Review Article

Combination of O_2 and CO_2-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 O_2 and CO_2-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 CO_2 ($Cv\text{-}aCO_2$) to arterial-to-venous O_2 content difference ($Ca\text{-}vO_2$), i.e., the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio, its potential clinical application, limitations and uncertainties. Finally, although biologically plausible, the potential applications of the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio in the clinical practice require to be confirmed.

Keywords: Tissue perfusion; venous-to-arterial carbon dioxide difference; anaerobic metabolism; respiratory quotient; venous-arterial CO_2 to arterial-venous O_2 difference ($Cv\text{-}aCO_2/Ca\text{-}vO_2$ 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 ($ScvO_2$) 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, $ScvO_2$ 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 (CO_2)-derived parameters could provide very important information about macro and micro hemodynamics, even when oxygen- derived variables resemble corrected. Importantly, variations in CO_2 occur faster than changes in lactate levels, which make the CO_2-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 CO_2 to arterial-venous O_2 ratio (Cv-aCO_2/Ca-vO_2 ratio)

Aerobic carbon dioxide production and the physiological rationale of the Cv-aCO_2/Ca-vO_2 ratio

Under normoxic conditions, carbon dioxide (CO_2) is generated during the tricarboxylic acid or Krebs cycle. The total CO_2 production (VCO_2) is directly related to the global oxygen consumption (VO_2), by the relationship: $VCO_2 = RQ \times VO_2$, where RQ symbolizes the respiratory quotient and represents the relationship between the total CO_2 generated and the oxygen (O_2) 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 VCO_2 should not exceed the O_2 availability. Indeed, RQ remains <1.0 even during metabolic rate rises (as long as aerobic metabolism is maintained), because the proportional increase in VCO_2 and VO_2.

According to the Fick equation, VO_2 and VCO_2 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 CO_2 content difference (Cv-aCO_2) and the arterial-to-venous O_2 content difference (Ca-vO_2), i.e., the Cv-aCO_2/Ca-vO_2 ratio, should reflect the VCO_2/VO_2 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, VCO_2 approaches VO_2, whereby the Cv-aCO_2 and the Ca-vO_2 should also do it. Consequently, VCO_2 should not exceed O_2 availability whereby the VCO_2/VO_2 ratio [i.e., the respiratory quotient (RQ)] should not be >1.0. Thus, VCO_2/VO_2 and Cv-aCO_2/Ca-vO_2 ratio >1.0 should be considered as abnormal and these could potentially reflect anaerobic CO_2 generation.

Anaerobic carbon dioxide production

Under hypoxia conditions, aerobic VCO_2 decreases while anaerobic VCO_2 turns on. Such anaerobic VCO_2 reflects the proton (H+) buffering by cytosolic and plasmatic bicarbonate (HCO_3–). 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 VCO_2 as the protons are captured by HCO_3– leading to carbonic acid (H_2CO_3) generation with subsequent dissociation into CO_2 and H_2O (*Figure 2*). Nevertheless, although anaerobic VCO_2 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 CO_2 produced at the tissues, thus masking the portion of increased anaerobic CO_2.

The hypothetical meaning of the Cv-aCO_2/Ca-vO_2 ratio

Experimental blockade of mitochondrial O_2 utilization and limitation of O_2 availability during severe tissue hypoperfusion have been related with "non-symmetrical" reductions in VCO_2 and VO_2 with the subsequent RQ increase. Such "asymmetric" VCO_2/VO_2 fall might be explained by an increase in anaerobic CO_2 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 VCO_2 can exceed the adaptive increment in VO_2 (20), thus leading to RQ values >1.0. Similar data have been described during experimental shock in which VCO_2 decreases slightly less than the VO_2 reduction, leading to increases in the VCO_2/VO_2 ratio (21,22). Interestingly, reversion of shock was related with returning VCO_2/VO_2 ratio to values <1.0. Thus, if considering the Cv-aCO_2/Ca-vO_2 ratio as a surrogate of the VCO_2/VO_2 ratio, a Cv-aCO_2/Ca-vO_2 ratio >1.0 could potentially identify the presence of anaerobic metabolism.

