Review Article

How can CO_2-derived indices guide resuscitation in critically ill patients?

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Abstract: Assessing the adequacy of oxygen delivery with oxygen requirements is one of the key-goal of haemodynamic resuscitation. Clinical examination, lactate and central or mixed venous oxygen saturation (S_vO_2 and $S_{cv}O_2$, respectively) all have their limitations. Many of them may be overcome by the use of the carbon dioxide (CO_2)-derived variables. The venoarterial difference in CO_2 tension ("ΔPCO_2" or "PCO_2 gap") is not an indicator of anaerobic metabolism since it is influenced by the oxygen consumption. By contrast, it reliably indicates whether blood flow is sufficient to carry CO_2 from the peripheral tissue to the lungs in view of its clearance: it, thus, reflects the adequacy of cardiac output with the metabolic condition. The ratio of the PCO_2 gap with the arteriovenous difference of oxygen content (PCO_2 gap/$C_{a-v}O_2$) might be a marker of anaerobiosis. Conversely to S_vO_2 and $S_{cv}O_2$, it remains interpretable if the oxygen extraction is impaired as it is in case of sepsis. Compared to lactate, it has the main advantage to change without delay and to provide a real-time monitoring of tissue hypoxia.

Keywords: PCO_2 gap; cardiac output; tissue hypoxia; lactate; respiratory quotient

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Introduction

In patients with acute circulatory failure, one of the goals of the treatment is to increase cardiac output. The aim is to improve the oxygen delivery to the tissues and correct the mismatch between oxygen demand and supply, which is the hallmark of shock (1). However, no absolute normal value of cardiac output or oxygen delivery can be defined, as their adequate value basically depends on the tissue oxygen requirements. The correct value of cardiac output is the one that ensures a flow of oxygen that meets the metabolic demand (2,3). Then, any treatment aimed at changing cardiac output, such as fluid or inotropes, must be driven by the assessment of the adequacy between oxygen demand and supply.

To assess this adequacy, clinical examination has still a limited value. Signs of skin hypoperfusion do not reliably detect tissue hypoxia (4). Urine output may reflect the kidney perfusion, but it might be altered by many other factors during shock. Moreover, it depends on the presence or absence of a prior renal failure, and it cannot be used anymore as an indicator of the kidney perfusion in the case of acute tubular necrosis (5). Blood lactate may increase due to many processes not related to tissue oxygenation, leading to false positives (6). Furthermore, the blood lactate concentration depends on the balance between lactate production and lactate clearance, thus the delay required by its metabolism precludes one using it as a real-time marker

of tissue metabolism (7). Oxygen saturation of the mixed (S_vO_2) or the central ($S_{cv}O_2$) venous blood is often in the normal range in septic shock despite anaerobic metabolism, because of the alteration of tissue oxygen extraction (8).

In this context, the indices derived from the arterial and central or mixed venous blood partial tension in carbon dioxide (CO_2) were proposed to overcome many of the limitations of the previous variables to indicate the adequacy of oxygen supply and requirements (9).

The meaning of PCO_2 gap

What is the PCO_2 gap?

The difference between the mixed venous content (C_vCO_2) and the arterial content (C_aCO_2) of CO_2 reflects the balance between its production by the tissues and its elimination through the lungs. This venoarterial difference in CO_2 content (CCO_2) can be estimated at the bedside by the venoarterial difference in PCO_2 ($P_vCO_2 - P_aCO_2$), named PCO_2 gap or ΔPCO_2.

It is not possible to understand its clinical value without understanding how CO_2 is produced, transported and eliminated, in aerobic and anaerobic conditions.

CO_2 production

Under normoxic conditions, CO_2 is produced in the cells during oxidative metabolism. The CO_2 production (VCO_2) is directly related to the global O_2 consumption (VO_2) by the relation:

$$VCO_2 = R \times VO_2 \quad [1]$$

where R is the respiratory quotient. R may vary from 0.7 to 1 depending on the predominant energetic substrate (0.7 for lipids, 1 for carbohydrates). Therefore, under aerobic conditions, CO_2 production should increase either because the aerobic metabolism increases or, for a given VO_2, because more carbohydrates are used as energetic substrates.

