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A Multi-Center Randomized Controlled Study Using $\Delta P_{CO2}/Ca\text{-}v_{O2}$ as the Target to Guide Early Tissue Hypoperfusion in Sepsis in Plateau Areas

Lianyu Zhang[1], Fabin Zhang[2]*, Huanying Bai[1], Huibin Yun[1], Zhao Zheng[1], Shuncai Liu[1], Shenghua A[1], Zhongshan Shi[3], Yuhai Hu[3]

[1]Department of Critical Care Medicine, The Third People's Hospital of Xining, Xining 810005, Qinghai Province, China
[2]Department of Public Health, Medical College of Qinghai University, Xining 810016, Qinghai Province, China
[3]Department of Critical Care Medicine, Golmud People's Hospital, Golmud 816099, Qinghai Province, China

Corresponding author: Fabin Zhang, qhmczfb@126.com

Abstract: *Objective:* To explore the value of using the venous-arterial carbon dioxide partial pressure difference and the arterial-venous oxygen content difference ratio ($\Delta P_{CO2}/Ca\text{-}v_{O2}$) as targets to guide early tissue hypoperfusion in sepsis in plateau areas. *Methods:* 90 sepsis patients admitted to the Third People's Hospital of Xining and Golmud People's Hospital from June 2017 to December 2022 were selected as the research subjects, and they were divided into the Scv_{O2} (central venous oxygen saturation) group and the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group, with 45 cases in each group. The two groups were treated with early shock resuscitation according to different protocols. The hemodynamic characteristics of the two groups of patients before and after resuscitation were observed, and the volume responsiveness was evaluated. The ROC (receiver operating characteristic) curve was used to analyze the significance of $\Delta P_{CO2}/Ca\text{-}v_{O2}$, Scv_{O2}, lactate, lactate clearance, and urine output in evaluating patient prognosis and the correlation between $\Delta P_{CO2}/Ca\text{-}v_{O2}$ and the above indicators was explored. *Results:* Compared with before resuscitation, after fluid resuscitation, the heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), lactate, lactate clearance rate, and urine output of the two groups of patients were significantly improved ($P < 0.05$); in terms of therapeutic effect, the 28-day mortality rate, 6-hour fluid balance, and lactic acid clearance of the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group were better than the Scv_{O2} group. The ROC characteristic curve showed that the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ value can effectively predict the prognosis of patients (AUC = 0.907, sensitivity was 97%, specificity was 72.4%, and critical value was 1.84). $\Delta P_{CO2}/Ca\text{-}v_{O2}$ significantly correlated with Scv_{O2}, lactic acid, and lactic acid clearance rate. *Conclusion:* The $\Delta P_{CO2}/Ca\text{-}v_{O2}$ value can be used to guide fluid resuscitation in early hypoperfusion in sepsis in plateau areas, improve patients' hemodynamics, reduce lactate indicators, and increase urine output. $\Delta P_{CO2}/Ca\text{-}v_{O2}$ level > 1.84 can effectively improve patient prognosis.

Keywords: $\Delta P_{CO2}/Ca\text{-}v_{O2}$; Scv_{O2}; Sepsis; Plateau area; Prognosis

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1. Introduction

Septic shock is a serious complication of severe infection. According to the "Chinese Sepsis/Septic Shock Emergency Treatment Guidelines (2018)," starting fluid resuscitation for patients as early as possible is crucial to the prognosis. Delayed resuscitation treatment can cause organ failure and severe cases leading to death [1]. Early identification and prompt fluid resuscitation are key factors in the treatment of septic shock patients. Therefore, finding effective indicators of early tissue hypoperfusion and providing fluid resuscitation are the primary factors in treating sepsis. In early studies, lactate, lactate clearance, and Scv_{O2} (central venous oxygen saturation) guided patients' fluid resuscitation [2]. Although lactate and lactate clearance played a key role in anaerobic glycolysis, they were not used to guide oxygen parameters. Lactate-directed resuscitation bundle strategies have had mixed results in resuscitation treatment.

Xining has an altitude of 2360 m, and Golmud has an altitude of 2780 m. The hemodynamic characteristics differ somewhat from patients in plain areas [3]. Hypoxia at the plateau can easily cause abnormal lactic acid metabolism. Therefore, tissue hypoperfusion cannot be detected early by relying on a single indicator for plateau sepsis. This paper studies the combination of Scv_{O2} and $\Delta P_{CO2}/Ca\text{-}v_{O2}$ as a guiding target for early tissue hypoperfusion and correlates it with Scv_{O2}, lactic acid, and lactic acid clearance rate, and explores the advantages of the value of $\Delta P_{CO2}/Ca\text{-}v_{O2}$ in guiding early hypoperfusion fluid resuscitation in plateau areas.

