World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.47

World J Crit Care Med 2016 February 4; 5(1): 47-56
ISSN 2220-3141 (online)

REVIEW

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

Jihad Mallat, Malcolm Lemyze, Laurent Tronchon, Benoît Vallet, Didier Thevenin

Jihad Mallat, Malcolm Lemyze, Laurent Tronchon, Benoît Vallet, Didier Thevenin, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, 62300 Lens, France

Author contributions: Mallat J contributed to conception, designed and wrote the paper; Lemyze M, Tronchon L, Vallet B and Thevenin D revised the manuscript critically for important intellectual content.

Conflict-of-interest statement: Authors declare no conflicts of interests for this article.

Correspondence to: Jihad Mallat, MD, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, 99 route de La Bassée, 62300 Lens, France. mallatjihad@gmail.com
Telephone: +33-321-691088
Fax: +33-321-691839

Received: August 5, 2015
Peer-review started: August 6, 2015
First decision: September 16, 2015
Revised: October 12, 2015
Accepted: December 3, 2015
Article in press: December 4, 2015
Published online: February 4, 2016

Abstract

The mixed venous-to-arterial carbon dioxide (CO_2) tension difference [P (v-a) CO_2] is the difference between carbon dioxide tension (PCO_2) in mixed venous blood (sampled from a pulmonary artery catheter) and the PCO_2 in arterial blood. P (v-a) CO_2 depends on the cardiac output and the global CO_2 production, and on the complex relationship between PCO_2 and CO_2 content. Experimental and clinical studies support the evidence that P (v-a) CO_2 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 CO_2 generated by the peripheral tissues. P (v-a) CO_2 can be replaced by the central venous-to-arterial CO_2 difference (ΔPCO_2), 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 ΔPCO_2 during the resuscitation of septic shock patients might be useful when deciding when to continue resuscitation despite a central venous oxygen saturation ($ScvO_2$) > 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 ΔPCO_2 (> 6 mmHg) could be used to identify patients who still remain inadequately resuscitated. Monitoring the ΔPCO_2 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 CO_2 production, or to choose between hemoglobin correction or fluid/inotrope infusion in patients with a too low $ScvO_2$ related to metabolic demand. The combination of P (v-a) CO_2 or ΔPCO_2 with oxygen-derived parameters through the calculation of the P (v-a) CO_2 or ΔPCO_2/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

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 O_2-derived parameters. In this regard, its monitoring should help the clinicians for the decision of giving therapy targeting at increasing cardiac output.

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 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/47.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.47

INTRODUCTION

A shock is a form of acute circulatory failure associated with an inequality between systemic oxygen delivery (DO_2) and oxygen consumption (VO_2), 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 (SvO_2) from a pulmonary artery catheter has been proposed as an indirect marker of global tissue oxygenation[2]. SvO_2 reflects the balance between oxygen demand and supply. A low SvO_2 represents a high oxygen extraction (O_2ER) in order to maintain aerobic metabolism and VO_2 constant in response to an acute decrease in DO_2. However, when DO_2 drops under a critical value, O_2ER is no longer capable of upholding VO_2, and global tissue hypoxia appears, as indicated by the occurrence of lactic acidosis[3-5].

Since the assessment of central venous oxygen saturation ($ScvO_2$) can be achieved more easily, and is less risky than from pulmonary artery catheter, it would be useful if $ScvO_2$ could function as an accurate reflection of SvO_2. In fact, SvO_2 is not similar to $ScvO_2$ because the latter primarily reflects the oxygenation of the upper side of the body. In normal patients, $ScvO_2$ is lower than SvO_2 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 $ScvO_2$ was more often reported to be higher than $ScvO_2$, probably due to the oxygen extraction increases in splanchnic and renal tissues[7-11]. This suggests that the existence of a decreased $ScvO_2$ implies an even smaller SvO_2. Because of the lack of agreement regarding absolute values, some authors questioned the clinical utility of $ScvO_2$[12,13]. However, despite absolute values differ, trends in $ScvO_2$ closely mirror trends in SvO_2[8,9], suggesting that monitoring $ScvO_2$ makes sense in critically ill patients.

It has been shown that an early hemodynamic optimization using a resuscitation bundle aimed at increasing $ScvO_2$ > 70% was related to an important reduction in septic shock mortality[14]. Since that, monitoring $ScvO_2$ 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 $ScvO_2$ > 70% was effective. Also, in these studies, the mean baseline $ScvO_2$ values were already above 70%. Thus, these findings do not indicate that clinicians should stop monitoring $ScvO_2$ and adjust DO_2 by optimizing $ScvO_2$ levels, particularly in septic shock patients with low $ScvO_2$, who are at the highest risk of death[19].

