Preface

CO_2-derived variables for hemodynamic management in critically ill patients

CO_2 measurement carries significant physiologic and clinical information when analyzing hemodynamic status and ventilation of patients. While much focus is on O_2 based data, CO_2 derived parameters can provide a wealth of additional information. This is becoming more readily available as technological advances are making headways in CO_2 measurements.

The classic targets clinicians follow in patients in shock have shortcomings. The central venous oxygen saturation ($ScVO_2$) was once hailed as the ideal target to guide resuscitation of patients in shock (1). More recent data challenged its role and reduced its value, although it remains a helpful physiologic parameter to follow (2,3). A normal $ScVO_2$ does not exclude tissue hypoperfusion and could misguide the clinician. Lactic acid is another closely monitored parameter which reflects tissue perfusion. It is also advocated for in multiple guidelines, but also has its own shortcomings: it can be elevated for reasons other than tissue perfusion such as adrenergic stimulation, increased glycolytic activity or reduced clearance from liver dysfunction (4-6). The venous-to-arterial CO_2 partial pressure difference (ΔPCO_2) and tissue CO_2 could help alleviate some of these limitations.

According to the Fick equation, and similar to O_2 metabolism, CO_2 production (VCO_2) is directly proportional to the cardiac output (CO) and the venous-to-arterial CO_2 content difference. The CO_2 content is linearly related to the partial pressure of CO_2 over the general physiological range of CO_2 content (7). Moreover, the mixed venous values correlate with the central venous values (8). Hence the Fick equation can be rewritten as follows: $\Delta PCO_2 = k \times VCO_2/CO$, where the k is a pseudo-linear coefficient supposed to be linear in physiological states.

Based on this modified Fick equation, and for patients in a steady state, ΔPCO_2 is inversely proportional to CO. ΔPCO_2 and its relation to the CO has been studied in a number of situations, including patients in shock on vasopressors, and found to be an appropriate target to titrate such agents (9,10).

ΔPCO_2 has similar value in the operating room, where optimizing tissue perfusion and O_2 delivery is essential to reduce post-operative complications. For high risk non cardiac surgical patients, ΔPCO_2 can be used to reflect CO, identify patients that are not adequately resuscitated and along with $\Delta PCO_2/C(a\text{-}v)O_2$ ratio predict post-operative complications (11). This might not be true with cardiac surgical patients, who have different macro and micro hemodynamic changes (12).

Tissue hypercarbia is a common observation in patients in circulatory failure. Tissue CO_2 values are a reflection of the adequacy of tissue perfusion, as reduced blood flow leads to blood stagnation and failure of CO_2 washout from the tissues. This stagnant hypercapnia phenomenon reflects tissue hypoperfusion, even earlier than systemic parameters (13). This is especially relevant in sepsis where the impaired microcirculation, arteriovenous shunting and reduction in capillary density culminate in heterogeneous tissue perfusion. Direct optical videoscopy permits to assess these microcirculatory changes, but is yet to reach the bedside for mainstream use. Tissue capnometry, on the other hand, might offer similar data and is becoming more readily available.

Gastric, sublingual, bladder and transcutaneous PCO_2 values have been assessed in critically ill patients. The stomach is easy to access, can be used to detect gastric hypoperfusion and splanchnic ischemia. The gastric PCO_2 correlates with outcomes in the critical care and operating room settings (14). The sublingual vasculature has drawn significant interest as it reflects pathologic changes seen during septic shock. Measuring sublingual CO_2 offers a way to assess the microcirculation in such patients (15). Overall, the tissue CO_2 gap seems to perform better than systemic parameters, paving the way to use it as a resuscitation target for septic shock.

Transcutaneous CO_2 ($tcPCO_2$) offers another non-invasive method to estimate $PaCO_2$ with many studies establishing a good correlation between the 2 values (16). Some restrictions persist including the optimal site for $tcPCO_2$ measurement (earlobe with its high vascularity seems to perform better than other sites), technological delays (time is needed to sensor equilibration) and a gap between $PaCO_2$ variations and reflection in the $tcPCO_2$ value. Nonetheless, when the appropriate conditions are met and the skin perfusion is normal, $tcPCO_2$ reflects $PcCO_2$. Similar to other tissues, and as was discussed in the prior section, for patients in shock, the transcutaneous CO_2 gap is a good reflection of tissue perfusion and as such can be used for hemodynamic measurements.

Based on the Fick equation as it applies to O_2 and CO_2, the $\Delta PCO_2/C(a\text{-}v)O_2$ ratio equals VCO_2/VO_2 and hence the respiratory quotient (RQ). While under aerobic conditions, RQ values ranges between 0.6 to less than 1, RQ changes with anaerobic metabolism. This is due to VCO_2 increases to a larger extent than VO_2 under anaerobic conditions. While this is of paramount importance diagnostically, it was also found to be valuable parameter to target during resuscitation (17,18).

The following review articles summarize the available literature on CO_2 physiology and clinical value, as it pertains to the critical care setting as well as the operating room.