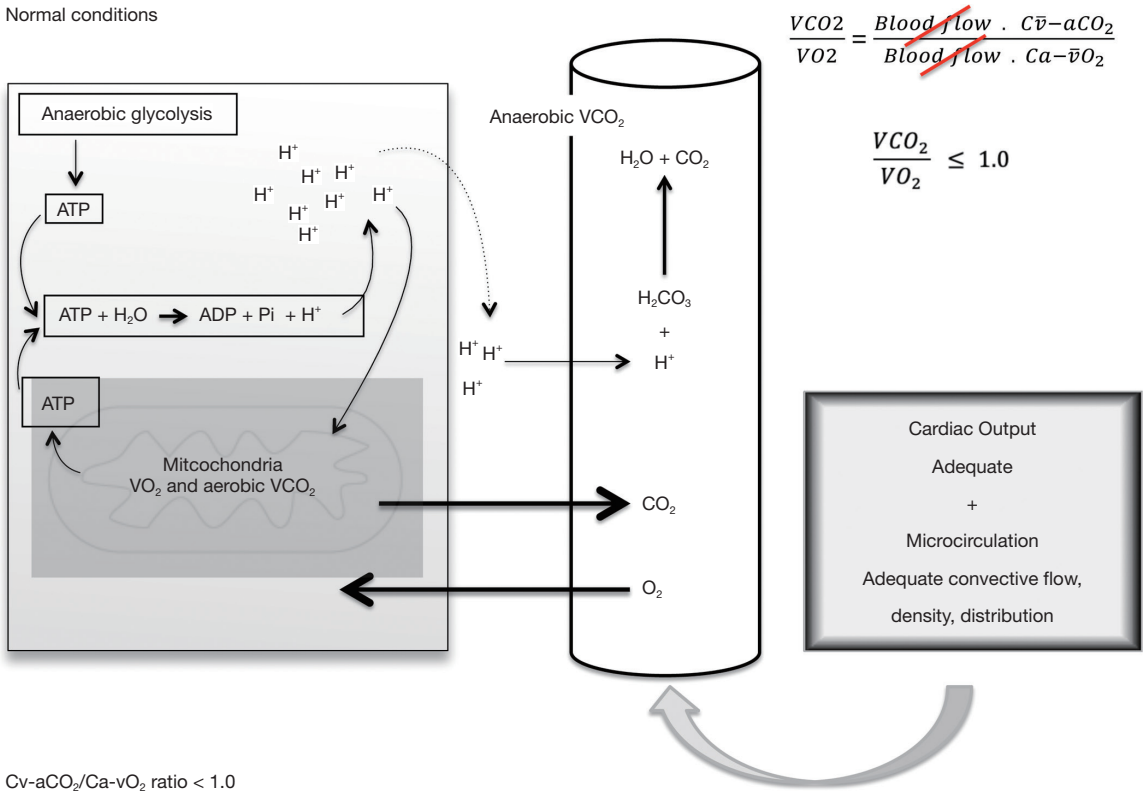

Figure 1 Normal resting conditions. Normal macro and micro hemodynamics lead to homogeneous distribution of oxygen to the tissues. Under preserved mitochondrial function, CO_2 is generated during the Krebs cycle (aerobic VCO_2). The ATP generated predominantly during the oxidative phosphorylation (and in a lesser extend, during glycolysis) is hydrolyzed thus liberating free hydrogenions (H+), which are normally recycled into the mitochondria to synthetize again ATP. Minor quantities of H+ pass the cell membrane reaching the circulation. Such H+ are buffered by the HCO_3- system and finally transformed into CO_2 and water. However, this last process accounts minimally for the total VCO_2 when oxidative phosphorylation functions normally. The relationship between the total CO_2 production (VCO_2) and oxygen consumption (VO_2) should be <1.0 under aerobic conditions. According to the Fick equation, VCO_2 and VO_2 are directly proportional to the cardiac output and their respective venous-to-arterial and arterial-to-venous content differences, respectively. Thus, the quotient between the venous-to-arterial CO_2 content difference (Cv-aCO_2) and the arterial-to-venous O_2 content difference (Ca-vO_2), i.e., the Cv-aCO_2/Ca-vO_2 ratio, should reflect in some extend the VCO_2/VO_2 fraction, independently of flow variations (since cardiac output is present at both numerator and denominator components of the formula).

