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UNDERSTANDING THE DISEASE

Understanding the venous–arterial CO_2 to arterial–venous O_2 content difference ratio

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Introduction

Early identification of tissue hypoperfusion is a cornerstone of shock management [1]. Normal macrohemodynamic and oxygen-derived parameters do not, however, rule out the presence of tissue hypoxia [2]. In this setting, carbon dioxide (CO_2)-derived variables may provide information on macro- and microvascular blood flow [3] and also on the presence of anaerobic metabolism [4, 5]. Importantly, variations in CO_2 occur more rapidly than changes in lactate kinetics, making the former an attractive biomarker for monitoring, especially during the early stages of resuscitation [6, 7].

The rationale of $C\bar{v}–aCO_2$ to $Ca\text{-}\bar{v}O_2$ ratio

According to the Fick equation, oxygen consumption (VO_2) and CO_2 production (VCO_2) are related to cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Thus, under aerobic steady-state conditions VCO_2 approximates VO_2 and, consequently, the mixed venous-to-arterial CO_2 content difference ($C\bar{v}\text{-}aCO_2$) approximates the arterial-to-mixed-venous O_2 content difference ($Ca\text{-}\bar{v}O_2$). In other words, CO_2 production should not be higher than O_2 availability and, therefore, the VCO_2/VO_2 ratio (i.e., the respiratory quotient) should not be higher than 1.0. Nonetheless, under under certain conditions, such as progressive exercise, in which VO_2 increases in response to metabolic demands, VCO_2 may surpass VO_2 when the anaerobic threshold is reached [8]. This situation arises as result of the disproportionate increase in the production of CO_2, which is released through the buffering of excess hydrogen ions, most of which derive from ATP hydrolysis [9] and the excessive liberation of protons due to accelerated anaerobic glycolysis [10]. Thus, during progressive exercise, both VO_2 and VCO_2, as well as the respiratory quotient increase. Interestingly, experimental blockage of mitochondrial O_2 utilization [11] leads to a simultaneous—but not symmetric—decrease in VO_2 and VCO_2 with subsequent increases in the respiratory quotient, also suggesting non-aerobic CO_2 generation.

During circulatory shock, a global decrease in VO_2 should be accompanied by a reduction in aerobic CO_2 production. However, experimental models demonstrate that VCO_2 exhibits a slighter decrease than VO_2 [12, 13], thus pathologically increasing the VCO_2/VO_2 ratio as consequence of predominant anaerobic metabolism (Fig. 1). Interestingly, after shock reversion, the VCO_2/VO_2 ratio returns to normal values, suggesting the potential reversibility of this phenomenon, at least during the early stages of shock.

The $C\bar{v}\text{-}aCO_2/Ca–\bar{v}O_2$ ratio could be used as a surrogate for VCO_2/VO_2. Remarkably, both the venous-to-arterial CO_2 difference and the arterial-to-venous O_2 content difference, i.e., the numerator and denominator of this quotient, are influenced by macro- and microblood flow alterations, which suggest that increases in the $C\bar{v}\text{-}aCO_2/Da\text{-}\bar{v}O_2$ ratio are to some extent independent of flow variations. It is well known that low cardiac output may increase venous CO_2 partial pressure ($PvCO_2$) even in the absence of extra CO_2 production due to the venous stagnation phenomenon [14]. Likewise, microcirculatory alterations, such as decreased percentage of perfused small vessels, decreased functional capillary density, and increased heterogeneity of flow, are associated with progressively increased $P\bar{v}\text{-}aCO_2$ and $C\bar{v}\text{-}aCO_2$ during septic shock [3]. Analogously, increasing heterogeneity of microvascular flow impairs oxygen extraction [15], and insufficient cardiac output might also limit VO_2 during periods of oxygen supply dependency. Consequently,