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Boulos Nassar[1,2], Jihad Mallat[1]

[1]*Department of Critical Care Medicine, Critical Care Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE;*
[2]*University of Iowa Hospitals and Clinics, Pulmonary and Critical Care Division, Iowa City, USA*
(*Email: boulosnassar@gmail.com; mallatjihad@gmail.com*)

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Review Article

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

Francesco Gavelli[1,2,3], Jean-Louis Teboul[1,2], Xavier Monnet[1,2]

[1]Service de médecine intensive-réanimation, Hôpital de Bicêtre, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France; [2]Université Paris-Sud, Faculté de médecine Paris-Sud, Inserm UMR S_999, Le Kremlin-Bicêtre, France; [3]Emergency Medicine Unit, Department of Translational Medicine, Università degli Studi del Piemonte Orientale, Novara, Italy

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Correspondence to: Dr. Francesco Gavelli, MD. Service de médecine intensive-réanimation, Hôpital de Bicêtre, 78, rue du Général Leclerc, F-94270 Le Kremlin-Bicêtre, France. Email: gavelli.francesco@gmail.com.

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

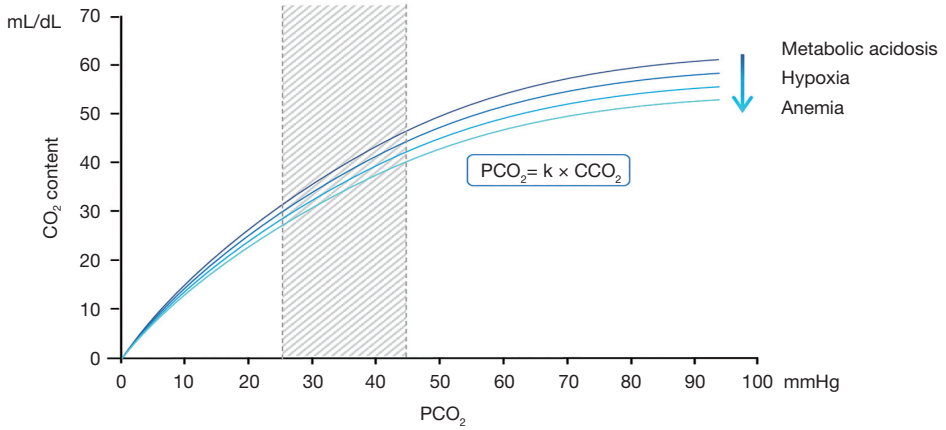

Figure 1 Relationship between content (CCO_2) and partial pressure (PCO_2) of carbon dioxide.

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 ($PCO_2 = k \times CCO_2$) 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

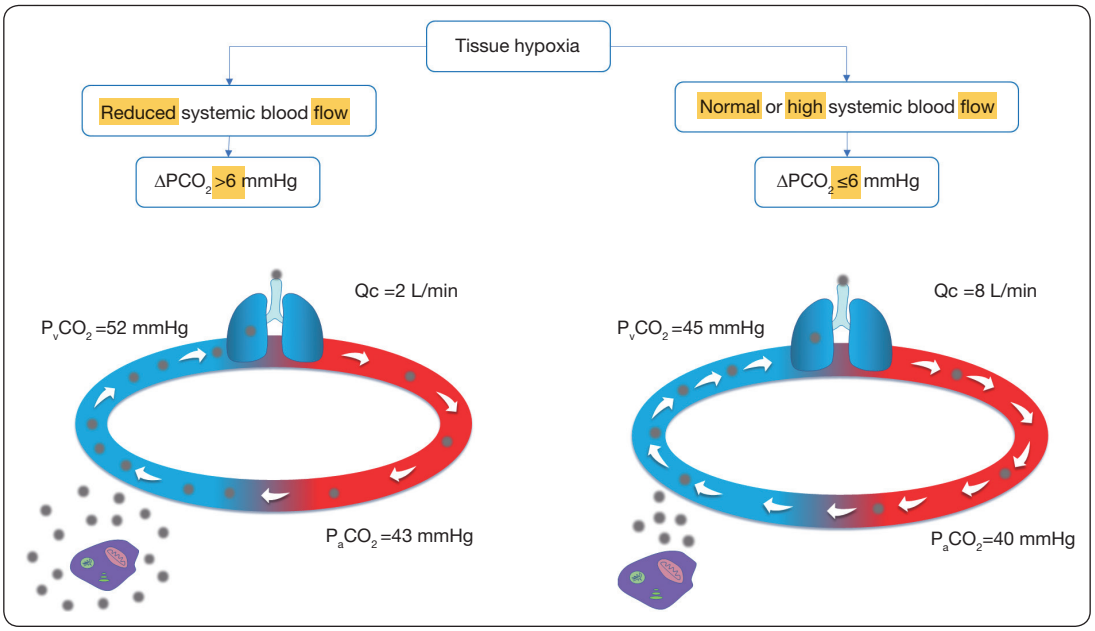

Figure 2 Illustration of the influence of cardiac output on the amplitude of the venoarterial difference of carbon dioxide partial pressure. P_aCO_2, arterial partial pressure in carbon dioxide; P_vCO_2, venous partial pressure in carbon dioxide; Qc, cardiac output; ΔPCO_2, venoarterial difference of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