The potential clinical use of the Cv-aCO_2/Ca-vO_2 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 CO_2 and O_2-derived parameters could theoretically help to identify, in some extend, the persistence or reversion of anaerobic metabolism.

Using CO_2 partial pressures (pCO_2) instead of CO_2 contents (CCO_2), Mekontso-Dessap *et al.* (27) demonstrated a good agreement between the Pv-aCO_2/Ca-vO_2 ratio (as surrogate of the Cv-aCO_2/Ca-vO_2 ratio) and lactate levels ≥2.0 mmol/L (accepting it as indicator of anaerobic metabolism). Nevertheless, far beyond a simple agreement, the Cv-aCO_2/Ca-vO_2 ratio might provide

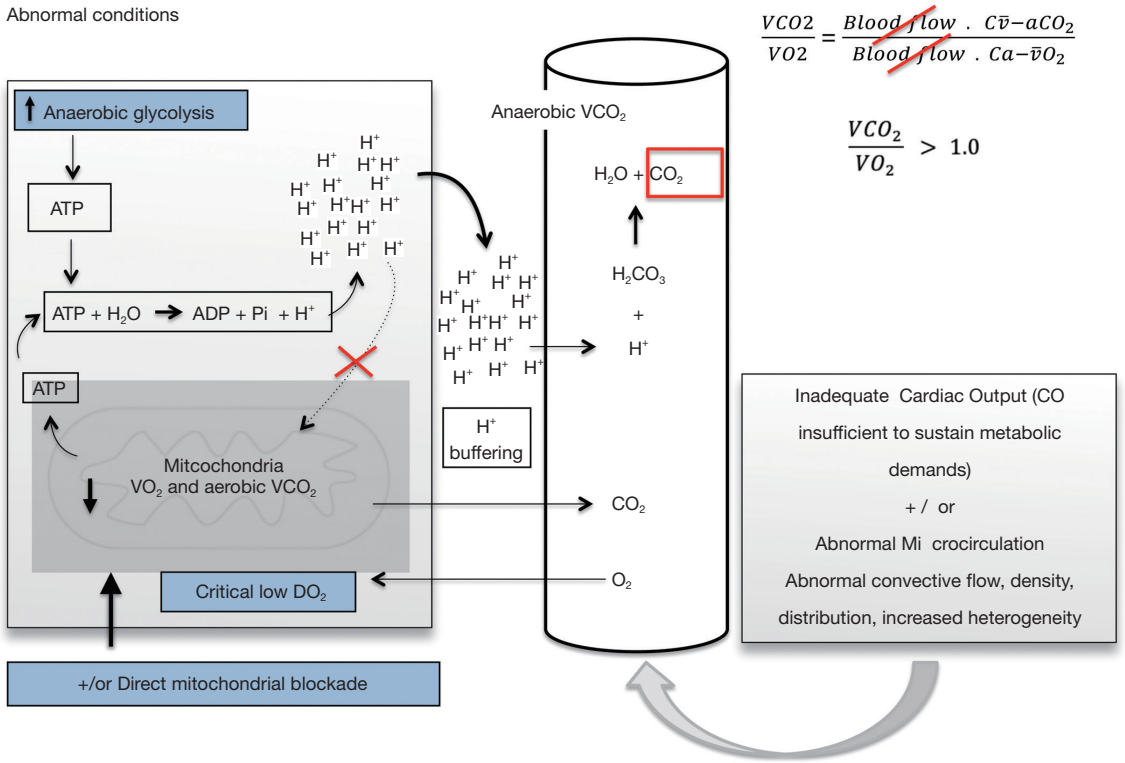

Figure 2 Abnormal conditions. When macro hemodynamics and/or microcirculatory blood distribution are inadequate or when mitochondrial machinery is blocked, the H+ generated during the ATP hydrolysis are not recycled during the oxidative phosphorylation. Thus, the excess of H+ will cross the cell membrane to finally be buffered by the HCO_3- system and thus, to be transformed into CO_2 and H_2O. This leads to increase VCO_2/VO_2 fraction and its surrogate, the Cv-aCO_2/Ca-vO_2 ratio. To minimize the influence of Haldane effect, CO_2 contents should be calculated instead of CO_2 partial pressures (for details, see at the text).

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 during early stages of shock. In fact, Cv-aCO_2/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 Cv-aCO_2/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 Cv-aCO_2/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 CO_2 dissociation curves and the criticism about the Cv-aCO_2/Ca-vO_2 ratio as a marker of anaerobic metabolism

The phenomenon whereby hemoglobin increases or decreases its affinity for CO_2 according to variations in its oxygenated or deoxygenated state is known as Haldane effect. Thus, when blood enters systemic capillaries and releases O_2, the CO_2-carrying capacity rises so that blood picks up extra CO_2. Conversely, as blood enters pulmonary capillaries and binds O_2, the CO_2-carrying capacity falls, thus facilitating pulmonary elimination of CO_2.

According to the Haldane effect, the total CO_2 content (CCO_2) rises at a given pCO_2 as O_2 hemoglobin saturation falls, thus indicating a non-linear relationship between pCO_2 and CCO_2. Likewise, changes in tissue oxygen extraction, pH, tissue VCO_2, and hemoglobin concentration can also influence the relationships between pCO_2 and CCO_2, making difficult the interpretation of the venous-to-arterial pCO_2 difference. In addition, depending on baseline SvO_2, the Haldane effect may increase or decrease Pv-aCO_2 in response to the same changes in blood flow or metabolism (34).

