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EDITORIAL

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# Venous–arterial $CO_2$ to arterial–venous $O_2$ difference ratio as a resuscitation target in shock states?

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In shock states, aerobically generated carbon dioxide ($CO_2$) decreases together with oxygen ($O_2$) consumption ($VO_2$). When $VO_2$ becomes dependent on $O_2$ delivery ($DO_2$), $CO_2$ can be produced anaerobically mostly due to bicarbonate buffering of protons produced in excess secondary to the hydrolysis of adenosine triphosphate, so that $VCO_2$ can exceed $VO_2$. It has been estimated that anaerobic ATP compensates approximately 6 % of the accumulated $O_2$ depth [1]. Therefore, a respiratory quotient (RQ) >1 may be interpreted as a sign of anaerobic metabolism, since it may indicate that more $CO_2$ is produced than $O_2$ is consumed (Fig. 1), although both are decreased. According to the Fick equation, $VCO_2$ equals the product of cardiac output by the difference between mixed venous and arterial $CO_2$ contents ($C_{mv-a}CO_2$) whereas $VO_2$ equals the product of cardiac output by the difference between arterial and mixed venous $O_2$ contents ($C_{a-mv}O_2$) (Fig. 1). By eliminating the cardiac output value, which is common to the numerator and denominator of the RQ (Fig. 1) and taking $PCO_2$ as a surrogate of $CO_2$ content, an increased ratio between mixed venous–arterial $PCO_2$ difference and $C_{mv-a}CO_2$ ($P_{mv-a}CO_2/C_{a-mv}O_2$) was shown to be a good indicator of anerobiosis assessed by hyperlactatemia [2]. However, the relationship between $CO_2$ content and $PCO_2$ is curvilinear rather than linear and is influenced by the degree of metabolic acidosis, the hematocrit and the $O_2$ saturation. In this issue of *ICM*, Ospina-Tascon et al. [3] demonstrate that a $C_{mv-a}CO_2/C_{a-mv}O_2$ >1 predicts outcome early in septic shock, similar to increased arterial lactate concentration. Patients with both an increased $C_{mv-a}CO_2/C_{a-mv}O_2$ and lactate concentration 6 h after the study start had the highest mortality [3]. The authors propose that the $C_{mv-a}CO_2/C_{a-mv}O_2$ could become a resuscitation target [3]. The authors should be congratulated on having conducted this study and having performed the relatively complex calculations of the $CO_2$ contents. However, before targeting to normalize the $C_{mv-a}CO_2/C_{a-mv}O_2$, several issues should be considered.

1. Calculating $VCO_2$ by multiplying $C_{mv-a}CO_2$ with blood flow is only valid under steady-state conditions. If poorly perfused tissues regain flow, $CO_2$ stores are washed out and calculated $CO_2$ production is likely to be overestimated. This may have happened in patients in the study of Ospina-Tascon et al. [3] who were in the resuscitation phase of septic shock.
2. The amount of anaerobically produced $CO_2$ is low compared to $CO_2$ produced under aerobic conditions. It is therefore be questioned whether such small amounts can increase the $VCO_2$ above $VO_2$. For instance, when $DO_2$ was stepwise reduced to 16 % of baseline values in an in situ, vascularly isolated, innervated dog limb, $VO_2$ remained above $VCO_2$ despite continually increasing RQ [4]. Admittedly, the hindlimb $VCO_2/VO_2$ relationship may not represent global RQ well.

