

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 (Δ 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 Δ 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 Δ PCO₂ (> 6 mmHg) could be used to identify patients who still remain inadequately resuscitated. Monitoring the Δ PCO₂ from the beginning of the reanimation 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 Δ PCO₂ with oxygen-derived parameters through the calculation of the P (v-a) CO₂ or Δ 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.

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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^[1]. 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^[2]. 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^[3-5].

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 splanchnic 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 ScvO₂ 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^[21,22]. 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^[23,24]. However, no benefits have been observed for lactate decrease-guided therapy over resuscitation guided by ScvO₂ in septic shock patients^[25]. 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.

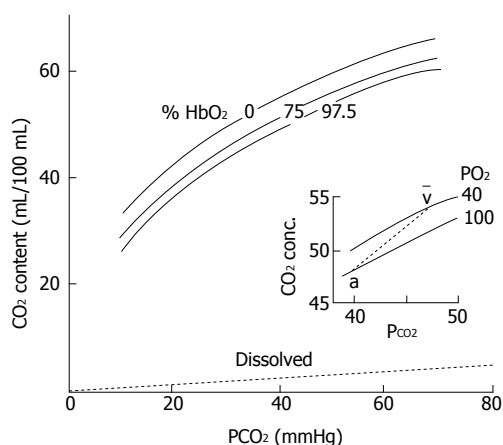


Figure 1 CO₂ dissociation curve. CO₂ content (mL/100 mL) vs CO₂ partial tension (PCO₂). Differences between the curves result in higher CO₂ content in the blood, and smaller PCO₂ differences between arterial and venous blood. Hemoglobin-O₂ saturation affects the position of the CO₂ dissociation curve (Haldane effect).

PHYSIOLOGICAL BACKGROUND

CO₂ transport in the blood

CO₂ is transported in the blood in three figures^[26]: 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 affe-

cting 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]. 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 (PaCO₂): P (v-a) CO₂ = PvCO₂ - PaCO₂; PvCO₂ and PaCO₂ 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 × (CvCO₂ - CaCO₂). In spite of a global curvilinear shape of the relation between PCO₂ and the total CCO₂, there is a rather linear association between CCO₂ and PCO₂ over the general physiological range of CO₂ content so that CCO₂ can be substituted by PCO₂ (PCO₂ = k × CCO₂)^[27-29]. 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^[30].

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

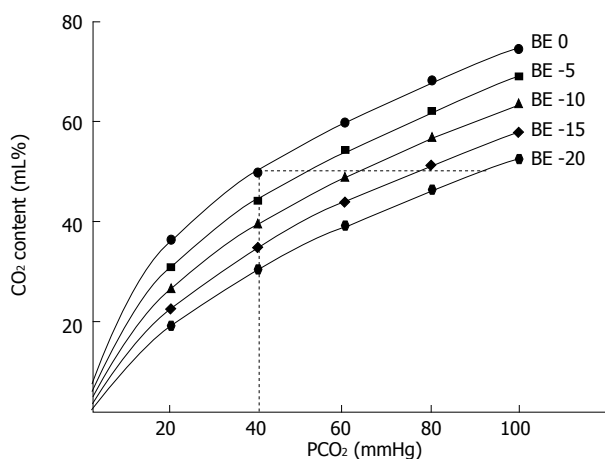


Figure 2 CO₂ dissociation curve. CO₂ content (mL/100 mL) vs CO₂ partial tension (PCO₂). Each curve is described at constant base excess (BE). As displayed, for the same CO₂ content, changing the BE results in a great change in PCO₂.

quotient varying among 0.7 and 1.0 according to the energy intake. Under circumstances of important carbohydrate consumption, R becomes close to 1.0. Thus, CO₂ generation should increase either with elevated oxidative metabolism or for a constant VO₂ when a balanced alimentation regime is substituted by a high carbohydrate consumption regime^[31]. Under both situations of increased VCO₂, P (v-a) CO₂ should increase unless cardiac output can increase to the same extent.

Anaerobic CO₂ production: Under conditions of tissue hypoxia, there is an increased generation of H⁺ ions from an excessive generation of lactic acid due to an acceleration of anaerobic glycolysis, and the hydrolysis of high-energy phosphates^[32]. These H⁺ ions will then be buffered by the bicarbonate existing in the cells so that CO₂ will be produced. Decarboxylation of metabolic intermediates such as α -ketoglutarate and oxaloacetate during hypoxia is, also, a possible but trivial cause of anaerobic CO₂ generation^[32].

