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Relationship of relevant factors to $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in critically ill patients

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Abstract

Objective: This study investigated the factors related to the ratio of the venoarterial carbon dioxide tension difference [$P(v\text{-}a)CO_2$] to the arteriovenous oxygen content difference [$C(a\text{-}v)O_2$] (hereafter termed "Ratio").

Methods: We retrospectively studied 1294 pairs of arterial and central venous blood gas measurements in 352 critically ill patients. A high Ratio was defined as > 1.68 based on published literature. Measurements were divided into four groups: Group I [$P(v\text{-}a)CO_2 \leq 6$ mmHg/central venous oxygen saturation ($ScvO_2$) $< 70\%$], Group II [$P(v\text{-}a)CO_2 \leq 6$ mmHg/$ScvO_2 \geq 70\%$], Group III [$P(v\text{-}a)CO_2 > 6$ mmHg/$ScvO_2 \geq 70\%$], and Group IV [$P(v\text{-}a)CO_2 > 6$ mmHg/$ScvO_2 < 70\%$].

Results: The Ratio's strongest correlation was with $P(v\text{-}a)CO_2$ when compared with $ScvO_2$ and hemoglobin in all data. The $P(v\text{-}a)CO_2$ and $ScvO_2$ were significantly higher and the hemoglobin and arterial oxygen saturation were significantly lower in the high Ratio measurements (>1.68) than low Ratio measurements (≤ 1.68). The $P(v\text{-}a)CO_2$ was best for predicting a high Ratio. A $P(v\text{-}a)CO_2$ threshold of 7 mmHg was associated with a sensitivity of 41.77% and specificity of 90.62% for predicting a high Ratio.

Conclusions: A high $P(v\text{-}a)CO_2$ is the most relevant contributor to a high Ratio among all related factors in critically ill patients.

Keywords

$ScvO_2$, $P(v\text{-}a)CO_2$, $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio, oxygen delivery (DO_2), oxygen consumption (VO_2), intensive care unit

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Introduction

The concept of an existing relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) has been the cornerstone of shock, and determining DO_2/VO_2 dependence is a key issue in shock resuscitation.[1,2] The ratio of the venoarterial carbon dioxide tension difference [$P(v\text{-}a)CO_2$] to the arteriovenous oxygen content difference [$C(a\text{-}v)O_2$] [i.e., the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio] has garnered much attention as a new marker that reflects the relationship between DO_2 and VO_2. The ratio between VO_2 and global carbon dioxide production (VCO_2) is lower in aerobic than anaerobic metabolism. First, a decrease in VO_2 accompanies a decrease in aerobically generated carbon dioxide in terms of tissue hypoxia. In a hypoxic cellular environment, however, anaerobic carbon dioxide generation increases as hydrogen ions generated by anaerobic sources of energy are buffered by bicarbonate.[3] Hence, the ratio between VCO_2 and VO_2 becomes mismatched, and the amount of VCO_2 generation becomes greater than the amount of VO_2. Consequently, a rise in the respiratory quotient (VCO_2/VO_2 ratio) reflects the presence of global anaerobic metabolism.[4]

Many studies have shown that the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio reflects the lactate level, lactate evolution, and lactate clearance and is associated with prognosis.[5–12] Furthermore, a high $C(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is an independent risk factor for mortality in critically ill patients.[8,10] A $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio cutoff of 1.68 is a better predictor of a $\geq 15\%$ increase in VO_2 induced by an acute increase in DO_2 when compared with lactate and central venous oxygen saturation ($ScvO_2$).[11,12]

The $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is calculated from several parameters based on a known formula that mainly involves $ScvO_2$, hemoglobin (Hb), arterial oxygen saturation (SaO_2), and $P(v\text{-}a)CO_2$.[13] A theoretical mathematical relationship exists among these parameters. However, calculation of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio may involve various combinations of relevant parameters depending on the clinical situation, which could cause a complicated inter-relationship between the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio and these related parameters. Therefore, a simple and rapid method for identification of a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio would be of substantial benefit, and the factors contributing to a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio are worthy of consideration in the clinical setting.

To our knowledge, the dependency of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio on $ScvO_2$ and $P(v\text{-}a)CO_2$ has not been sufficiently explored in clinical practice. The present study was performed to determine the relationships of $ScvO_2$, Hb, SaO_2, and $P(v\text{-}a)CO_2$ with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio; define the corresponding factors that contribute to a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (>1.68) according to the published literature in critically ill patients;[9] and investigate the behavior of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in given settings based on specific cutoff values of $P(v\text{-}a)CO_2$ (6 mmHg) and $ScvO_2$ (70%) for tissue perfusion according to the published literature.[14–16]

Patients and methods

Patients and data

The Institutional Research and Ethics Committee of the Peking Union Medical College Hospital approved this study. Because this retrospective study involved only the collection of clinical data, the Institutional Research and Ethics Committee waived the need to obtain consent.