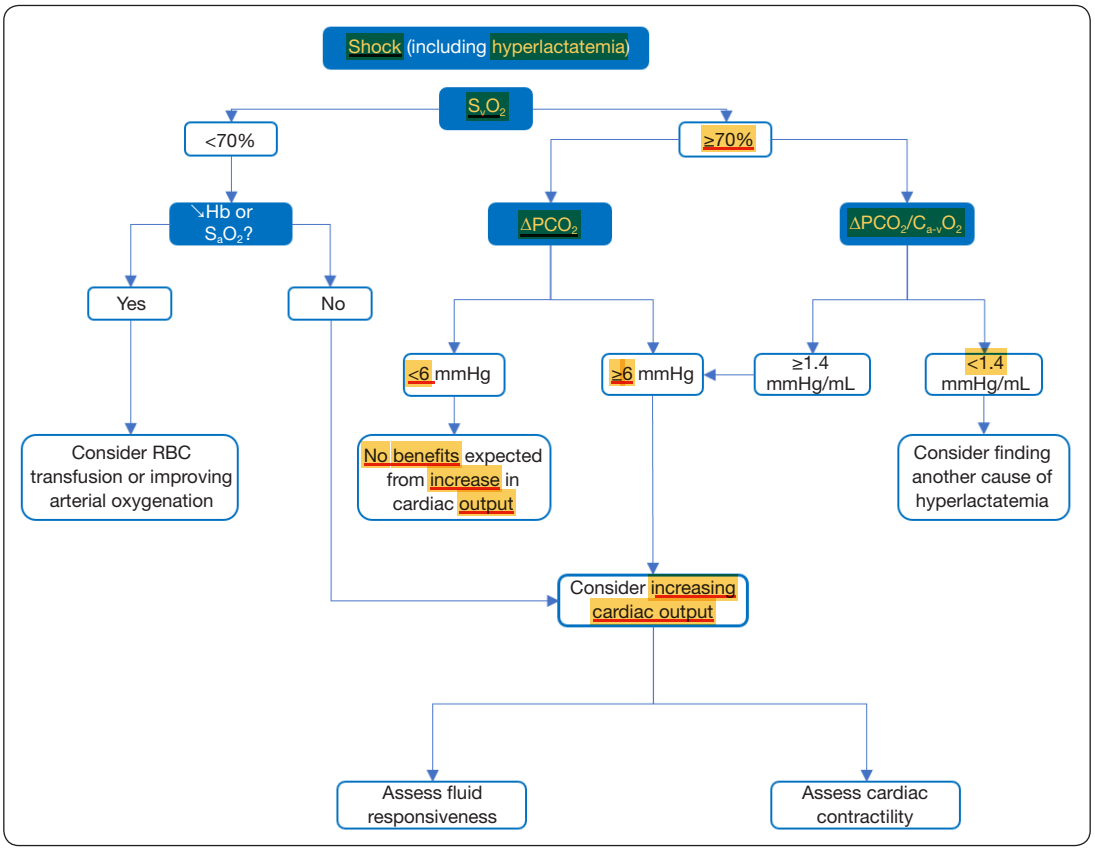

Figure 3 Interpretation of indices of tissue oxygenation. Hb, haemoglobin; S_vO_2, venous oxygen saturation; S_aO_2, arterial oxygen saturation; $C_{a-v}O_2$, arteriovenous difference in oxygen content; ΔPCO_2, venoarterial difference in carbon dioxide partial pressure.

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_2 remains 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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Review Article

Interpretation of venous-to-arterial carbon dioxide difference in the resuscitation of septic shock patients

Siyi Yuan, Huaiwu He, Yun Long

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Beijing 100730, China

Contributions: (I) Conception and design: H He; (II) Administrative support: Y Long; (III) Provision of study materials or patients: Y Long, H He; (IV) Collection and assembly of data: S Yuan; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Huaiwu He. Department of Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. Email: tjmuhhw@163.com; Yun Long. Department of Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China. Email: iculong_yun@163.com.

Abstract: The venous-to-arterial carbon dioxide difference [P(v-a)CO_2] was calculated from the difference of venous CO_2 and arterial CO_2, which has been used to reflect the global flow in the circulatory shock. Moreover, recent clinical studies found the P(v-a)CO_2 was related to the sublingual microcirculation perfusion in the sepsis. However, it is still controversial that whether P(v-a)CO_2 could be used to assess the microcirculatory flow in septic patients. Moreover, the related influent factors should be taken into account when interpreting P(v-a)CO_2 in clinical practice. This paper reviews the relevant experimental and clinical scenarios of P(v-a)CO_2 with the aim to help intensivists to use this parameter in the resuscitation of septic shock patients. Furthermore, we propose a conceptual framework to manage a high P(v-a)CO_2 value in the resuscitation of septic shock. The triggers of correcting an elevated P(v-a)CO_2 should take into consideration the other tissue perfusion parameters. Additionally, more evidence is required to validate that a decreasing in P(v-a)CO_2 by increasing cardiac output would result in improvement of microcirculation. Further investigations are necessary to clarify the relationship between P(v-a)CO_2 and microcirculation.

Keywords: Septic shock; venous-to-arterial carbon dioxide difference [P(v-a)CO_2]; microcirculation; resuscitation

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Introduction

The evaluation and correction of macrocirculatory and microcirculatory flow play an important role in the resuscitation of circulatory shock (1). The venous-to-arterial carbon dioxide difference [P(v-a)CO_2] has gained great attentions in the resuscitation of sepsis. The P(v-a)CO_2 is determined by cardiac output and metabolic status, and it has been taken as an indicator of the adequacy of the venous blood flow to remove the CO_2 produced by the peripheral tissues (2,3).