Anaerobic CO₂ generation in hypoxic tissues is not simple to identify. Indeed, the effluent venous blood flow can be sufficiently high to wash out the CO₂ generated under these conditions of a significant decline in aerobic CO₂ production^[33]. Consequently, PCO₂ could be not increased in the efferent vein, and anaerobic CO₂ generation not recognized from the calculation of P (v-a) CO₂. Nevertheless, if afferent and efferent blood flows are artificially arrested, hypoxia will happen inside the organ and the sustained CO₂ production would then be disclosed by measuring an augmented PCO₂ in the sluggish efferent blood flow, in spite of the drop in CO₂ generation from the aerobic pathway^[34,35].

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^[33,36,37]. 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. 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^[38]. This finding underscores the utility of calculating P (v-a) CO₂ rather than simply assessing PvCO₂, particularly in the case of spontaneous breathing^[39].

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^[40]. Furthermore, higher P (v-a) CO₂ values were observed in patients with circulatory failure compared with those without circulatory failure^[41]. 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^[33,36]. 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^[37]. Nevertheless, since the k factor should rise during tissue hypoxia^[33] while VCO₂ must decrease, the resultant effect on P (v-a) CO₂ depends mainly on the flow state (cardiac output)^[27].

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^[33,36,37,42]. 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^[33,36,42] assumed that this brisk increase in P (v-a) CO₂ can be utilized as a good indicator of tissue dysoxia. However, since both VCO₂ (aerobic production) and venous efferent blood flow decrease, P (v-a) CO₂ should not be considerably

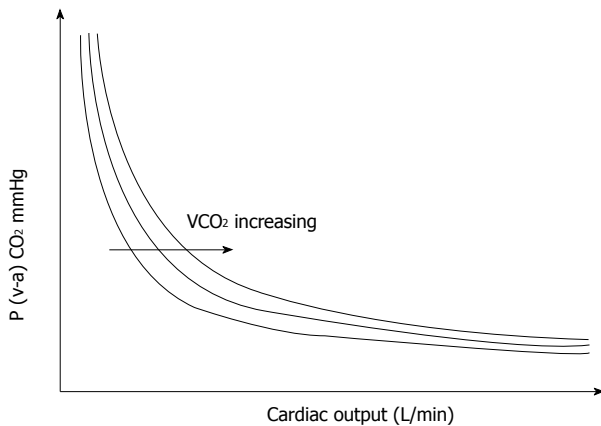


Figure 3 Relationship between the mixed venous-to-arterial PCO₂ difference P (v-a) CO₂ and cardiac output. For a constant total CO₂ production (VCO₂), changes in cardiac output result in large changes in P (v-a) CO₂ in the low values of cardiac output, whereas changes in cardiac output will not result in significant changes in P (v-a) CO₂ 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) CO₂ 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 two following reasons.

Since the association between P (v-a) CO₂ and cardiac output is curvilinear (Fick equation), an enormous rise in P (v-a) CO₂ 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 VCO₂, it should be moderated in hypoxic states because the decline in VCO₂ leftward shift the isopleth which describes the P (v-a) CO₂/cardiac output relationship (Figure 3).

The curvilinearity of the relationship between CvCO₂ and PvCO₂ may be another cause for this sharp increase in P (v-a) CO₂. Indeed, due to this particular relationship, PvCO₂ changes are greater than CvCO₂ changes at the highest range of CCO₂^[29]. Furthermore, the disproportions between CCO₂ and PCO₂ at high values of CCO₂ are magnified in the presence of an elevated O₂ saturation and by the decrease in venous pH^[29], which is frequently associated with the increase in PvCO₂ and may be of greater significance if metabolic acidosis coexists (Figure 2). Therefore, in the case of low flow states, P[v-a]CO₂ can substantially increase resulting from CO₂ stagnation in spite of the decrease in VCO₂ 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 CO₂ generated by the hypoxic cells, so that P (v-a) CO₂ should not increase even if the CO₂ production is not decreased. Conversely, low flow states can result in a widening of P (v-a) CO₂