On the other hand, normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion and does not preclude evolution to multi-organ dysfunction and death[20]. The obvious limitation of $ScvO_2$ is that normal/high values cannot distinguish if DO_2 is sufficient or in excess to demand. In septic conditions, normal/high $ScvO_2$ 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 $ScvO_2$ is measured downstream from tissues, when a given tissue receives inadequate DO_2, the resulting low local oxygen venous saturations may be "masked" by admixture with highly saturated venous blood from tissues with better perfusion and DO_2, resulting overall in normal or even high $ScvO_2$. Although $ScvO_2$ may thus not miss any global DO_2 dysfunction, it may stay "blind" to local perfusion disturbances, which exist in abundance in sepsis due to damaged microcirculation. Indeed, high $ScvO_2$ values have been associated with increased mortality in septic shock patients[21,22]. Thus, in some circumstances the use of $ScvO_2$ 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 $ScvO_2$ 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 $ScvO_2$ 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.

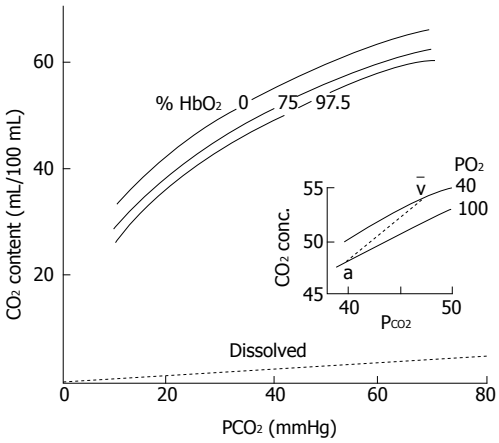

Figure 1 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Differences between the curves result in higher CO_2 content in the blood, and smaller PCO_2 differences between arterial and venous blood. Hemoglobin-O_2 saturation affects the position of the CO_2 dissociation curve (Haldane effect).

PHYSIOLOGICAL BACKGROUND

CO_2 transport in the blood

CO_2 is transported in the blood in three figures[26]: Dissolved, in combination with proteins as carbamino compounds, and as bicarbonate. Physically dissolved CO_2 is a function of CO_2 solubility in blood, which is about 20 times that of oxygen (O_2); therefore, considerably more CO_2 than O_2 is present in simple solution at equal partial pressures. However, dissolved CO_2 shares only around 5% of the whole CO_2 concentration in arterial blood.

Carbamino compounds comprise the second form of CO_2 in the blood. These compounds occur when CO_2 combines with terminal amine groups in blood proteins, especially with the globin of hemoglobin. However, this chemical combination between CO_2 and hemoglobin is much less important than haemoglobin-O_2 binding, so carbamino compounds comprise only 5% of the total CO_2 in the arterial blood.

The bicarbonate ion (HCO_3^-) is the most significant form of the CO_2 carriage in the blood. CO_2 combines with water (H_2O) to form carbonic acid (H_2CO_3), and this dissociates to HCO_3^- and hydrogen ion (H^+): $CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$. 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 H_2CO_3 dissociates to H^+ and HCO_3^-, and the H^+ is buffered primarily by hemoglobin while the excess HCO_3^- is transported out the RBC into plasma by an electrically neutral bicarbonate-chloride exchanger. The fast conversion of CO_2 to HCO_3^- results in nearly 90% of the CO_2 in arterial blood being transported in that manner.

Hemoglobin-O_2 saturation is the major factor affecting the capacity of hemoglobin to fix CO_2 (Haldane effect). Consequently, CO_2 concentration increases when blood is deoxygenated, or CO_2 concentration diminishes when blood is oxygenated, at any assumed carbon dioxide tension (PCO_2)[26] (Figure 1). H^+ ions from CO_2 can be deemed as competing with O_2 for hemoglobin binding. Accordingly, rising oxygen reduces the affinity of hemoglobin for H^+ and blood CO_2 concentration (Haldane effect). The physiological assets of the Haldane effect are that it promotes removing of CO_2 in the lungs when blood is oxygenated and CO_2 filling in the blood when oxygen is delivered to tissues. Additionally, the Haldane effect leads to a sharper physiologic CO_2 blood equilibrium curve that has the physiologic interest of rising CO_2 concentration differences for a given PCO_2 difference.

CO_2 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 PCO_2 and the total blood CO_2 content (CCO_2) is curvilinear even though more linear than the oxygen dissociation curve[26]. Oxygen saturation, hematocrit, temperature, and the degree of metabolic acidosis influence the PCO_2/CCO_2 relationship[26]. Hence, for a given value of CCO_2, PCO_2 is higher in the case of metabolic acidosis than in the case of normal pH (Figure 2).

Determinant of venous-to-arterial CO_2 tension difference

The venous-to-arterial CO_2 tension difference [P (v-a) CO_2] is the gradient between PCO_2 in mixed venous blood ($PvCO_2$) and PCO_2 in arterial blood ($PaCO_2$): P (v-a) $CO_2 = PvCO_2 - PaCO_2$; $PvCO_2$ and $PaCO_2$ are partial pressures of the dissolved CO_2 in the mixed venous and arterial blood, respectively.