The simultaneous arterial and central venous blood gas measurements that were obtained from critically ill patients during their first week of intensive care unit admission from July 2013 to December 2014 were

retrospectively reviewed. The blood gas analysis data were stored in an electrical information system in our department. The attending intensivists decided on the placement of arterial and central venous catheters according to the severity of the patient's condition. The $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio has been considered a relevant marker of global anaerobic metabolism, and calculation of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio was suggested during resuscitation in our department.

Standard measurement of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio involves the following two steps. First, a central venous catheter is inserted via the jugular or subclavian vein, and placement of the central venous catheter in the superior vena cava is confirmed by chest radiography. Second, arterial and central venous blood gas samples are anaerobically collected in 3-mL heparinized syringes, which are analyzed using a bedside blood gas machine (GEM Premier 3000, model 5700; Instrumentation Laboratory, Bedford, MA, USA or ABL90; Radiometer, Copenhagen, Denmark). The same blood gas machine was used to measure both the arterial and central venous blood gas.

Study definitions

Pairs of arterial and central venous blood samples were used determine the following variables: arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), central venous oxygen tension (PvO_2), central venous carbon dioxide tension ($PvCO_2$), SaO_2, and $ScvO_2$. The Hb and lactate concentrations were measured from the arterial blood. The arterial oxygen content (CaO_2), central venous oxygen content (CvO_2), $C(a\text{-}v)O_2$, $P(v\text{-}a)CO_2$, $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio, and oxygen extraction percentage (EO_2) were defined as follows:

- $CaO_2 = (1.34 \times SaO_2 \times Hb) + (0.0031 \times PaO_2)$
- $CvO_2 = (1.34 \times ScvO_2 \times Hb) + (0.0031 \times PvO_2)$
- $C(a\text{-}v)O_2 = CaO_2 - CvO_2$
- $P(v\text{-}a)CO_2 = PvCO_2 - PaCO_2$
- $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio $= (PvCO_2 - PaCO_2)/(CaO_2 - CvO_2)$
- $EO_2 = (SaO_2 - SvO_2)/SaO_2$

Moreover, a low and high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio was defined as ≤ 1.68 and > 1.68, respectively; a low and high $P(v\text{-}a)CO_2$ was defined as ≤ 6 and > 6 mmHg, respectively; and a low and high $ScvO_2$ was defined as $< 70\%$ and $\geq 70\%$, respectively.

Statistical analysis

Descriptive statistics for continuous variables were presented as mean ± standard deviation when the variables were normally distributed and as median and interquartile range (25%–75%) when the variables had a skewed distribution. The Mann–Whitney test was used to compare continuous variables between the groups, and the chi-squared test and Fisher's exact test were used to compare categorical variables. Comparison of two continuous variables was performed using Spearman's correlation. The areas under the receiver operating characteristic (ROC) curves were compared using the Hanley–McNeil test.[17] The statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 11.4.3.0 (MedCalc Software bvba, Ostend, Belgium). All statistical tests were two-sided, and a P-value of < 0.05 was considered statistically significant.

Results

In total, 1294 pairs of simultaneous arterial and central venous blood gas measurements in 352 patients were retrospectively selected for analysis (mean age, 59 years; range,

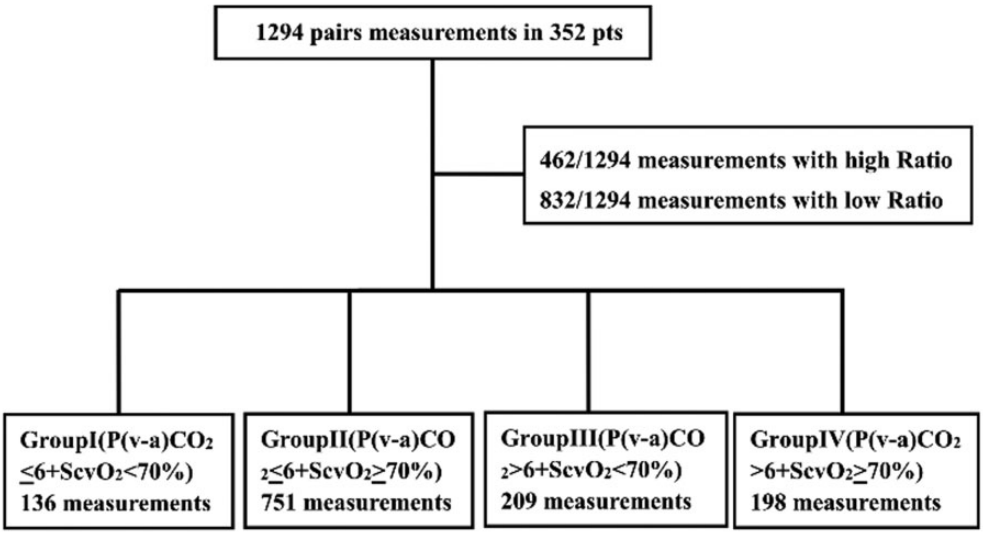

Figure 1. Flow diagram.

