Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock

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Abstract

The mixed venous-to-arterial carbon dioxide (CO2) tension difference [P (v-a) CO2] is the difference between carbon dioxide tension (PCO2) in mixed venous blood (sampled from a pulmonary artery catheter) and the PCO2 in arterial blood. P (v-a) CO2 depends on the cardiac output and the global CO2 production, and on the complex relationship between PCO2 and CO2 content. Experimental and clinical studies support the evidence that P (v-a) CO2 cannot serve as an indicator of tissue hypoxia, and should be regarded as an indicator of the adequacy of venous blood to wash out the total CO2 generated by the peripheral tissues. P (v-a) CO2 can be replaced by the central venous-to-arterial CO2 difference (∆PCO2), which is calculated from simultaneous sampling of central venous blood from a central vein catheter and arterial blood and, therefore, more easy to obtain at the bedside. Determining the ∆PCO2 during the resuscitation of septic shock patients might be useful when deciding when to continue resuscitation despite a central venous oxygen saturation (ScvO2) > 70% associated with elevated blood lactate levels. Because high blood lactate levels is not a discriminatory factor in determining the source of that stress, an increased ∆PCO2 (> 6 mmHg) could be used to identify patients who still remain inadequately resuscitated. Monitoring the ∆PCO2 from the beginning of the resuscitation of septic shock patients might be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy. In this respect, it can aid to titrate inotropes to adjust oxygen delivery to CO2 production, or to choose between hemoglobin correction or fluid/inotrope infusion in patients with a too low ScvO2 related to metabolic demand. The combination of P (v-a) CO2 or ∆PCO2 with oxygen-derived parameters through the calculation of the P (v-a) CO2 or ∆PCO2/arteriovenous oxygen content difference ratio can detect the presence of global anaerobic metabolism.

Key words: Venous-to-arterial carbon dioxide tension difference; Carbon dioxide production; Oxygen supply dependency; Cardiac output; tissue hypoxia; Anaerobic metabolism; Oxygen consumption; Resuscitation; Septic shock

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Core tip: Early recognition and correction of tissue hypoperfusion are cornerstones in the management of septic shock patients. The venous-to-arterial carbon dioxide tension difference, which is a marker of the adequacy of cardiac output to global metabolic demand, is a helpful additional means to detect patients who stay under-resuscitated after optimization of O2-derived parameters. In this regard, its monitoring should help the clinicians for the decision of giving therapy targeting at increasing cardiac output.

INTRODUCTION

A shock is a form of acute circulatory failure associated with an inequality between systemic oxygen delivery (DO2) and oxygen consumption (VO2), which result in tissue hypoxia[13]. Early recognition and adequate resuscitation of tissue hypoperfusion are of particular importance in the management of septic shock to avoid the development of tissue hypoxia and multi-organ failure. Assessment of mixed venous oxygen saturation (SvO2) from a pulmonary artery catheter has been proposed as an indirect marker of global tissue oxygenation[12]. SvO2 reflects the balance between oxygen demand and supply. A low SvO2 represents a high oxygen extraction (O2ER) in order to maintain aerobic metabolism and VO2 constant in response to an acute decrease in DO2. However, when DO2 drops under a critical value, O2ER is no longer capable of upholding VO2, and global tissue hypoxia appears, as indicated by the occurrence of lactic acidosis[12-14].

Since the assessment of central venous oxygen saturation (ScvO2) can be achieved more easily, and is less risky than from pulmonary artery catheter, it would be useful if ScvO2 could function as an accurate reflection of SvO2. In fact, SvO2 is not similar to ScvO2 because the latter primarily reflects the oxygenation of the upper side of the body. In normal patients, ScvO2 is lower than SvO2 by about 2% to 3%, largely because of the less rate of oxygen extraction by the kidneys[6]. In shock state, the absolute value of ScvO2 was more often reported to be higher than SvO2, probably due to the oxygen extraction increases in splanchic and renal tissues[7-11]. This suggests that the existence of a decreased ScvO2 implies an even smaller SvO2. Because of the lack of agreement regarding absolute values, some authors questioned the clinical utility of ScvO2[12,13]. However, despite absolute values differ, trends in ScvO2 closely mirror trends in SvO2[8,9], suggesting that monitoring ScvO2 makes sense in critically ill patients.