2. Materials and methods

2.1. Research information

A total of 90 sepsis patients admitted to the Department of Critical Care Medicine of the Third People's Hospital of Xining and Golmud People's Hospital from June 2017 to December 2022 were selected as the research subjects. Inclusion criteria: Patients diagnosed with sepsis; patients who have lived in plateau areas for a long time and are > 18 years old; patients who voluntarily participate in this study and give informed consent; Exclusion criteria: Patients with other serious diseases, including but not limited to liver and kidney insufficiency, lung disease, etc.; patients with short expected survival period (< 24 hours); the patient or family members refuse invasive procedures. Patients who met the inclusion criteria were divided into the Scv_{O2} group and the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group according to random numbers. The basic information of the two groups of patients is shown in **Table 1**. There was no statistically significant difference between the basic information, and they were comparable ($P > 0.05$); the ethics committees of the two hospitals had approved the study.

2.2. Research methods

Superior vena deep vein catheters and arterial catheters were established and early resuscitation treatment for septic shock was performed according to different plans.

Fluid resuscitation plan: Crystalloid was the first choice for fluid resuscitation; albumin could also be used, while hydroxyethyl starch was not recommended. The volume expansion speed was to input 500 ml of crystalloid within 30 minutes, and the cumulative volume could reach 30 ml/kg or more.

Resuscitation plan for patients in the Scv_{O2} group:

(1) 6-hour resuscitation goal: Central venous pressure (CVP) 8–12 mmHg (for patients with mechanical ventilation or abdominal hypertension, the CVP goal can be increased to 12–15 mmHg); mean arterial pressure (MAP) ≥ 65 mmHg; urine output ≥ 0.5 ml/kg/h; central venous oxygen saturation (Scv_{O2}) ≥ 70%.

(2) Monitoring and evaluation were done at least once an hour before reaching the standard.

(3) If CVP reached 8–12 mmHg after fluid resuscitation, and MAP was less than 65 mmHg,

norepinephrine titration treatment was given to MAP ≥ 65 mmHg (when it is difficult to maintain blood pressure with norepinephrine alone, epinephrine may be considered); for some patients with low risk of arrhythmia or bradycardia, dopamine could be used.

(4) If Scv_{O2} did not reach 70%, it was necessary to infuse concentrated red blood cells to increase the hemoglobin (Hb) level to more than 90 g/L, or infuse dobutamine [1–20 μg/kg/min] / milrinone [0.1–1.0 μg/kg/min] to achieve the goal.

(5) The above recovery goal was maintained for at least 24 hours.

Resuscitation plan for patients in the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group (**Figure 1**):

(1) 6-hour resuscitation goal: CVP 8 to 12 mmHg. For patients with mechanical ventilation or abdominal hypertension, the CVP target can be increased to 12 to 15 mmHg; MAP ≥ 65 mmHg; urine output ≥ 0.5 ml/kg/h; $\Delta P_{CO2}/Ca\text{-}v_{O2} < 1.8$;

(2) Step (2) is the same as Scv_{O2} group.

(3) Step (3) is the same as Scv_{O2} group.

(4) If $\Delta P_{CO2}/Ca\text{-}v_{O2} \geq 1.8$ and Hb < 90 g/L, concentrated red blood cells were transfused until Hb ≥ 90 g/L (if blood transfusion requirements cannot be met due to tight blood sources, this step of the resuscitation process can be skipped).

(5) If $\Delta P_{CO2}/Ca\text{-}v_{O2} \geq 1.8$ and $\Delta P_{CO2} < 6$ mmHg, on the premise of maintaining MAP ≥ 65 mmHg, nitroglycerin 5–40 μg/min was used to improve cardiac compliance and ΔP_{CO2} was re-evaluated.

(6) If $\Delta P_{CO2}/Ca\text{-}v_{O2}$ remained ≥ 1.8 and $\Delta P_{CO2} < 6$ mmHg, oxygen consumption was actively reduced (sedation: Ramsay score 2–4 points, SAS score 3–4 points; cooling: axillary temperature drops to 36.0–37.0°C), so that $\Delta P_{CO2}/Ca\text{-}v_{O2} < 1.4$.