18–91 years; female, n = 163; male, n = 189). The study population comprised 96 postoperative patients, 236 patients with sepsis, and 20 patients with other diseases. The flow diagram in Figure 1 shows the data analysis of all the measurements.

Correlation between relevant parameters and P(v-a)CO_2/C(a-v)O_2 ratio in all measurements

The distribution of all data reflecting the P(v-a)CO_2/C(a-v)O_2 ratio measurements was skewed (median, 1.45; interquartile range, 0.93). There was a significant and strong correlation between P(v-a)CO_2 and P(v-a)CO_2/C(a-v)O_2 ($r = 0.692$, $P < 0.0001$) among the 1294 sets of measurements. Both the $ScvO_2$ ($r = 0.104$, $P < 0.0001$) and Hb ($r = -0.159$, $P < 0.0001$) were significantly correlated with P(v-a)CO_2/C(a-v)O_2, but these relationships were weak. However, P(v-a)CO_2/C(a-v)O_2, P(v-a)CO_2, and $ScvO_2$ were not significantly associated with the arterial lactate level.

Difference between high and low P(v-a)CO_2/C(a-v)O_2 measurements

Thirty-six percent (462/1294) of the measurements had a high P(v-a)CO_2/C(a-v)O_2 ratio (>1.68). There was a significantly higher P(v-a)CO_2 ($P < 0.0001$), lower Hb ($P < 0.0001$), higher $ScvO_2$, ($P < 0.0001$), and lower SaO_2 ($P = 0.045$) among the high than low P(v-a)CO_2/C(a-v)O_2 ratio measurements (Figure 2(a)–(d)). However, there was no significant difference in lactate (2.7 ± 2.8 vs. 2.7 ± 3.3) between the low and high P(v-a)CO_2/C(a-v)O_2 ratio measurements.

The P(v-a)CO_2 (area under ROC curve, 0.793) was the best predictor of a high ratio (>1.68) and was significantly better than $ScvO_2$ (area under ROC curve, 0.62) and Hb (area under ROC curve, 0.606) (Figure 3). The areas under the curve of the related variables used to predict a high ratio are shown in Table 1. A P(v-a)CO_2 threshold of 7 mmHg was associated with a sensitivity of 41.77% and a specificity of 90.62% for predicting a high P(v-a)CO_2/C(a-v)O_2 ratio (>1.68).

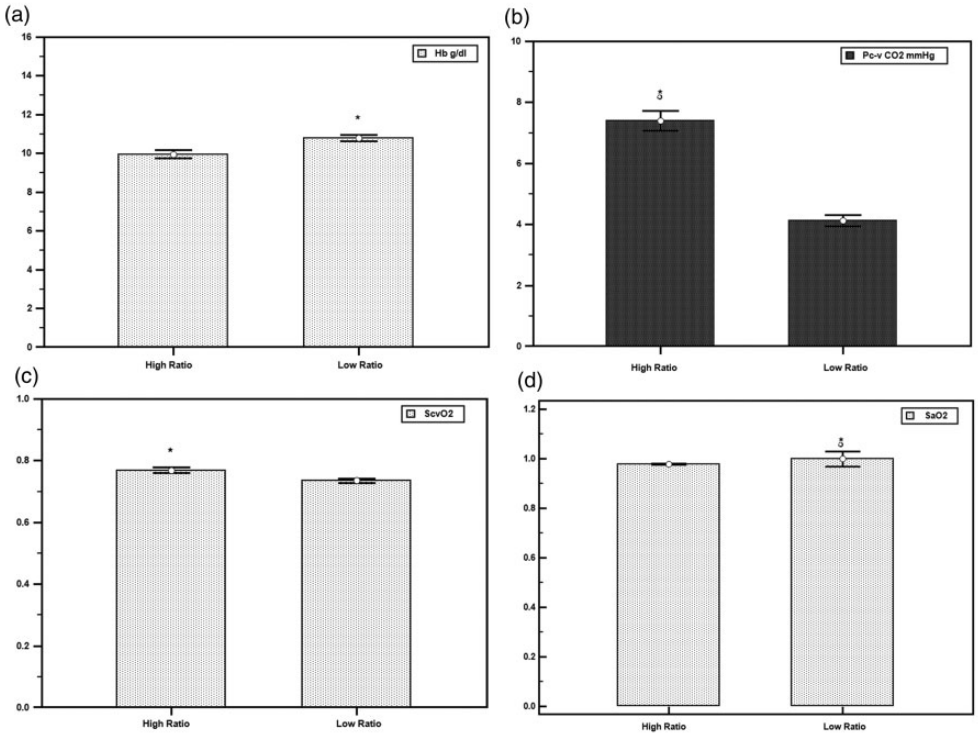

Figure 2. Difference in (a) hemoglobin, (b) P(v-a)CO_2, (c) $ScvO_2$, and (d) SaO_2 between high and low P(v-a)CO_2/C(a-v)O_2 ratio measurements. *P <0.05. P(v-a)CO_2, venoarterial carbon dioxide tension difference; $ScvO_2$, central venous oxygen saturation; SaO_2, arterial oxygen saturation; C(a-v)O_2, arteriovenous oxygen content difference.

