Introduction

The evaluation and correction of macrocirculatory and microcirculatory flow play an important role in the resuscitation of circulatory shock (1). The venous-to-arterial carbon dioxide difference \([P(v-a)CO_2]\) has gained great attentions in the resuscitation of sepsis. The \(P(v-a)CO_2\) is determined by cardiac output and metabolic status, and it has been taken as an indicator of the adequacy of the venous blood flow to remove the \(CO_2\) produced by the peripheral tissues (2,3).

The \(P(v-a)CO_2\) was calculated as the difference between venous PCO\(_2\) and arterial PCO\(_2\). The venous PCO\(_2\) could be obtained from the mixed venous blood through a pulmonary artery catheter or from the central venous blood through a central venous catheter. Researches (4,5) had shown that central venous-arterial PCO\(_2\) difference \([P(cv-a)CO_2]\) was consistent with mixed venous-arterial PCO\(_2\) difference \([P(mv-a)CO_2]\) and both of them were inversely related to cardiac index (CI). Nowadays, the central venous PCO\(_2\) is commonly used to calculate \(P(v-a)CO_2\) in clinical practice. Recent study found that \(P(mv-a)CO_2\) might be a potential indicator to reflect microcirculatory flow in septic shock patients (6). In this paper, we review the literatures of...
P(v-a)CO₂ and try to answer the question how to interpret and manage the P(v-a)CO₂ in the resuscitation of sepsis.

**P(v-a)CO₂ and prognosis in sepsis**

Based on the physiological background of P(v-a)CO₂, it is easy to understand that a high P(v-a)CO₂ indicate an impaired cardiac output and tissue hypoperfusion. Hence, a persistent P(v-a)CO₂ after resuscitation is related to a poor prognosis in septic shock patients (6). A cutoff 6 mmHg of P(v-a)CO₂ has been suggested as an indicator to reflect the adequacy of cardiac output to tissue perfusion in critically ill patients (3). Several studies had reported that a high P(v-a)CO₂ (>6 mmHg) was related to poor outcome in septic shock condition (4,7-12). van Beest et al. (4) found that a high P(cv-a)CO₂ (≥6 mmHg) in the first 24 h after ICU admission was related to a higher hospital mortality rate (OR 5.3, P=0.08) in 53 septic shock patients. Vallee et al. (7) further reported that the septic shock patients with a higher P(cv-a)CO₂ had a poor lactate clearance, higher SOFA score, and a lower mortality rate, in the normalized central venous oxygen saturation (ScvO₂) (>70%) condition, than patients with a normal P(cv-a)CO₂ value (<6 mmHg). Moreover, Mallat et al. (8) reported that P(cv-a)CO₂ was not related to 28-day mortality in septic shock patients. The authors found that normalization of both P(cv-a)CO₂ gap and ScvO₂, during the first 6 hours of resuscitation, was associated with a better lactate clearance than the normalization of ScvO₂ alone (8). Therefore, P(cv-a)CO₂ was suggested as an additional goal of resuscitation when ScvO₂ target had been achieved (>70%) in septic shock patients (7,8).

Moreover, our study found a lower P(cv-a)CO₂ (3.5 mmHg but not 6 mmHg) had a good ability for predicting ICU mortality in septic shock patients with a high ScvO₂ (>80%) (13). The non-survivor group had a low P(v-a)CO₂ (mean 4.8 mmHg) <6 mmHg and high lactate level (mean 3.1 mmol/L) in our study. Hence, the normal cutoff value of P(v-a)CO₂ requires further investigations to be validated in septic shock patients with a high ScvO₂ (>80%) and signs of tissue hypoxia.

Recently, a systematic review showed that P(v-a)CO₂ was correlated with mortality and other clinical outcomes in septic shock patients (14). Furthermore, Muller et al. (12) found that P(cv-a)CO₂ was only associated with mortality in patients with impaired cardiac function (defined as atrial fibrillation and/or left ventricular ejection fraction less than 50%) but not with patients with normal cardiac function.

The authors found that patients with septic shock and impaired cardiac function were more prone to a persistent high P(cv-a)CO₂, even when initial resuscitation succeeded in normalizing mean arterial pressure, central venous pressure, and ScvO₂ (12). In other words, a high P(cv-a)CO₂ might mainly result from a poor cardiac function in the resuscitation of septic shock patients. Further clinical investigation is required to clarify the predictive meaning of P(cv-a)CO₂ in normal cardiac function. The relevant clinical studies of P(cv-a)CO₂ and outcome were summarized in the Table 1.