The P(v-a)CO_2 was calculated as the difference between venous PCO_2 and arterial PCO_2. The venous PCO_2 could be obtained from the mixed venous blood through a pulmonary artery catheter or from the central venous blood through a central venous catheter. Researches (4,5) had shown that central venous-arterial PCO_2 difference [P(cv-a)CO_2] was consistent with mixed venous-arterial PCO_2 difference [P(mv-a)CO_2] and both of them were inversely related to cardiac index (CI). Nowadays, the central venous PCO_2 is commonly used to calculate P(v-a)CO_2 in clinical practice. Recent study found that P(mv-a)CO_2 might be a potential indicator to reflect microcirculatory flow in septic shock patients (6). In this paper, we review the literatures of

$P(v\text{-}a)CO_2$ and try to answer the question how to interpret and manage the $P(v\text{-}a)CO_2$ in the resuscitation of sepsis.

$P(v\text{-}a)CO_2$ and prognosis in sepsis

Based on the physiological background of $P(v\text{-}a)CO_2$, it is easy to understand that a high $P(v\text{-}a)CO_2$ indicate an impaired cardiac output and tissue hypoperfusion. Hence, a persistent $P(v\text{-}a)CO_2$ after resuscitation is related to a poor prognosis in septic shock patients (6). A cutoff 6 mmHg of $P(v\text{-}a)CO_2$ has been suggested as an indicator to reflect the adequacy of cardiac output to tissue perfusion in critically ill patients (3). Several studies had reported that a high $P(v\text{-}a)CO_2$ (>6 mmHg) was related to poor outcome in septic shock condition (4,7-12). van Beest *et al.* (4) found that a high $P(cv\text{-}a)CO_2$ (≥6 mmHg) in the first 24 h after ICU admission was related to a higher hospital mortality rate (OR 5.3, P=0.08) in 53 septic shock patients. Vallee *et al.* (7) further reported that the septic shock patients with a higher $P(cv\text{-}a)CO_2$ had a poor lactate clearance, higher SOFA score, and a lower mortality rate, in the normalized central venous oxygen saturation ($ScvO_2$) (>70%) condition, than patients with a normal $P(cv\text{-}a)CO_2$ value (<6 mmHg). Moreover, Mallat *et al.* (8) reported that $P(cv\text{-}a)CO_2$ was not related to 28-day mortality in septic shock patients. But the authors found that normalization of both $P(cv\text{-}a)CO_2$ gap and $ScvO_2$, during the first 6 hours of resuscitation, was associated with a better lactate clearance than the normalization of $ScvO_2$ alone (8). Therefore, $P(cv\text{-}a)CO_2$ was suggested as an additional goal of resuscitation when $ScvO_2$ target had been achieved (>70%) in septic shock patients (7,8).

Moreover, our study found a lower $P(cv\text{-}a)CO_2$ (3.5 mmHg but not 6 mmHg) had a good ability for predicting ICU mortality in septic shock patients with a high $ScvO_2$ (>80%) (13). The non-survivor group had a low $P(v\text{-}a)CO_2$ (mean 4.8 mmHg) <6 mmHg and high lactate level (mean 3.1 mmol/L) in our study. Hence, the normal cutoff value of $P(v\text{-}a)CO_2$ requires further investigations to be validated in septic shock patients with a high $ScvO_2$ (>80%) and signs of tissue hypoxia.

Recently, a systematic review showed that $P(v\text{-}a)CO_2$ was correlated with mortality and other clinical outcomes in septic shock patients (14). Furthermore, Muller *et al.* (12) found that $P(cv\text{-}a)CO_2$ was only associated with mortality in patients with impaired cardiac function (defined as atrial fibrillation and/or left ventricular ejection fraction less than 50%) but not with patients with normal cardiac function. The authors found that patients with septic shock and impaired cardiac function were more prone to a persistent high $P(cv\text{-}a)CO_2$, even when initial resuscitation succeeded in normalizing mean arterial pressure, central venous pressure, and $ScvO_2$ (12). In other words, a high $P(cv\text{-}a)CO_2$ might mainly result from a poor cardiac function in the resuscitation of septic shock patients. Further clinical investigation is required to clarify the predictive meaning of $P(cv\text{-}a)CO_2$ in normal cardiac function. The relevant clinical studies of $P(cv\text{-}a)CO_2$ and outcome were summarized in the *Table 1*.

Pitfalls of $P(v\text{-}a)CO_2$ in assessing global flow and tissue perfusion

There were some potential pitfalls of using $P(v\text{-}a)CO_2$ to identify global flow and tissue perfusion in clinical situations.

(I) Hyperoxia: Saludes *et al.* (15) found that an elevated $P(v\text{-}a)CO_2$ could independently result from a hyperoxia (caused by breathing 100% O_2 for 5 min) but not from an inadequate cardiac output in the septic patients. Several potential mechanisms should be taken on how hyperoxia cause an increase in $P(v\text{-}a)CO_2$ are as following: firstly, a high $P(v\text{-}a)CO_2$ could be derived from the impaired microcirculatory flow caused by arterial hyperoxia (16). It has been shown that normobaric hyperoxia decreases capillary perfusion and VO_2 and increases the heterogeneity of the perfusion (17). Secondly, Haldane effect, a phenomenon known as the increase in venous oxygen saturation would cause a decrease in the affinity of hemoglobin (Hb) for CO_2 (18). The CO_2 would unbind from Hb and, in the venous hyperoxia condition, would further produce an increase in the free form of CO_2 in the venous site. Consequently, the $P(v\text{-}a)CO_2$ would elevate in the high venous saturation condition resulted from hyperoxia (19).