P(v-a)CO_2/C(a-v)O_2 in different groups based on $ScvO_2$ (70%) and P(v-a)CO_2 (6 mmHg)

Based on the cutoffs of $ScvO_2$ (70%) and P(v-a)CO_2 (6 mmHg), we assigned all measurements to four categories: Group I [P(v-a)$CO_2 \leq 6$ mmHg and $ScvO_2 < 70\%$], Group II [P(v-a)$CO_2 \leq 6$ mmHg and $ScvO_2 \geq 70\%$], Group III [P(v-a)$CO_2 > 6$ mmHg and $ScvO_2 \geq 70\%$], and Group IV [P(v-a)$CO_2 > 6$ mmHg and $ScvO_2 < 70\%$]. The characteristics of the P(v-a)CO_2/C(a-v)O_2 ratio in the different groups are shown in Table 2. Group I ($n = 136$) had the lowest P(v-a)CO_2/C(a-v)O_2 ratio (1.00 ± 0.46), and Group III ($n = 209$) had the highest P(v-a)CO_2/C(a-v)O_2 ratio [2.32 (1.9–3.4)]. Moreover, the lowest percentage of a high P(v-a)CO_2/C(a-v)O_2 ratio (>1.68) was present in Group I [5.8% (8/136)], and the highest percentage was present in Group III [84% (176/209)] (Figure 4). Group I had a significantly higher lactate level and lower Hb and SaO_2 than the other groups ($P < 0.05$), and Groups I and IV had a significantly higher EO_2 than the other groups (Figure 5).

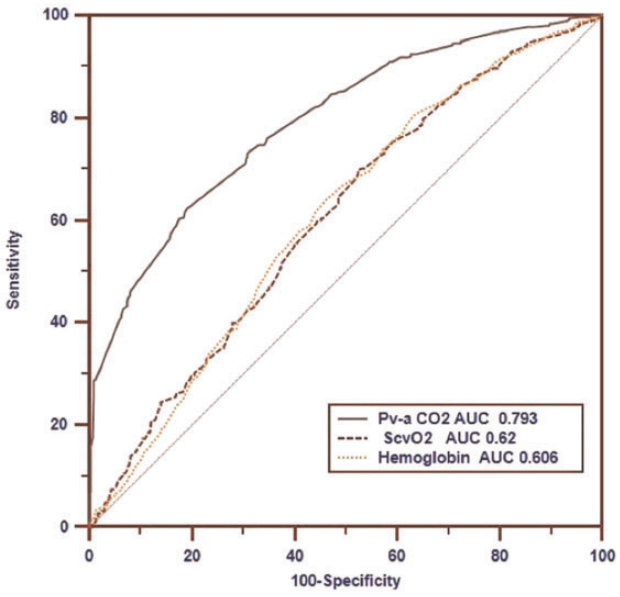

Figure 3. Receiving operating characteristic curves showing the ability of $ScvO_2$, $P(v\text{-}a)CO_2$, and hemoglobin to predict a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio of >1.68. $ScvO_2$, central venous oxygen saturation; $P(v\text{-}a)CO_2$, venoarterial carbon dioxide tension difference; $C(a\text{-}v)O_2$, arteriovenous oxygen content difference.

Table 1. Comparison of AUCs for predicting a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (>1.68) in all measurements.

Parameters	AUC	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
Hemoglobin	0.606	0.579–0.633	9.7 g/dL	53.70	64.30
$P(v\text{-}a)CO_2$	0.793*	0.769–0.814	7 mmHg	41.77	90.62
$ScvO_2$	0.620	0.468–0.762	79.6%	47.60	69.80
SaO_2	0.557	0.525–0.588	99%	42.90	69.20

AUC, area under the receiver operating characteristic curve; $P(v\text{-}a)CO_2$, venoarterial carbon dioxide tension difference; PaO_2, arterial oxygen tension; $ScvO_2$, central venous oxygen saturation; SaO_2, arterial oxygen saturation; CI, confidence interval. *P <0.05 for comparison of $P(v\text{-}a)CO_2$.