Under hypoxic conditions, CO_2 is produced in the cells through buffering of excessively produced protons by local bicarbonate ions (HCO_3^-). Protons are generated by two mechanisms (10). First, CO_2 increases because of the hydrolysis of adenosine triphosphate and of adenosine diphosphate that occurs in anaerobic conditions. Second, a potential but minor source of CO_2 production under anaerobic conditions is the decarboxylation of some substrates produced by intermediate metabolism (α ketoglutarate or oxaloacetate) (10).

How is CO_2 transported?

CO_2 is transported in the blood in three forms: dissolved (10%), carried in bicarbonate ions (60%) and associated with proteins as carbamino compounds (30%). Compared to what happens for O_2, the dissolved form of CO_2 plays a more significant role in its transport because CO_2 is approximately 20 to 30 times more soluble than O_2. However, the main proportion of CO_2 is carried in bicarbonates, which result from the reaction of CO_2 and water molecules:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+ \quad [2]$$

From the tissues, CO_2 diffuses into the red blood cells, where erythrocytic carbonic anhydrase catalyses CO_2 hydration, converting most CO_2 and H_2O to HCO_3^- and H^+ (11). In the red blood cells, dissolved CO_2 can also be fixed by haemoglobin. This fixation depends on the oxidation state of haemoglobin, since CO_2 has a greater affinity for reduced than for oxygenated haemoglobin (12). This is called the "Haldane effect" (13,14). In the peripheral capillaries this phenomenon facilitates the loading of CO_2 by the blood, while O_2 is delivered to the tissues. By contrast, in the lungs, the Haldane effect enhances the unloading of CO_2 while O_2 is transferred to haemoglobin.

Finally, the carbamino compounds are formed by combining the CO_2 with the terminal NH_2 groups of proteins, especially with the globin of haemoglobin. This reaction is also favoured by haemoglobin deoxygenation.

How is CO_2 eliminated?

The three forms of CO_2 are carried by the blood flow to pulmonary circulation and eliminated by ventilation. Passive diffusion from the capillaries to the alveoli eliminates CO_2, depending on the difference in the gas tension between both spaces.

What is the relationship between CCO_2 and PCO_2?

Since CCO_2 results from the combination of the three forms by which CO_2 is transported, the formula to calculate it is complex and not practical for clinical purposes (15). In this regard, the possibility to derive CCO_2 from one single component, notably the PCO_2, is useful:

$$PCO_2 = k \times CCO_2 \quad [3]$$

The k value is influenced by the degree of blood pH, haematocrit and the arterial oxygen saturation (16-18) (*Figure 1*). As a matter of fact, the relationship between

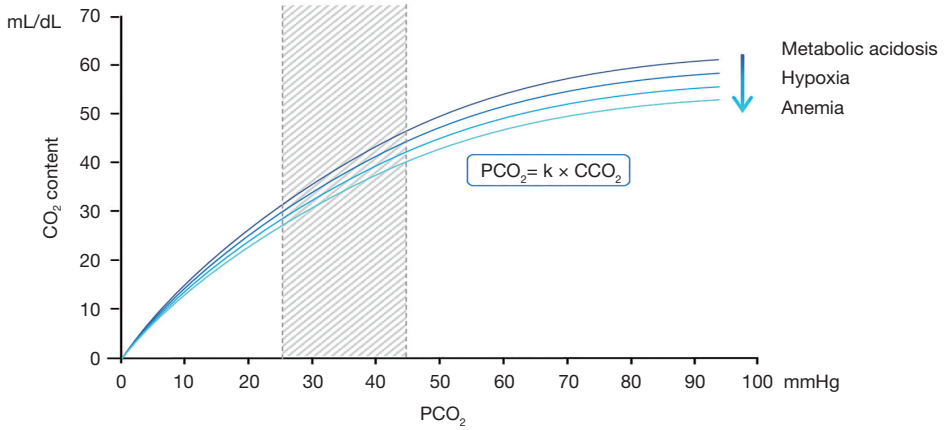

Figure 1 Relationship between content (CCO_2) and partial pressure (PCO_2) of carbon dioxide.

CCO_2 and PCO_2 is almost linear over the physiological range (*Figure 1*). Then, in clinical practice, the PCO_2 gap is an estimate of the difference between venous and arterial CO_2 content ($C_{v\text{-}a}CO_2$).

