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Original Contribution

Persistent hyperlactatemia-high central venous-arterial carbon dioxide to arterial-venous oxygen content ratio is associated with poor outcomes in early resuscitation of septic shock

Juandi Zhou [a,1], Jia Song [b,1], Shijin Gong [b,*], Li Li [b], Haixiang Zhang [b], Minjia Wang [b]

[a] Department of General Surgery, Zhejiang Hospital, Hangzhou, Zhejiang 310013, China
[b] Department of Critical Care Medicine, Zhejiang Hospital, Hangzhou, Zhejiang 310013, China

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ABSTRACT

Objective: Several studies reported Pv-aCO_2/Ca-vO_2 ratio as a surrogate of VCO_2/VO_2 to detect global tissue hypoxia. The present study aimed to evaluate the prognostic value of Pv-aCO_2/Ca-vO_2 ratio combined with lactate levels during the early phases of resuscitation in septic shock.
Methods: A retrospective study was conducted in 144 septic shock patients in a 30-bed mixed ICU. A Pv-aCO_2/Ca-vO_2 ratio > 1.4 was considered abnormal. Patients were classified into four predefined groups according to lactate levels and Pv-aCO_2/Ca-vO_2 ratio after the first 6 h of resuscitation. Sequential Organ Failure Assessment (SOFA) score at day 3 was assessed. A Kaplan-Meier curve showed the survival probabilities at day 28 using a log-rank test to evaluate the differences between groups. A receiver operating characteristics (ROC) curve evaluated the ability of lactate, Pv-aCO_2/Ca-vO_2 ratio and Pv-aCO_2/Ca-vO_2 ratio combined with lactate to predict mortality at day 28.
Results: Combination of hyperlactatemia and high Pv-aCO_2/Ca-vO_2 ratio was associated with poor SOFA scores and low survival rates at day 28 ($P < 0.001$). The Cox multivariate survival analysis demonstrated that Pv-aCO_2/Ca-vO_2 ratio and lactate at T6 were independent predictors of mortality at day 28. The area under the ROC curve of the Pv-aCO_2/Ca-vO_2 ratio combined with lactate for predicting mortality at day 28 was highest and superior to that of lactate and Pv-aCO_2/Ca-vO_2 ratios.
Conclusion: Combination of Pv-aCO_2/Ca-vO_2 ratio and lactate at early stages of resuscitation of septic shock can better predict the prognosis of patients. The Pv-aCO_2/Ca-vO_2 ratio may become a useful parameter supplementary to lactate in the resuscitation of septic shock.

1. Introduction

Early identification of tissue hypoperfusion and adequate resuscitation are key factors in the management of patients with septic shock [1]. As a marker of anaerobic metabolism, lactate may putatively be elevated in case of oxygen debt. Not only the baseline lactate level [2] but also its evolution under the influence of therapy [3,4] has been associated with clinical outcomes. However, hyperlactatemia does not necessarily reflect anaerobic metabolism secondary to tissue hypoxia, especially in septic states [5]. Other nonhypoxic mechanisms such as accelerated aerobic glycolysis induced by sepsis-associated inflammation [6], inhibition of pyruvate dehydrogenase [7], and liver dysfunction [8] may also contribute to hyperlactatemia in septic patients. Accordingly, search for other markers of ongoing tissue hypoxia during the resuscitation of septic shock is the current focus. Mekontso-Dessap et al. [9] reported that venous arterial carbon dioxide difference (Pv-aCO_2) to arterial venous oxygen content difference (Ca-vO_2) ratio could be used as an alternative marker of global anaerobic metabolism in critically ill patients. Importantly, Pv-aCO_2/Ca-vO_2 ratio variations are faster than lactate change, which makes it an attractive variable to identify patients at the risk of anaerobic metabolism.

Considering that the Pv-aCO_2/Ca-vO_2 ratio could indicate the persistence of tissue hypoperfusion and/or anaerobic metabolism, we

* Corresponding author at: Department of Critical Care Medicine, Zhejiang Hospital, 12 Lingyin Road, Hangzhou, Zhejiang 310013, China.
E-mail address: gsj801@126.com (S. Gong).
[1] Co-first authors.

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conducted the present study to examine whether an increased $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio is related to the development of severe multiorgan dysfunction and worse outcomes during the early phases of septic shock.

2. Patients and methods

2.1. Patients

This retrospective observational study was carried out in a 30-bed mixed Intensive Care Unit (ICU) between September 2013 and September 2016. Patients with a new septic shock episode admitted to the Department of Critical Care Medicine were eligible for the study. Septic shock was defined according to the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference [10]. The exclusion criteria were as follows: <18 years old, pregnant women, moribund, advanced liver cirrhosis (Child–Pugh C), or drop-out of therapy during the study.