(7) If $\Delta P_{CO2}/Ca\text{-}v_{O2} \geq 1.8$ and $\Delta P_{CO2} \geq 6$ mmHg, fluid resuscitation was chosen or dobutamine [1–20 μg/kg/min] / milrinone [0.1–1.0 μg/kg/min] was increased so that $\Delta P_{CO2} < 6$ mmHg.

(8) The above recovery goal was maintained for at least 24 hours.

Volume responsiveness assessment plan:

(1) Passive leg raising test: In a quiet state, the body position changed from a semi-recumbent 45° to a supine position with the legs raised 45°, and an increase of ≥ 10% in the invasive blood pressure and pulse pressure was observed for 30–90 seconds, indicating the presence of volume responsiveness.

(2) Bedside ultrasound monitoring: In the controlled ventilation mode without autonomous triggering of mechanical ventilation, the expansion index of the inferior vena cava (IVC) = (Dmax during inspiration – Dmin during expiration) / Dmin during expiration × 100%, IVC expansion index > 18% indicated volume responsiveness.

(3) PiCCO monitoring: SVV (stroke volume variation) = (SVmax–SVmin) / [(SVmax + SVmin)/2] × 100%, PPV (pulse pressure variation) = (PPmax–PPmin) / [(PPmax + PPmin)/2] × 100%, under sedation, without arrhythmia, and in a controlled ventilation mode without autonomous triggering of mechanical ventilation, SVV and PPV ≥ 11% indicated the presence of volume responsiveness.

(4) End-expiratory occlusion test (EEOT) mechanical ventilation: In patients with controlled ventilation mode without spontaneous triggering, holding the breath for > 15 seconds at the end of expiration, and observing an increase in invasive blood pressure and pulse pressure of ≥ 5% indicated the presence of volume responsiveness.

(5) The passive leg raising test was preferred for the assessment of volume responsiveness. IVC expansion index, SVV, PPV, and EEOT can be selected as auxiliary assessments if conditions permit.

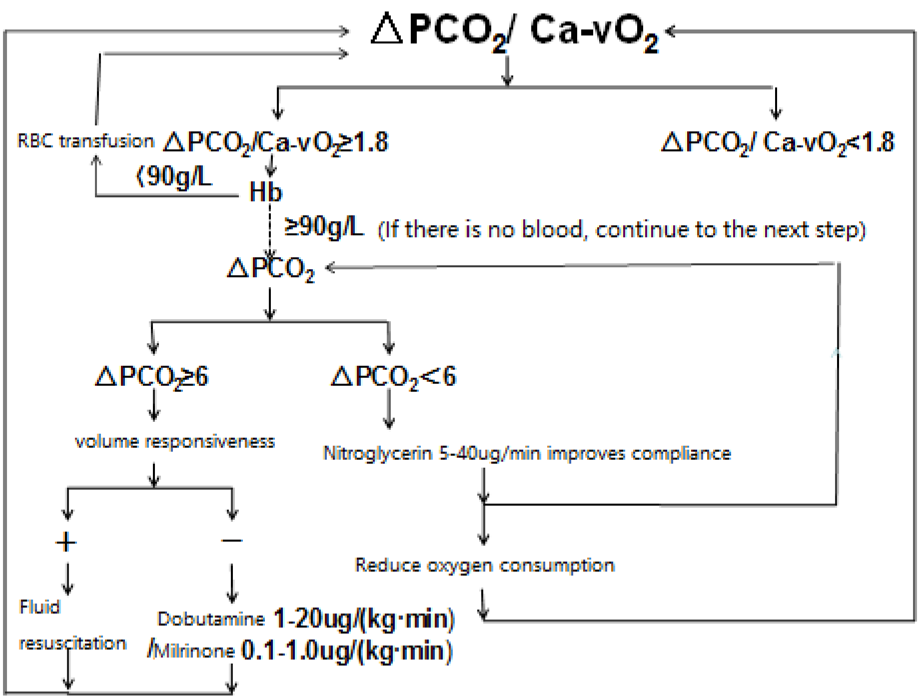

Figure 1. $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group patient resuscitation flow chart

2.3. Observation indicators

Two groups of patients were treated according to the septic shock treatment bundle.

(1) Hemodynamic change indicators of the two groups of patients before and after resuscitation, including heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), Scv_{O2}, lactic acid, lactic acid clearance, and other indicators.

(2) $\Delta P_{CO2}/Ca\text{-}v_{O2}$ calculation method:
$\Delta P_{CO2} = Pv_{CO2} - Pa_{CO2}Ca\text{-}v_{O2} = Ca_{O2} - Cv_{O2} = (1.34 \times Hb \times Sa_{O2} + Pa_{O2} \times 0.003) - (1.34 \times Hb \times Sv_{O2} + Pv_{O2} \times 0.003)$.