What are the determinants of the PCO_2 gap?

According to the Fick equation applied to CO_2, the CO_2 excretion (which equals CO_2 production—VCO_2—in steady state) equals the product of cardiac output by the difference between mixed venous CCO_2 (C_vCO_2) and arterial CCO_2 (C_aCO_2):

$$VCO_2 = \text{cardiac output} \times (C_vCO_2 - C_aCO_2) \quad [4]$$

As mentioned above, under physiological conditions, CCO_2 can be substituted by PCO_2 (PCO_2= k × CCO_2) so that:

$$\Delta PCO_2 = k \times (C_vCO_2 - C_aCO_2) \quad [5]$$

and

$$VCO_2 = \text{cardiac output} \times \Delta PCO_2/k \quad [6]$$

Thus, ΔPCO_2 can be calculated from a modified Fick equation:

$$\Delta PCO_2 = (k \times VCO_2)/\text{cardiac output} \quad [7]$$

where k is the factor cited above in the relationship between PCO_2 and CCO_2.

This relationship between ΔPCO_2 and cardiac output expresses the fact that, if cardiac output is low, the CO_2 clearance decreases, CO_2 stagnates at the venous side and P_vCO_2 increases relatively to P_aCO_2 at the venous level: this leads to an increase in the PCO_2 gap.

In other words, for a given VCO_2, a decrease in cardiac output results in an increased PCO_2 gap and *vice versa*. This was found by experimental studies in which, when cardiac output was gradually reduced under conditions of stable VO_2, the PCO_2 gap was observed to concomitantly increase (9,19). Conversely, in a clinical study performed in normolactatemic patients with cardiac failure, the increase in cardiac index induced by dobutamine was associated with a decrease in the PCO_2 gap, while VO_2 was unchanged (20).

How to use the PCO_2 gap in clinical practice?

Can ΔPCO_2 be used as a marker of tissue hypoxia? No!

During cardiac arrest large increases in ΔPCO_2 were reported suggesting that ΔPCO_2 can increase during tissue hypoxia (21,22). However, because of the physiologic facts explained above, ΔPCO_2 is not a straightforward indicator of anaerobic metabolism.

Indeed, in case of tissue hypoxia, ΔPCO_2 can increase, decrease or remain unchanged, since the determinants of ΔPCO_2 can change in opposite directions.

First, as mentioned above, the k factor (defining the relationship between PCO_2 and CCO_2) increases in case of tissue hypoxia, increasing the PCO_2 gap even if the venoarterial difference in CCO_2 does not change (artefactual increase of ΔPCO_2).

Second, during tissue hypoxia, CO_2 production should decrease as a result of the decrease in VO_2: the less O_2 is consumed, the less CO_2 is produced. In an animal study where cardiac output was experimentally decreased by tamponade, Zhang and Vincent observed that, below a critical level of O_2 delivery, the further decrease in both cardiac output and O_2 delivery resulted in a progressive decrease in VCO_2 along with the decrease in VO_2 (9).