It has been shown that an early hemodynamic optimization using a resuscitation bundle aimed at increasing ScvO2 > 70% was related to an important reduction in septic shock mortality[14]. Since that, monitoring ScvO2 has become widely recommended[1,14,15]. Recently, three large multicenter studies[16-18] failed to demonstrate any benefits of the early goal-directed therapy approach. Nevertheless, the design of these trials was not to answer the question of whether targeting an ScvO2 > 70% was effective. Also, in these studies, the mean baseline SvO2 values were already above 70%. Thus, these findings do not indicate that clinicians should stop monitoring ScvO2 and adjust DO2 by optimizing ScvO2 levels, particularly in septic shock patients with low ScvO2, who are at the highest risk of death[19].

On the other hand, normalization of ScvO2 does not rule out persistent tissue hypoperfusion and does not preclude evolution to multi-organ dysfunction and death[20]. The obvious limitation of ScvO2 is that normal/high values cannot distinguish if DO2 is sufficient or in excess to demand. In septic conditions, normal/high ScvO2 values might be due to the heterogeneity of the microcirculation that generates capillary shunting and/or mitochondrial damage responsible of disturbances in tissue oxygen extraction. Because ScvO2 is measured downstream from tissues, when a given tissue receives inadequate DO2, the resulting low local oxygen venous saturations may be “masked” by admixture with highly saturated venous blood from tissues with better perfusion and DO2, resulting overall in normal or even high ScvO2. Although ScvO2 may thus not miss any global DO2 dysfunction, it may stay “blind” to local perfusion disturbances, which exist in abundance in sepsis due to damaged microcirculation. Indeed, high ScvO2 values have been associated with increased mortality in septic shock patients[14,15]. Thus, in some circumstances the use of ScvO2 might erroneously drive a clinician to conclude that the physiologic state of the patient has ameliorated when, in fact, it may not have improved.

Lactate has also been proposed as a resuscitation endpoint[15,16]. However, no benefits have been observed for lactate decrease-guided therapy over resuscitation guided by ScvO2 in septic shock patients[20]. Moreover, given the nonspecific nature of lactate level elevation, hyperlactatemia alone is not a discriminatory factor in establishing the source of the circulatory failure. Hence, additional circulatory parameters such as the venous-to-arterial carbon dioxide tension difference are needed to identify patients with septic shock who presently may still insufficiently reanimated, especially when ScvO2 values are normal/high in the context of hyperlactatemia. The purpose of this review is to discuss the physiologic background and the potential clinical usefulness of the venous-to-arterial carbon dioxide tension difference in septic shock.
**PHYSIOLOGICAL BACKGROUND**

**CO₂ transport in the blood**

CO₂ is transported in the blood in three figures:\(^{26,27}\). Dissolved, in combination with proteins as carbamino compounds, and as bicarbonate. Physically dissolved CO₂ is a function of CO₂ solubility in blood, which is about 20 times that of oxygen (O₂); therefore, considerably more CO₂ than O₂ is present in simple solution at equal partial pressures. However, dissolved CO₂ shares only around 5% of the whole CO₂ concentration in arterial blood.

Carbamino compounds comprise the second form of CO₂ in the blood. These compounds occur when CO₂ combines with terminal amine groups in blood proteins, especially with the globin of hemoglobin. However, this chemical combination between CO₂ and hemoglobin is much less important than haemoglobin-O₂ binding, so carbamino compounds comprise only 5% of the total CO₂ in the arterial blood.

The bicarbonate ion (HCO₃⁻) is the most significant form of the CO₂ carriage in the blood. CO₂ combines with water (H₂O) to form carbonic acid (H₂CO₃), and this dissociates to HCO₃⁻ and hydrogen ion (H⁺): CO₂ + H₂O = H₂CO₃ = HCO₃⁻ + H⁺. Carbonic anhydrase is the enzyme that catalyzes the first reaction, making it almost instantaneous. Carbonic anhydrase occurs mainly in red blood cells (RBC), but it also occurs on pulmonary capillary endothelial cells, and it accelerates the reaction in plasma in the lungs. The uncatalyzed reaction will occur in plasma, but at a much slower rate. The second reaction happens immediately inside RBC and does not require any enzyme. The H₂CO₃ dissociates to H⁺ and HCO₃⁻, and the H⁺ is buffered primarily by hemoglobin while the excess HCO₃⁻ is transported out the RBC into plasma by an electrically neutral bicarbonate-chloride exchanger. The fast conversion of CO₂ to HCO₃⁻ results in nearly 90% of the CO₂ in arterial blood being transported in that manner.