Discussion

This is the largest clinical study to date evaluating the correlation of $ScvO_2$ and $P(v\text{-}a)CO_2$ with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in critically ill patients. The most important finding of the present study is that the relationships of $ScvO_2$ and $P(v\text{-}a)CO_2$ with the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio were validated and that the characteristics of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio were described in the real-world setting. These data are meaningful for interpretation of this ratio in clinical practice.

Factors contributing to a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (>1.68)

In the present study, $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ showed a significantly stronger relationship with $P(v\text{-}a)CO_2$ than $ScvO_2$, Hb, and SaO_2. Importantly, a high $P(v\text{-}a)CO_2$ is the most relevant factor contributing to the high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio among these

Table 2. Related parameters in the different groups according to cutoffs of $ScvO_2$ (70%) and P(v-a)CO_2 (6 mmHg).

Parameters	Group I P(v-a)$CO_2 \leq 6$ mmHg and $ScvO_2 < 70\%$ (n = 136)	Group II P(v-a)$CO_2 \leq 6$ mmHg and $ScvO_2 \geq 70\%$ (n = 751)	Group III P(v-a)$CO_2 > 6$ mmHg and $ScvO_2 \geq 70\%$ (n = 209)	Group IV P(v-a)$CO_2 > 6$ mmHg and $ScvO_2 < 70\%$ (n = 198)
$ScvO_2$, %	66 (61–67)	80 (76–84)[a]	78 ± 6[a]	61 (54–67)[b,c]
P(v-a)CO_2, mmHg	4 (2–5)	3.9 (2–5)	8 (7–9.6)[a,b]	8 (7–10)[a,b]
Ratio index	1.00 ± 0.46	1.26 (0.87–1.7)[a,c]	2.32 (1.9–3.4)[a,b]	1.6 (1.4–1.9)[a,c]
Incidence of a high ratio	8 (5.8)	195 (25.9)[a,c]	176 (84.0)[a]	83 (42.0)[a,c]
Hemoglobin, g/dL	9.9 ± 2.2	10 (8.8–11.6)[a]	11.1 ± 2.5[a]	11 ± 2.8[a]
Lactate, mmol/L	5 (3–6)	1.7 (1.1–2.8)[a]	1.7 (1.1–2.8)[a]	2.3 (1.3–4.2)[a]
SaO_2, %	97 (93–99)	99 (97–100)[a]	99 (98–100)[a]	98 (95–100)[a]
EO_2, %	34 ± 0.08	22 ± 0.08[a,c]	21 ± 0.06[a,c]	39 ± 0.09[a]

Data are presented as median (interquartile range), mean ± standard deviation, or n (%).
$ScvO_2$, central venous oxygen saturation; P(v-a)CO_2, venoarterial carbon dioxide tension difference; SaO_2, arterial oxygen saturation; EO_2, oxygen extraction percentage.
[a]$P < 0.05$ vs. Group I.
[b]$P < 0.05$ vs. Group II.
[c]$P < 0.05$ vs. Group III.

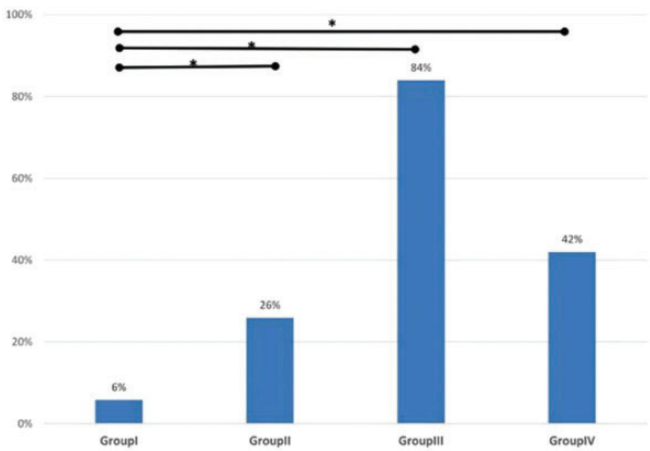

Figure 4. Percentages of a high P(v-a)CO_2/C(a-v)O_2 ratio (>1.68) in different groups based on the cutoffs of $ScvO_2$ (70%) and P(v-a)CO_2 (6 mmHg). *$P < 0.05$. P(v-a)CO_2, venoarterial carbon dioxide tension difference; C(a-v)O_2, arteriovenous oxygen content difference; $ScvO_2$, central venous oxygen saturation.

related parameters. Therefore, the first priority might be to address the high P(v-a)CO_2 level to restore the P(v-a)CO_2/C(a-v)O_2 ratio in critically ill patients. It could be argued that the variations in these parameters would impact the relationship between the included parameters and the P(v-a)CO_2/C(a-v)O_2 ratio. Additionally, both the P(v-a)CO_2 and $ScvO_2$ measurements had an abnormal distribution, and