The application of Fick equation to CO_2 shows that the CO_2 elimination (identical to CO_2 generation in a stable condition) equals the product of the difference between mixed venous blood CO_2 content ($CvCO_2$) and arterial blood CO_2 content ($CaCO_2$) and cardiac output: Total CO_2 production (VCO_2) = cardiac output × ($CvCO_2$ - $CaCO_2$). In spite of a global curvilinear shape of the relation between PCO_2 and the total CCO_2, there is a rather linear association between CCO_2 and PCO_2 over the general physiological range of CO_2 content so that CCO_2 can be substituted by PCO_2 ($PCO_2 = k \times CCO_2$)[27-29]. Therefore, VCO_2 can be calculated from a modified Fick equation as: VCO_2 = cardiac output × k × P (v-a) CO_2 so that P (v-a) $CO_2 = k \times VCO_2$/cardiac output, where k is the pseudo-linear coefficient supposed to be constant in physiological states[27]. Therefore, P (v-a) CO_2 would be linearly linked to CO_2 generation and inversely associated to cardiac output. Under normal conditions, P (v-a) CO_2 values range between 2 and 6 mmHg[30].

Influence of CO_2 production on P (v-a) CO_2

Aerobic CO_2 production: Oxidative phosphorylation proceeds with the formation of energy-laden molecules, CO_2 and water. Total CO_2 production is directly related to VO_2: $VCO_2 = R \times VO_2$, where R is the respiratory

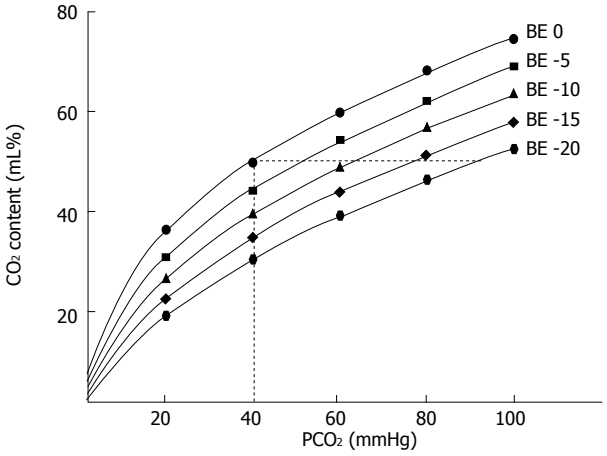

Figure 2 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Each curve is described at constant base excess (BE). As displayed, for the same CO_2 content, changing the BE results in a great change in PCO_2.

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, CO_2 generation should increase either with elevated oxidative metabolism or for a constant VO_2 when a balanced alimentation regime is substituted by a high carbohydrate consumption regime[31]. Under both situations of increased VCO_2, P (v-a) CO_2 should increase unless cardiac output can increase to the same extent.

Anaerobic CO_2 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 CO_2 will be produced. Decarboxylation of metabolic intermediates such as α-ketoglutarate and oxaloacetate during hypoxia is, also, a possible but trivial cause of anaerobic CO_2 generation[32].

Anaerobic CO_2 generation in hypoxic tissues is not simple to identify. Indeed, the effluent venous blood flow can be sufficiently high to wash out the CO_2 generated under these conditions of a significant decline in aerobic CO_2 production[33]. Consequently, PCO_2 could be not increased in the efferent vein, and anaerobic CO_2 generation not recognized from the calculation of P (v-a) CO_2. Nevertheless, if afferent and efferent blood flows are artificially arrested, hypoxia will happen inside the organ and the sustained CO_2 production would then be disclosed by measuring an augmented PCO_2 in the sluggish efferent blood flow, in spite of the drop in CO_2 generation from the aerobic pathway[34,35].

Influence of cardiac output on P (v-a) CO_2

According to the modified Fick equation, P (v-a) CO_2 is related to VCO_2 and inversely linked to cardiac output. Under steady states of both VO_2 and VCO_2, P (v-a) CO_2 was observed to increase in parallel with the reduction in cardiac output[33,36,37]. In other words, when cardiac output is adapted to VO_2, P (v-a) CO_2 should not increase due to increased clearance of CO_2, whereas P (v-a) CO_2 should be high following cardiac output reduction because of a low flow-induced tissue CO_2 stagnation phenomenon. Due to the decreasing of transit time a higher than usual addition of CO_2 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 $PvCO_2$ and $PaCO_2$. However, under spontaneous breathing situations, hyperventilation, stimulated by the decreased blood flow, may reduce $PaCO_2$ and thus may prevent the CO_2 stagnation-induced rise in $PvCO_2$[38]. This finding underscores the utility of calculating P (v-a) CO_2 rather than simply assessing $PvCO_2$, particularly in the case of spontaneous breathing[39].

Can P (v-a) CO_2 be used as a marker of tissue hypoxia?

Marked increases in P (v-a) CO_2 were reported in patients during cardiopulmonary resuscitation[40]. Furthermore, higher P (v-a) CO_2 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 CO_2 production. Thus, it has been suggested that P (v-a) CO_2can 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 VO_2, the relationship between changes in cardiac output and P (v-a) CO_2 are much more complex. Indeed, in these circumstances, the increase in CO_2 production related to the anaerobic pathway is counterbalanced by a reduced aerobic CO_2 production, so that VCO_2 and hence P (v-a) CO_2 could be at best unchanged or decreased[37]. Nevertheless, since the k factor should rise during tissue hypoxia[33] while VCO_2 must decrease, the resultant effect on P (v-a) CO_2 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) CO_2 following the reduction in DO_2 was reported, while a constant VO_2 was measured[33,36,37,42]. In this state of O_2 supply-independency and steady CO_2 generation, rising of P (v-a) CO_2 after flow decrease can be explained clearly by CO_2 stagnation.