Since during tissue hypoxia, k must increase (tending

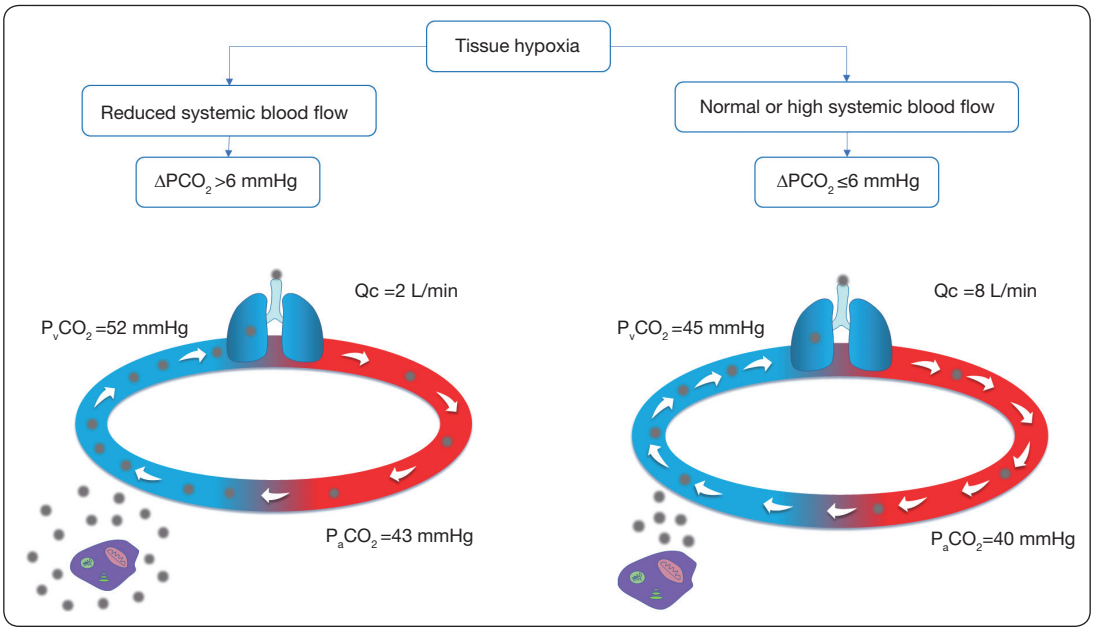

Figure 2 Illustration of the influence of cardiac output on the amplitude of the venoarterial difference of carbon dioxide partial pressure. P_aCO_2, arterial partial pressure in carbon dioxide; P_vCO_2, venous partial pressure in carbon dioxide; Qc, cardiac output; ΔPCO_2, venoarterial difference of carbon dioxide partial pressure.

to increase ΔPCO_2) and VCO_2 must decrease (tending to decrease ΔPCO_2), the resultant effect on ΔPCO_2 will mainly depend on cardiac output [$\Delta PCO_2 = (k \times VCO_2)$/cardiac output] (23).

Therefore, two situations should be distinguished: tissue hypoxia with reduced blood flow and tissue hypoxia with preserved or high blood flow (*Figure 2*).

In cases of *tissue hypoxia with reduced systemic blood flow*, P_vCO_2 increases relatively to P_aCO_2 due to the venous stagnation phenomenon, which increases ΔPCO_2. In this regard, in experimental studies where tissue hypoxia was induced by reducing blood flow, high values of ΔPCO_2 were found (19,24).

On the other hand, in cases of *tissue hypoxia with preserved or high systemic blood flow* ΔPCO_2 should be normal or even reduced. The high efferent venous blood flow should be sufficient to wash out the CO_2 produced by the tissues, preventing stagnation and ΔPCO_2 increase.

Results from several clinical studies have supported this hypothesis. Bakker *et al.* (25) found that most patients with septic shock had a ΔPCO_2 ≤6 mmHg. Cardiac index obtained in this subgroup of patients was significantly higher than that obtained in the subgroup of patients with a ΔPCO_2 >6 mmHg. Interestingly, the two subgroups did not differ in terms of blood lactate. Although VCO_2 and VO_2 were not directly measured, these data suggest that differences in CO_2 production did not account for differences in ΔPCO_2. In other words, many patients had a normal ΔPCO_2 despite tissue hypoxia, probably because their high blood flow had easily removed CO_2 produced by the tissues. Similar findings were reported by Mecher *et al.* (26). Clearly, these latter studies (25,26) underline the poor sensitivity of ΔPCO_2 to detect tissue hypoxia.

Normal or low ΔPCO_2 values were also reported in hypotensive patients with fulminant hepatic failure with tissue hypoxia, as strongly suggested by the increase in VO_2 after prostacyclin infusion (27). At baseline ΔPCO_2 was very low, which was probably due to the fact that VCO_2 was low—as suggested by the low VO_2—and that cardiac output was very high. These findings strongly support the fact that high flow states shock should result in a decrease, rather than an increase, of the PCO_2 gap.