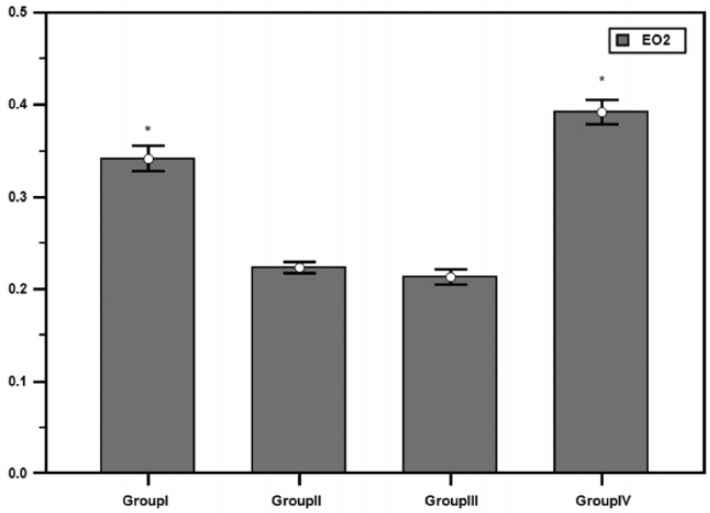

Figure 5. EO_2 in different groups based on the cutoffs of $ScvO_2$ (70%) and $P(v\text{-}a)CO_2$ (6 mmHg). *Group I vs. Groups II, III, and IV; $P < 0.05$. Group IV vs. Groups II and III; $P < 0.05$. EO_2, oxygen extraction percentage; $ScvO_2$, central venous oxygen saturation; $P(v\text{-}a)CO_2$, venoarterial carbon dioxide tension difference.

the variation in the $P(v\text{-}a)CO_2$ and $ScvO_2$ might have been comparable in this large-sample study. Therefore, our study suggests that the priority should be paying close attention to $P(v\text{-}a)CO_2$ to correct the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in critically ill patients. Further prospective studies are required to investigate the effects of variations of other related parameters on the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio.

Behavior of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in present classification based on $ScvO_2$ and $P(v\text{-}a)CO_2$

$ScvO_2$ is a well-known marker that reflects whether DO_2 meets the demand of VO_2.[18] Additionally, $P(v\text{-}a)CO_2$ functions as a global flow parameter that reflects whether the systemic flow meets the needs of tissue perfusion.[19,20] In Group I of the present study, the combination of low $P(v\text{-}a)CO_2$ and low $ScvO_2$ indicated that the global flow was sufficient but that DO_2 did not meet the demand of VO_2. This group had a significantly lower SaO_2 and Hb and higher EO_2 than the other groups. Both arterial hypoxia and hemodilution could contribute to low $ScvO_2$ resulting from insufficient DO_2 with a high EO_2 and low $P(v\text{-}a)CO_2$ from high compensatory cardiac output. Interestingly, Group I had the lowest $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (1.00 ± 0.46) and lowest percentage of a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio [5.8% (8/136)]. Theoretically, using a low $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio to reflect the absence of anaerobic metabolism should be done with caution in patients with low $ScvO_2$ together with low $P(v\text{-}a)CO_2$, who have special hemodilution and arterial blood hypoxemia conditions with high VO_2. A potential pathophysiologic mechanism is as follows. First, the cardiac output shows a compensatory increase to restore DO_2 under conditions of hypoxemia and/or hemodilution, which could cause a decrease in the $P(v\text{-}a)CO_2$ gap. Second, a low $ScvO_2$ commonly

indicates an compensatory increase in the EO_2 because of high oxygen demand. Third, the $P(v\text{-}a)CO_2$ might further decrease in the presence of low $ScvO_2$ through the Haldane effect.[21] Hence, in Group I of the present study, the "pseudo-normalization" of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio might have been related to high cardiac output together with high VO_2.[22] A recent experimental study also showed that the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio might be a misleading surrogate for anaerobic metabolism in the presence of hemodilution.[23] Further clinical studies are required to validate the meaning of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in the Group I condition.

Group II had high $ScvO_2$ and low $P(v\text{-}a)CO_2$. In this case, both global flow and DO_2 appeared to be adequate to meet tissue cell needs. Sepsis may have been a common cause of the results seen in Group II, especially given the hyperdynamic hemodynamic status after early resuscitation. Studies have supported that normal $ScvO_2$ does not exclude tissue hypoxia, and even high $ScvO_2$ has been associated with poor clinical outcomes.[24–28] Moreover, 25.9% (195/751) of the measurements had a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in Group II. In other words, normalization of both $ScvO_2$ and $P(v\text{-}a)CO_2$ could not totally exclude the independence of the presence of anaerobic metabolism. Here, we stress that a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio cannot be simply taken as a marker of increased DO_2 to meet the tissue perfusion needs under conditions of high $ScvO_2$ and low $P(v\text{-}a)CO_2$. First, oxygen cannot be effectively transported into tissue cells through the microcirculation when there is a loss of coherence between the macro- and microcirculation.[29,30] Second, if a disassociation exists between cellular oxygen utilization and tissue perfusion, an increase in DO_2 would not help to correct the high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio. Further study is required to determine whether correction of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio can improve tissue perfusion and/or the clinical outcome when $ScvO_2$ and $P(v\text{-}a)CO_2$ have been normalized.

