long B, Koyfman A, Modisett KL and Woods CJ: Practical considerations in sepsis resuscitation. J Emerg Med 52: 472-483, 2017.

Zhonghua Yi Xue Za Zhi 94: 994‑998, 2015.

Guideline of bundle therapy by key points of control strategies for children initiated at triage. Pediatrics 127: e1585‑e1592, 2011.

EXPERIMENTAL AND THERAPEUTIC MEDICINE  18:  3631-3635,  2019