2.4. Statistical analysis

SPSS16.0 statistical software was used for relevant statistical processing and analysis. Count data: Comparison of count data among patients' general data was performed using c^2 test; measurement data were expressed in mean ± standard deviation (SD). The mean *t*-test was used to draw a receiver operating characteristic curve (ROC curve) to calculate relevant variable indicators to determine sepsis. The prognostic area under the curve (AUC), sensitivity, specificity, and Youden index were compared using the *z*-test. Pearson analysis was used for correlation analysis; $P < 0.05$ indicated a statistically significant difference.

3. Results

3.1. Comparison of the basic information of the two groups of patients

Statistics of the basic information of 90 patients in the two groups, including gender, age, body shape, and other basic information. There is no significant difference in the basic information of the two groups of patients, and they are comparable (**Table 1**).

Table 1. Comparison of basic information of the two groups of patients (n = 90)

Clinical information		Scv_{O2} group (n = 45)	$\Delta P_{CO2}/Ca\text{-}v_{O2}$ group (*n* = 45)	*t*/c[2] value	*P* value
Gender (cases)	Male	24	25	0.034	1.000
	Female	21	20		
Age (years)		67.43 ± 6.04	68.21 ± 8.73	0.392	0.697
APACHE II score		20.61 ± 2.73	19.32 ± 3.90	1.430	0.158
SOFA score		11.21 ± 2.56	11.00 ± 3.47	0.263	0.794
Primary infection site	Respiratory tract	16	18	0.701	0.873
	Abdominal cavity	12	12		
	Urinary tract	10	6		
	Other	7	9		
Basic illness	Malignant tumor	8	6	2.439	0.659
	COPD	18	15		
	Diabetes	10	12		
	Cirrhosis	4	3		
	Other	5	8		

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease

3.2. Hemodynamic change characteristics of the two groups of patients before and after resuscitation

HR, MAP, CVP, lactate, and lactate clearance rates of the two groups of patients after fluid resuscitation were significantly better than those before resuscitation ($P < 0.05$); the CVP and CI (cardiac index) of patients in the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group after resuscitation were better than those in the Scv_{O2} group ($P < 0.05$), as shown in **Table 2**.

Table 2. Hemodynamic changes characteristics of the two groups of patients

Parameter	$\Delta P_{CO2}/Ca\text{-}v_{O2}$ group		Scv_{O2} group	
	Before resuscitation	After resuscitation	Before resuscitation	After resuscitation
HR (times/min)	109.78 ± 11.26	103.81 ± 7.74*	108.91 ± 10.52	104.53 ± 8.39*
MAP (mmHg)	53.38 ± 5.50	79.52 ± 7.89*	54.68 ± 6.23	80.56 ± 8.65*
CVP (mmHg)	4.98 ± 1.25	14.38 ± 3.69*#	5.14 ± 1.36	11.15 ± 2.67*
Lactic acid	5.29 ± 3.49	2.56 ± 1.47*	5.38 ± 2.58	2.67 ± 1.82*
Clearance of lactate acid	20.28 ± 3.56	35.46 ± 4.15*	21.25 ± 2.97	32.12 ± 3.57*
CI	5.32 ± 0.76	7.25 ± 1.02*#	5.18 ± 0.94	5.84 ± 1.29
Urine volume (ml/h)	1.47 ± 1.23	3.23 ± 1.66	1.44 ± 1.32	4.16 ± 1.78

*$P < 0.05$ compared with the same group before fluid resuscitation; #$P < 0.05$ compared with the control group after 6 hours of fluid resuscitation

3.3. Comparison of treatment results between the two groups of patients

The $\Delta P_{CO2}/Ca\text{-}v_{O2}$ group had better ICU (intensive care unit) admission time, mechanical ventilation time, and 6-hour fluid balance than the Scv_{O2} group, and the difference was statistically significant ($P < 0.05$), as presented in **Table 3**.