Group III had a high $P(v\text{-}a)CO_2$ of > 6 mmHg and high $ScvO_2$ of $\geq 70\%$, indicating that the global flow might be insufficient for tissue perfusion, although the DO_2 had reached the threshold for the physiologic requirements. Eighty-four percent (176/209) of the measurements had a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio (>1.68) in Group III, and a high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio indicates a high possibility of anaerobic metabolism. A high $ScvO_2$ might result from dysfunction of the microcirculation (shunting) and oxygen utilization.[26–28] Moreover, an elevated $P(v\text{-}a)CO_2$ is not only dependent on the effect of the global flow related to tissue hypoxia but is also dependent on the ability of the microcirculatory blood flow to clear the additional carbon dioxide even during normal/high global flow. Recent clinical research has shown that the $P(v\text{-}a)CO_2$ gap may also reflect alterations in the microcirculation in patients with septic shock.[16] Therefore, we suggest that restoration of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio should focus on both global flow and microcirculation flow in the Group III condition. Some might argue the lactate level was not higher in Group III and that lactate is always taken as a marker of anaerobic metabolism. However, the agreement between the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio and lactate level should not be interpreted as representative of anaerobic metabolism. Studies have shown the hyperlactatemia is not always of hypoxic origin in critically ill patients.[31–33]

Group IV had a high $P(v\text{-}a)CO_2$ of > 6 mmHg and low $ScvO_2$ of $< 70\%$, indicating that both global flow and DO_2 were insufficient for the body's demand. Interestingly, only 42% (83/198) of the

measurements had a high P(v-a)CO_2/C(a-v)O_2 ratio in Group IV. In contrast, 58% of the P(v-a)CO_2/C(a-v)O_2 ratio measurements were normal ($\leq$1.68). In other words, among patients with high P(v-a)CO_2 and low $ScvO_2$, there might be a more than 50% possibility for the absence of anaerobic metabolism. Hence, calculation of the P(v-a)CO_2/C(a-v)O_2 ratio might also provide information that would help to avoid over-resuscitation in patients with a high P(v-a)CO_2 of >6 mmHg and low $ScvO_2$ of $<70\%$. Moreover, low $ScvO_2$ and high P(v-a)CO_2 might result from a high VO_2 condition; in such cases, both the EO_2 and VCO_2 are increased. Our study also showed that Group IV had the highest EO_2. The potential clinical meaning of the P(v-a)CO_2/C(a-v)O_2 ratio in the four groups is summarized in Table 3.

Disassociation of lactate and P(v-a)CO_2/C(a-v)O_2 ratio

A significant relationship between lactate and the P(v-a)CO_2/C(a-v)O_2 ratio was not found in the present study. Moreover, there was no significant difference in the lactate level between low and high P(v-a)CO_2/C(a-v)O_2 ratio measurements. This result seems to oppose those of published studies,[4–7] and it should be interpreted with caution. The ability of the P(v-a)CO_2/C(a-v)O_2 ratio and lactate to reflect anaerobic metabolism was not questioned and/or compared in our study. Several factors could have confounded the relationship between lactate and the P(v-a)CO_2/C(a-v)O_2 ratio in the present study, such as the lactate clearance ability, washout effect, and stress factors. However, our study supports the notion that incoherence of lactate and the P(v-a)CO_2/C(a-v)O_2 ratio might be common in critically ill patients. We stress that attention should be paid to the disassociation of lactate and the P(v-a)CO_2/C(a-v)O_2 ratio in clinical practice. Traditionally, a high lactate level is always taken as a marker of anaerobic metabolism and an indicator of the need for resuscitation. This viewpoint has been challenging because high lactate cannot result from cellular hypoxia in the intensive care unit. A recent study showed that the P(v-a)CO_2/C(a-v)O_2 ratio can provide additional information on anaerobic metabolism when compared with the lactate level.[9] Further study is required to validate how to combine lactate and the P(v-a)CO_2/C(a-v)O_2 ratio to identify cellular hypoxia and guide resuscitation.

In summary, the P(v-a)CO_2/C(a-v)O_2 ratio is a potential marker of global anaerobic metabolism that could provide additional information regarding the relationship of global DO_2/VO_2 when combined with $ScvO_2$ and P(v-a)CO_2 in clinical practice. The above-described findings could be of interest and should be considered in the application of the P(v-a)CO_2/C(a-v)O_2 ratio in clinical practice.

