How can CO₂-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 (S₅O₂ and SₓO₂, respectively) all have their limitations. Many of them may be overcome by the use of the carbon dioxide (CO₂)-derived variables. The venoarterial difference in CO₂ tension (“ΔPCO₂” or “PCO₂ 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 CO₂ 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 PCO₂ gap with the arteriovenous difference of oxygen content (PCO₂ gap/Cₐ-vO₂) might be a marker of anaerobiosis. Conversely to S₅O₂ and SₓO₂, 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: PCO₂ 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,O₂) or the central (S,c,O₂) 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 (CO₂) 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 PCO₂ gap

What is the PCO₂ gap?

The difference between the mixed venous content (Cv,CO₂) and the arterial content (Ca,CO₂) of CO₂ reflects the balance between its production by the tissues and its elimination through the lungs. This venoarterial difference in CO₂ content (CCO₂) can be estimated at the bedside by the venoarterial difference in PCO₂ (Pv,CO₂ − Pa,CO₂), named PCO₂ gap or ΔPCO₂.

It is not possible to understand its clinical value without understanding how CO₂ is produced, transported and eliminated, in aerobic and anaerobic conditions.

CO₂ production

Under normoxic conditions, CO₂ is produced in the cells during oxidative metabolism. The CO₂ production (VCO₂) is directly related to the global O₂ consumption (VO₂) by the relation:

\[ VCO₂ = R \times VO₂ \]  

[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, CO₂ production should increase either because the aerobic metabolism increases or, for a given VO₂, because more carbohydrates are used as energetic substrates.

Under hypoxic conditions, CO₂ is produced in the cells through buffering of excessively produced protons by local bicarbonate ions (HCO₃⁻). Protons are generated by two mechanisms (10). First, CO₂ increases because of the hydrolysis of adenosine triphosphate and of adenosine diphosphate that occurs in anaerobic conditions. Second, a potential but minor source of CO₂ production under anaerobic conditions is the decarboxylation of some substrates produced by intermediate metabolism (α-ketoglutarate or oxaloacetate) (10).

How is CO₂ transported?

CO₂ 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 O₂, the dissolved form of CO₂ plays a more significant role in its transport because CO₂ is approximately 20 to 30 times more soluble than O₂. However, the main proportion of CO₂ is carried in bicarbonates, which result from the reaction of CO₂ and water molecules:

\[ CO₂ + H₂O ↔ H₂CO₃ ↔ HCO₃⁻ + H⁺ \]  

[2]

From the tissues, CO₂ diffuses into the red blood cells, where erythrocytic carbonic anhydrase catalyses CO₂ hydration, converting most CO₂ and H₂O to HCO₃⁻ and H⁺ (11). In the red blood cells, dissolved CO₂ can also be fixed by haemoglobin. This fixation depends on the oxidation state of haemoglobin, since CO₂ 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 CO₂ by the blood, while O₂ is delivered to the tissues. By contrast, in the lungs, the Haldane effect enhances the unloading of CO₂ while O₂ is transferred to haemoglobin.

Finally, the carbamino compounds are formed by combining the CO₂ with the terminal NH₃ groups of proteins, especially with the globin of haemoglobin. This reaction is also favoured by haemoglobin deoxygenation.

How is CO₂ eliminated?

The three forms of CO₂ are carried by the blood flow to pulmonary circulation and eliminated by ventilation. Passive diffusion from the capillaries to the alveoli eliminates CO₂, depending on the difference in the gas tension between both spaces.

What is the relationship between CCO₂ and PCO₂?

Since CCO₂ results from the combination of the three forms by which CO₂ is transported, the formula to calculate it is complex and not practical for clinical purposes (15). In this regard, the possibility to derive CCO₂ from one single component, notably the PCO₂, is useful:

\[ PCO₂ = k \times CCO₂ \]  

[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
Carbon dioxide in shock states

CCO₂ and PCO₂ is almost linear over the physiological range (Figure 1). Then, in clinical practice, the PCO₂ gap is an estimate of the difference between venous and arterial CO₂ content (Cv-aCO₂).

What are the determinants of the PCO₂ gap?

