Combination of O₂ and CO₂-derived variables to detect tissue hypoxia in the critically ill patient

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Abstract: Oxygen-derived parameters have been traditionally used to guide resuscitation during shock states. Nevertheless, normalization of venous oxygen saturation does not exclude the persistence of tissue hypoperfusion and tissue hypoxia. Combination of O₂ and CO₂-derived variables has consistently demonstrated to be related with clinical outcomes and its variations could anticipate changes in lactate and also predict fluid responsiveness in terms of oxygen consumption. Here we discuss the potential mechanisms leading to increase the venous-to-arterial CO₂ (Cv-aCO₂) to arterial-to-venous O₂ content difference (Ca-vO₂), i.e., the Cv-aCO₂/Ca-vO₂ ratio, its potential clinical application, limitations and uncertainties. Finally, although biologically plausible, the potential applications of the Cv-aCO₂/Ca-vO₂ ratio in the clinical practice require to be confirmed.

Keywords: Tissue perfusion; venous-to-arterial carbon dioxide difference; anaerobic metabolism; respiratory quotient; venous-arterial CO₂ to arterial-venous O₂ difference (Cv-aCO₂/Ca-vO₂ difference)

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Introduction

Early detection and prompt reversion of tissue hypoperfusion are key factors to prevent progression to multiorgan dysfunction and death during shock states (1). Techniques commonly used to monitor tissue perfusion have focused mainly on systemic blood flow and the balance between oxygen demand and supply to the tissues (2,3). Indeed, quantitative resuscitation targeting central venous oxygen saturation (ScvO₂) and some macro hemodynamic parameters was related with a significant reduction of mortality in an initial single-center randomized controlled trial including patients with septic shock (4). Subsequent studies on implementation of resuscitation bundles targeting similar hemodynamic goals in septic shock were also apparently beneficial (5,6). Nevertheless, the utility of oxygen-derived parameters was promptly challenged (7), and recent clinical trials failed to demonstrate their clinical benefit (8-10). In fact, ScvO₂ is often normal at the ICU admission (11), and attaining macro hemodynamic goals and/or normalization of global oxygen-derived parameters in septic shock do not exclude the occurrence or persistence of tissue hypoxia. In this context, other variables such as carbon dioxide (CO₂)-derived parameters could provide very important information about macro and micro hemodynamics, even when oxygen-derived variables resemble corrected. Importantly, variations in CO₂ occur faster than changes in lactate levels, which make the CO₂-derived parameters an attractive tool to monitor tissue perfusion and potentially, cell oxygenation during the early stages of shock.
The theoretical basics of the venous-arterial CO₂ to arterial-venous O₂ ratio (Cv-aCO₂/ Ca-vO₂ ratio)

Aerobic carbon dioxide production and the physiological rationale of the Cv-aCO₂/ Ca-vO₂ ratio

Under normoxic conditions, carbon dioxide (CO₂) is generated during the tricarboxylic acid or Krebs cycle. The total CO₂ production (VCO₂) is directly related to the global oxygen consumption (VO₂), by the relationship: VCO₂ = RQ × VO₂, where RQ symbolizes the respiratory quotient and represents the relationship between the total CO₂ generated and the oxygen (O₂) consumed throughout metabolic processes. Under normal rest conditions, RQ fluctuates from 0.6 to 1.0 depending on the predominant energetic substrate utilized (i.e., amino acids, lipids or carbohydrates). Thus, under resting aerobic conditions RQ should not be >1.0 since VCO₂ should not exceed the O₂ availability. Indeed, RQ remains <1.0 even during metabolic rate rises (as long as aerobic metabolism is maintained), because the proportional increase in VCO₂ and VO₂.

According to the Fick equation, VO₂ and VCO₂ are directly proportional to the cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Following this rationale, the quotient between the venous-to-arterial CO₂ content difference (Cv-aCO₂) and the arterial-to-venous O₂ content difference (Ca-vO₂), i.e., the Cv-aCO₂/Ca-vO₂ ratio, should reflect the VCO₂/VO₂ fraction and it should be theoretically independent of flow variations, as cardiac output is present at both numerator and denominator components of the formula (Figure 1).

