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Editorial

Venous-arterial CO_2 to arterial-venous O_2 differences: A physiological meaning debate

Current techniques for monitoring tissue perfusion have largely focused on systemic blood flow and the balance between oxygen demand and supply to the tissues [1]. Nevertheless, the relative value of resuscitation targets such as oxygen-derived parameters has been widely questioned [2] and recent studies failed to demonstrate any benefit on clinical outcomes with its use [3]. In this context, variables such as carbon dioxide-derived parameters might provide additional and very important information about macro and micro blood flow alterations [4,5] or even about the presence of anaerobic metabolism [6,7]. Particularly, the venous-arterial carbon dioxide to arterial-venous oxygen contents difference ratio ($Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio) could add some prognostic information to lactate levels at very early stages of resuscitation in septic shock [7]. However, the physiological meaning and mechanisms leading to increase $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio might be widely debated [8,9].

According to the Fick equation, oxygen consumption (VO_2) and CO_2 production (VCO_2) are directly proportional to the cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Under aerobic steady-state conditions, VCO_2 should not exceed O_2 availability and, therefore, the VCO_2/VO_2 ratio (i.e., the respiratory quotient – RQ –) should not be >1.0. Consequently, if considering $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio as a surrogate of the VCO_2/VO_2 ratio, the mixed venous-to-arterial CO_2 content difference ($Cv\text{-}aCO_2$) should approximate to and do not exceed the arterial-to-mixed-venous O_2 content difference ($Ca\text{-}vO_2$) independently of blood flow variations, since according to the Fick's equation, cardiac output is present in both the numerator and denominator components of such ratio. Importantly, over physiological range of blood CO_2 partial pressures (PCO_2), i.e., along the steep portion of the CO_2 dissociation curve, PCO_2 maintains a quasi-linear relationship with blood CO_2 contents (CCO_2), so the $Pv\text{-}aCO_2$ could be theoretically used as an equivalent of the $Cv\text{-}aCO_2$. However, the relationship between PCO_2 and CCO_2 becomes non linear in conditions of hypoxia and altered pH, which could limit its interchangeability.

In this issue, Dubin et al. [9] retrospectively evaluated the equivalence of the venous-arterial CO_2 to arterial-venous O_2 differences calculated in central venous ($Pcv\text{-}aCO_2/Ca\text{-}cvO_2$) and mixed-venous ($Pmv\text{-}aCO_2/Ca\text{-}mvO_2$) blood samples from 23 patients with septic shock, concluding that such variables are not interchangeable. Although mathematical differences between these two variables are evident and, consequently, disagreement between $Pcv\text{-}aCO_2/Ca\text{-}vO_2$ and $Pmv\text{-}aCO_2/Ca\text{-}vO_2$ ratios might be expected, clinical information provided by calculation of venous-arterial CO_2 to arterial-venous O_2 differences ratio (by using both PCO_2 and CCO_2 values) might be highly valuable in the clinical setting [6,7,10-12]. Previous studies suggested some agreement or interchangeability between $Pcv\text{-}aCO_2$ and $Pmv\text{-}aCO_2$, i.e., the numerator components of its respective ratios [11,13-16], although certainly, small disparities between them could induce wide differences in their respective venous-arterial CO_2 to arterial-venous O_2 differences, such as proposed by Dubin et al. [9]. Nevertheless, this could be an insufficient argument to deny the clinical relevance of venous-arterial CO_2 to arterial-venous O_2 differences ratio previously suggested in observational studies including patients in septic shock [6,7,10-12,17].

$Pcv\text{-}aCO_2/Ca\text{-}vO_2$ ratio was initially proposed as a marker of global anaerobic metabolism because its relationship with increased lactate levels in critically ill patients [6,11]. Subsequently, venous-arterial CO_2 to arterial-venous O_2 contents difference ratio (i.e., the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio) showed to be able to give additional prognostic information to that provided by lactate levels during early stages of septic shock [7,17]. Interestingly, high $Pcv\text{-}aCO_2/Ca\text{-}vO_2$ ratios were also associated with a delayed lactate clearance during initial resuscitation of septic shock [17], but most importantly, $Pcv\text{-}aCO_2/Ca\text{-}vO_2$ ratios demonstrated to predict the response to fluid load in terms of changes in systemic VO_2 [10,11]. However, whether $Pcv\text{-}aCO_2/Ca\text{-}vO_2$ ratios could detect oxygen supply dependence is a more complex discussion beyond the scope of this manuscript.

Dubin et al. also propose that high $Pcv\text{-}aCO_2/Ca\text{-}vO_2$ ratio obeys mainly to variations in hemoglobin levels. Furthermore, according to their previous experimental observations estimating respiratory quotient (RQ) by using analysis of expired gases, they suggest a weak correlation between $Pv\text{-}aCO_2/Ca\text{-}vO_2$ and anaerobic metabolism [18] attributing this to the combination of the Haldane effect, hemoglobin levels and persistent hyperlactatemia. Nevertheless, they did not provide information about the venous-to-arterial CO_2 content differences ($Cv\text{-}aCO_2$), which precisely include pH, temperature and hemoglobin levels for its calculation. Indeed, to the extend that $Pv\text{-}aCO_2$ is greater >6.0, differences between $Pv\text{-}aCO_2$ and its respective contents ($Cv\text{-}aCO_2$) are deeper [5], and such as it has been showed in previous observations, calculations of venous-arterial CO_2 to arterial-venous O_2 differences correlates differently with clinical outcomes when using PCO_2 vs. CCO_2 values in the numerator [7]. Furthermore, under non-steady-state conditions, RQ is easily influenced by a wide array of physiologic and pathophysiologic events that can alter the relationship between the true metabolic activity and measurements of RQ by indirect calorimetry (RQ_{ic}) [19]. Thus, changes in ventilation (V), perfusion (Q) and pulmonary V/Q relationships might lead to temporary differences between