In those studies, when DO_2 was more diminished under its critical value, a drop in VO_2 was noticed, insinuating O_2 supply-dependency and occurrence of anaerobic metabolism. The progressive widening of P (v-a) CO_2 seen before DO_2 had achieved the critical point, was amplified by an acute rise in $PvCO_2$ when DO_2 declined below that point. The authors[33,36,42] assumed that this brisk increase in P (v-a) CO_2 can be utilized as a good indicator of tissue dysoxia. However, since both VCO_2 (aerobic production) and venous efferent blood flow decrease, P (v-a) CO_2 should not be considerably

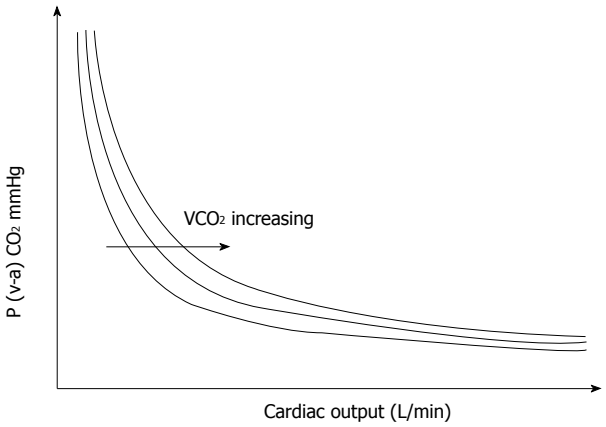

Figure 3 Relationship between the mixed venous-to-arterial PCO_2 difference P (v-a) CO_2 and cardiac output. For a constant total CO_2 production (VCO_2), changes in cardiac output result in large changes in P (v-a) CO_2 in the low values of cardiac output, whereas changes in cardiac output will not 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 two 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[29], 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[40]. 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[37,38]. Mecher *et al*[47] 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 $\leqslant$ 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*[48] 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 PCO_2 levels. Thus, there is a clear relation between tissue CO_2 accumulation and blood flow leading to increasing venous-arterial CO_2 gradients.

In short, altogether, these results strengthen the conception that low flow situations act a crucial part in the enlargement of P (v-a) CO_2 in states of tissue hypoxia. Elevated P (v-a) CO_2 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 CO_2 in spite of the existence of normal/high cardiac output.

The P (v-a) CO_2 should, therefore, be regarded as an indicator of the ability of an adequate venous blood flow return to clear the CO_2 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) CO_2 ($\geqslant$ 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) CO_2 used as a resuscitation endpoint would be associated with improved outcomes.

Central venous-to-arterial PCO_2 difference as a target in resuscitation of septic shock

The measurement of P (v-a) CO_2 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 (ΔPCO_2) is greatly easier and similarly helpful. Interestingly, a strong agreement between P (v-a) CO_2 and ΔPCO_2, calculated as the difference between central venous PCO_2 sampled from a central vein catheter and arterial PCO_2, was reported in critically ill patients[52] and severe sepsis and septic shock patients[53].

As emphasized above, high values of $ScvO_2$ do not preclude the presence of tissue hypoperfusion and hypoxia in cases of impaired O_2ER capabilities that can occur in septic shock[21,22]. Since the solubility of CO_2 is very high (around 20 times than O_2), 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 O_2 diffusion difficulties (resulting from shunted and obstructed capillaries), "covering" reduced O_2ER and increased tissue O_2 debt, CO_2 still diffuses to the efferent veins, "uncovering" the hypoperfusion situation for the clinician when ΔPCO_2 is evaluated[54]. Accordingly, Vallée *et al*[55] tested the hypothesis that the ΔPCO_2 can be used as a global indicator of tissue hypoperfusion in reanimated septic shock patients in whom $ScvO_2$ was already greater than 70%. They showed that despite a normalized DO_2/VO_2 ratio, patients who had impaired tissue perfusion with blood lactate concentration > 2 mmol/L remained with an elevated ΔPCO_2 (> 6 mmHg). Also, patients with low ΔPCO_2 values had greater lactate decrease and cardiac index values and exhibited a significantly higher reduction in SOFA score than patients with high ΔPCO_2. In a prospective study that included 80 patients, we recently examined the usefulness of measuring ΔPCO_2 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 ΔPCO_2 ($\leqslant$ 6 mmHg) after six hours of resuscitation had greater decreases in blood lactate and in SOFA score than those who failed to normalize ΔPCO_2 (> 6 mmHg). Interestingly, patients who achieved the goals of both $\Delta PCO_2 \leqslant$ 6 mmHg and $ScvO_2$ > 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 $ScvO_2$ and ΔPCO_2 seems to be a better prognostic factor of outcome after reanimation from septic shock than $ScvO_2$ 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 ΔPCO_2 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 $ScvO_2$, an augmented ΔPCO_2 is suggestive of the involvement of low cardiac output, and assessing ΔPCO_2 could assist in expediting treatments intended at increasing cardiac output, rather than the arterial O_2 saturation and hemoglobin concentration. When $ScvO_2$ is normal/high ($\geqslant$ 70%), the presence of elevated ΔPCO_2 is indicative of the persisting impaired perfusion. ΔPCO_2 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 ΔPCO_2 in septic shock sates?

