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The ratio of venoarterial PCO_2 to arteriovenous O_2 content difference: There is no place for simplistic interpretations

We completely agree with the comments from Drs. Chiarla and Giovaninni. They help to a more comprehensive understanding of the ratio of venoarterial PCO_2 to arteriovenous O_2 content difference ($P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$). In a rather simplistic way, $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ is frequently considered a surrogate for respiratory quotient (RQ) and anaerobic metabolism. Thus, a panel of experts invited by the Editorial Board of the journal *Intensive Care Medicine* incorporated $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ in an algorithm for the assessment of tissue oxygenation [1]. As Dr. Chiarla and Giovaninni described in their database of patients with sepsis, changes in $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ are almost completely explained by factors different to anaerobic metabolism. This finding might be expected in stable patients, in whom tissue hypoxia is not present. Nevertheless, in experimental models of ischemic and anemic hypoxia, the actual RQ, measured by expired gases analysis, was only a minor contributor to $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ [2,3]. On the other hand, changes in the dissociation of CO_2 from Hb induced by hemoglobin, metabolic acidosis and Haldane effect, were the main determinants of $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ [2]. These effects were magnified at the flattened portion of the CO_2Hb dissociation curve as shown by the impact of mixed venous PCO_2 in the model. The Letter to the Editor submitted by Drs. Chiarla and Giovaninni correctly emphasizes the occurrence of pathophysiological and mathematical coupling. Of note, it has been suggested that $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ might help to identify the source of lactate, whether aerobic or anaerobic [4]. Regardless of its origin, lactate itself can increase $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$. In a sheep model of hemorrhagic shock, we showed that retransfusion normalized oxygen consumption and RQ, while lactate levels persisted elevated [5]. Despite that tissue oxygenation was normalized, there was a concurrent increase in $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$, which might have incorrectly been considered a proof of remaining tissue hypoxia. In this setting, $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ was not an indicator of anaerobic metabolism.

The main drawback of $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ for the monitoring of tissue oxygenation, however, is that it ignores basic physiology. The increase in RQ is a dramatic event associated with impending death. For example, the RQ increases when Hb decreases to 1.2 ± 0.1 g% in hemodilution (Fig. 1), and when mean arterial blood pressure falls to 27 ± 2 mmHg in progressive hemorrhage [2,3]. These are extreme and obvious conditions, which do not require additional monitoring or sensitive assessment of tissue oxygenation to be identified. Accordingly, high values of $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ in patients with stable conditions seldom reflect anaerobic metabolism but the presence of factors that modify the dissociation of CO_2 from Hb. In summary, since $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ is a composite variable with multiple determinants and complex interactions, there is no place for mechanistic interpretations.

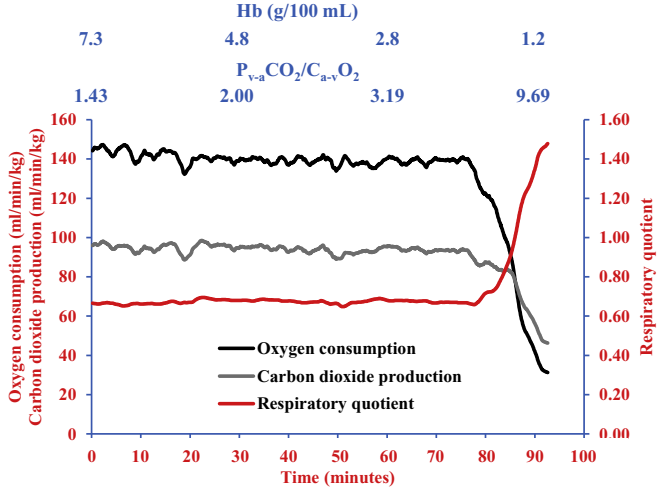

Fig. 1. Behavior of O_2 consumption (VO_2), CO_2 production (VCO_2) and respiratory quotient (RQ) measured by means of breath-by-breath analysis of expired gases, during stepwise hemodilution. Values of Hb and the ratio of venoarterial PCO_2 to arteriovenous O_2 content difference ($P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$) correspond to the last portion of each period of hemodilution. VO_2, VCO_2 and RQ only increased after the last stage of hemodilution when Hb reached 1.2 g/100 mL In contrast, $P_{v\text{-}a}CO_2/C_{v\text{-}a}O_2$ significantly increased after each stage of hemodilution. Data are from references [2] and [3].

Declaration of Competing Interest

The authors have not disclosed any potential conflicts of interest.

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