due to the tissue CO₂ stagnation phenomenon^[43] even if no additional CO₂ production occurs. This point was nicely demonstrated by Vallet *et al.*^[44] in a canine model of isolated limb in which a diminished DO₂ by reducing blood flow (ischemic hypoxia) was related to a rise in P (v-a) CO₂. On the other hand, when blood flow was preserved, but arterial PO₂ was decreased by lowering the input oxygen concentration (hypoxic hypoxia), P (v-a) CO₂ did not rise despite a significant decline in VO₂. This because the preserved blood flow was sufficient to clear the generated CO₂^[40]. Accordingly, Nevière *et al.*^[45] demonstrated that for the same level of induced oxygen supply dependency, P (v-a) CO₂ was risen only in ischemic hypoxia but not in hypoxic hypoxia, indicating that augmented P (v-a) CO₂ was mostly linked to the reduction in cardiac output. These studies clearly show that the absence of elevated P (v-a) CO₂ does not preclude the presence of tissue hypoxia and hence underline the good value of P (v-a) CO₂ 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) CO₂^[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) CO₂^[37,38]. Mecher *et al.*^[47] observed that septic shock patients with P (v-a) CO₂ > 6 mmHg had a significantly lower mean cardiac output when compared to patients with P (v-a) CO₂ ≤ 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) CO₂ associated with an increase in cardiac output only in patients with elevated P (v-a) CO₂. Moreover, the changes in cardiac output induced by volume expansion were correlated with changes in P (v-a) CO₂ (R = 0.46, P < 0.01). The authors rightly concluded that in patients with septic shock, an elevated P (v-a) CO₂ is related to a decreased systemic blood flow. In septic shock patients, Bakker *et al.*^[48] similarly found a significant negative correlation between cardiac output and P (v-a) CO₂. Thus, a strong association between cardiac output and P (v-a) CO₂ is also well documented in septic shock. Furthermore, increased P (v-a) CO₂ was found merely in patients with lower cardiac output. In that study, the dissimilarities in P (v-a) CO₂ cannot be explained by the inequalities in CO₂ production, as implied by the identical VO₂ 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) CO₂ despite the presence of tissue hypoxia, presumably since their elevated cardiac output had simply washed out the CO₂ generated in the peripheral circulation.

Creteur *et al.*^[49] examined the association between impairment in microcirculatory perfusion and tissue PCO₂. 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 (Δ PCO₂) is greatly easier and similarly helpful. Interestingly, a strong agreement between P (v-a) CO₂ and Δ 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 Δ PCO₂ is evaluated^[54]. Accordingly, Vallée *et al.*^[55] tested the hypothesis that the Δ 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 Δ PCO₂ (> 6 mmHg). Also, patients with low Δ PCO₂ values had greater lactate decrease and cardiac index values and exhibited a significantly higher reduction in SOFA score than patients with high Δ PCO₂. In a prospective study that included 80 patients, we recently examined the usefulness of measuring Δ 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 Δ PCO₂ (≤ 6 mmHg) after six hours of resuscitation had greater decreases in blood lactate and in SOFA score than those who failed to normalize Δ PCO₂ (> 6 mmHg). Interestingly, patients who achieved the goals of both Δ 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 Δ 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 Δ 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 Δ PCO₂ is suggestive of the involvement of low cardiac output, and assessing Δ 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 ($\geq 70\%$), the presence of elevated Δ PCO₂ is indicative of the persisting impaired perfusion. Δ 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 Δ PCO₂ in septic shock states?

As developed extensively above, the Δ 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 Δ 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 Δ 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