Limitations

Several limitations of this study should be acknowledged. First, this was a retrospective study, and we only focused on the relationships between relevant parameters and the P(v-a)CO_2/C(a-v)O_2 ratio. Validation of the P(v-a)CO_2/C(a-v)O_2 ratio as a marker of cellular hypoxia was not the aim of this study; therefore, information regarding prognosis, other tissue perfusion parameters, cellular hypoxia indicators, DO_2, and cardiac output are unavailable. Importantly, the most significant points of this study were demonstration of the profile of the P(v-a)CO_2/C(a-v)O_2 ratio and identification of the risk factors contributing to changes in parameters used in calculation of the ratio in clinical practice. Second, we acknowledge that some conclusions in this study are speculative according to reasonable pathophysiologic principles. Hence,

Table 3. Characteristics and potential meaning of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in the four groups.

Items	Group I Low $P(v\text{-}a)CO_2$ + low $ScvO_2$	Group II Low $P(v\text{-}a)CO_2$ + high $ScvO_2$	Group III High $P(v\text{-}a)CO_2$ + high $ScvO_2$	Group IV High $P(v\text{-}a)CO_2$ + low $ScvO_2$
Behavior of ratio	96% of the measurements of the ratio were normal with a low value	25% of the measurements of the ratio were abnormal with a high value	84% of the measurements of the ratio were abnormal with a high value	Almost 50% of the measurements of the ratio were abnormal with a high value
Global circulation	Sufficient global flow but insufficient DO_2 for the high oxygen demand	Insufficient global flow and DO_2	Sufficient DO_2 but insufficient global flow	Insufficient global flow and DO_2
Interpretation of ratio	The low ratio might not reliably reflect the absence of anaerobic metabolism	The high ratio reflects the presence of anaerobic metabolism, possibly secondary to mitochondrial dysfunction or microcirculation shunting	The high ratio reflects anaerobic metabolism secondary to poor microcirculatory perfusion and/or mitochondrial dysfunction	The high ratio reflects anaerobic metabolism secondary to low DO_2 and flow and/or high VO_2 with poor cardiac output
Potential etiology	Hemodilution and hypoxemia together with high EO_2 and oxygen demand	Sepsis, inflammation, ischemia–reperfusion	Sepsis, inflammation, ischemia–reperfusion	Hypovolemic shock, cardiac shock, obstructive shock
Therapy	Decrease oxygen demand with sedation, low temperature, or other; transfusion for hemodilution; negative fluid balance with volume overload; improve SaO_2 with increased FiO_2 and/or PEEP	Recruit microcirculation with vasodilators	Improve global flow using fluid therapy, inotropic therapy, or other; recruit microcirculation with vasodilators	Improve global flow and DO_2 using fluid therapy, inotropic therapy, or other; decrease oxygen demand with sedation, low temperature, or other

$P(v\text{-}a)CO_2$, venoarterial carbon dioxide tension difference; $ScvO_2$, central venous oxygen saturation; DO_2, oxygen delivery; VO_2, oxygen consumption; EO_2, oxygen extraction percentage; SaO_2, arterial oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

further investigations are required to validate that hemodilution and hypoxemia with a high VO_2 result in pseudo-normalization of the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio. Third, the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio functions as a parameter to predict the response of an increase in DO_2 according to the concept of oxygen transport. The DO_2 challenge test is the related method used to evaluate DO_2/VO_2 dependence. The limitations of the global DO_2 challenge test must be taken into consideration; namely, the balance time of the DO_2 challenge and the mathematical coupling of data when using the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio.[34]

Conclusion

The $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is always low in a low $ScvO_2$ + low $P(v\text{-}a)CO_2$ condition, and the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is always high in a high $ScvO_2$ + low $P(v\text{-}a)CO_2$ condition. A high $P(v\text{-}a)CO_2$ is the most relevant factor that contributes to the high $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in critically ill patients. Before the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is used for shock resuscitation in the clinical setting, further prospective studies are required to validate the $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio in different clinical conditions.

Abbreviations

DO_2 = oxygen delivery; VO_2 = oxygen consumption; $P(v\text{-}a)CO_2$ = venoarterial carbon dioxide tension difference; $C(a\text{-}v)O_2$ = arteriovenous oxygen content difference; VCO_2 = global carbon dioxide production; $C(v\text{-}a)CO_2$ = venoarterial carbon dioxide content difference; $ScvO_2$ = central venous oxygen saturation; SaO_2 = arterial oxygen saturation; PaO_2 = arterial oxygen tension; $PaCO_2$ = arterial carbon dioxide tension; PvO_2 = central venous oxygen tension; $PvCO_2$ = central venous carbon dioxide tension; Hb = hemoglobin; CaO_2 = arterial oxygen content; CvO_2 = central venous oxygen content; EO_2 = oxygen extraction percentage.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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