According to the Fick equation applied to CO₂, the CO₂ excretion (which equals CO₂ production—VCO₂—in steady state) equals the product of cardiac output by the difference between mixed venous CCO₂ (CvCO₂) and arterial CCO₂ (CaCO₂):

\[ VCO₂ = \text{cardiac output} \times (CvCO₂ - CaCO₂) \]  \[ 4 \]

As mentioned above, under physiological conditions, CCO₂ can be substituted by PCO₂ (PCO₂ = k × CCO₂) so that:

\[ \Delta \text{PCO₂} = k \times (CvCO₂ - CaCO₂) \]  \[ 5 \]

and

\[ VCO₂ = \text{cardiac output} \times \Delta \text{PCO₂}/k \]  \[ 6 \]

Thus, ΔPCO₂ can be calculated from a modified Fick equation:

\[ \Delta \text{PCO₂} = (k \times VCO₂)/\text{cardiac output} \]  \[ 7 \]

where k is the factor cited above in the relationship between PCO₂ and CCO₂.

This relationship between ΔPCO₂ and cardiac output expresses the fact that, if cardiac output is low, the CO₂ clearance decreases, CO₂ stagnates at the venous side and P₂CO₂ increases relatively to P₁CO₂ at the venous level: this leads to an increase in the PCO₂ gap.

In other words, for a given VCO₂, a decrease in cardiac output results in an increased PCO₂ gap and vice versa. This was found by experimental studies in which, when cardiac output was gradually reduced under conditions of stable VO₂, the PCO₂ 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 PCO₂ gap, while VO₂ was unchanged (20).

How to use the PCO₂ gap in clinical practice?

Can ΔPCO₂ be used as a marker of tissue hypoxia? No!

During cardiac arrest large increases in ΔPCO₂ were reported suggesting that ΔPCO₂ can increase during tissue hypoxia (21,22). However, because of the physiologic facts explained above, ΔPCO₂ is not a straightforward indicator of anaerobic metabolism.

Indeed, in case of tissue hypoxia, ΔPCO₂ can increase, decrease or remain unchanged, since the determinants of ΔPCO₂ can change in opposite directions.

First, as mentioned above, the k factor (defining the relationship between PCO₂ and CCO₂) increases in case of tissue hypoxia, increasing the PCO₂ gap even if the venoarterial difference in CCO₂ does not change (artefactual increase of ΔPCO₂).

Second, during tissue hypoxia, CO₂ production should decrease as a result of the decrease in VO₂: the less O₂ is consumed, the less CO₂ is produced. In an animal study where cardiac output was experimentally decreased by tamponade, Zhang and Vincent observed that, below a critical level of O₂ delivery, the further decrease in both cardiac output and O₂ delivery resulted in a progressive decrease in VCO₂ along with the decrease in VO₂ (9). Since during tissue hypoxia, k must increase (tending...
to increase ∆PCO$_2$ and VCO$_2$ must decrease (tending to decrease ∆PCO$_2$), the resultant effect on ∆PCO$_2$ will mainly depend on cardiac output \[ ∆PCO_2 = \frac{k \times VCO_2}{\text{cardiac output}} \] (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$_{aCO_2}$ increases relatively to P$_{vCO_2}$ due to the venous stagnation phenomenon, which increases ∆PCO$_2$. In this regard, in experimental studies where tissue hypoxia was induced by reducing blood flow, high values of ∆PCO$_2$ were found (19,24).

On the other hand, in cases of tissue hypoxia with preserved or high systemic blood flow ∆PCO$_2$ 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 ∆PCO$_2$ increase.

Results from several clinical studies have supported this hypothesis. Bakker et al. (25) found that most patients with septic shock had a ∆PCO$_2$ ≤6 mmHg. Cardiac index obtained in this subgroup of patients was significantly higher than that obtained in the subgroup of patients with a ∆PCO$_2$ >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 ∆PCO$_2$. In other words, many patients had a normal ∆PCO$_2$ 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 ∆PCO$_2$ to detect tissue hypoxia.

