Review Article

Interpretation of venous-to-arterial carbon dioxide difference in the resuscitation of septic shock patients

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Abstract: The venous-to-arterial carbon dioxide difference [P(v-a)CO_2] was calculated from the difference of venous CO_2 and arterial CO_2, which has been used to reflect the global flow in the circulatory shock. Moreover, recent clinical studies found the P(v-a)CO_2 was related to the sublingual microcirculation perfusion in the sepsis. However, it is still controversial that whether P(v-a)CO_2 could be used to assess the microcirculatory flow in septic patients. Moreover, the related influent factors should be taken into account when interpreting P(v-a)CO_2 in clinical practice. This paper reviews the relevant experimental and clinical scenarios of P(v-a)CO_2 with the aim to help intensivists to use this parameter in the resuscitation of septic shock patients. Furthermore, we propose a conceptual framework to manage a high P(v-a)CO_2 value in the resuscitation of septic shock. The triggers of correcting an elevated P(v-a)CO_2 should take into consideration the other tissue perfusion parameters. Additionally, more evidence is required to validate that a decreasing in P(v-a)CO_2 by increasing cardiac output would result in improvement of microcirculation. Further investigations are necessary to clarify the relationship between P(v-a)CO_2 and microcirculation.

Keywords: Septic shock; venous-to-arterial carbon dioxide difference [P(v-a)CO_2]; microcirculation; resuscitation

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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

$P(v\text{-}a)CO_2$ and try to answer the question how to interpret and manage the $P(v\text{-}a)CO_2$ in the resuscitation of sepsis.

$P(v\text{-}a)CO_2$ and prognosis in sepsis

Based on the physiological background of $P(v\text{-}a)CO_2$, it is easy to understand that a high $P(v\text{-}a)CO_2$ indicate an impaired cardiac output and tissue hypoperfusion. Hence, a persistent $P(v\text{-}a)CO_2$ after resuscitation is related to a poor prognosis in septic shock patients (6). A cutoff 6 mmHg of $P(v\text{-}a)CO_2$ 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 $P(v\text{-}a)CO_2$ (>6 mmHg) was related to poor outcome in septic shock condition (4,7-12). van Beest *et al.* (4) found that a high $P(cv\text{-}a)CO_2$ (≥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 $P(cv\text{-}a)CO_2$ had a poor lactate clearance, higher SOFA score, and a lower mortality rate, in the normalized central venous oxygen saturation ($ScvO_2$) (>70%) condition, than patients with a normal $P(cv\text{-}a)CO_2$ value (<6 mmHg). Moreover, Mallat *et al.* (8) reported that $P(cv\text{-}a)CO_2$ was not related to 28-day mortality in septic shock patients. But the authors found that normalization of both $P(cv\text{-}a)CO_2$ gap and $ScvO_2$, during the first 6 hours of resuscitation, was associated with a better lactate clearance than the normalization of $ScvO_2$ alone (8). Therefore, $P(cv\text{-}a)CO_2$ was suggested as an additional goal of resuscitation when $ScvO_2$ target had been achieved (>70%) in septic shock patients (7,8).

Moreover, our study found a lower $P(cv\text{-}a)CO_2$ (3.5 mmHg but not 6 mmHg) had a good ability for predicting ICU mortality in septic shock patients with a high $ScvO_2$ (>80%) (13). The non-survivor group had a low $P(v\text{-}a)CO_2$ (mean 4.8 mmHg) <6 mmHg and high lactate level (mean 3.1 mmol/L) in our study. Hence, the normal cutoff value of $P(v\text{-}a)CO_2$ requires further investigations to be validated in septic shock patients with a high $ScvO_2$ (>80%) and signs of tissue hypoxia.

Recently, a systematic review showed that $P(v\text{-}a)CO_2$ was correlated with mortality and other clinical outcomes in septic shock patients (14). Furthermore, Muller *et al.* (12) found that $P(cv\text{-}a)CO_2$ 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 $P(cv\text{-}a)CO_2$, even when initial resuscitation succeeded in normalizing mean arterial pressure, central venous pressure, and $ScvO_2$ (12). In other words, a high $P(cv\text{-}a)CO_2$ 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 $P(cv\text{-}a)CO_2$ in normal cardiac function. The relevant clinical studies of $P(cv\text{-}a)CO_2$ and outcome were summarized in the *Table 1*.