Hemoglobin-O₂ saturation is the major factor affecting the capacity of hemoglobin to fix CO₂ (Haldane effect). Consequently, CO₂ concentration increases when blood is deoxygenated, or CO₂ concentration diminishes when blood is oxygenated, at any assumed carbon dioxide tension (PCO₂)\(^{26}\) (Figure 1). H⁺ ions from CO₂ can be deemed as competing with O₂ for hemoglobin binding. Accordingly, rising oxygen reduces the affinity of hemoglobin for H⁺ and blood CO₂ concentration (Haldane effect). The physiological assets of the Haldane effect are that it promotes removing of CO₂ in the lungs when blood is oxygenated and CO₂ filling in the blood when oxygen is delivered to tissues. Additionally, the Haldane effect leads to a sharper physiologic CO₂ blood equilibrium curve that has the physiologic interest of rising CO₂ concentration differences for a given PCO₂ difference.

CO₂ is rapidly excreted from the circulation by the lungs by passive diffusion from the capillaries to the alveoli, and its production approximately matches excretion.

The relationship between PCO₂ and the total blood CO₂ content (CCO₂) is curvilinear even though more linear than the oxygen dissociation curve\(^{26}\). Oxygen saturation, hematocrit, temperature, and the degree of metabolic acidosis influence the PCO₂/CCO₂ relationship\(^{26,28}\). Hence, for a given value of CCO₂, PCO₂ is higher in the case of metabolic acidosis than in the case of normal pH (Figure 2).

**Determinant of venous-to-arterial CO₂ tension difference**

The venous-to-arterial CO₂ tension difference [P (v-a) CO₂] is the gradient between PCO₂ in mixed venous blood (PVCO₂) and PCO₂ in arterial blood (PA CO₂): P (v-a) CO₂ = PVCO₂ - PA CO₂. PVCO₂ and PA CO₂ are partial pressures of the dissolved CO₂ in the mixed venous and arterial blood, respectively.

The application of Fick equation to CO₂ shows that the CO₂ elimination (identical to CO₂ generation in a stable condition) equals the product of the difference between mixed venous blood CO₂ content (CvCO₂) and arterial blood CO₂ content (CaCO₂) and cardiac output: Total CO₂ production (VCO₂) = cardiac output × k × P (v-a) CO₂ so that P (v-a) CO₂ = k × VCO₂/CaCO₂

Therefore, VCO₂ can be calculated from a modified Fick equation as: VCO₂ = cardiac output × k × P (v-a) CO₂ so that P (v-a) CO₂ = k × VCO₂/cardiac output, where k is the pseudo-linear coefficient supposed to be constant in physiological states\(^{27}\). Therefore, P (v-a) CO₂ would be linearly linked to CO₂ generation and inversely associated to cardiac output. Under normal conditions, P (v-a) CO₂ values range between 2 and 6 mmHg\(^{28}\).

**Influence of CO₂ production on P (v-a) CO₂**

**Aerobic CO₂ production:** Oxidative phosphorylation proceeds with the formation of energy-laden molecules, CO₂ and water. Total CO₂ production is directly related to VO₂: VCO₂ = R × VO₂, where R is the respiratory

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**Figure 1 CO₂ dissociation curve.** CO₂ content (mL/100 mL) vs CO₂ partial tension (PCO₂). Differences between the curves result in higher CO₂ content in the blood, and smaller PCO₂ differences between arterial and venous blood. Hemoglobin-O₂ saturation affects the position of the CO₂ dissociation curve (Haldane effect).
output. Under steady states of both VO2 and VCO2, is related to VCO2 and inversely linked to cardiac output. According to the modified Fick equation, P (v-a) CO2 should not increase due to increased clearance of CO2, whereas P (v-a) CO2 should be high following cardiac output reduction because of a low flow-induced tissue CO2 stagnation phenomenon. Due to the decreasing of transit time a higher than usual addition of CO2 per unit of blood passing the efferent microvessels leads to produce hypercapnia in the venous blood. As long as alveolar respiration is sufficient, a gradient will occur between PvCO2 and PaCO2. However, under spontaneous breathing situations, hyperventilation, stimulated by the decreased blood flow, may reduce PaCO2 and thus may prevent the CO2 stagnation-induced rise in PvCO2. This finding underscores the utility of calculating P (v-a) CO2 rather than simply assessing PvCO2, particularly in the case of spontaneous breathing.