Table 3. Comparison of treatment results between the two groups of patients

Clinical information	$\Delta P_{CO2}/Ca\text{-}v_{O2}$ group	Scv_{O2} group	t/c^2 value	P value
Time of admission to ICU (days)	13.32 ± 3.28	16.21 ± 4.33	2.818	0.007
Mechanical ventilation time (days)	9.07 ± 2.37	11.32 ± 2.37	3.548	0.001
28-day mortality rate [n (%)]	15 (25)	22 (36.67)	1.915	0.235
6-hour liquid balance (ml)	2092.85 ± 229	3001.61 ± 324	4.815	0.000

3.4. The application value of $\Delta P_{CO2}/Ca\text{-}v_{O2}$ and other indicators in predicting patient prognosis

The AUC of $\Delta P_{CO2}/Ca\text{-}v_{O2}$ in predicting patient prognosis was 0.907, and the optimal cut-off value was 1.84. Compared with the other three indicators, the difference was statistically significant ($P < 0.05$) (**Figure 2** and **Table 4**).

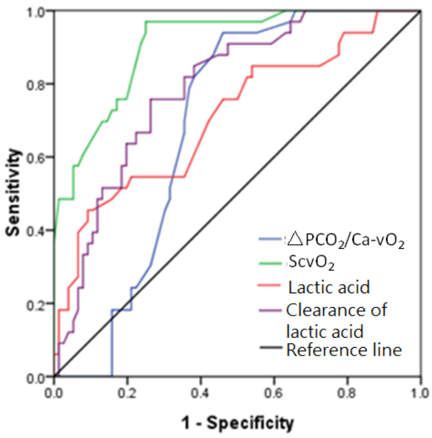

Figure 2. ΔROC curves of $\Delta P_{CO2}/Ca\text{-}v_{O2}$, Scv_{O2}, and other indicators

Table 4. The clinical application value of $\Delta P_{CO2}/Ca\text{-}v_{O2}$, Scv_{O2}, and other indicators on the prognosis of patients with sepsis

Category	Area under curve	Sensitivity	Specificity	Diagnostic cutoff
$\Delta P_{CO2}/Ca\text{-}v_{O2}$	0.907	0.970	0.724	1.84
Scv_{O2}	0.686*	0.939	0.539	0.69
Lactic acid	0.710*	0.455	0.908	2.14
Lactate clearance	0.790*	0.758	0.737	22.07

3.5. Correlation analysis between $\Delta P_{CO2}/Ca\text{-}v_{O2}$ and $Scv_{O2,}$ lactic acid, and lactic acid clearance

Pearson correlation analysis of $\Delta P_{CO2}/Ca\text{-}v_{O2}$ and Scv_{O2}, lactic acid, and lactic acid clearance in 90 patients showed that the $\Delta P_{CO2}/Ca\text{-}v_{O2}$ value was significantly correlated with Scv_{O2}, lactic acid, and lactic acid clearance rate.

Table 5. Correlation between $\Delta P_{CO2}/Ca\text{-}v_{O2}$ and Scv_{O2}, lactic acid, and lactic acid clearance rate

Index	r	*P* value
Scv_{O2}	-0.230	0.016
Lactic acid	0.209	0.029
Lactate clearance	0.246	0.010

4. Discussion

Although precise anti-infective therapy and early goal-directed therapy (EGDT) fluid resuscitation can greatly improve the prognosis of septic patients, septic shock is still a disease with high mortality in hospital ICUs [4]; Wang *et al.* found that it may be unable to accurately identify tissue hypoxia in patients, thereby delaying fluid resuscitation. For patients who have lived in plateau areas for a long time, the atmospheric pressure and the partial pressure of inhaled oxygen are low, and the partial pressure of arterial oxygen and blood oxygen saturation decrease. However, chronic hypoxia can compensate for increased hemoglobin and CO_2 max. Ca-vO_2 is near normal [5], and using traditional indicators to judge tissue hypoperfusion in patients in plateau areas is inappropriate. Therefore, finding suitable tissue hypoperfusion indicators for patients with sepsis in plateau areas is important to improve patient prognosis. Our hospital jointly carried out a multi-center randomized study in many hospitals in Xining City using $\Delta P_{CO2}/Ca\text{-}v_{O2}$ as the target to guide early tissue hypoperfusion in sepsis. The results showed that $\Delta P_{CO2}/Ca\text{-}v_{O2}$ was the target for determining plateau areas. Indicators of tissue hypoperfusion have a certain significance in stabilizing the patient's hemodynamic characteristics. The ROC curve showed that $\Delta P_{CO2}/Ca\text{-}v_{O2}$ has the largest area under the curve when predicting patient death, which is better than Scv_{O2}, lactic acid, and lactic acid clearance. The $\Delta P_{CO2}/Ca\text{-}v_{O2}$ correlates with Scv_{O2}, lactic acid, and lactate clearance, suggesting that $\Delta P_{CO2}/Ca\text{-}v_{O2}$ can reflect the degree of tissue hypoxia and hypoperfusion in patients, and the results are reliable.