(II) Hyper-ventilation: Mallat *et al.* (20) investigated the effect of acute hyperventilation on $P(cv\text{-}a)CO_2$ gap in hemodynamically stable septic shock patients. The authors found that acute hyperventilation could increase $P(cv\text{-}a)CO_2$ gap, which may be a result of increases in VO_2. In other words, the acute changes in respiratory status could contribute to a high $P(v\text{-}a)CO_2$, which might be independent of the changes in cardiac output. (III) Hypoxia: the cellular hypoxia could be caused by ischemic or hypoxic hypoxia. Vallet *et al.* found that $P(v\text{-}a)CO_2$ increase in ischemic hypoxia induced by a decrease in blood flow, but not in hypoxic hypoxia conditions where

Table 1 P(v-a)CO_2 and outcome in clinical studies

Author	Year	Population	Types of study	Outcome [low P(v-a)CO_2 group *vs.* high P(v-a)CO_2 group]	Note
Bakker *et al.* (9)	1992	64 pts with septic shock	Prospective observational study	N/A	Non-survivors had a significantly higher P(v-a)CO_2 than survivors (5.9±3.4 *vs.* 4.4±2.3 mmHg, P<0.05)
Vallee *et al.* (7)	2008	50 pts with septic shock with SvO_2 ≥70%	Prospective observational study	12 h lactate clearance: –38%±39% *vs.* –17%±33% (P=0.04); 24 h SOFA: 11±4 *vs.* 15±4 (P<0.05)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=26; Pts with high P(v-a)CO_2 (>6 mmHg) n=24
Troskot *et al.* (11)	2010	71 pts with septic shock	Retrospective analysis	N/A	High P(v-a)CO_2 (>6 mmHg) is related to mortality (P=0.015) in non-ventilated patients (P=0.015), not in ventilated patients (P=0.27)
van Beest *et al.* (4)	2013	53 pts with septic shock	Post hoc analysis	28 d mortality: 21% *vs.* 29% (P=0.53)	The mixed P(v-a)CO_2 underestimated the central P(v-a)CO_2 by a mean bias of 0.03±0.32 kPa (–0.62–0.58 kPa)
Ospina-Tascon *et al.* (6)	2013	85 pts with septic shock	Prospective observational study	Persistence of high P(v-a)CO_2 was associated with a higher 3 d SOFA (P<0.001) and 28 d mortality log rank test: 19.21 (P<0.001)	Pts with persistence of high P(v-a)CO_2 (both T0, T6 >6 mmHg) n=24
Du *et al.* (10)	2013	172 pts with septic shock, including 122 pts with SvO_2 ≥70%	Retrospective analysis	6 h lactate clearance: 21%±31% *vs.*1%±61% (P=0.016); 28 d mortality: 16.1% *vs.* 56.1% (P<0.001)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=81; Pts with high P(v-a)CO_2 (>6 mmHg) n=41 with $ScvO_2$ ≥70%
Mallat *et al.* (8)	2014	80 pts with septic shock	Prospective observational study	6 h lactate clearance: 28%±31% *vs.* –0.2%±34% (P<0.0001); 28 d mortality: 20% *vs.* 24% (P=0.003)	Pts with low P(v-a)CO_2 (≤6 mmHg) n=48; Pts with high P(v-a)CO_2 (>6 mmHg) n=32
Muller *et al.* (12)	2017	114 pts in cardiac group; 236 pts in non-cardiac group	Prospective cohort study	28 d mortality: 20% *vs.* 35% (P=0.024) (cardiac group); 28 d mortality: 26% *vs.* 28% (P=0.8) (non-cardiac group)	Cardiac group: patients had AF and/or LVEF <50%

Pts, patients; N/A, not applicable; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; P(v-a)CO_2, venous-to-arterial carbon dioxide difference; $ScvO_2$, central venous oxygen saturation.

the blood flow was maintained constant, even in a state of VO_2/DO_2 dependency, in a canine model of isolated limb (21). Hence, P(v-a)CO_2 could serve as a marker of the adequacy of venous blood flow to wash-out the CO_2 produced by the tissues (tissue hypoperfusion marker) rather than a marker of tissue hypoxia.

P(v-a)CO_2 and microcirculation

Both $ScvO_2$ and lactate have been well accepted as targets to guide resuscitation in sepsis (22). However, sometimes there might be some limitations in using $ScvO_2$ and lactate to reflect tissue perfusion (23). For example, when capillary shunting occurred, $ScvO_2$ could be elevated and mask the presence of tissue hypoperfusion or tissue hypoxia. Recently, P(v-a)CO_2 has gained attention as a complementary tool to reflect global perfusion in the resuscitation of septic shock patients when $ScvO_2$ is more than 70% (24).