Can P (v-a) CO2 be used as a marker of tissue hypoxia? Marked increases in P (v-a) CO2 were reported in patients during cardiopulmonary resuscitation. Furthermore, higher P (v-a) CO2 values were observed in patients with circulatory failure compared with those without circulatory failure. These observations were attributed to the decrease of blood flow and the development of anaerobic metabolism with anaerobic CO2 production. Thus, it has been suggested that P (v-a) CO2 can be used to detect the presence of tissue hypoxia in patients with acute circulatory failure. In fact, under conditions of tissue hypoxia with a decreased VO2, the relationship between changes in cardiac output and P (v-a) CO2 are much more complex. Indeed, in these circumstances, the increase in CO2 production related to the anaerobic pathway is counterbalanced by a reduced aerobic CO2 production, so that VCO2 and hence P (v-a) CO2 could be at best unchanged or decreased. Nevertheless, since the k factor should rise during tissue hypoxia while VCO2 must decrease, the resultant effect on P (v-a) CO2 depends mainly on the flow state (cardiac output).

Tissue hypoxia with low blood flow Experimental studies in which blood flow was progressively reduced, an elevation in P (v-a) CO2 following the reduction in DO2 was reported, while a constant VO2 was measured. In this state of O2 supply-independency and steady CO2 generation, rising of P (v-a) CO2 after flow decrease can be explained clearly by CO2 stagnation. In those studies, when DO2 was more diminished under its critical value, a drop in VO2 was noticed, insinuating O2 supply-dependency and occurrence of anaerobic metabolism. The progressive widening of P (v-a) CO2 seen before DO2 had achieved the critical point, was amplified by an acute rise in PvCO2 when DO2 declined below that point. The authors assumed that this brisk increase in P (v-a) CO2 can be utilized as a good indicator of tissue dysxia. However, since both VCO2 (aerobic production) and venous efferent blood flow decrease, P (v-a) CO2 should not be considerably

Influence of cardiac output on P (v-a) CO2
According to the modified Fick equation, P (v-a) CO2 is related to VCO2 and inversely linked to cardiac output. Under steady states of both VO2 and VCO2, P (v-a) CO2 was observed to increase in parallel with the reduction in cardiac output. In other words, when cardiac output is adapted to VO2, P (v-a) CO2 should not increase due to increased clearance of CO2, whereas P (v-a) CO2 should be high following cardiac output reduction because of a low flow-induced tissue CO2 stagnation phenomenon.
low flow states can result in a widening of $P_{(v-a)} CO_2$ even if the CO$_2$ production is not decreased. Conversely, the hypoxic cells, so that $P_{(v-a)} CO_2$ should not increase to assure adequate clearance of the CO$_2$ generated by the tissues. Under conditions of tissue hypoxia with maintained flow, changes in cardiac output result in large changes in $P_{(v-a)} CO_2$ when the CO$_2$ production is not decreased. However, changes in cardiac output will not result in significant changes in $P_{(v-a)} CO_2$ in the high values of cardiac output.

changed unless very low values of blood flow were achieved during the supply dependent period. Therefore, from the analysis of the data of these experimental studies$^{[33,36,37,42]}$, it can be reasonably supposed that an abrupt increase in $P_{(v-a)} CO_2$ should not be easily attributed to the outset of hypoxia but rather to an additional decrease in cardiac output. This fact can be explained by the following reasons.

Since the association between $P_{(v-a)} CO_2$ and cardiac output is curvilinear (Fick equation), an enormous rise in $P_{(v-a)} CO_2$ must be noticed for a reduction in cardiac output in its lowest scale. In fact, even if this mathematical phenomenon may be robust under conditions of maintained VCO$_2$, it should be moderated in hypoxic states because the decline in VCO$_2$ leftward shift the isopleth which describes the $P_{(v-a)} CO_2$/cardiac output relationship (Figure 3).

The curvilinearity of the relationship between CvCO$_2$ and PvCO$_2$ may be another cause for this sharp increase in $P_{(v-a)} CO_2$. Indeed, due to this particular relationship, PvCO$_2$ changes are greater than CvCO$_2$ changes at the highest range of CCO$_2$.$^{[29]}$ Furthermore, the disproportions between CCO$_2$ and PCO$_2$ at high values of CCO$_2$ are magnified in the presence of an elevated O$_2$ saturation and by the decrease in venous pH.$^{[20]}$, which is frequently associated with the increase in PvCO$_2$ and may be of greater significance if metabolic acidosis coexists (Figure 2). Therefore, in the case of low flow states, P[v-a]CO$_2$ can substantially increase resulting from CO$_2$ stagnation in spite of the decrease in VCO$_2$ as reported in those experimental studies$^{[33,36,37,42]}$.