Under aerobic steady state conditions, VCO₂ approaches VO₂, whereby the Cv-aCO₂ and the Ca-vO₂ should also do it. Consequently, VCO₂ should not exceed O₂ availability whereby the VCO₂/VO₂ ratio [i.e., the respiratory quotient (RQ)] should not be >1.0. Thus, VCO₂/VO₂ and Cv-aCO₂/Ca-vO₂ ratio >1.0 should be considered as abnormal and these could potentially reflect anaerobic CO₂ generation.

Anaerobic carbon dioxide production

Under hypoxia conditions, aerobic VCO₂ decreases while anaerobic VCO₂ turns on. Such anaerobic VCO₂ reflects the proton (H+) buffering by cytosolic and plasmatic bicarbonate (HCO₃⁻). The “gross H+ release” results from the sum of all cellular reactions liberating H+ [e.g., the ATPase, hexokinase (HK), phosphofructokinase (PFK), and glyceraldehyde-3-phosphate dehydrogenase (G3PDH) reactions], which are counterbalanced by metabolic reactions consuming H+ [e.g., AMP deaminase (AMPDase), the creatine kinase (CK), pyruvate kinase (PK), and lactate dehydrogenase (LDH) reactions]. Thus, the balance between the “gross H+ release” and chemical reactions consuming H+ (i.e., the “metabolic buffering”) results in the “net H+ release”, which is ultimately regulated by the intra and extracellular structural buffering (e.g., amino acids) and the bicarbonate buffering system (12).

Interestingly, the hydrolysis of the ATP has been proposed as the most important source of hydrogen ions during intense exercise (13), prolonged ischemia (14) or increased Na+-K+ ATPase activity (15-19). Thus, non-recycled H+ due either to slowdown, blocking or overshoot of oxidative phosphorylation, progressively accumulate to be finally buffered by the bicarbonate system. This later will be responsible for the anaerobic VCO₂ as the protons are captured by HCO₃⁻ leading to carbonic acid (H₂CO₃) generation with subsequent dissociation into CO₂ and H₂O (Figure 2). Nevertheless, although anaerobic VCO₂ is a biologically plausible process, its clinical demonstration is quite complex since the efferent venous blood flow might be sufficient to wash out the total CO₂ produced at the tissues, thus masking the portion of increased anaerobic CO₂.

The hypothetical meaning of the Cv-aCO₂/Ca-vO₂ ratio

Experimental blockade of mitochondrial O₂ utilization and limitation of O₂ availability during severe tissue hypoperfusion have been related with “non-symmetrical” reductions in VCO₂ and VO₂ with the subsequent RQ increase. Such “asymmetric” VCO₂/VO₂ fall might be explained by an increase in anaerobic CO₂ production resulting from the buffering of protons delivered from the ATP hydrolysis that are not recycled during oxidative phosphorylation (Figure 2). Similarly, when anaerobic threshold is achieved after an excessive increased metabolic demand, total VCO₂ can exceed the adaptive increment in VO₂ (20), thus leading to RQ values >1.0. Similar data have been described during experimental shock in which VCO₂ decreases slightly less than the VO₂ reduction, leading to increases in the VCO₂/VO₂ ratio (21,22). Interestingly, reversion of shock was related with returning VCO₂/VO₂ ratio to values <1.0. Thus, if considering the Cv-aCO₂/Ca-vO₂ ratio as a surrogate of the VCO₂/VO₂ ratio, a Cv-aCO₂/ Ca-vO₂ ratio >1.0 could potentially identify the presence of anaerobic metabolism.
Ospina-Tascón and Madriñán. Combination of O₂ and CO₂-derived variables in the critical ill

The potential clinical use of the Cv-aCO₂/Ca-vO₂ ratio

Although hyperlactatemia has been traditionally used as a marker of anaerobic metabolism, lactate levels might frequently increase by causes different to tissue hypoxia (23). Indeed, high lactate levels can result from increased glycolytic activity, abnormal pyruvate metabolism and altered metabolic lactate reuptake (24-26). Thus, interpretation of hyperlactatemia during the resuscitation and post resuscitation periods of septic shock is not straightforward. In this sense, the use of combined CO₂ and O₂-derived parameters could theoretically help to identify, in some extend, the persistence or reversion of anaerobic metabolism.