**Pitfalls of P(v-a)CO₂ in assessing global flow and tissue perfusion**

There were some potential pitfalls of using P(v-a)CO₂ to identify global flow and tissue perfusion in clinical situations.

(I) Hyperoxia: Saludes et al. (15) found that an elevated P(v-a)CO₂ could independently result from a hyperoxia (caused by breathing 100% O₂ for 5 min) but not from an inadequate cardiac output in the septic patients. Several potential mechanisms should be taken on how hyperoxia cause an increase in P(v-a)CO₂ are as following: firstly, a high P(v-a)CO₂ could be derived from the impaired microcirculatory flow caused by arterial hyperoxia (16). It has been shown that normobaric hyperoxia decreases capillary perfusion and VO₂ and increases the heterogeneity of the perfusion (17). Secondly, Haldane effect, a phenomenon known as the increase in venous oxygen saturation would cause a decrease in the affinity of hemoglobin (Hb) for CO₂ (18). The CO₂ would unbind from Hb and, in the venous hyperoxia condition, would further produce an increase in the free form of CO₂ in the venous site. Consequently, the P(v-a)CO₂ would elevate in the high venous saturation condition resulted from hyperoxia (19).

(II) Hyper-ventilation: Mallat et al. (20) investigated the effect of acute hyperventilation on P(cv-a)CO₂ gap in hemodynamically stable septic shock patients. The authors found that acute hyperventilation could increase P(cv-a)CO₂ gap, which may be a result of increases in VO₂. In other words, the acute changes in respiratory status could contribute to a high P(v-a)CO₂, which might be independent of the changes in cardiac output. (III) Hypoxia: the cellular hypoxia could be caused by ischemic or hypoxic hypoxia. Vallet et al. found that P(v-a)CO₂ increase in ischemic hypoxia induced by a decrease in blood flow, but not in hypoxic hypoxia conditions where
the blood flow was maintained constant, even in a state of VO₂/DO₂ dependency, in a canine model of isolated limb (21). Hence, P(v-a)CO₂ could serve as a marker of the adequacy of venous blood flow to wash-out the CO₂ produced by the tissues (tissue hypoperfusion marker) rather than a marker of tissue hypoxia.

### P(v-a)CO₂ and microcirculation

Both ScvO₂ and lactate have been well accepted as targets to guide resuscitation in sepsis (22). However, sometimes there might be some limitations in using ScvO₂ and lactate to reflect tissue perfusion (23). For example, when capillary shunting occurred, ScvO₂ could be elevated and mask the presence of tissue hypoperfusion or tissue hypoxia. Recently, P(v-a)CO₂ has gained attention as a complementary tool to reflect global perfusion in the resuscitation of septic shock patients when ScvO₂ is more than 70% (24).

Ospina-Tascon et al. (25) conducted a prospective study involving 75 septic shock patients with the aim to