Pitfalls of $P(v\text{-}a)CO_2$ in assessing global flow and tissue perfusion

There were some potential pitfalls of using $P(v\text{-}a)CO_2$ to identify global flow and tissue perfusion in clinical situations.

(I) Hyperoxia: Saludes *et al.* (15) found that an elevated $P(v\text{-}a)CO_2$ could independently result from a hyperoxia (caused by breathing 100% O_2 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 $P(v\text{-}a)CO_2$ are as following: firstly, a high $P(v\text{-}a)CO_2$ could be derived from the impaired microcirculatory flow caused by arterial hyperoxia (16). It has been shown that normobaric hyperoxia decreases capillary perfusion and VO_2 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 CO_2 (18). The CO_2 would unbind from Hb and, in the venous hyperoxia condition, would further produce an increase in the free form of CO_2 in the venous site. Consequently, the $P(v\text{-}a)CO_2$ 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 $P(cv\text{-}a)CO_2$ gap in hemodynamically stable septic shock patients. The authors found that acute hyperventilation could increase $P(cv\text{-}a)CO_2$ gap, which may be a result of increases in VO_2. In other words, the acute changes in respiratory status could contribute to a high $P(v\text{-}a)CO_2$, 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 $P(v\text{-}a)CO_2$ increase in ischemic hypoxia induced by a decrease in blood flow, but not in hypoxic hypoxia conditions where

Table 1 P(v-a)CO_2 and outcome in clinical studies

Author	Year	Population	Types of study	Outcome [low P(v-a)CO_2 group *vs.* high P(v-a)CO_2 group]	Note
Bakker *et al.* (9)	1992	64 pts with septic shock	Prospective observational study	N/A	Non-survivors had a significantly higher P(v-a)CO_2 than survivors (5.9±3.4 *vs.* 4.4±2.3 mmHg, P<0.05)
Vallee *et al.* (7)	2008	50 pts with septic shock with SvO_2 ≥70%	Prospective observational study	12 h lactate clearance: –38%±39% *vs.* –17%±33% (P=0.04); 24 h SOFA: 11±4 *vs.* 15±4 (P<0.05)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=26; Pts with high P(v-a)CO_2 (>6 mmHg) n=24
Troskot *et al.* (11)	2010	71 pts with septic shock	Retrospective analysis	N/A	High P(v-a)CO_2 (>6 mmHg) is related to mortality (P=0.015) in non-ventilated patients (P=0.015), not in ventilated patients (P=0.27)
van Beest *et al.* (4)	2013	53 pts with septic shock	Post hoc analysis	28 d mortality: 21% *vs.* 29% (P=0.53)	The mixed P(v-a)CO_2 underestimated the central P(v-a)CO_2 by a mean bias of 0.03±0.32 kPa (–0.62–0.58 kPa)
Ospina-Tascon *et al.* (6)	2013	85 pts with septic shock	Prospective observational study	Persistence of high P(v-a)CO_2 was associated with a higher 3 d SOFA (P<0.001) and 28 d mortality log rank test: 19.21 (P<0.001)	Pts with persistence of high P(v-a)CO_2 (both T0, T6 >6 mmHg) n=24
Du *et al.* (10)	2013	172 pts with septic shock, including 122 pts with SvO_2 ≥70%	Retrospective analysis	6 h lactate clearance: 21%±31% *vs.*1%±61% (P=0.016); 28 d mortality: 16.1% *vs.* 56.1% (P<0.001)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=81; Pts with high P(v-a)CO_2 (>6 mmHg) n=41 with $ScvO_2$ ≥70%
Mallat *et al.* (8)	2014	80 pts with septic shock	Prospective observational study	6 h lactate clearance: 28%±31% *vs.* –0.2%±34% (P<0.0001); 28 d mortality: 20% *vs.* 24% (P=0.003)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=48; Pts with high P(v-a)CO_2 (>6 mmHg) n=32
Muller *et al.* (12)	2017	114 pts in cardiac group; 236 pts in non-cardiac group	Prospective cohort study	28 d mortality: 20% *vs.* 35% (P=0.024) (cardiac group); 28 d mortality: 26% *vs.* 28% (P=0.8) (non-cardiac group)	Cardiac group: patients had AF and/or LVEF <50%