**Tissue hypoxia with maintained or high blood flow**

Under conditions of tissue hypoxia with maintained flow state, venous blood flow should be sufficiently elevated to assure adequate clearance of the CO$_2$ generated by the hypoxic cells, so that $P_{(v-a)} CO_2$ should not increase even if the CO$_2$ production is not decreased. Conversely, low flow states can result in a widening of $P_{(v-a)} CO_2$ due to the tissue CO$_2$ stagnation phenomenon$^{[43]}$ even if no additional CO$_2$ production occurs. This point was nicely demonstrated by Vallet et al.$^{[44]}$ in a canine model of isolated limb in which a diminished DO$_2$ by reducing blood flow (ischemic hypoxia) was related to a rise in $P_{(v-a)} CO_2$. On the other hand, when blood flow was preserved, but arterial PO$_2$ was decreased by lowering the input oxygen concentration (hypoxic hypoxia), $P_{(v-a)} CO_2$ did not rise despite a significant decline in VO$_2$. This because the preserved blood flow was sufficient to clear the generated CO$_2$. Accordingly, Nevière et al.$^{[45]}$ demonstrated that for the same level of induced oxygen supply dependency, $P_{(v-a)} CO_2$ was risen only in ischemic hypoxia but not in hypoxic hypoxia, indicating that augmented $P_{(v-a)} CO_2$ was mostly linked to the reduction in cardiac output. These studies clearly show that the absence of elevated $P_{(v-a)} CO_2$ does not preclude the presence of tissue hypoxia and hence underline the good value of $P_{(v-a)} CO_2$ to detect inadequate tissue perfusion related to its metabolic production but also its poor sensitivity to detect tissue hypoxia. A mathematical model analysis also established that cardiac output plays the key role in the widening of $P_{(v-a)} CO_2$.$^{[46]}$

**Clinical studies**

Results from clinical investigations in septic shock patients have also supported that the decreased cardiac output is the major determinant in the elevation of $P_{(v-a)} CO_2$. Mecher et al.$^{[37,38]}$ observed that septic shock patients with $P_{(v-a)} CO_2 > 6$ mmHg had a significantly lower mean cardiac output when compared to patients with $P_{(v-a)} CO_2 \leq 6$ mmHg. No differences in blood lactate levels were found between the two subgroups. Interestingly, the volume expansion engendered a reduction in $P_{(v-a)} CO_2$ associated with an increase in cardiac output only in patients with elevated $P_{(v-a)} CO_2$. Moreover, the changes in cardiac output induced by volume expansion were correlated with changes in $P_{(v-a)} CO_2 (R = 0.46, P < 0.01)$. The authors rightly concluded that in patients with septic shock, an elevated $P_{(v-a)} CO_2$ is related to a decreased systemic blood flow. In septic shock patients, Bakker et al.$^{[47]}$ similarly found a significant negative correlation between cardiac output and $P_{(v-a)} CO_2$. Thus, a strong association between cardiac output and $P_{(v-a)} CO_2$ is also well documented in septic shock. Furthermore, increased $P_{(v-a)} CO_2$ was found merely in patients with lower cardiac output. In that study, the dissimilarities in $P_{(v-a)} CO_2$ cannot be explained by the inequalities in CO$_2$ production, as implied by the identical VO$_2$ and lactate concentration found in the two groups of patients$^{[48]}$. On the other hand, many patients in those studies$^{[47,48]}$ had normal $P_{(v-a)} CO_2$ despite the presence of tissue hypoxia, presumably since their elevated cardiac output had simply washed out the CO$_2$ generated in the peripheral circulation.

Creteur et al.$^{[49]}$ examined the association between impairment in microcirculatory perfusion and tissue PCO$_2$. They showed that the reperfusion of damaged...
microcirculation (assessed using orthogonal polarized spectroscopy) was associated with normalized sublingual tissue PCO2 levels. Thus, there is a clear relation between tissue CO2 accumulation and blood flow leading to increasing venous-arterial CO2 gradients.