The major role of cardiac output in the value of ΔPCO_2 was demonstrated in animal studies that compared ΔPCO_2 changes between models of ischemic hypoxia and models of hypoxic hypoxia (28,29). Ischemic hypoxia was created by reducing blood flow using progressive bleeding in pigs (28) or in sheep (29). Hypoxic hypoxia was created either by a

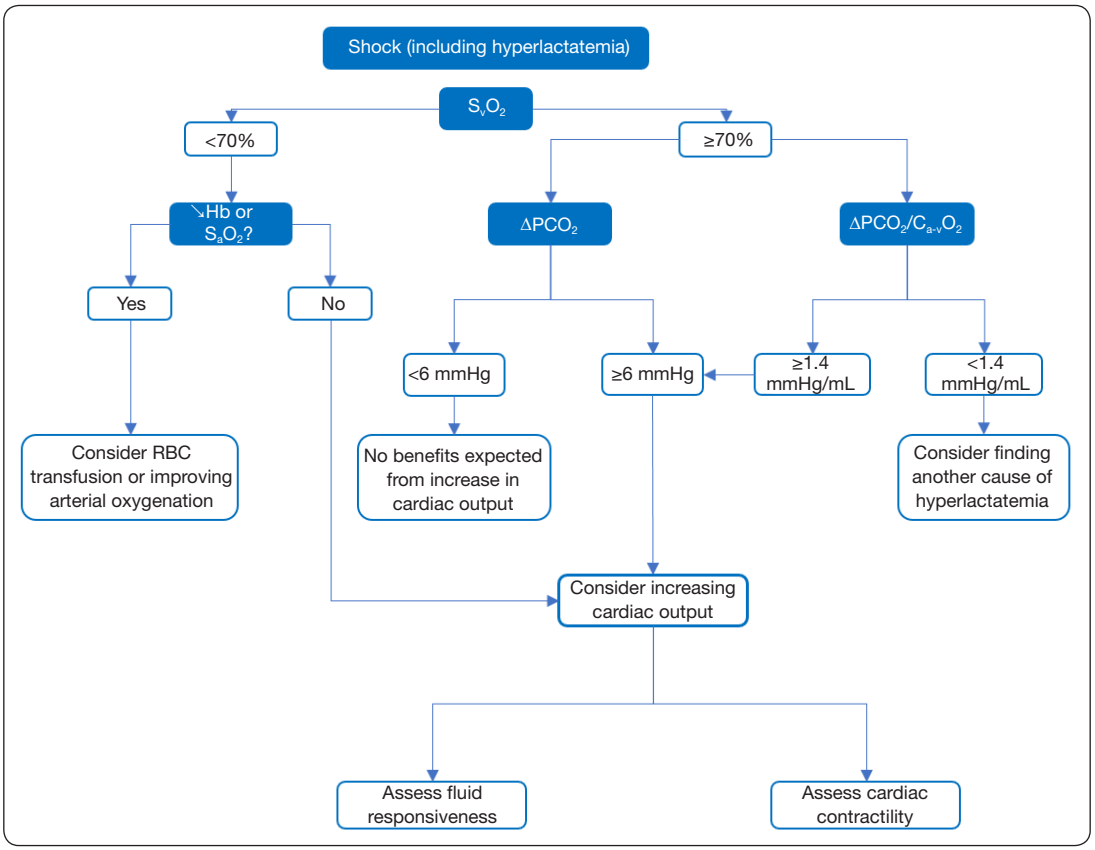

Figure 3 Interpretation of indices of tissue oxygenation. Hb, haemoglobin; S_vO_2, venous oxygen saturation; S_aO_2, arterial oxygen saturation; $C_{a-v}O_2$, arteriovenous difference in oxygen content; ΔPCO_2, venoarterial difference in carbon dioxide partial pressure.

progressive reduction of inspired oxygen concentration (28) or by progressive intratracheal instillation of hydrochloric acid (29). In both studies, cardiac output remained unchanged in the hypoxic hypoxia group. Significantly, ΔPCO_2 increased in the ischemic hypoxia group whereas it remained unchanged in the hypoxic hypoxia group (28,29). Similar results were reported by Vallet *et al.* in a model of vascular isolated dog hind limb (30). Indeed, ΔPCO_2 significantly increased when limb hypoxia was induced by ischemia while it remained unchanged when hypoxia was induced by hypoxemia with maintained limb blood flow (30).

All these experimental (28-30) and clinical (25-27) studies have confirmed that during tissue hypoxia, ΔPCO_2 can be either high or normal depending on cardiac output. Thus, a normal ΔPCO_2 cannot exclude the absence of tissue hypoxia in high blood flow states. On the other hand, ΔPCO_2 can be elevated in cases of low cardiac output, even in the absence of tissue hypoxia.