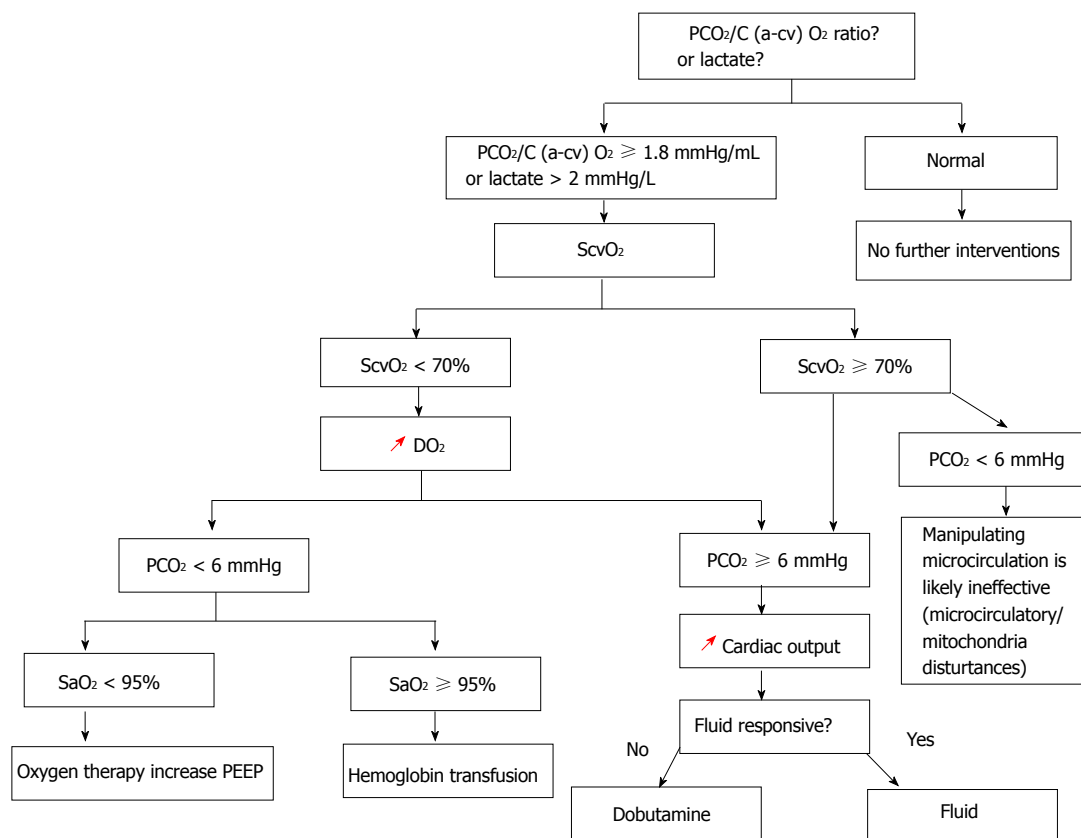


Figure 4 ScvO₂-ΔPCO₂ guided protocol. ScvO₂: Central venous oxygen saturation; ΔPCO₂: Central venous-to-arterial carbon dioxide tension difference; SaO₂: Arterial oxygen saturation; C (a-cv) O₂: Central arteriovenous oxygen content difference; DO₂: Oxygen delivery; PEEP: Positive end expiratory pressure; red arrows: Increasing.

values not only failed to demonstrate any benefit but could also be potentially harmful in septic shock patients^[58,59]; and (2) A normal ΔPCO₂ (< 6 mmHg) would suggest that blood flow is sufficiently high to remove the global CO₂ 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 ΔPCO₂ with high cardiac output did not preclude the inadequacy of regional blood flow.

The change in ΔPCO₂- as an index of VCO₂/cardiac output ratio- should be interpreted in line with changes in cardiac output and VCO₂. Under aerobic conditions, ΔPCO₂ along with ScvO₂ and O₂ER 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 VO₂, and therefore VCO₂, through its potential thermogenic effects related to its β₁-adrenergic properties^[61]. Recently, we showed that during the stepwise increase of dobutamine dose from 0-10 μg/kg per minute, ΔPCO₂ decreased in parallel with an increase in cardiac output. However, an unchanged ΔPCO₂ was observed when dobutamine was increased from 10-15 μg/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, ΔPCO₂ 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) CO₂^[43].

Otherwise, the increase in systemic blood flow can affect VCO₂ production under situations of tissue hypoxia. Indeed, under conditions of O₂ supply dependency, an increase in cardiac output may lead to an increase in aerobic VCO₂ production through the supply-dependent increase in VO₂. In this situation, the changes in cardiac output may have no effect on the time-course of ΔPCO₂. Accordingly, almost unaffected ΔPCO₂ 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 ΔPCO₂ that would imply that the critical value of DO₂ has been overcome.

Moreover, the clinicians should be aware that because the relationship between ΔPCO₂ and cardiac output is curvilinear, large variations in cardiac output will not necessarily engender important variations in ΔPCO₂ (Figure 3). In other words, the interpretation should be cautious in case of high flow states.

Limitations of ΔPCO₂

There are many pre-analytical sources of errors in PCO₂ measurement that should be avoided to interpret ΔPCO₂ 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 have taken all precautions to minimize the pre-analytical and analytical errors, we, recently, found, in a prospective study^[62], that the measurement error for ΔPCO_2 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 ΔPCO_2 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 ΔPCO_2 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 [$\Delta\text{PCO}_2/\text{C}$ (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 $\Delta\text{PCO}_2/\text{C}$ (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 $\Delta\text{PCO}_2/\text{C}$ (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 $\Delta\text{PCO}_2/\text{C}$ (a-cv) O₂ ratio. In a recent prospective study that included 135 septic shock patients^[67], Ospina-Tascon *et al.*^[50] found that the mixed venous-to-arterial CCO₂ 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/CCO₂ 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 CCO₂ 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 $\Delta\text{PCO}_2/\text{C}$ (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 ΔPCO_2 . ΔPCO_2 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 ΔPCO_2 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 $\Delta\text{PCO}_2/\text{C}$ (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 ΔPCO_2 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 ($\geq 70\%$), an elevated ΔPCO_2 still suggests that rising cardiac output can be indicated with the purpose of reducing global tissue hypoxia (Figure 4). However, if both ScvO₂ and ΔPCO_2 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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