In short, altogether, these results strengthen the conception that low flow situations act a crucial part in the enlargement of P (v-a) CO2 in states of tissue hypoxia. Elevated P (v-a) CO2 might imply that: (1) cardiac output is not enough under states of supposed tissue hypoxia; and (2) microcirculatory flow is not sufficiently high or adequately distributed to remove the additional CO2 in spite of the existence of normal/high cardiac output.

The P (v-a) CO2 should, therefore, be regarded as an indicator of the ability of an adequate venous blood flow return to clear the CO2 excess rather than as a marker of tissue hypoxia.

Recently, Ospina-Tascon et al.[50] have shown that the persistence of high P (v-a) CO2 (≥ 6 mmHg) during the first six hours of reanimation of septic shock patients was linked to more severe multiple organ failure and higher mortality rate (Relative Risk = 2.23, P = 0.01). However, further studies are required to test if P (v-a) CO2 used as a resuscitation endpoint would be associated with improved outcomes.

**Central venous-to-arterial PCO2: difference as a target in resuscitation of septic shock**

The measurement of P (v-a) CO2 requires the presence of a pulmonary artery catheter, which is rarely practiced nowadays[51]. Since the central venous catheter is implanted in most septic shock patients, the usage of central venous-arterial carbon dioxide partial pressure difference (∆PCO2) is greatly easier and similarly helpful. Interestingly, a strong agreement between P (v-a) CO2 and ∆PCO2, calculated as the difference between central venous PCO2 sampled from a central vein catheter and arterial PCO2, was reported in critically ill patients[52] and severe sepsis and septic shock patients[53].

As emphasized above, high values of ScvO2 do not preclude the presence of tissue hypoperfusion and hypoxia in cases of impaired O2ER capabilities that can occur in septic shock[21,22]. Since the solubility of CO2 is very high (around 20 times than O2), its capability of spreading out of ischemic tissues into the efferent veins is phenomenal, making it an extremely sensitive indicator of hypoperfusion. Consequently, in conditions where there are O2 diffusion difficulties (resulting from shunted and obstructed capillaries), “covering” reduced O2ER and increased tissue O2 debt, CO2 still diffuses to the efferent veins, “uncovering” the hypoperfusion situation for the clinician when ∆PCO2 is evaluated[54].

Accordingly, Vallée et al.[55] tested the hypothesis that the ∆PCO2 can be used as a global indicator of tissue hypoperfusion in reanimated septic shock patients in whom ScvO2 was already greater than 70%. They showed that despite a normalized DO2/VO2 ratio, patients who had impaired tissue perfusion with blood lactate concentration > 2 mmol/L remained with an elevated ∆PCO2 (> 6 mmHg). Also, patients with low ∆PCO2 values had greater lactate decrease and cardiac index values and exhibited a significantly higher reduction in SOFA score than patients with high ∆PCO2. In a prospective study that included 80 patients, we recently examined the usefulness of measuring ∆PCO2 during the initial resuscitation period of septic shock[56]. We found that during the very early period of septic shock, patients who reached a normal ∆PCO2 (< 6 mmHg) after six hours of resuscitation had greater decreases in blood lactate and in SOFA score than those who failed to normalize ∆PCO2 (> 6 mmHg). Interestingly, patients who achieved the goals of both ∆PCO2 ≤ 6 mmHg and ScvO2 > 70% after the first six hours of resuscitation had the greatest blood lactate decrease, which was found to be an independent prognostic factor of ICU mortality[56]. In addition, Du et al.[57], in a retrospective study, showed that the normalization of both ScvO2 and ∆PCO2 seems to be a better prognostic factor of outcome after reanimation from septic shock than ScvO2 only. Patients who achieved both targets seemed to clear blood lactate more efficiently[57].

Taken all these studies together[55-57], we believe that monitoring the ∆PCO2 from the beginning of the reanimation of patients with septic shock may be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy (Figure 4). Indeed, in patients with decreased ScvO2, an augmented ∆PCO2 is suggestive of the involvement of low cardiac output, and assessing ∆PCO2 could assist in expediting treatments intended at increasing cardiac output, rather than the arterial O2 saturation and hemoglobin concentration. When ScvO2 is normal/high (≥ 70%), the presence of elevated ∆PCO2 is indicative of the persisting impaired perfusion. ∆PCO2 provides further assistance in making the relevant choices about inotropes and fluids. Randomized clinical trial, however, is required to validate this hypothesis.

**How to interpret ∆PCO2 in septic shock states?**

As developed extensively above, the ∆PCO2 should be considered as a marker of tissue perfusion (i.e., the adequacy of blood flow to wash out the CO2 generated by the tissues) rather than a marker of tissue hypoxia.