In summary, how to interpret the PCO_2 gap in practice?

An increased PCO_2 gap (>6 mmHg) suggests that cardiac output is not high enough with respect to the global metabolic conditions:

- In cases of shock (e.g., increased blood lactate), a high PCO_2 gap could prompt clinicians to increase cardiac output with the aim of reducing tissue hypoxia (*Figure 3*);
- In the absence of shock, a high PCO_2 gap can be associated with an increased oxygen demand.

In a patient with a high initial value of ΔPCO_2, following the time-course of ΔPCO_2 can also be helpful to assess the global metabolic effects of a therapy aiming at increasing cardiac output. Under conditions of oxygen supply-dependency, when cardiac output increases, the decrease in anaerobic metabolism tends to decrease ΔPCO_2 but the increase in VO_2 tends to increase ΔPCO_2. As a result, ΔPCO_2 is expected to decrease to a lesser extent than in

$$\text{Respiratory quotient}=\frac{CO_2\text{produced}}{O_2\text{consumed}}=\frac{VCO_2\times K}{VO_2}=\frac{\text{Cardiac output}\times C_{v\text{-}a}CO_2}{\text{Cardiac output}\times C_{a\text{-}v}O_2}\approx\frac{\text{Cardiac output}\times P_{v\text{-}a}CO_2}{\text{Cardiac output}\times C_{a\text{-}v}O_2}=\frac{PCO_2\text{gap}}{C_{a\text{-}v}O_2}$$

Figure 4 Estimation of the respiratory quotient from the ratio between venoarterial difference in carbon dioxide partial pressure and arteriovenous difference in oxygen content. $C_{a\text{-}v}O_2$, arteriovenous difference in oxygen content; CO_2, carbon dioxide; $C_{v\text{-}a}CO_2$, venoarterial difference in carbon dioxide content; $P_{v\text{-}a}CO_2$, venoarterial difference in carbon dioxide partial pressure.

the case of oxygen supply independence. Consequently, unchanged ΔPCO_2 with therapy should not mean that the therapy has failed but rather that the treatment should be intensified until obtaining a frank decrease in ΔPCO_2, indicating that the critical level of O_2 delivery has been actually overcome.

On the other hand, a normal PCO_2 gap (≤6 mmHg) suggests that cardiac output is high enough to wash out the amount of the CO_2 produced from the peripheral tissues (*Figure 2*). Thus, increasing cardiac output has little chance to improve global oxygenation and such a strategy should not be a priority.

Combined analysis of ΔPCO_2 and oxygen-derived variables

Even though ΔPCO_2 cannot directly identify the presence of anaerobic metabolism, its combination with oxygen-derived variables has been suggested to overcome this issue (31). Indeed, as mentioned above, in case of anaerobic metabolism, VCO_2 tends to increase because of the buffering of excessively produced protons, but also tends to decrease because of the decrease in VO_2. Then, indexing VCO_2 by VO_2 should help detect the excess in CO_2 produced due to the occurrence of anaerobic metabolism. In other words, dividing VCO_2 by VO_2 may help detect the production of CO_2 which is not due to VO_2.

The issue is then to estimate the ratio VCO_2/VO_2 at the bedside. As shown on *Figure 4*, using the Fick equation, and substituting CCO_2 by PCO_2, as suggested above, this ratio can be estimated by the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio, where $C_{a\text{-}v}O_2$ stands for the arteriovenous difference in O_2 content.

In a series of 89 critically ill patients (148 measurements) where the mixed venous blood was sampled through a pulmonary catheter, a close correlation was found between blood lactate concentration and the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio, while no correlation was found between blood lactate concentration and ΔPCO_2 alone and between blood lactate concentration and $C_{a\text{-}v}O_2$ alone (31). Similarly, in 51 septic shock patients, Monnet *et al.* showed a significant correlation between blood lactate and the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio when the venous blood gas analysis was performed on the central, not the mixed venous blood (8). Similar results were found by Mesquida *et al.* who also demonstrated an increased mortality among patients with higher $\Delta PCO_2/C_{a\text{-}v}O_2$ ratios, whereas no difference was observed for ΔPCO_2 and $S_{cv}O_2$ (32).