Using CO₂ partial pressures (pCO₂) instead of CO₂ contents (CCO₂), Mekontso-Dessap et al. (27) demonstrated a good agreement between the Pv-aCO₂/Ca-vO₂ ratio (as surrogate of the Cv-aCO₂/Ca-vO₂ ratio) and lactate levels ≥2.0 mmol/L (accepting it as indicator of anaerobic metabolism). Nevertheless, far beyond a simple agreement, the Cv-aCO₂/Ca-vO₂ ratio might provide...
additional information to that offered by lactate levels. A recent study (28) suggested that combination of persistent hyperlactatemia and Cv-aCO$_2$/Ca-vO$_2$ ratios >1.0 is related with more severe multiorgan dysfunction and higher mortality rates in patients with septic shock. Remarkably, patients attaining normalization of lactate levels but with Cv-aCO$_2$/Ca-vO$_2$ ratios >1.0 depicted similar clinical outcomes than those with persistent hyperlactatemia but with normal Cv-aCO$_2$/Ca-vO$_2$ ratios. Nevertheless, this study did not elucidate whether Cv-aCO$_2$/Ca-vO$_2$ ratios >1.0 might anticipate increases in lactate levels.

Subsequent studies corroborated the prognostic value of the Pv-aCO$_2$/Ca-vO$_2$ ratio in sepsis and septic shock (29,30). Importantly, an increased Pv-aCO$_2$/Ca-vO$_2$ ratio was related with delayed lactate clearance (29,30), which suggests that Cv-aCO$_2$/Ca-vO$_2$ ratio could anticipate lactate variations. Other studies showed that combined hyperlactatemia and high Cv-aCO$_2$/Ca-vO$_2$ ratio (or its equivalent, the Pv-aCO$_2$/Ca-vO$_2$ ratio) could identify ongoing supply dependency of O$_2$ consumption (i.e., VO$_2$/DO$_2$ dependency) (31,32). In agreement with this concept, oxygen consumption (VO$_2$) was increased after a fluid load only in patients with acute circulatory failure and an abnormal Pv-aCO$_2$/Ca-vO$_2$ ratio at the baseline (31,32).

An experimental model of septic shock secondary to peritonitis demonstrated that regional mesenteric Cv-aCO$_2$/Ca-vO$_2$ ratio tracks the instauration and reversion of anaerobic metabolism following the variations in microcirculatory blood flow distribution at jejunal mucosa and serosa and also tracking the variations in mesenteric lactate levels (33). Hence, anaerobic metabolism reflected by increases in Cv-aCO$_2$/Ca-vO$_2$ ratio can be reversed by improvement of O$_2$ distribution at microcirculatory level, at least during very early stages of septic shock (33).

Combined CO$_2$ and O$_2$-derived variables might add prognostic information to that provided by lactate levels.
levels during early stages of shock. In fact, \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio reacts faster than lactate levels to short-term hemodynamic changes, which makes it an attractive variable to be monitored and, although difficult to be calculated, its interpretation is easier, with values >1.0 suggesting ongoing anaerobic metabolism. Thus, an increased lactate accompanied by a \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio >1.0 might suggest “ongoing” tissue hypoxia, whereby clinicians should be encouraged to optimize macro and micro hemodynamics. Conversely, increased lactate levels accompanied by \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratios ≤1.0 could suggest that such lactate increase results from slow lactate clearance more than from ongoing tissue hypoxia, whereby additional resuscitation efforts should be discouraged. Nevertheless, such hypothesis must be tested in prospective clinical trials before to translate into the clinical practice.

The Haldane effect, the \( \text{CO}_2 \) dissociation curves and the criticism about the \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio as a marker of anaerobic metabolism

The phenomenon whereby hemoglobin increases or decreases its affinity for \( \text{CO}_2 \) according to variations in its oxygenated or deoxygenated state is known as Haldane effect. Thus, when blood enters systemic capillaries and releases \( \text{O}_2 \), the \( \text{CO}_2 \)-carrying capacity rises so that blood picks up extra \( \text{CO}_2 \). Conversely, as blood enters pulmonary capillaries and binds \( \text{O}_2 \), the \( \text{CO}_2 \)-carrying capacity falls, thus facilitating pulmonary elimination of \( \text{CO}_2 \).