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RQ_{ic} and the true metabolic RQ, until a new steady state is attained [20]. Additionally, because the high solubility of CO_2 in tissues and blood, VCO_2 obtained by indirect calorimetry will rise slowly and consequently, RQ_{ic} will momentarily differ from the true RQ. Consequently, denying the relationship between venous-arterial CO_2 to arterial-venous O_2 differences and anaerobic metabolism based on measurements by indirect calorimetry or attributing high $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratios just to variations in hemoglobin levels could be physiologically misleading. Indeed, at very low hemoglobin values, small errors in hemoglobin measurements will amplify the error of calculation of $Pv\text{-}aCO_2/Ca\text{-}vO_2$ or $Cv\text{-}aCO_2/Ca\text{-}vO_2$ values.

Thus, computing $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratios imply the theoretical correction of factors involved in the Haldane effect, independently of systemic blood flow variations, pulmonary ventilation or blood flow distributions, whereby estimation of venous-arterial CO_2 to arterial-venous O_2 differences should approximate the RQ and it could be used as a global estimation of cell respiration.

In conclusion, the proposal by Dubin et al. about the inaccuracies in the calculation of venous-arterial CO_2 to arterial-venous O_2 differences by using central instead of mixed-venous blood samples is fairly logic. However, beyond the mathematical disagreement between $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ and $Pmv\text{-}aCO_2/Ca\text{-}mvO_2$ and the discussion about the relationship between $Pv\text{-}aCO_2/Ca\text{-}vO_2$ or $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratios and the presence of anaerobic metabolism, venous-arterial CO_2 to arterial-venous O_2 differences have demonstrated to be consistent through several observations in the clinical setting. Nevertheless, exact mechanisms leading to increase venous-arterial CO_2 to arterial-venous O_2 differences ratio and its possible application in the clinical practice should deserve future research efforts.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

[1] Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369(18):1726–34.
[2] Bellomo R, Reade MC, Warrillow SJ. The pursuit of a high central venous oxygen saturation in sepsis: growing concerns. Crit Care 2008;12(2):130.
[3] Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, Canter RR, et al. Early, Goal-Directed Therapy for Septic shock - a patient-level meta-analysis. N Engl J Med 2017; 376(23):2223–34.
[4] Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 2008;34(12):2218–25.
[5] Ospina-Tascón GA, Umaña M, Bermúdez WF, Bautista-Rincón DF, Valencia JD, Madriñán HJ, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive Care Med 2016;42 (2):211–21.
[6] Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002;28(3): 272–7.
[7] Ospina-Tascón GA, Umaña M, Bermúdez W, Bautista-Rincón DF, Hernandez G, Bruhn A, et al. Combination of arterial lactate levels and venous-arterial CO2 to arterial-venous O 2 content difference ratio as markers of resuscitation in patients with septic shock. Intensive Care Med 2015;41(5):796–805.
[8] Ospina-Tascón GA, Hernández G, Cecconi M. Understanding the venous-arterial CO. Intensive Care Med 2016;42(11):1801–4.
[9] Dubin A, Ferrara G, Kanoore Edul VS, Martins E, Canales HS, Canullán C, et al. Venoarterial PCO2-to-arteriovenous oxygen content difference ratio is a poor surrogate for anaerobic metabolism in hemodilution: an experimental study. Ann Intensive Care 2017;7(1):65.
[10] Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med 2013;41(6):1412–20.
[11] Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Ann Intensive Care 2016;6(1):10.
[12] Mesquida J, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. Crit Care 2015;19:126.
[13] Cuschieri J, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 2005;31(6):818–22.
[14] Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. World J Crit Care Med 2016;5(1):47–56.
[15] Ospina-Tascón GA, Bautista-Rincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, et al. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care 2013;17(6): R294.
[16] Guinot PG, Badoux L, Bernard E, Abou-Arab O, Lorne E, Dupont H. Central Venous-to-Arterial Carbon Dioxide Partial pressure Difference in patients Undergoing Cardiac Surgery is not Related to Postoperative Outcomes. J Cardiothorac Vasc Anesth 2017;31(4):1190–6.
[17] He HW, Liu DW, Long Y, Wang XT. High central venous-to-arterial CO2 difference/arterial-central venous O2 difference ratio is associated with poor lactate clearance in septic patients after resuscitation. J Crit Care 2016;31(1):76–81.
[18] Ferrara G, Edul VSK, Canales HS, Martins E, Canullán C, Murias G, et al. Systemic and microcirculatory effects of blood transfusion in experimental hemorrhagic shock. Intensive Care Med Exp 2017;5(1):24.
[19] Cohen IL, Roberts KW, Perkins RJ, Feustel PJ, Shah DM. Fick-derived hemodynamics. Oxygen consumption measured directly vs oxygen consumption calculated from CO2 production under steady state and dynamic conditions. Chest 1992;102(4): 1124–7.
[20] Henneberg S, Söderberg D, Groth T, Stjernström H, Wiklund L. Carbon dioxide production during mechanical ventilation. Crit Care Med 1987;15(1):8–13.

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