Pts, patients; N/A, not applicable; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; P(v-a)CO_2, venous-to-arterial carbon dioxide difference; $ScvO_2$, central venous oxygen saturation.

the blood flow was maintained constant, even in a state of VO_2/DO_2 dependency, in a canine model of isolated limb (21). Hence, P(v-a)CO_2 could serve as a marker of the adequacy of venous blood flow to wash-out the CO_2 produced by the tissues (tissue hypoperfusion marker) rather than a marker of tissue hypoxia.

P(v-a)CO_2 and microcirculation

Both $ScvO_2$ and lactate have been well accepted as targets to guide resuscitation in sepsis (22). However, sometimes there might be some limitations in using $ScvO_2$ and lactate to reflect tissue perfusion (23). For example, when capillary shunting occurred, $ScvO_2$ could be elevated and mask the presence of tissue hypoperfusion or tissue hypoxia. Recently, P(v-a)CO_2 has gained attention as a complementary tool to reflect global perfusion in the resuscitation of septic shock patients when $ScvO_2$ is more than 70% (24).

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

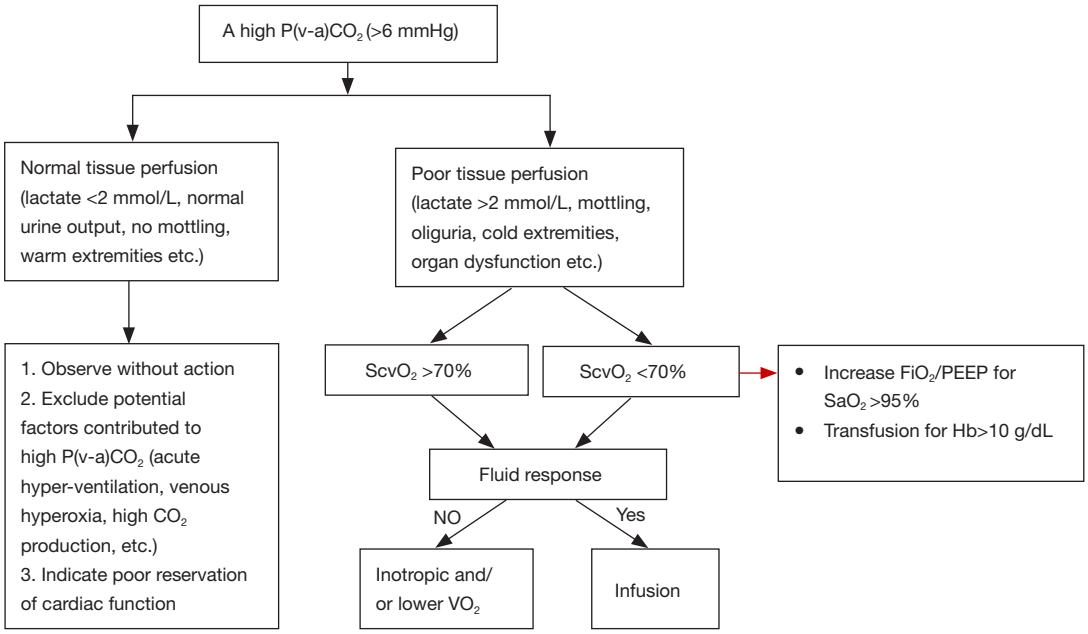

Figure 1 A recursive and regression tree to interpret and manage a high P(v-a)CO_2 (>6 mmHg). P(v-a)CO_2, venous-to-arterial carbon dioxide difference; $ScvO_2$, central venous oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

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/m^2) 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

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