Ospina-Tascon *et al.* (25) conducted a prospective study involving 75 septic shock patients with the aim to

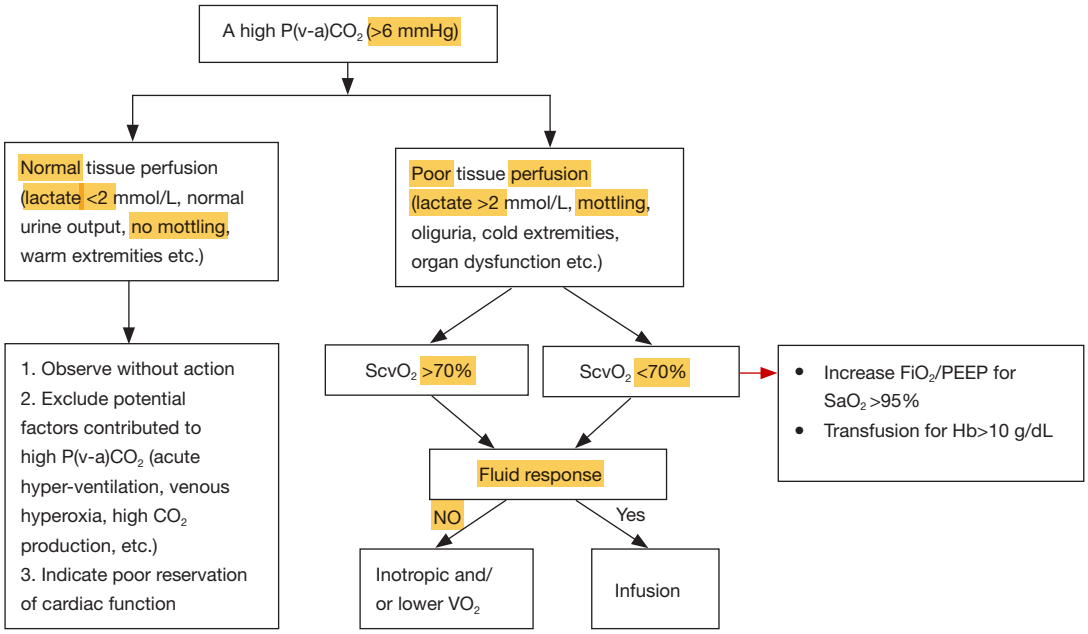

Figure 1 A recursive and regression tree to interpret and manage a high P(v-a)CO_2 (>6 mmHg). P(v-a)CO_2, venous-to-arterial carbon dioxide difference; ScvO_2, central venous oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

investigate the relationship between P(mv-a)CO_2 and sublingual microcirculation assessed by sidestream dark-field device. They found that high P(mv-a)CO_2 values were associated with low percentages of small perfused vessels (PPV), low functional capillary density, and high heterogeneity of microvascular blood flow. Interestingly, the relationship between P(v-a)CO_2 and microcirculation was independent of the effects of cardiac output in that study. In summary, a high P(v-a)CO_2 might be caused by an inadequate microcirculatory flow to clear the excess CO_2 production, even in the presence of normal (or high) cardiac output in septic shock patients. Moreover, Kanoore *et al.* (26) found sepsis patients with a high CI (>4 L/min/m^2) showed a lower P(v-a)CO_2 (5±3 *vs.* 7±2 mmHg) than those with normal cardiac output. However, there were no differences in sublingual perfused vascular density, proportion of perfused vessels, or microvascular flow index in both groups in that study. Hence, an impaired microcirculation could be persistent even in a low P(v-a)CO_2 and a high cardiac output condition. The loss of coherence between macrocirculation and microcirculation is common in septic shock patients (27). Importantly, it is uncertain if the decrease in P(v-a)CO_2, observed after an increase in cardiac output, is related to the improvement of microcirculation. Further studies are needed to investigate this issue.

How to Interpret and manage a high P(v-a)CO_2 (>6 mmHg)

An elevated P(v-a)CO_2 could result from different reasons in septic shock patients, such as low cardiac output, poor microcirculatory perfusion or acute hyperventilation (28). Hence, a high P(v-a)CO_2 should be taken as an alarm trigger of inadequate blood flow in the resuscitation of septic shock patients. It remains a challenge for intensivists to correctly interpret and manage an elevated P(v-a)CO_2 (>6 mmHg) condition. In *Figure 1*, we summarized a recursive and regression approach of resuscitation of septic shock patients. The usefulness of this resuscitation protocol needs to be validated in clinical trials.

Conclusions

During recent years, P(v-a)CO_2 has gained great attention and more frequently used in the resuscitation of septic shock patients. The intensivists should take other tissue perfusion parameters into consideration before correcting an elevated P(v-a)CO_2 in the resuscitation of septic shock patients. Moreover, further investigations are necessary to clarify the relationship between P(v-a)CO_2 and microcirculation.

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Footnote

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Review Article

Combination of O_2 and CO_2-derived variables to detect tissue hypoxia in the critically ill patient

Gustavo A. Ospina-Tascón, Humberto J. Madriñán

Department of Intensive Care, Fundación Valle del Lili University Hospital-Universidad Icesi, Cali, Colombia

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Correspondence to: Dr. Gustavo A. Ospina-Tascón. Department of Intensive Care, Fundación Valle del Lili University Hospital-Universidad Icesi, Av. Simón Bolívar Cra. 98, Cali, Colombia. Email: gusospin@gmail.com.

Abstract: Oxygen-derived parameters have been traditionally used to guide resuscitation during shock states. Nevertheless, normalization of venous oxygen saturation does not exclude the persistence of tissue hypoperfusion and tissue hypoxia. Combination of O_2 and CO_2-derived variables has consistently demonstrated to be related with clinical outcomes and its variations could anticipate changes in lactate and also predict fluid responsiveness in terms of oxygen consumption. Here we discuss the potential mechanisms leading to increase the venous-to-arterial CO_2 ($Cv\text{-}aCO_2$) to arterial-to-venous O_2 content difference ($Ca\text{-}vO_2$), i.e., the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio, its potential clinical application, limitations and uncertainties. Finally, although biologically plausible, the potential applications of the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio in the clinical practice require to be confirmed.