The clinical inferences of this approach can be outlined as follows: (1) in a patient with an initially increased ∆PCO2 (≥ 6 mmHg), clinicians should be aware that blood flow might not be sufficient despite apparent normal macrocirculatory parameters, including ScvO2. Thus, with respect to the metabolic states, an elevated ∆PCO2 could encourage clinicians to rise cardiac output in order to improve tissue perfusion, especially under suspected hypoxic conditions (elevated blood lactate levels). Nevertheless, we should stress out that, in the absence of suspected conditions of tissue ischemia, increasing cardiac output to supranormal
values not only failed to demonstrate any benefit but could also be potentially harmful in septic shock patients \[58,59\]; and (2) A normal $\Delta$PCO$_2$ (< 6 mmHg) would suggest that blood flow is sufficiently high to remove the global CO$_2$ production from the peripheral circulation, and increasing cardiac output could not be a first concern in the management approach even in the presence of tissue hypoxia. On the other hand, clinicians should keep in mind that a normal $\Delta$PCO$_2$ with high cardiac output did not preclude the inadequacy of regional blood flow. The change in $\Delta$PCO$_2$ - as an index of VCO$_2$/cardiac output ratio - should be interpreted in line with changes in cardiac output and VCO$_2$. Under aerobic conditions, $\Delta$PCO$_2$ along with ScvO$_2$ and O$_2$ER can serve to guide therapy with dobutamine better than cardiac output in septic shock patients \[60\]. Indeed, dobutamine in parallel to its effects on systemic hemodynamics may increase VO$_2$, and therefore VCO$_2$, through its potential thermogenic effects related to its $\beta_1$-adrenergic properties \[61\]. Recently, we showed that during the stepwise increase of dobutamine dose from 0-10 $\mu$g/kg per minute, $\Delta$PCO$_2$ decreased in parallel with an increase in cardiac output. However, an unchanged $\Delta$PCO$_2$ was observed when dobutamine was increased from 10-15 $\mu$g/kg per minute in spite of the further increase in cardiac output because of the thermogenic effects of the drug at that rate \[60\]. Thus, $\Delta$PCO$_2$ can assist the clinician in distinguishing between the hemodynamic and the metabolic effects of dobutamine. Similar results were reported in stable chronic heart failure patients, but with P (v-a) CO$_2$ \[43\].

Otherwise, the increase in systemic blood flow can affect VCO$_2$ production under situations of tissue hypoxia. Indeed, under conditions of O$_2$ supply dependency, an increase in cardiac output may lead to an increase in aerobic VCO$_2$ production through the supply-dependent increase in VO$_2$. In this situation, the changes in cardiac output may have no effect on the time-course of $\Delta$PCO$_2$. Accordingly, almost unaffected $\Delta$PCO$_2$ with treatment would not indicate that the treatment has been unsuccessful. In such situation, the therapeutic approach would be preferably kept until achieving a significant drop in $\Delta$PCO$_2$ that would imply that the critical value of DO$_2$ has been overcome.

Moreover, the clinicians should be aware that because the relationship between $\Delta$PCO$_2$ and cardiac output is curvilinear, large variations in cardiac output will not necessarily engender important variations in $\Delta$PCO$_2$. (Figure 3). In other words, the interpretation should be cautious in case of high flow states.

**Limitations of $\Delta$PCO$_2$**

There are many pre-analytical sources of errors in PCO$_2$ measurement that should be avoided to interpret $\Delta$PCO$_2$ correctly: inappropriate sample container, insufficient
sample volume compared to anticoagulant volume, and contaminated sample with resident fluid in the line or with air or venous blood, etc. Even after having taken all precautions to minimize the pre-analytical and analytical errors, we, recently, found, in a prospective study[62], that the measurement error for ∆PCO2 was ± 1.4 mmHg and the smallest detectable difference, which is the least change that requires to be measured by a laboratory analyzer to identify a genuine change of measurement, was ± 2 mmHg. This means that the changes in ∆PCO2 should be more than ± 2 mmHg to be considered as real changes and not due to natural variation[62].

Combined analysis of P (v-a) CO2 or ∆PCO2 and O2-derived parameters

Under situations of tissue hypoxia, a drop in VO2 is associated with a decline in aerobic CO2 generation while an anaerobic CO2 generation can still arise[36,37]. Therefore, the VCO2 being reduced less than the VO2, a rise of the respiratory quotient (VCO2/VO2 ratio) can be observed[37,63]. Therefore, the rise in the respiratory quotient was suggested to identify global tissue hypoxia[63].