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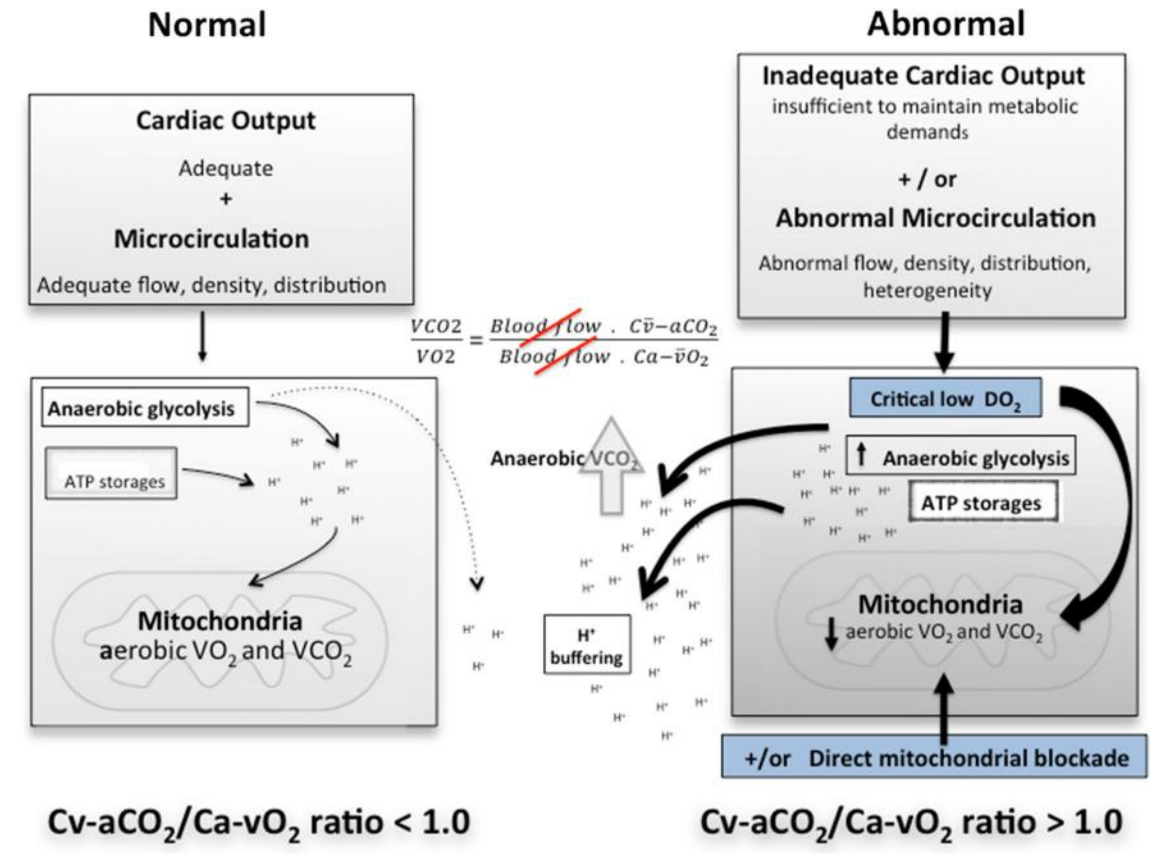

Fig. 1 A comparison of the mixed venous-to-arterial carbon dioxide (CO_2) content difference ($C\bar{v}$-aCO_2)/arterial-to-mixed-venous oxygen (O_2) content difference (Ca–$\bar{v}O_2$) ratio during normal (*left side*) and abnormal conditions (*right side*). Normal aerobic mitochondrial function leads to a normal C $\bar{v}$-aCO_2/Ca–$\bar{v}O_2$ (i.e., < 1.0). In contrast, during progressive hypoperfusion, insufficient cardiac output, abnormal microcirculation or direct mitochondrial blockade, both O_2 consumption and aerobic CO_2 generation are depressed but the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio increases (>1.0) due to an increase in anaerobic CO_2 generation as a consequence of the buffering of hydrogen ions (H^+) coming from anaerobic glycolysis and ATP hydrolysis . *VO_2*: oxygen consumption; *VCO_2* CO_2 production; *DO_2* oxygen delivery

an increased $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio reflects the relative increase of VCO_2 over VO_2 secondary to the buffering of hydrogen ions due to anaerobic metabolism [16], while the isolated Pv-aCO_2 (or $C\bar{v}$-aCO_2) reflects the blood flow conditions at both the macro- and microvascular levels [3, 7].

