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Shedding light on venoarterial PCO_2 gradient

Arnaldo Dubin* and Mario Omar Pozo

As an expression on Fick's principle, the reduction in cardiac output is associated with a parallel increase in both mixed venoarterial CO_2 content difference ($C_{mv\text{-}a}CO_2$) and arterial-mixed venous oxygen content difference ($C_{a\text{-}mv}O_2$). Nevertheless, disproportioned elevations in $C_{mv\text{-}a}CO_2$ compared to those of $C_{a\text{-}mv}O_2$ ensue when the anaerobic threshold is reached. This results from anaerobic CO_2 production, secondary to the buffering of anaerobically generated protons by bicarbonate.

The clinical approach to venoarterial CO_2 differences usually relies on partial pressure rather than content difference. Unfortunately, the attempts to track $C_{mv\text{-}a}CO_2$ through mixed venoarterial PCO_2 difference ($P_{mv\text{-}a}CO_2$) might be misleading. The relationship between CO_2 content and partial pressure is intricate. Moreover, the estimation of CO_2 content from PCO_2 is troublesome, and calculation algorithms frequently produce unreliable results. Since several factors can modify the dissociation of CO_2 from Hb, $P_{mv\text{-}a}CO_2$ can fail to reflect $C_{mv\text{-}a}CO_2$ changes. For example, hemodilution induces opposite changes in $P_{mv\text{-}a}CO_2$ and $C_{mv\text{-}a}CO_2$. The high cardiac output that develops in such situation increases $P_{mv\text{-}a}CO_2$ and reduces $C_{mv\text{-}a}CO_2$ [1]. Other factors, such as metabolic acidosis and Haldane effect, can also play a major role in this relationship and have strong effects on $P_{mv\text{-}a}CO_2$, regardless of cardiac output changes [2].

Another focus of confusion might reside in the actual meaning of venoarterial PCO_2 difference. Differently to tissue-arterial PCO_2 difference, $P_{mv\text{-}a}CO_2$ primarily reflects the changes in systemic blood flow and not in microcirculatory perfusion. Physiologic research helps to understand this question. In an experimental model of endotoxemia, all the PCO_2 differences—$P_{mv\text{-}a}CO_2$, mesenteric venoarterial and mucosal villi-arterial—increased during the phase of hypodynamic shock [3]. After fluid resuscitation, $P_{mv\text{-}a}CO_2$ and mesenteric venoarterial PCO_2 difference normalized following the improvement in cardiac output and superior mesenteric artery blood flow. Tissue hypercarbia, however, remained present as an expression of villi microcirculatory hypoperfusion.

Although mixed venous and central venous gases are not interchangeable [4], central venoarterial PCO_2 difference ($P_{vc\text{-}a}CO_2$) has been used a surrogate for $P_{mv\text{-}a}CO_2$. It might thus be a good marker of cardiac output, even more sensitive than central venous oxygen saturation [5]. Nevertheless, an observational study found that $P_{vc\text{-}a}CO_2$ did not correlate with cardiac output but with sublingual microvascular perfusion [6]. It was therefore claimed by some authors that $P_{vc\text{-}a}CO_2$ might reflect tissue perfusion. This speculation is supported neither by physiology [3] nor by relevant clinical studies. In septic shock, patients with a hyperdynamic profile showed lower $P_{vc\text{-}a}CO_2$ than those with normal systemic hemodynamics, even though the microcirculatory alterations were similar in both groups [7]. So, the lack of correlation between cardiac output and $P_{vc\text{-}a}CO_2$ found in septic patients [6] should be explained by modifications in the dissociation of CO_2 from Hb. Disorders such as hemodilution and lactic acidosis are commonly present in septic shock and frequently display microvascular abnormalities. Certainly, the relationship between $P_{vc\text{-}a}CO_2$ and microcirculation should not be interpreted as a causal phenomenon.

In this issue of *Annals of Intensive Care*, Mallat et al. [8] report that an acute reduction in arterial PCO_2 from 44 to 34 mm Hg was associated with an increase of 2 mm Hg in $P_{vc\text{-}a}CO_2$. The authors attributed this finding to the concomitant increase in oxygen consumption (VO_2). Unfortunately, methodological issues might limit the relevance of the conclusions: First, the increase in $P_{cv\text{-}a}CO_2$ not only was quantitatively minor and insignificant from a clinical point of view, but mainly stayed within the error of the method of PCO_2 measurement. This is especially true when taking into account the error propagation produced during the calculation of the PCO_2 difference.

*Correspondence: arnaldodubin@gmail.com
Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, 60 y 120, calle 42 No 577, 1900 La Plata, Argentina

Furthermore, the use of central venous instead of mixed venous gases for computation of VO_2 is questionable [4]. In addition, the subtle change in base excess that appeared during hyperventilation might also explain part of the change in $P_{cv\text{-}a}CO_2$ [2]. Modifications in Hb levels before and after hyperventilation, which might have affected $P_{cv\text{-}a}CO_2$ [1], were not reported. A comprehensive discussion about any $P_{cv\text{-}a}CO_2$ change should consider all its determinants.

The effects of hypocapnia on $P_{vc\text{-}a}CO_2$ have been previously reported in stable cardiac surgery patients [9]. An experimental study also showed that severe hypocapnia increased gut intramucosal-arterial PCO_2 as a probable consequence of regional and tissue hypoperfusion. In contrast, systemic and regional venoarterial PCO_2 gradients did not change [10]. In this way, the effects of hypocapnia on $P_{vc\text{-}a}CO_2$ are uncertain.

Although the study from Mallat et al. [8] does not add new physiologic information and has major limitations, it emphasizes that $P_{vc\text{-}a}CO_2$ is not a straightforward surrogate for blood flow. The messages for physiologists and practitioners should be that $P_{vc\text{-}a}CO_2$ monitoring might contribute to the assessment of systemic hemodynamics but requires a comprehensive interpretation.

Abbreviations

$C_{mv\text{-}a}CO_2$: mixed venoarterial CO_2 content difference; $C_{a\text{-}mv}O_2$: arterial-mixed venous oxygen content difference; $P_{mv\text{-}a}CO_2$: mixed venoarterial PCO_2 difference; $P_{vc\text{-}a}CO_2$: central venoarterial PCO_2 difference; VO_2: oxygen consumption.

Authors' contributions

AD and MOP wrote the manuscript. Both authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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