Admittedly, Pv-aCO_2/Ca-vO_2 could be equivalent to the Cv-aCO_2/Ca-vO_2 ratio when PCO_2, pH, and SvO_2 approximate to normality, which occurs in many cases. Nevertheless, during low pCO_2 and SvO_2 conditions, Cv-aCO_2 might profoundly differ from Pv-aCO_2. Indeed, clinical observations during very early stages of resuscitation of septic shock suggest that persistence of a high Cv-aCO_2/Ca-vO_2 ratio is related to unfavorable clinical outcomes but not its equivalent, the Pv-aCO_2/Ca-vO_2 ratio (28). Thus, although the influence of the Haldane effect is negligible at low Pv-aCO_2, the disagreement of Cv-aCO_2 and Pv-aCO_2 increases at higher Pv-aCO_2 values (28).

Some authors have proposed that high Pcv-aCO_2/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, RQ is easily influenced by a number of physiologic events that can alter the agreement between measurements of RQ by indirect calorimetry (RQic) and the true metabolic activity. Thus, the high solubility of CO_2 in tissues and blood, and the variations in pulmonary ventilation/perfusion (V/Q) relationships might lead to momentary discordant results between RQic and the true RQ, until a new stead- state is attained (36). Consequently, the relationship between venous-arterial CO_2 to arterial-venous O_2 differences and anaerobic metabolism should not be rejected based just on measurements of VCO_2 by RQic. Similarly, attributing high Pv-aCO_2/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 Pv-aCO_2/Ca-vO_2 or Cv-aCO_2/Ca-vO_2 values.

Conclusions

Physiological determinants of combined CO_2 and O_2-derived variables are quite complex. Theoretically, the Cv-aCO_2/Ca-vO_2 ratio is independent of systemic blood flow variations and it should approach the RQ or at least, it should approximates cell respiration state. Although venous-arterial CO_2 to arterial-venous O_2 differences have demonstrated to predict fluid responsiveness in terms of 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.

Acknowledgments

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Footnote

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

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