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Types of study</th>
<th>Outcome [low P(v-a)CO₂ group vs. high P(v-a)CO₂ group]</th>
<th>Note</th>
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</thead>
<tbody>
<tr>
<td>Bakker et al. (9)</td>
<td>1992</td>
<td>64 pts with septic shock</td>
<td>Prospective observational study</td>
<td>N/A</td>
<td>Non-survivors had a significantly higher P(v-a)CO₂ than survivors (5.9±3.4 vs. 4.4±2.3 mmHg, P&lt;0.05)</td>
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<td>Vallee et al. (7)</td>
<td>2008</td>
<td>50 pts with septic shock with SvO₂ ≥70%</td>
<td>Prospective observational study</td>
<td>12 h lactate clearance: −38%±39% vs. −17%±33% (P=0.04); 24 h SOFA: 11±4 vs. 15±4 (P&lt;0.05)</td>
<td>Pts with low P(v-a)CO₂ (&lt;6 mmHg) n=26; Pts with high P(v-a)CO₂ (&gt;6 mmHg) n=24</td>
</tr>
<tr>
<td>Troskot et al. (11)</td>
<td>2010</td>
<td>71 pts with septic shock</td>
<td>Retrospective analysis</td>
<td>N/A</td>
<td>High P(v-a)CO₂ (&gt;6 mmHg) is related to mortality (P=0.015) in non-ventilated patients (P=0.015), not in ventilated patients (P=0.27)</td>
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<td>van Beest et al. (4)</td>
<td>2013</td>
<td>53 pts with septic shock</td>
<td>Post hoc analysis</td>
<td>28 d mortality: 21% vs. 29% (P=0.53)</td>
<td>The mixed P(v-a)CO₂ underestimated the central P(v-a)CO₂ by a mean bias of 0.03±0.32 kPa (−0.62–0.58 kPa)</td>
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<td>Ospina-Tascon et al. (6)</td>
<td>2013</td>
<td>85 pts with septic shock</td>
<td>Prospective observational study</td>
<td>Persistence of high P(v-a)CO₂ was associated with a higher 3 d SOFA (P&lt;0.001) and 28 d mortality log rank test: 19.21 (P&lt;0.001)</td>
<td>Pts with persistence of high P(v-a)CO₂ (both T0, T6 &gt;6 mmHg) n=24</td>
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<tr>
<td>Du et al. (10)</td>
<td>2013</td>
<td>172 pts with septic shock, including 122 pts with SvO₂ ≥70%</td>
<td>Retrospective analysis</td>
<td>6 h lactate clearance: 21%±31% vs. 11%±61% (P=0.016); 28 d mortality: 16.1% vs. 56.1% (P&lt;0.001)</td>
<td>Pts with low P(v-a)CO₂ (&lt;6 mmHg) n=81; Pts with high P(v-a)CO₂ (&gt;6 mmHg) n=41 with ScvO₂ ≥70%</td>
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<tr>
<td>Mallat et al. (8)</td>
<td>2014</td>
<td>80 pts with septic shock</td>
<td>Prospective observational study</td>
<td>6 h lactate clearance: 28%±31% vs. −0.2%±34% (P&lt;0.001); 28 d mortality: 20% vs. 24% (P=0.003)</td>
<td>Pts with low P(v-a)CO₂ (&lt;6 mmHg) n=48; Pts with high P(v-a)CO₂ (&gt;6 mmHg) n=32</td>
</tr>
<tr>
<td>Muller et al. (12)</td>
<td>2017</td>
<td>114 pts in cardiac group; 236 pts in non-cardiac group</td>
<td>Prospective cohort study</td>
<td>28 d mortality: 20% vs. 35% (P=0.024) (cardiac group); 28 d mortality: 26% vs. 28% (P=0.8) (non-cardiac group)</td>
<td>Cardiac group: patients had AF and/or LVEF &lt;50%</td>
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Pts, patients; N/A, not applicable; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; P(v-a)CO₂, venous-to-arterial carbon dioxide difference; ScvO₂, central venous oxygen saturation.
investigate the relationship between \( P(mv-a)CO_2 \) and sublingual microcirculation assessed by sidestream dark-field device. They found that high \( P(mv-a)CO_2 \) values were associated with low percentages of small perfused vessels (PPV), low functional capillary density, and high heterogeneity of microvascular blood flow. Interestingly, the relationship between \( P(v-a)CO_2 \) and microcirculation was independent of the effects of cardiac output in that study. In summary, a high \( P(v-a)CO_2 \) might be caused by an inadequate microcirculatory flow to clear the excess \( CO_2 \) production, even in the presence of normal (or high) cardiac output in septic shock patients. Moreover, Kanoore et al. (26) found sepsis patients with a high CI (>4 L/min/m²) showed a lower \( P(v-a)CO_2 \) (5±3 vs. 7±2 mmHg) than those with normal cardiac output. However, there were no differences in sublingual perfused vascular density, proportion of perfused vessels, or microvascular flow index in both groups in that study. Hence, an impaired microcirculation could be persistent even in a low \( P(v-a)CO_2 \) and a high cardiac output condition. The loss of coherence between macrocirculation and microcirculation is common in septic shock patients (27). Importantly, it is uncertain if the decrease in \( P(v-a)CO_2 \) observed after an increase in cardiac output, is related to the improvement of microcirculation. Further studies are needed to investigate this issue.

**How to Interpret and manage a high \( P(v-a)CO_2 \) (>6 mmHg)**

An elevated \( P(v-a)CO_2 \) could result from different reasons in septic shock patients, such as low cardiac output, poor microcirculatory perfusion or acute hyperventilation (28). Hence, a high \( P(v-a)CO_2 \) should be taken as an alarm trigger of inadequate blood flow in the resuscitation of septic shock patients. It remains a challenge for intensivists to correctly interpret and manage an elevated \( P(v-a)CO_2 \) (>6 mmHg) condition. In Figure 1, we summarized a recursive and regression approach of resuscitation of septic shock patients. The usefulness of this resuscitation protocol needs to be validated in clinical trials.

**Conclusions**

During recent years, \( P(v-a)CO_2 \) has gained great attention and more frequently used in the resuscitation of septic shock patients. The intensivists should take other tissue perfusion parameters into consideration before correcting an elevated \( P(v-a)CO_2 \) in the resuscitation of septic shock patients. Moreover, further investigations are necessary to clarify the relationship between \( P(v-a)CO_2 \) and microcirculation.
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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References