As developed extensively above, the ΔPCO_2 should be considered as a marker of tissue perfusion (*i.e.,* the adequacy of blood flow to wash out the CO_2 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 ΔPCO_2 ($\geqslant$ 6 mmHg), clinicians should be aware that blood flow might not be sufficient despite apparent normal macrocirculatory parameters, including $ScvO_2$. Thus, with respect to the metabolic states, an elevated ΔPCO_2 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

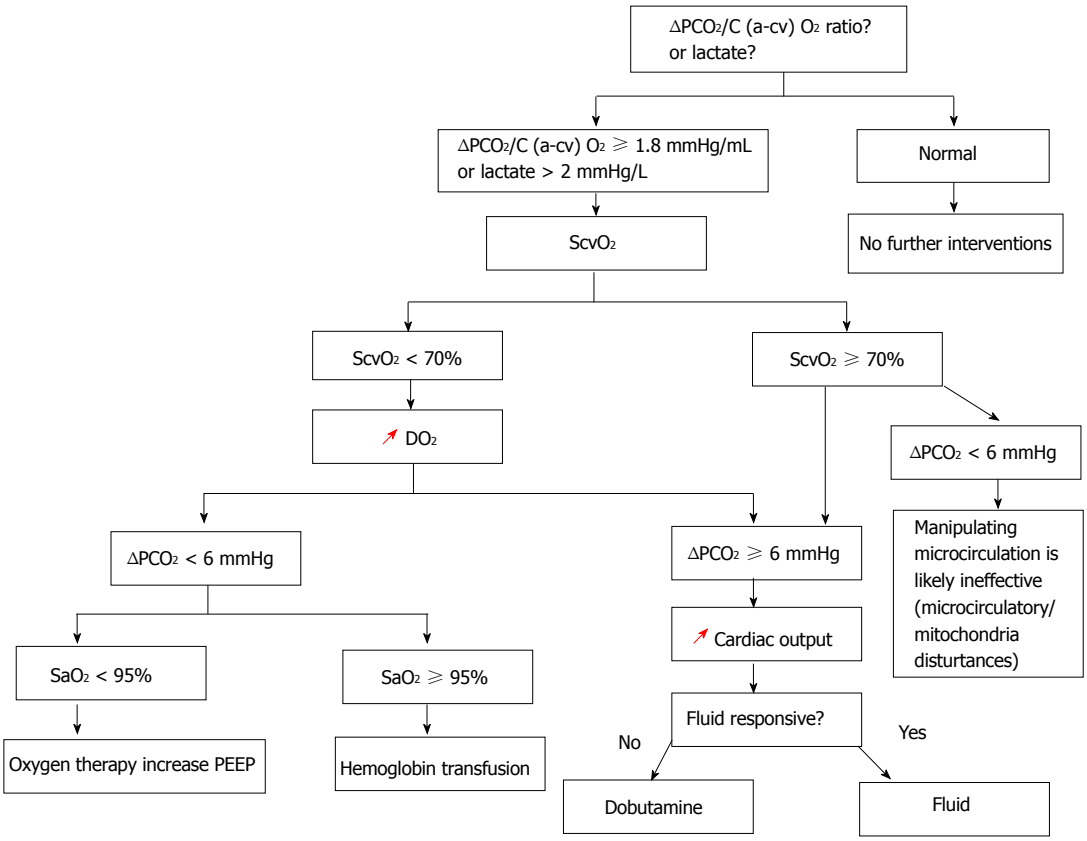

Figure 4 $ScvO_2$-ΔPCO_2 guided protocol. $ScvO_2$: Central venous oxygen saturation; ΔPCO_2: Central venous-to-arterial carbon dioxide tension difference; SaO_2: Arterial oxygen saturation; C (a-cv) O_2: Central arteriovenous oxygen content difference; DO_2: Oxygen delivery; PEEP: Positive end expiratory 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 ΔPCO_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 ΔPCO_2 with high cardiac output did not preclude the inadequacy of regional blood flow.

The change in ΔPCO_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, ΔPCO_2 along with $ScvO_2$ and O_2ER 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 β_1-adrenergic properties[61]. Recently, we showed that during the stepwise increase of dobutamine dose from 0-10 μg/kg per minute, ΔPCO_2 decreased in parallel with an increase in cardiac output. However, an unchanged ΔPCO_2 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, ΔPCO_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 ΔPCO_2. Accordingly, almost unaffected ΔPCO_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 ΔPCO_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 ΔPCO_2 and cardiac output is curvilinear, large variations in cardiac output will not necessary engender important variations in ΔPCO_2 (Figure 3). In other words, the interpretation should be cautious in case of high flow states.