In summary, an increase in the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio above 1.4 mmHg/mL (31,32) should be considered as a marker of global anaerobic metabolism. Its normalization during resuscitation has been suggested as a therapeutic target (33). In the latter study, only lactate and $\Delta PCO_2/C_{a\text{-}v}O_2$ resulted to be independently associated to mortality at multivariate analysis, among a series of haemodynamic variables in septic shock. Furthermore, mortality was significantly higher among patients with increase in both lactate and $\Delta PCO_2/C_{a\text{-}v}O_2$, compared to the one of those with only elevated lactate levels and a normal $\Delta PCO_2/C_{a\text{-}v}O_2$.

$S_{cv}O_2$ *vs.* PCO_2-derived indices

An advantage of the PCO_2 gap over $S_{cv}O_2$ is that it remains a valid marker of the adequacy of cardiac output to the metabolic conditions even if the microcirculation is injured and the oxygen extraction is impaired. This could be due to the fact that CO_2 is about 20 times more soluble than O_2 (34). The microcirculatory impairment, with large venoarterial shunts, impedes the diffusion of O_2 between cells and red blood cells, while the diffusion of CO_2 remains unaltered (34). A confirmation comes from the study performed by Ospina-Tascón *et al.*, where, in the early phases of septic shock, ΔPCO_2 was actually able to detect the adequacy of microvascular blood flow (35).

Aiming at illustrating the superiority of the PCO_2 gap over S_vO_2, Vallée *et al.* included 50 septic shock patients where a $S_{cv}O_2$ higher than 70% had been achieved (36). The central venous PCO_2-arterial PCO_2 difference (PCO_2 gap) was abnormally high (>6 mmHg) in half of the patients (36).

In that subgroup, blood lactate level tended to be higher and cardiac output to be lower compared to patients with a central PCO_2 gap ≤6 mmHg. The authors concluded that $S_{cv}O_2$ may not be sufficient to guide therapy and that, when the 70% $S_{cv}O_2$ value is reached, the presence of a central PCO_2 gap >6 mmHg might be useful to identify patients who still remain inadequately resuscitated (36). Another study showed that the combination of $S_{cv}O_2$ and central PCO_2 gap predicted outcome in 172 critically ill patients resuscitated from septic shock better than $S_{cv}O_2$ alone (37). Patients who met both targets appeared to clear lactate more efficiently (37). Similar results were reported in a series of septic shock patients (38).

Regarding the comparison of $S_{cv}O_2$ with the central $\Delta PCO_2/C_{a-v}O_2$ ratio, our team performed a study where 51 critically ill patients received fluid (8). In patients in whom volume expansion increased cardiac output, central PCO_2 gap was able to follow the changes in cardiac output. Among patients in whom cardiac output increased, VO_2 increased in around half of the cases (indicating dependency between VO_2 and O_2 delivery) while VO_2 remained stable in the other ones (indicating independence between VO_2 and O_2 delivery). The increase of VO_2 was detected by changes in the $\Delta PCO_2/C_{a-v}O_2$ ratio but not by the changes in ΔPCO_2 (8). Interestingly, in our cohort, $S_{cv}O_2$ could not detect changes in VO_2, because it included a large proportion of septic shock patients in whom $S_{cv}O_2$ was in the normal range due to oxygen extraction impairment. This confirmed the superiority of the $\Delta PCO_2/C_{a-v}O_2$ ratio over $ScvO_2$ to detect tissue hypoxia in septic shock patients. Finally, the changes in lactate were also able to detect changes in VO_2. However, lactate was measured three hours after fluid administration while the $\Delta PCO_2/C_{a-v}O_2$ ratio was measured immediately after its end (8). This suggests that one advantage of the $\Delta PCO_2/C_{a-v}O_2$ ratio over lactate is that it changes immediately after changes in VO_2. However, Mallat *et al.* observed in septic shock patients that the increase in VO_2 after volume expansion was detected much better by both the $\Delta PCO_2/C_{a-v}O_2$ and the $C_{v-a}CO_2/C_{a-v}O_2$ ratio than by blood lactate (39).