Normal or low ∆PCO$_2$ 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 ∆PCO$_2$ 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 ∆PCO$_2$ was demonstrated in animal studies that compared ∆PCO$_2$ 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
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, ∆PCO2 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, ∆PCO2 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, ∆PCO2 can be either high or normal depending on cardiac output. Thus, a normal ∆PCO2 cannot exclude the absence of tissue hypoxia in high blood flow states. On the other hand, ∆PCO2 can be elevated in cases of low cardiac output, even in the absence of tissue hypoxia.

In summary, how to interpret the PCO2 gap in practice?

An increased PCO2 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 PCO2 gap could prompt clinicians to increase cardiac output with the aim of reducing tissue hypoxia (Figure 3);
- In the absence of shock, a high PCO2 gap can be associated with an increased oxygen demand.

In a patient with a high initial value of ∆PCO2, following the time-course of ∆PCO2 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 ∆PCO2 but the increase in VO2 tends to increase ∆PCO2. As a result, ∆PCO2 is expected to decrease to a lesser extent than in...
the case of oxygen supply independence. Consequently, unchanged ΔPCO₂ with therapy should not mean that the therapy has failed but rather that the treatment should be intensified until obtaining a frank decrease in ΔPCO₂, indicating that the critical level of O₂ delivery has been actually overcome.

On the other hand, a normal PCO₂ gap (≤ 6 mmHg) suggests that cardiac output is high enough to wash out the amount of the CO₂ 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 ΔPCO₂ and oxygen-derived variables**

Even though ΔPCO₂ 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, VCO₂ tends to increase because of the buffering of excessively produced protons, but also tends to decrease because of the decrease in VO₂. Then, indexing VCO₂ by VO₂ should help detect the excess in CO₂ produced due to the occurrence of anaerobic metabolism. In other words, dividing VCO₂ by VO₂ may help detect the production of CO₂ which is not due to VO₂.

The issue is then to estimate the ratio VCO₂/VO₂ at the bedside. As shown on Figure 4, using the Fick equation, and substituting CCO₂ by PCO₂, as suggested above, this ratio can be estimated by the ΔPCO₂/Cvₐ,O₂ ratio, where Cvₐ,O₂ stands for the arteriovenous difference in O₂ 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 ΔPCO₂/Cvₐ,O₂ ratio, while no correlation was found between blood lactate concentration and ΔPCO₂ alone and between blood lactate concentration and Cvₐ,O₂ alone (31). Similarly, in 51 septic shock patients, Monnet et al. showed a significant correlation between blood lactate and the ΔPCO₂/Cvₐ,O₂ 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 ΔPCO₂/Cvₐ,O₂ ratios, whereas no difference was observed for ΔPCO₂ and Sv, O₂ (32).

In summary, an increase in the ΔPCO₂/Cvₐ,O₂ 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 ΔPCO₂/Cvₐ,O₂ 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 ΔPCO₂/Cvₐ,O₂, compared to the one of those with only elevated lactate levels and a normal ΔPCO₂/Cvₐ,O₂.

**Sv, O₂ vs. PCO₂-derived indices**

An advantage of the PCO₂ gap over Sv, O₂ 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 CO₂ is about 20 times more soluble than O₂ (34). The microcirculatory impairment, with large venoarterial shunts, impedes the diffusion of O₂ between cells and red blood cells, while the diffusion of CO₂ remains unaltered (34). A confirmation comes from the study performed by Ospina-Tascón et al., where, in the early phases of septic shock, ΔPCO₂ was actually able to detect the adequacy of microvascular blood flow (35).