Limitations of ΔPCO_2

There are many pre-analytical sources of errors in PCO_2 measurement that should be avoided to interpret ΔPCO_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 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 O_2-derived parameters

Under situations of tissue hypoxia, a drop in VO_2 is associated with a decline in aerobic CO_2 generation while an anaerobic CO_2 generation can still arise[36,37]. Therefore, the VCO_2 being reduced less than the VO_2, a rise of the respiratory quotient (VCO_2/VO_2 ratio) can be observed[37,63]. Therefore, the rise in the respiratory quotient was suggested to identify global tissue hypoxia[63]. Because VO_2 is equal to the product of cardiac output by the difference between arterial and mixed venous O_2 content C (a-mv) O_2, and VCO_2 is proportional to the product of cardiac output and P (v-a) CO_2 the P (v-a) CO_2/C (a-mv) O_2 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 DO_2. The authors found a good correlation between P (v-a) CO_2/C (a-mv) O_2 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) CO_2 alone and between blood lactate and C (a-mv) O_2 alone. Moreover, for a threshold value > 1.4 the P (v-a) CO_2/C (a-mv) O_2 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 [ΔPCO_2/C (a-cv) O_2], predicted an increase in VO_2 after a fluid-induced increase in DO_2 (VO_2/DO_2 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 $ScvO_2$. In a series of 60 fluid-responder patients, we recently found that ΔPCO_2/C (a-cv) O_2 ratio at baseline predicted accurately the presence of VO_2/DO_2 dependency phenomenon and better than blood lactate (unpublished data).

In a population of 35 septic shock patients with normalized mean arterial pressure and $ScvO_2$, Mesquida *et al*[66] showed that the presence of elevated ΔPCO_2/C (a-cv) O_2 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 ΔPCO_2/C (a-cv) O_2 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 CCO_2 difference/C (a-mv) O_2 ratio at baseline and six hours after resuscitation was an independent prognostic factor of 28 d mortality, but not P (v-a) CO_2/C (a-mv) O_2 ratio. The authors attributed this discrepancy to the fact that the PCO_2/CCO_2 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 CCO_2 difference/C (a-mv) O_2 ratio might not be equivalent to P (v-a) CO_2/C (a-mv) O_2 ratio.

From the results of those above studies[64-67], we believe that we can reasonably admit that the ΔPCO_2/C (a-cv) O_2 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 CO_2 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 O_2-derived parameters in order to calculate the ΔPCO_2/C (a-cv) O_2, which can be used to detect the presence of global anaerobic metabolism. In such situation, the presence of low $ScvO_2$ (< 70%) should push the physician to increase DO_2, 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 $ScvO_2$ (⩾ 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 $ScvO_2$ 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).

REFERENCES

1 **Cecconi M**, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014; **40**: 1795-1815 [PMID: 25392034 DOI: 10.1007/s00134-014-3525-z]