In summary, all these arguments suggest that, in case of septic shock with O_2 extraction impairment, in contrast with S_vO_2 or $S_{cv}O_2$, ΔPCO_2remains a reliable marker of the adequacy of cardiac output with the metabolic condition and that the $\Delta PCO_2/C_{a-v}O_2$ ratio remains a valid indicator of the adequacy between O_2 delivery and VO_2. Moreover, compared to lactate, the CO_2-derived variables have the advantage to change without delay and to follow the metabolic condition in real time.

Errors and pitfalls of the PCO_2 gap

Although many studies confirmed the association between an elevation in both ΔPCO_2 and $\Delta PCO_2/C_{a-v}O_2$ ratio and poor outcome in terms of lactate clearance, changes in VO_2 and mortality (40-42), some other ones showed a limited or even a negative correlation between elevated ΔPCO_2 and increase in blood lactate or mortality (43-45). Part of the discrepancy might be related to the fact that the latter studies were performed in post-cardiac surgery patients.

Haemodilution was recently investigated by Dubin *et al.* in an experimental model (46): the reliability of the $\Delta PCO_2/C_{a-v}O_2$ ratio was compared between sheep with progressive haemorrhage and sheep with progressive haemodilution. Interestingly, the authors observed that in the haemodilution group, the $\Delta PCO_2/C_{a-v}O_2$ ratio increased despite the absence of anaerobic metabolism. These findings, together with the high correlation with haemoglobin changes (R^2=0.79; P<0.001), suggest that changes were explained by a rightward shift of the relationship between PCO_2 and CCO_2 (46).

In this regard, conflicting results have been reported also in terms of prognostic value of $\Delta PCO_2/C_{a-v}O_2$ and $\Delta CCO_2/C_{a-v}O_2$: while some authors observed that the $\Delta CCO_2/C_{a-v}O_2$ ratio was an independent predictor of mortality, contrary to the $\Delta PCO_2/C_{a-v}O_2$ ratio (33), others observed that the $\Delta PCO_2/C_{a-v}O_2$ ratio but not the $\Delta CCO_2/C_{a-v}O_2$ was associated with increased mortality (42).

Other authors investigated possible causes of misleading interpretation of both ΔPCO_2 and the $\Delta PCO_2/C_{a-v}O_2$ ratio. Mallat *et al.* showed that hyperventilation creates an increase in ΔPCO_2 in healthy volunteers (47). Saludes *et al.* tested the effects of a hyperoxygenation trial on ΔPCO_2 (48), and observed that, even though oxygen parameters increased both on the arterial and venous side, PCO_2 augmented only in the venous blood, leading to an increase in both ΔPCO_2 and $\Delta PCO_2/C_{a-v}O_2$ ratio which was probably not related to changes in blood flow (48).

In addition, some technical aspects should be kept in mind when these indices are used in clinical practice. First, some errors in the PCO_2 gap measurements may occur when sampling the venous blood: incorrect sample container, contaminated sample by air or venous blood or catheter fluid (49). Second, a too long delay of transport of blood sampling may significantly change the blood gas content at the venous and the arterial site (50).

Third, it is important to remind that variations in both ΔPCO_2 and the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio are submitted to a certain degree of variability. In this regard, in a series of 192 patients, Mallat *et al.* showed that the smallest detectable difference of ΔPCO_2 was ±1.8 mmHg, corresponding to a least significant change of 32%. For the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio, the smallest detectable difference was ±0.57 mmHg/mL, corresponding to a least significant change of 38% (51).

Conclusions

A proper analysis of the physiology of CO_2 metabolism reveals that the PCO_2 gap indicates the adequacy of cardiac output with the metabolic condition while the adequacy between O_2 delivery and O_2 consumption is better indicated by the $\Delta PCO_2/C_{a\text{-}v}O_2$ ratio in critically ill patients. The CO_2-derived indices seem to be quite reliable when measured in the central venous blood. In contrast to S_vO_2 or $S_{cv}O_2$, they remain useful in septic shock patients with an impaired O_2 extraction.

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None.

Footnote

Conflicts of Interest: JL Teboul and X Monnet are members of the Medical Advisory Board of Pulsion Medical Systems, Getinge. F Gavelli has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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