Aiming at illustrating the superiority of the PCO₂ gap over Sv, O₂, Vallée et al. included 50 septic shock patients where a Sv, O₂ higher than 70% had been achieved (36). The central venous PCO₂-arterial PCO₂ difference (PCO₂ 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\textsubscript{2} gap ≤ 6 mmHg. The authors concluded that S\textsubscript{a}O\textsubscript{2} may not be sufficient to guide therapy and that, when the 70% S\textsubscript{a}O\textsubscript{2} value is reached, the presence of a central PCO\textsubscript{2} gap > 6 mmHg might be useful to identify patients who still remain inadequately resuscitated (36). Another study showed that the combination of S\textsubscript{a}O\textsubscript{2} and central PCO\textsubscript{2} gap predicted outcome in 172 critically ill patients resuscitated from septic shock better than S\textsubscript{a}O\textsubscript{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\textsubscript{a}O\textsubscript{2} with the central ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{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\textsubscript{2} gap was able to follow the changes in cardiac output. Among patients in whom cardiac output increased, VO\textsubscript{2} increased in around half of the cases (indicating dependency between VO\textsubscript{2} and O\textsubscript{2} delivery) while VO\textsubscript{2} remained stable in the other ones (indicating independence between VO\textsubscript{2} and O\textsubscript{2} delivery). The increase of VO\textsubscript{2} was detected by changes in the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio but not by the changes in ΔPCO\textsubscript{2} (8). Interestingly, in our cohort, S\textsubscript{a}O\textsubscript{2} could not detect changes in VO\textsubscript{2}, because it included a large proportion of septic shock patients in whom S\textsubscript{a}O\textsubscript{2} was in the normal range due to oxygen extraction impairment. This confirmed the superiority of the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio over ScvO\textsubscript{2} to detect tissue hypoxia in septic shock patients. Finally, the changes in lactate were also able to detect changes in VO\textsubscript{2}. However, lactate was measured three hours after fluid administration while the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio was measured immediately after its end (8). This suggests that one advantage of the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio over lactate is that it changes immediately after changes in VO\textsubscript{2}. However, Mallat et al. observed in septic shock patients that the increase in VO\textsubscript{2} after volume expansion was detected much better by both the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} and the C\textsubscript{a}CO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio than by blood lactate (39).

In summary, all these arguments suggest that, in case of septic shock with O\textsubscript{2} extraction impairment, in contrast with S\textsubscript{a}O\textsubscript{2} or S\textsubscript{v}O\textsubscript{2}, ΔPCO\textsubscript{2} remains a reliable marker of the adequacy of cardiac output with the metabolic condition and that the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio remains a valid indicator of the adequacy between O\textsubscript{2} delivery and VO\textsubscript{2}. Moreover, compared to lactate, the CO\textsubscript{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\textsubscript{2} gap**

Although many studies confirmed the association between an elevation in both ΔPCO\textsubscript{2} and ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio and poor outcome in terms of lactate clearance, changes in VO\textsubscript{2} and mortality (40-42), some other ones showed a limited or even a negative correlation between elevated ΔPCO\textsubscript{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 ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio was compared between sheep with progressive haemorrhage and sheep with progressive haemodilution. Interestingly, the authors observed that in the haemodilution group, the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio increased despite the absence of anaerobic metabolism. These findings, together with the high correlation with haemoglobin changes (R\textsuperscript{2}=0.79; P<0.001), suggest that changes were explained by a rightward shift of the relationship between PCO\textsubscript{2} and CCO\textsubscript{2} (46).

In this regard, conflicting results have been reported also in terms of prognostic value of ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} and ΔCCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2}: while some authors observed that the ΔCCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio was an independent predictor of mortality, contrary to the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio (33), others observed that the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio but not the ΔCCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} was associated with increased mortality (42).

Other authors investigated possible causes of misleading interpretation of both ΔPCO\textsubscript{2} and the ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{2} ratio. Mallat et al. showed that hyperventilation creates an increase in ΔPCO\textsubscript{2} in healthy volunteers (47). Saludes et al. tested the effects of a hyperoxegenation trial on ΔPCO\textsubscript{2} (48), and observed that, even though oxygen parameters increased both on the arterial and venous side, PCO\textsubscript{2} augmented only in the venous blood, leading to an increase in both ΔPCO\textsubscript{2} and ΔPCO\textsubscript{2}/C\textsubscript{a}O\textsubscript{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\textsubscript{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 $\Delta PCO_2$ and the $\Delta PCO_2/Ca-vO_2$ 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 $\Delta PCO_2$ was $\pm 1.8$ mmHg, corresponding to a least significant change of 32%. For the $\Delta PCO_2/Ca-vO_2$ ratio, the smallest detectable difference was $\pm 0.57$ 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 $\Delta PCO_2/Ca-vO_2$ 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 $SvO_2$ or $ScvO_2$, they remain useful in septic shock patients with an impaired O$_2$ extraction.

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Footnote

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References


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