2 **Krafft P**, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest* 1993; **103**: 900-906 [PMID: 8449089]
3 **Schumacker PT**, Cain SM. The concept of a critical oxygen delivery. *Intensive Care Med* 1987; **13**: 223-229 [PMID: 3301969]
4 **Nelson DP**, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of systemic and intestinal O2 uptake during endotoxemia. *J Appl Physiol* (1985) 1988; **64**: 2410-2419 [PMID: 3136126]
5 **Zhang H**, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. *Circ Shock* 1993; **40**: 168-176 [PMID: 8348680]
6 **Bloos F**, Reinhart K. Venous oximetry. *Intensive Care Med* 2005; **31**: 911-913 [PMID: 15937678]
7 **Chawla LS**, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 2004; **126**: 1891-1896 [PMID: 15596689]
8 **Reinhart K**, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med* 2004; **30**: 1572-1578 [PMID: 15197435]
9 **Dueck MH**, Klimek M, Appenrodt S, Weigand C, Boerner U. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology* 2005; **103**: 249-257 [PMID: 16052106]
10 **Varpula M**, Karlsson S, Ruokonen E, Pettilä V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Med* 2006; **32**: 1336-1343 [PMID: 16826387]
11 **van Beest PA**, van Ingen J, Boerma EC, Holman ND, Groen H, Koopmans M, Spronk PE, Kuiper MA. No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin. *Crit Care* 2010; **14**: R219 [PMID: 21114844 DOI: 10.1186/cc9348]
12 **Martin C**, Auffray JP, Badetti C, Perrin G, Papazian L, Gouin F. Monitoring of central venous oxygen saturation versus mixed venous oxygen saturation in critically ill patients. *Intensive Care Med* 1992; **18**: 101-104 [PMID: 1613187]
13 **Edwards JD**, Mayall RM. Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. *Crit Care Med* 1998; **26**: 1356-1360 [PMID: 9710094]
14 **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169]
15 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]
16 **Yealy DM**, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683-1693 [PMID: 24635773 DOI: 10.1056/NEJMoa1401602]
17 **Peake SL**, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371**: 1496-1506 [PMID: 25272316 DOI: 10.1056/NEJMoa1404380]
18 **Mouncey PR**, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301-1311 [PMID: 25776532 DOI: 10.1056/NEJMoa1500896]
19 **Boulain T**, Garot D, Vignon P, Lascarrou JB, Desachy A, Botoc V, Follin A, Frat JP, Bellec F, Quenot JP, Mathonnet A, Dequin PF. Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. *Crit Care* 2014; **18**: 609 [PMID: 25529124 DOI: 10.1186/s13054-014-0609-7]
20 **Puskarich MA**, Trzeciak S, Shapiro NI, Heffner AC, Kline JA, Jones AE. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. *Resuscitation* 2011; **82**: 1289-1293 [PMID: 21752522 DOI: 10.1016/j.resuscitation.2011.06.015]
21 **Pope JV**, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; **55**: 40-46.e1 [PMID: 19854541 DOI: 10.1016/j.annemergmed.2009.08.014]
22 **Textoris J**, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, Leone M. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. *Crit Care* 2011; **15**: R176 [PMID: 21791065 DOI: 10.1186/cc10325]
23 **Gu WJ**, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med* 2015; **41**: 1862-1863 [PMID: 26154408 DOI: 10.1007/s00134-015-3955-2]
24 **Zhang Z**, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis*. *Crit Care Med* 2014; **42**: 2118-2125 [PMID: 24797375 DOI: 10.1097/CCM.0000000000000405]
25 **Jones AE**, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739-746 [PMID: 20179283 DOI: 10.1001/jama.2010.158]
26 **West JB**. Gas transport to the periphery: how gases are moved to the peripheral tissues? In: West JB, editor. Respiratory physiology. The essential. 4th ed. Williams & Wilkins: Baltimore, 1990: 69-85
27 **Lamia B**, Monnet X, Teboul JL. Meaning of arterio-venous PCO2 difference in circulatory shock. *Minerva Anestesiol* 2006; **72**: 597-604 [PMID: 16682934]
28 **Giovannini I**, Chiarla C, Boldrini G, Castagneto M. Calculation of venoarterial CO2 concentration difference. *J Appl Physiol* (1985) 1993; **74**: 959-964 [PMID: 8458820]
29 **McHardy GJ**. The relationship between the differences in pressure and content of carbon dioxide in arterial and venous blood. *Clin Sci* 1967; **32**: 299-309 [PMID: 6022823]
30 **Groeneveld AB**. Interpreting the venous-arterial PCO2 difference. *Crit Care Med* 1998; **26**: 979-980 [PMID: 9635634]
31 **Herve P**, Simonneau G, Girard P, Cerrina J, Mathieu M, Duroux P. Hypercapnic acidosis induced by nutrition in mechanically ventilated patients: glucose versus fat. *Crit Care Med* 1985; **13**: 537-540 [PMID: 3924480]
32 **Randall HM**, Cohen JJ. Anaerobic CO2 production by dog kidney in vitro. *Am J Physiol* 1966; **211**: 493-505 [PMID: 4288380]
33 **Zhang H**, Vincent JL. Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. *Am Rev Respir Dis* 1993; **148**: 867-871 [PMID: 8214940]
34 **von Planta M**, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Myocardial acidosis associated with CO2 production during cardiac arrest and resuscitation. *Circulation* 1989; **80**: 684-692 [PMID: 2504512]
35 **Kette F**, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Intramyocardial hypercarbic acidosis during cardiac arrest and resuscitation. *Crit Care Med* 1993; **21**: 901-906 [PMID: 8504660]
36 **Van der Linden P**, Rausin I, Deltell A, Bekrar Y, Gilbart E, Bakker J, Vincent JL. Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. *Anesth Analg* 1995; **80**: 269-275 [PMID: 7818112]
37 **Groeneveld AB**, Vermeij CG, Thijs LG. Arterial and mixed venous blood acid-base balance during hypoperfusion with incremental positive end-expiratory pressure in the pig. *Anesth Analg* 1991; **73**:

576-582 [PMID: 1952138]
38 **Rackow EC**, Astiz ME, Mecher CE, Weil MH. Increased venous-arterial carbon dioxide tension difference during severe sepsis in rats. *Crit Care Med* 1994; **22**: 121-125 [PMID: 8124954]
39 **Benjamin E**. Venous hypercarbia: a nonspecific marker of hypoperfusion. *Crit Care Med* 1994; **22**: 9-10 [PMID: 8124982]
40 **Weil MH**, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med* 1986; **315**: 153-156 [PMID: 3088448]
41 **Adrogué HJ**, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. *N Engl J Med* 1989; **320**: 1312-1316 [PMID: 2535633]
42 **Bowles SA**, Schlichtig R, Kramer DJ, Klions HA. Arteriovenous pH and partial pressure of carbon dioxide detect critical oxygen delivery during progressive hemorrhage in dogs. *J Crit Care* 1992; **7**: 95-105
43 **Teboul JL**, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. *Crit Care Med* 1998; **26**: 1007-1010 [PMID: 9635647]
44 **Vallet B**, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol* (1985) 2000; **89**: 1317-1321 [PMID: 11007564]
45 **Nevière R**, Chagnon JL, Teboul JL, Vallet B, Wattel F. Small intestine intramucosal PCO(2) and microvascular blood flow during hypoxic and ischemic hypoxia. *Crit Care Med* 2002; **30**: 379-384 [PMID: 11889315]
46 **Gutierrez G**. A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. *Am J Respir Crit Care Med* 2004; **169**: 525-533 [PMID: 14656752]
47 **Mecher CE**, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. *Crit Care Med* 1990; **18**: 585-589 [PMID: 2111753]
48 **Bakker J**, Vincent JL, Gris P, Leon M, Coffernils M, Kahn RJ. Veno-arterial carbon dioxide gradient in human septic shock. *Chest* 1992; **101**: 509-515 [PMID: 1735281]
49 **Creteur J**, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 2006; **32**: 516-523 [PMID: 16485092]
50 **Ospina-Tascón GA**, Bautista-Rincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, Bermúdez W, Granados M, Arango-Dávila C, Hernández G. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. *Crit Care* 2013; **17**: R294 [PMID: 24330804 DOI: 10.1186/cc13160]
51 **Richard C**, Monnet X, Teboul JL. Pulmonary artery catheter monitoring in 2011. *Curr Opin Crit Care* 2011; **17**: 296-302 [PMID: 21499096 DOI: 10.1097/MCC.0b013e3283466b85]
52 **Cuschieri J**, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med* 2005; **31**: 818-822 [PMID: 15803301]
53 **van Beest PA**, Lont MC, Holman ND, Loef B, Kuiper MA, Boerma EC. Central venous-arterial pCO2 difference as a tool in resuscitation of septic patients. *Intensive Care Med* 2013; **39**: 1034-1039 [PMID: 23559077 DOI: 10.1007/s00134-013-2888-x]
54 **Vallet B**, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! *Intensive Care Med* 2013; **39**: 1653-1655 [PMID: 23812340 DOI: 10.1007/s00134-013-2998-5]
55 **Vallée F**, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii K, Fourcade O, Genestal M. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med* 2008; **34**: 2218-2225 [PMID: 18607565 DOI: 10.1007/s00134-008-1199-0]
56 **Mallat J**, Pepy F, Lemyze M, Gasan G, Vangrunderbeeck N, Tronchon L, Vallet B, Thevenin D. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. *Eur J Anaesthesiol* 2014; **31**: 371-380 [PMID: 24625464 DOI: 10.1097/EJA.0000000000000064]
57 **Du W**, Liu DW, Wang XT, Long Y, Chai WZ, Zhou X, Rui X. Combining central venous-to-arterial partial pressure of carbon dioxide difference and central venous oxygen saturation to guide resuscitation in septic shock. *J Crit Care* 2013; **28**: 1110.e1-1110.e5 [PMID: 24216336 DOI: 10.1016/j.jcrc.2013.07.049]
58 **Hayes MA**, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330**: 1717-1722 [PMID: 7993413]
59 **Gattinoni L**, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med* 1995; **333**: 1025-1032 [PMID: 7675044]
60 **Mallat J**, Benzidi Y, Salleron J, Lemyze M, Gasan G, Vangrunderbeeck N, Pepy F, Tronchon L, Vallet B, Thevenin D. Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine. *Intensive Care Med* 2014; **40**: 404-411 [PMID: 24306082 DOI: 10.1007/s00134-013-3170-y]
61 **Ruffolo RR**. The pharmacology of dobutamine. *Am J Med Sci* 1987; **294**: 244-248 [PMID: 3310640]
62 **Mallat J**, Lazkani A, Lemyze M, Pepy F, Meddour M, Gasan G, Temime J, Vangrunderbeeck N, Tronchon L, Thevenin D. Repeatability of blood gas parameters, PCO2 gap, and PCO2 gap to arterial-to-venous oxygen content difference in critically ill adult patients. *Medicine* (Baltimore) 2015; **94**: e415 [PMID: 25621691 DOI: 10.1097/MD.0000000000000415]
63 **Cohen IL**, Sheikh FM, Perkins RJ, Feustel PJ, Foster ED. Effect of hemorrhagic shock and reperfusion on the respiratory quotient in swine. *Crit Care Med* 1995; **23**: 545-552 [PMID: 7874908]
64 **Mekontso-Dessap A**, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, Teboul JL. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. *Intensive Care Med* 2002; **28**: 272-277 [PMID: 11904655]
65 **Monnet X**, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, Persichini R, Anguel N, Richard C, Teboul JL. 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**: 1412-1420 [PMID: 23442986 DOI: 10.1097/CCM.0b013e318275cece]
66 **Mesquida J**, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, Artigas A. 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 [PMID: 25888382 DOI: 10.1186/s13054-015-0858-0]
67 **Ospina-Tascón GA**, Umaña M, Bermúdez W, Bautista-Rincón DF, Hernandez G, Bruhn A, Granados M, Salazar B, Arango-Dávila C, De Backer D. 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**: 796-805 [PMID: 25792204 DOI: 10.1007/s00134-015-3720-6]

P- Reviewer: Zhang ZH **S- Editor**: Qiu S **L- Editor**: A
E- Editor: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com