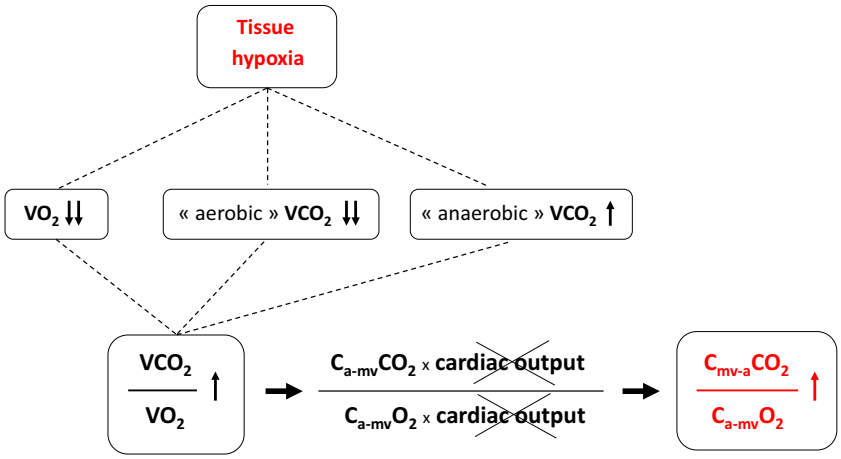


**Fig. 1** In cases of shock states, tissue hypoxia results in decreased oxygen consumption ($VO_2$) and aerobically generated carbon dioxide ($CO_2$) production ($VCO_2$). However, the global $VCO_2$ decreased to a lesser extent than $VO_2$ due to production of anaerobically generated $CO_2$. Consequently, the $VCO_2$ over $VO_2$ ratio increases. Therefore, after elimination of cardiac output (present in both numerator and denominator), the difference between mixed venous and arterial $CO_2$ contents ($C_{mv-a}CO_2$) over the difference between arterial and mixed venous $O_2$ contents ($C_{a-mv}O_2$) should increase in such hypoxic conditions

3. The treatment may have influenced the findings of Ospina-Tascon et al. [3]. Patients with high lactate values at 6 h received more norepinephrine than those with normal values, despite a greater number of the former (around 50 %) being treated with vasopressin. Vasopressin may constrict the mesenteric vascular bed [5, 6]. If global blood flow is low, increasing mesenteric lactate production may not be cleared by the liver and arterial lactate may increase. Conversely, if the liver is able to metabolize the excess of lactate, systemic RQ may rise as a consequence of mesenteric dysoxia. Since the groups at study baseline ($T_0$) and after 6 h ($T_6$) do not represent the same population, it would be interesting to know the treatment in patients who increased versus decreased their $C_{mv-a}CO_2/C_{a-mv}O_2$ and lactate values between $T_0$ and $T_6$.
4. Computation of $CO_2$ content seems to be cumbersome and subject to errors due to the number of variables included in the formula. This raises the question of its practical use in routine. More than a decade ago, Mekontso-Dessap et al. [2] proposed to calculate the $P_{mv-a}CO_2/C_{a-mv}O_2$ ratio to detect the presence of global anaerobiosis and showed that a value of $P_{mv-a}CO_2/C_{a-mv}O_2 > 1.4$ can reliably predict the presence of hyperlactatemia in the general population of critically ill patients. In spite of this interesting finding, the use of this ratio did not become popular for managing critically ill patients, maybe because measurements of blood lactate concentration are easier to obtain. In addition, determination of the $P_{mv-a}CO_2/C_{a-mv}O_2$ ratio as well as the $C_{mv-a}CO_2/C_{a-mv}O_2$ ratio require combined samplings of arterial blood and mixed venous blood and thus require pulmonary artery catheterization, which is less and less performed in the intensive care unit. Central venous blood variables are becoming more popular than mixed venous blood variables. Central venous blood $O_2$ saturation and the difference between central venous $PCO_2$ and arterial $PCO_2$ ($P_{cv-a}CO_2$) are recommended to be used to assess the adequacy of cardiac output to the global metabolic conditions, although the quality of evidence is only moderate [7]. During sepsis, where central venous $O_2$ content ($C_{cv}O_2$) and $ScvO_2$ can be in the normal range despite global tissue hypoxia owing to low $O_2$ extraction, it has recently been shown that hyperlactatemia and increased $P_{cv-a}CO_2/C_{a-cv}O_2$ ratio can predict the presence of $VO_2/DO_2$ dependence, whereas $ScvO_2$ cannot [8]. This may suggest that the $P_{cv-a}CO_2/C_{a-cv}O_2$ ratio could be used as a surrogate for the $P_{mv-a}CO_2/C_{a-mv}O_2$ ratio to assess global tissue hypoxia. It must be further shown that taking central venous $CO_2$ content instead of pressure, which would be more physiological, can be easily done at the bedside by using simple software able to avoid cumbersome calculations of $CO_2$ content. For a routine use of these surrogates of RQ, it must also be shown that they respond to changes in global tissue oxygenation faster than blood lactate concentration. Finally, one must keep in mind that all these parameters allow the assessing of global but not regional or local tissue oxygenation, knowing that dissociation between systemic and local blood flows may exist in patients with septic shock [9].

In conclusion, the paper by Ospina-Tascon et al. [3] adds interesting information to metabolic consequences of septic shock in the phase when treatment is administered with the aim to improve $DO_2$ and $VO_2$. Whether a

$C_{mv-a}CO_2/C_{a-mv}O_2$ ratio above 1 indicates anaerobic metabolism in unstable patients in septic shock and, if yes, why it can be associated with and without arterial hyperlactatemia, should be evaluated in more detail.

**Conflicts of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

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