$C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio and its relationship with anaerobic metabolism during tissue hypoxia

Interpretation of lactate levels during the resuscitation and post-resuscitation periods is sometimes very difficult since hyperlactatemia may not always represent anaerobic metabolism. Mekontso-Dessap et al. [4] demonstrated a good correlation between the $P\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio (a surrogate of $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio calculated by using CO_2 pressures instead of CO_2 contents) and lactate levels [4] using a cutoff of ≥2.0 mmol/L to indicate anaerobic metabolism. However, rather than predicting lactate elevation, the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio could provide important prognostic information to lactate variations during early stages of resuscitation due to its ability to detect "ongoing" anaerobic metabolism and to react faster than lactate to short-term hemodynamic changes. In a recent study, Ospina-Tascón et al. [5] demonstrated the strong prognostic significance of persistent hyperlactatemia combined with an increased $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio when compared to hyperlactemia with a normal ratio. The $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio could therefore be a useful tool with which to differentiate hypoxia-driven lactate accumulation versus other non-flow-dependent causes of hyperlactatemia.

Does the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio differ from the $P\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio?

Over the physiological range of CO_2 contents, i.e., along the steep portion of the CO_2 dissociation curve, the partial pressure of CO_2 (PCO_2) maintains a quasi-linear relationship with CO_2 content (CCO_2); theoretically, therefore, $P\bar{v}$-aCO_2 could be used as a surrogate for the $C\bar{v}$-aCO_2 ratio. The relationship between PCO_2 and CCO_2, however, becomes non-linear at abnormal $P\bar{v}$-aCO_2 values [3]. Thus, the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio may be superior to the $P\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio in predicting outcomes during very early phases of resuscitation of septic shock [5] since at deeper tissue hypoxia and acidosis, disparity between $P\bar{v}$-aCO_2 and $C\bar{v}$-aCO_2 increases according to the Haldane effect.

Limitations in clinical practice

First, calculation of VCO_2 according to Fick's approach is valid under steady-state conditions. Conversely, the regain of flow after tissue ischemia could overstimulate the VCO_2, leading to increases in VCO_2/VO_2. However, the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio integrates global CO_2 accumulation, O_2 consumption, and blood flow; therefore, the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio ratio should also be less influenced by pulmonary ventilation/perfusion abnormalities. Second, calculation of the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio is cumbersome and subject to an important risk of error. Nevertheless, the influence of such potential error is limited as it correctly identifies patients at increased risk of death [5]. Third, calculating $P\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ is relatively easy, and the value should be equivalent to $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ when PCO_2 and mixed venous oxygen saturation (SvO_2) approximates normality, which occurs frequently. The $P\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio is, however, largely subject to determinants of the Haldane effect, and thus its interchangeability with the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio is debatable. Fourth, information regarding global CO_2/O_2 relationships comes from studies using pulmonary artery catheter monitoring [4, 5], so its equivalence with central venous sample calculations is not yet proven, despite the relative good agreement between central venous and mixed venous CO_2 to calculate the Pv-aCO_2 [17]. Fifth, while the physiology might appear robust and the results coming from small single-center physiological studies studies sound biologically plausible, notwithstanding its complexities, the clinical applicability of the $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio remains to be confirmed.

Conclusion

The $C\bar{v}$-aCO_2/Ca-$\bar{v}O_2$ ratio can be used as an approximation of the respiratory quotient and may detect ongoing anaerobic CO_2 generation in patients with septic shock. Computations of CO_2 and O_2 contents are, admittedly, cumbersome, but the significance of the $C\bar{v}$-aCO_2/Ca-vO_2 ratio and its biological plausibility deserves future research efforts.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflicts of interest.

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