Scv_{O2} is an index that reflects the oxygen balance of the human upper body. It is critical in EGDT and is often used to guide fluid resuscitation [6]. However, because Scv_{O2} is easily affected by hemoglobin, oxygen consumption, and cardiac output, recent studies have shown that the ability of Scv_{O2} to reflect anaerobic metabolism in patients with septic shock is very limited, and there is no significant correlation between Scv_{O2} and lactate clearance after early resuscitation. Zhang *et al.* [7] have shown that too high or too low Scv_{O2} can indicate tissue hypoxia. Therefore, if Scv_{O2} is used as a separate indicator, when the Scv_{O2} value reaches the standard, medical staff will still face the dilemma of whether to continue fluid resuscitation. Lactate and lactate clearance can reflect tissue hypoxia [8]; compared with Scv_{O2}, lactate, and lactate clearance are more reliable indicators of fluid resuscitation in septic shock patients. However, in patients with septic shock, elevated lactate is not limited to tissue hypoxia. Other reasons, such as the release of inflammatory mediators to promote glycolysis, inhibition of related active enzyme functions, and impaired lactate clearance, can cause an increase in lactic acid [9]. In some patients with septic shock, even if the lactate level increases, it does not necessarily mean that the patient's body is hypoxic, thus using lactate as a detection target may induce excessive resuscitation [10].

In recent years, the venous-arterial carbon dioxide partial pressure difference [ΔP_{CO2} ($Pv\text{-}a_{CO2}$) = $Pv_{CO2} - Pa_{CO2}$] has been recommended by many researchers as one of the indicators reflecting tissue hypoperfusion [11,12]. Continuously elevated ΔP_{CO2} is an independent predictor of poor prognosis and is well correlated with lactate levels [13]. However, in septic shock, the early decrease in peripheral resistance and increased cardiac output prevent the accumulation of CO_2 in the venous blood. Even if there is severe tissue hypoperfusion, ΔP_{CO2} still appears normal [14]; plus, due to the Haldane effect, when patients have elevated ΔP_{CO2}, tissue hypoperfusion may not exist. Therefore, it is more reliable to evaluate CO_2 through changes in O_2. In the state of aerobic metabolism, the utilization of O_2 should exceed the production of CO_2 [15] so that the ΔP_{CO2}/Ca-v_{O2} value can replace the ratio of V_{CO2}/V_{O2} (respiratory quotient); that is, it can identify patients who are at risk of anaerobic metabolism [16]. Previous studies have proven that applying the ΔP_{CO2}/Ca-v_{O2} index in predicting tissue hypoperfusion in critically ill patients is significantly better than Pv-a_{CO2}, Sv_{O2}, and Ca-v_{O2} [17]. Moreover, ΔP_{CO2}/Ca-v_{O2} changes are more sensitive than lactic acid, making it a more reliable monitoring indicator of the body's anaerobic metabolism. Therefore, the combined use of ΔP_{CO2}/Ca-v_{O2} can better determine the anaerobic metabolism of tissues. When lactate and ΔP_{CO2}/Ca-v_{O2} increase, patients with hyperlactatemia tend to have anaerobic metabolism. However, if the ΔP_{CO2}/Ca-v_{O2} value is normal in a high lactate state, the patient's high lactate may come from other reasons, and fluid resuscitation cannot be performed blindly [18].

5. Conclusion

In summary, ΔP_{CO2}/Ca-v_{O2} value can guide fluid resuscitation for early hypoperfusion in sepsis in plateau areas. At the same time, combined with the changing direction of blood lactate levels, it can improve patients' hemodynamics and urine output and reduce lactate index, ΔP_{CO2}/Ca-v_{O2} level > 1.84 can effectively improve patient prognosis.

However, this study has certain shortcomings. Firstly, this study only included patients from plateau areas and failed to compare ΔP_{CO2}/Ca-v_{O2} between patients from plain areas, sub-plateau areas, and plateau areas. Secondly, it only observed a single indicator as a sign of tissue hypoperfusion; we will observe the combination of different indicators in the later stage and use them as effective indicators to judge the patient's tissue perfusion, which may benefit patients more. Lastly, the survival rate of patients in the ΔP_{CO2}/Ca-v_{O2} group did not increase significantly. Specifically, the reasons and improvement measures still need to be studied with a large sample size.

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Disclosure statement

The authors declare no conflict of interest.

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