According to the Haldane effect, the total \( \text{CO}_2 \) content (\( \text{CCO}_2 \)) rises at a given \( \text{pCO}_2 \) as \( \text{O}_2 \) hemoglobin saturation falls, thus indicating a non-linear relationship between \( \text{pCO}_2 \) and \( \text{CCO}_2 \). Likewise, changes in tissue oxygen extraction, \( \text{pH} \), tissue \( \text{VCO}_2 \), and hemoglobin concentration can also influence the relationships between \( \text{pCO}_2 \) and \( \text{CCO}_2 \), making difficult the interpretation of the venous-to-arterial \( \text{pCO}_2 \) difference. In addition, depending on baseline \( \text{SvO}_2 \), the Haldane effect may increase or decrease \( \text{Pv-aCO}_2 \) in response to the same changes in blood flow or metabolism (34).

Admittedly, \( \text{Pv-aCO}_2/\text{Ca-vO}_2 \) could be equivalent to the \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio when \( \text{PCO}_2 \), \( \text{pH} \), and \( \text{SvO}_2 \) approximate to normality, which occurs in many cases. Nevertheless, during low \( \text{pCO}_2 \) and \( \text{SvO}_2 \) conditions, \( \text{Cv-aCO}_2 \) might profoundly differ from \( \text{Pv-aCO}_2 \). Indeed, clinical observations during very early stages of resuscitation of septic shock suggest that persistence of a high \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio is related to unfavorable clinical outcomes but not its equivalent, the \( \text{Pv-aCO}_2/\text{Ca-vO}_2 \) ratio (28). Thus, although the influence of the Haldane effect is negligible at low \( \text{Pv-aCO}_2 \), the disagreement of \( \text{Cv-aCO}_2 \) and \( \text{Pv-aCO}_2 \) increases at higher \( \text{Pv-aCO}_2 \) values (28).

Some authors have proposed that high \( \text{PcV-aCO}_2/\text{Ca-vO}_2 \) ratio does not reflect anaerobic metabolism and obeys mainly to variations in hemoglobin levels (35), according to observations based on the analysis of expired gases by indirect calorimetry. Nevertheless, under non-steady-state conditions such as during shock states, \( \text{RQ} \) is easily influenced by a number of physiologic events that can alter the agreement between measurements of \( \text{RQ} \) by indirect calorimetry (\( \text{RQic} \)) and the true metabolic activity. Thus, the high solubility of \( \text{CO}_2 \) in tissues and blood, and the variations in pulmonary ventilation/perfusion (\( \text{V/Q} \)) relationships might lead to momentary discordant results between \( \text{RQic} \) and the true \( \text{RQ} \), until a new steady-state is attained (36). Consequently, the relationship between venous-arterial \( \text{CO}_2 \) to arterial-venous \( \text{O}_2 \) differences and anaerobic metabolism should not be rejected based just on measurements of \( \text{VCO}_2 \) by \( \text{RQic} \). Similarly, attributing high \( \text{Pv-aCO}_2/\text{Ca-vO}_2 \) ratios just to variations in hemoglobin levels could be physiologically misleading, since at very low hemoglobin values, small errors in hemoglobin measurements will amplify the error of calculation of \( \text{Pv-aCO}_2/\text{Ca-vO}_2 \) or \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) values.

Conclusions

Physiological determinants of combined \( \text{CO}_2 \) and \( \text{O}_2 \)-derived variables are quite complex. Theoretically, the \( \text{Cv-aCO}_2/\text{Ca-vO}_2 \) ratio is independent of systemic blood flow variations and it should approach the \( \text{RQ} \) or at least, it should approximates cell respiration state. Although venous-arterial \( \text{CO}_2 \) to arterial-venous \( \text{O}_2 \) differences have demonstrated to predict fluid responsiveness in terms of \( \text{VO}_2 \), to anticipate slowly lactate clearance and to be related with clinical outcomes, its potential application in the clinical practice needs to be confirmed.

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Footnote

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References

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