Because VO2 is equal to the product of cardiac output by the difference between arterial and mixed venous O2 content (C (a-mv) O2) and VCO2 is proportional to the product of cardiac output and P (v-a) CO2, the P (v-a) CO2/C (a-mv) O2 ratio could be utilized as indicator of the presence of global tissue hypoxia in critically ill patients. Accordingly, Mekontso-Dessap et al[64] tested this hypothesis in a retrospective study of critically ill patients with normalized cardiac output values and DO2. The authors found a good correlation between P (v-a) CO2/C (a-mv) O2 ratio, presented as a substitute of the respiratory quotient, and arterial blood lactate level, while no correlation was found between blood lactate and P (v-a) CO2 alone and between blood lactate and C (a-mv) O2 alone. Moreover, for a threshold value > 1.4 the P (v-a) CO2/C (a-mv) O2 ratio was able to predict with reliability the presence of hyperlactatemia[64]. The authors concluded that this ratio could be utilized as a reliable indicator of the presence of global anaerobic metabolism in critically ill patients. In a more recent study, Monnet et al[65] found that this ratio, calculated from central venous blood [∆PCO2/C (a-cv) O2], predicted an increase in VO2 after a fluid-induced increase in DO2 (VO2/DO2 dependency), and thus, can be able to detect the presence of global tissue hypoxia as accurately as the blood lactate level and far better than ScvO2. In a series of 60 fluid-responder patients, we recently found that ∆PCO2/C (a-cv) O2 ratio at baseline predicted accurately the presence of VO2/DO2 dependency phenomenon and better than blood lactate (unpublished data).

In a population of 35 septic shock patients with normalized mean arterial pressure and ScvO2, Mesquida et al[66] showed that the presence of elevated ∆PCO2/C (a-cv) O2 values at baseline was associated with the absence of lactate clearance within the following hours, and this condition was also associated with mortality. However, this was a retrospective study and it was not powered to explore the prognostic value of the ∆PCO2/C (a-cv) O2 ratio. In a recent prospective study that included 135 septic shock patients[67], Ospina-Tascon et al[60] found that the mixed venous-to-arterial CO2 difference/C (a-mv) O2 ratio at baseline and six hours after resuscitation was an independent prognostic factor of 28 d mortality, but not P (v-a) CO2/C (a-mv) O2 ratio. The authors attributed this discrepancy to the fact that the PCO2/CO2 ratio relationship is curvilinear rather than linear and is influenced by many factors such as pH and oxygen saturation (Haldane effect), and under these conditions, the mixed venous-to-arterial CO2 difference/C (a-mv) O2 ratio might not be equivalent to P (v-a) CO2/C (a-mv) O2 ratio.

From the results of those above studies[64-67], we believe that we can reasonably admit that the ∆PCO2/C (a-cv) O2 ratio can be used as an indicator of the presence of global tissue hypoxia in critically ill patients. Further clinical trials are needed to assess its prognostic value in patients with septic shock.

CONCLUSION

Early identification and improvement of tissue hypoperfusion are critical factors in the treatment of septic shock patients. The deficit in tissue perfusion with reduced blood flow should be considered as the primary determinant of an increase in ∆PCO2. ∆PCO2 should be seen as an indicator of the adequacy of venous blood flow (cardiac output) to clear the CO2 generated by the peripheral tissues rather than as a marker of tissue hypoxia. Thus, monitoring ∆PCO2 could be a useful complementary tool to guide the resuscitation in the early phase of septic shock (Figure 4). It can also be combined with the O2-derived parameters in order to calculate the ∆PCO2/C (a-cv) O2, which can be used to detect the presence of global anaerobic metabolism. In such situation, the presence of low ScvO2 (< 70%) should push the physician to increase DO2, and if ∆PCO2 is increased (≥ 6 mmHg), that indicates that increasing cardiac output is the rational choice to achieve this target (Figure 4). In the presence of a normal/high ScvO2 (≥ 70%), an elevated ∆PCO2 still suggests that rising cardiac output can be indicated with the purpose of reducing global tissue hypoxia (Figure 4). However, if both ScvO2 and ∆PCO2 are normal in a state of global anaerobic metabolism, manipulating the microcirculation will probably be ineffective to reduce oxygen deficit (Figure 4).

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