Keywords: Tissue perfusion; venous-to-arterial carbon dioxide difference; anaerobic metabolism; respiratory quotient; venous-arterial CO_2 to arterial-venous O_2 difference ($Cv\text{-}aCO_2/Ca\text{-}vO_2$ difference)

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Introduction

Early detection and prompt reversion of tissue hypoperfusion are key factors to prevent progression to multiorgan dysfunction and death during shock states (1). Techniques commonly used to monitor tissue perfusion have focused mainly on systemic blood flow and the balance between oxygen demand and supply to the tissues (2,3). Indeed, quantitative resuscitation targeting central venous oxygen saturation ($ScvO_2$) and some macro hemodynamic parameters was related with a significant reduction of mortality in an initial single-center randomized controlled trial including patients with septic shock (4). Subsequent studies on implementation of resuscitation bundles targeting similar hemodynamic goals in septic shock were also apparently beneficial (5,6). Nevertheless, the utility of oxygen-derived parameters was promptly challenged (7), and recent clinical trials failed to demonstrate their clinical benefit (8-10). In fact, $ScvO_2$ is often normal at the ICU admission (11), and attaining macro hemodynamic goals and/or normalization of global oxygen-derived parameters in septic shock do not exclude the occurrence or persistence of tissue hypoxia. In this context, other variables such as carbon dioxide (CO_2)-derived parameters could provide very important information about macro and micro hemodynamics, even when oxygen- derived variables resemble corrected. Importantly, variations in CO_2 occur faster than changes in lactate levels, which make the CO_2-derived parameters an attractive tool to monitor tissue perfusion and potentially, cell oxygenation during the early stages of shock.

The theoretical basics of the venous-arterial CO_2 to arterial-venous O_2 ratio (Cv-aCO_2/Ca-vO_2 ratio)

Aerobic carbon dioxide production and the physiological rationale of the Cv-aCO_2/Ca-vO_2 ratio

Under normoxic conditions, carbon dioxide (CO_2) is generated during the tricarboxylic acid or Krebs cycle. The total CO_2 production (VCO_2) is directly related to the global oxygen consumption (VO_2), by the relationship: $VCO_2 = RQ \times VO_2$, where RQ symbolizes the respiratory quotient and represents the relationship between the total CO_2 generated and the oxygen (O_2) consumed throughout metabolic processes. Under normal rest conditions, RQ fluctuates from 0.6 to 1.0 depending on the predominant energetic substrate utilized (i.e., amino acids, lipids or carbohydrates). Thus, under resting aerobic conditions RQ should not be >1.0 since VCO_2 should not exceed the O_2 availability. Indeed, RQ remains <1.0 even during metabolic rate rises (as long as aerobic metabolism is maintained), because the proportional increase in VCO_2 and VO_2.

According to the Fick equation, VO_2 and VCO_2 are directly proportional to the cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Following this rationale, the quotient between the venous-to-arterial CO_2 content difference (Cv-aCO_2) and the arterial-to-venous O_2 content difference (Ca-vO_2), i.e., the Cv-aCO_2/Ca-vO_2 ratio, should reflect the VCO_2/VO_2 fraction and it should be theoretically independent of flow variations, as cardiac output is present at both numerator and denominator components of the formula (*Figure 1*).

Under aerobic steady state conditions, VCO_2 approaches VO_2, whereby the Cv-aCO_2 and the Ca-vO_2 should also do it. Consequently, VCO_2 should not exceed O_2 availability whereby the VCO_2/VO_2 ratio [i.e., the respiratory quotient (RQ)] should not be >1.0. Thus, VCO_2/VO_2 and Cv-aCO_2/Ca-vO_2 ratio >1.0 should be considered as abnormal and these could potentially reflect anaerobic CO_2 generation.

Anaerobic carbon dioxide production

Under hypoxia conditions, aerobic VCO_2 decreases while anaerobic VCO_2 turns on. Such anaerobic VCO_2 reflects the proton (H+) buffering by cytosolic and plasmatic bicarbonate (HCO_3–). The "gross H+ release" results from the sum of all cellular reactions liberating H+ [e.g., the ATPase, hexokinase (HK), phosphofructokinase (PFK), and glyceraldehyde-3-phosphate dehydrogenase (G3PDH) reactions], which are counterbalanced by metabolic reactions consuming H^+ [e.g., AMP deaminase (AMPDase), the creatine kinase (CK), pyruvate kinase (PK), and lactate dehydrogenase (LDH) reactions]. Thus, the balance between the "gross H+ release" and chemical reactions consuming H+ (i.e., the "metabolic buffering") results in the "net H+ release", which is ultimately regulated by the intra and extracellular structural buffering (e.g., amino acids) and the bicarbonate buffering system (12).

Interestingly, the hydrolysis of the ATP has been proposed as the most important source of hydrogen ions during intense exercise (13), prolonged ischemia (14) or increased Na+-K+ ATPase activity (15-19). Thus, non-recycled H+ due either to slowdown, blocking or overshoot of oxidative phosphorylation, progressively accumulate to be finally buffered by the bicarbonate system. This later will be responsible for the anaerobic VCO_2 as the protons are captured by HCO_3– leading to carbonic acid (H_2CO_3) generation with subsequent dissociation into CO_2 and H_2O (*Figure 2*). Nevertheless, although anaerobic VCO_2 is a biologically plausible process, its clinical demonstration is quite complex since the efferent venous blood flow might be sufficient to wash out the total CO_2 produced at the tissues, thus masking the portion of increased anaerobic CO_2.