2.2. Measurements

All patients followed an early quantitative resuscitation protocol adapted from the Surviving Sepsis Campaign [11] in order to target (a) mean arterial pressure (MAP) ≥ 65 mm Hg; (b) urine output ≥0.5 mL/kg/min; (c) central venous oxygen saturation ($ScvO_2$) ≥ 70%; (d) central venous pressure (CVP): 8–12 mm Hg; (e) normalization of lactate levels. CVP was measured after a central venous catheter was inserted. The investigators confirmed the accurate positioning of the venous catheter tip on chest X-ray examinations. Tissue oxygenation variables included lactate, $ScvO_2$, arterial blood saturation (SaO_2) was estimated after arterial and central venous blood sampling and analysis by the GEM Premier 3000 (IL, Boston, USA). The arterial oxygen content (CaO_2), central venous oxygen content ($CcvO_2$), arteriovenous oxygen content difference ($Ca\text{-}vO_2$), and venoarterial CO_2 tension difference ($Pv\text{-}aCO_2$) were calculated using the following formulas:

$$CaO_2 = (1.34 \times SaO_2 \times Hb) + (0.003 \times PaO_2)$$

$$CcvO_2 = (1.34 \times ScvO_2 \times Hb) + (0.003 \times PcvO_2)$$

$$Ca\text{-}vO_2 = CaO_2 - CcvO_2$$

$$Pv\text{-}aCO_2 = PcvCO_2 - PaCO_2$$

2.3. Study protocol

Time 0 (T0) was declared when the blood gas of arterial blood and central venous blood were detected. Hemodynamic, oxygen, and tissue oxygenation variables were reviewed retrospectively at T0 and after 6 h (T6). Organ dysfunction at days 1 and 3 was evaluated using the Sequential Organ Failure Assessment (SOFA) score. If the patient survived for <3 days, the SOFA score was recorded on the day of death. We also calculated the survival at day 28.

Mekontso-Dessap et al. [9] reported that an optimal cut-off value of 1.4 was determined for the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio to predict the presence of hyperlactatemia. Our study used this threshold as the grouping criteria. All patients were classified into four groups according to the lactate levels and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio attained after the first 6 h of resuscitation: group A, lactate ≥ 2.0 mmol/L and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio > 1.4; group B, lactate ≥ 2.0 mmol/L and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio ≤ 1.4; group C, lactate < 2.0 mmol/L and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio > 1.4; and group D, lactate < 2.0 mmol/L and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio ≤ 1.4.

2.4. Statistical analysis

The statistical analysis was performed by IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, New York, USA). All data are expressed as mean ± SD when normally distributed, or as median [25–75%, interquartile range, (IQR)] when non-normally distributed. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. We used one-way ANOVA test to compare continuous variables with LSD test for multiple comparisons among the four groups. The chi-square test was used to compare the categorical variables (or Fisher's exact test). Pairwise comparisons between different study durations were assessed using paired Student's *t*-test. Survival curves up to day 28 were illustrated using the Kaplan–Meier method and log-rank (Mantel–Cox) test were used to estimate the differences among the predefined groups.

General demographics, hemodynamics, and blood gasses parameters at T0 and T6 were introduced into a Cox's proportional hazards regression model to analyze the prediction of mortality at day 28.

Receiver operating characteristics (ROC) curves were constructed to evaluate the ability of lactate, $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio combined with lactate at T6 to predict mortality at day 28. The areas under the ROC curves (AUCs) were compared using Hanley-McNeil test [12].

3. Results

144 septic shock patients (Fig. 1) comprised of 89 males and 55 females, with a median age of (74.4 ± 9.3) years. The primary characteristics of the cohort are summarized in Table 1. 52 patients were classified as group A, 30 into group B, 36 into group C, and 26 into group D. The primary source of infection was pneumonia (64.6%) and mortality at day 28 was 51.4%.

We did not observe any significant difference with regard to Acute Physiology and Chronic Health Evaluation II (APACHE II) score, demographics, or the ratio of patients receiving antibiotics and norepinephrine among the four groups, and also not for the dose of norepinephrine received before inclusion (T0). Patients from group A had a highest SOFA score among the four groups at day 1. Patients with group B and C received more fluids than group A during the first 6 h of resuscitation.

All hemodynamic, blood gasses, oxygen parameters at both T0 and T6 are presented in Table 2. Patients from groups A and C had higher $Pv\text{-}aCO_2$ and $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratios than groups B and D at T6. At baseline, no significant differences were noted between the four groups regarding the lactate levels. After the first 6 h of resuscitation, patients from groups A and B showed higher lactate levels than groups C and D.

Patients from group A with the highest SOFA scores at day 3 also had a significantly lower survival at day 28 as compared to the other groups. Patients from group D had the lowest SOFA scores at day 3 and mortality

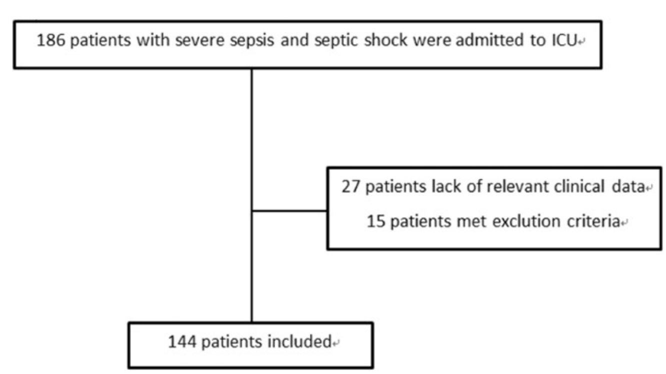

Fig. 1. Schematic representation demonstrating screening and inclusion/exclusion for the study.