The hypothetical meaning of the Cv-aCO_2/Ca-vO_2 ratio

Experimental blockade of mitochondrial O_2 utilization and limitation of O_2 availability during severe tissue hypoperfusion have been related with "non-symmetrical" reductions in VCO_2 and VO_2 with the subsequent RQ increase. Such "asymmetric" VCO_2/VO_2 fall might be explained by an increase in anaerobic CO_2 production resulting from the buffering of protons delivered from the ATP hydrolysis that are not recycled during oxidative phosphorylation (*Figure 2*). Similarly, when anaerobic threshold is achieved after an excessive increased metabolic demand, total VCO_2 can exceed the adaptive increment in VO_2 (20), thus leading to RQ values >1.0. Similar data have been described during experimental shock in which VCO_2 decreases slightly less than the VO_2 reduction, leading to increases in the VCO_2/VO_2 ratio (21,22). Interestingly, reversion of shock was related with returning VCO_2/VO_2 ratio to values <1.0. Thus, if considering the Cv-aCO_2/Ca-vO_2 ratio as a surrogate of the VCO_2/VO_2 ratio, a Cv-aCO_2/Ca-vO_2 ratio >1.0 could potentially identify the presence of anaerobic metabolism.

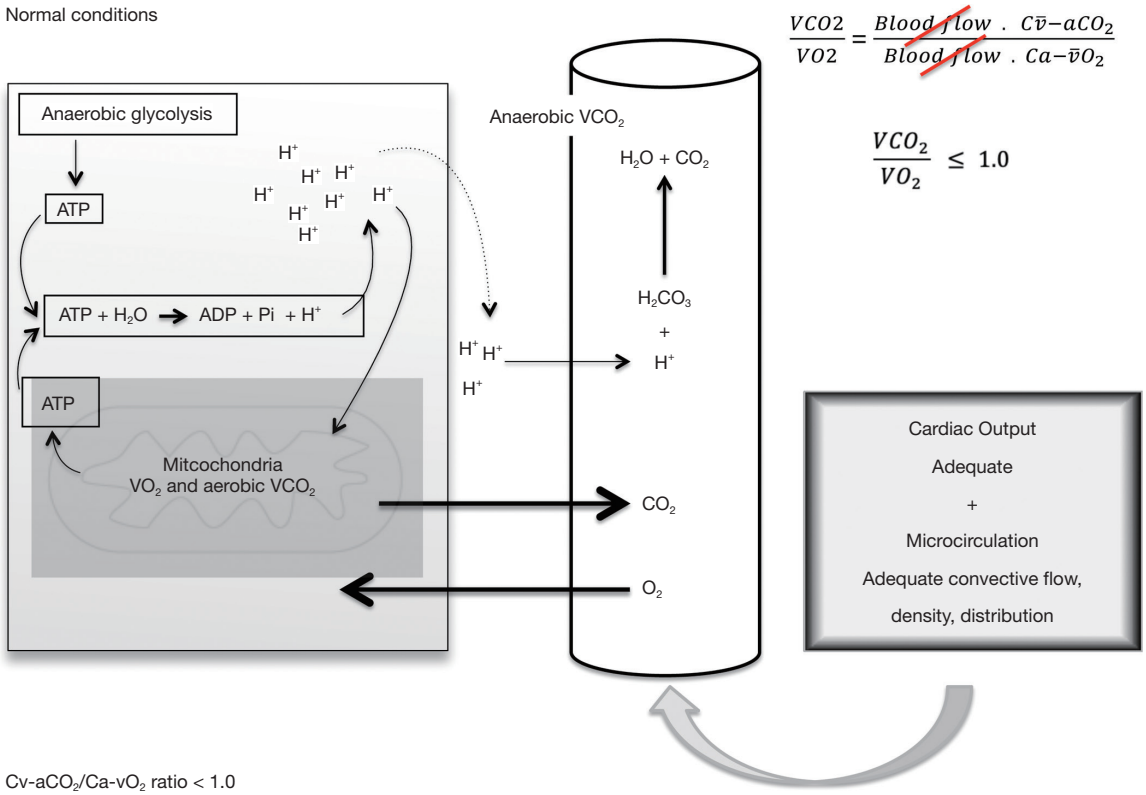

Figure 1 Normal resting conditions. Normal macro and micro hemodynamics lead to homogeneous distribution of oxygen to the tissues. Under preserved mitochondrial function, CO_2 is generated during the Krebs cycle (aerobic VCO_2). The ATP generated predominantly during the oxidative phosphorylation (and in a lesser extend, during glycolysis) is hydrolyzed thus liberating free hydrogenions (H+), which are normally recycled into the mitochondria to synthetize again ATP. Minor quantities of H+ pass the cell membrane reaching the circulation. Such H+ are buffered by the HCO_3- system and finally transformed into CO_2 and water. However, this last process accounts minimally for the total VCO_2 when oxidative phosphorylation functions normally. The relationship between the total CO_2 production (VCO_2) and oxygen consumption (VO_2) should be <1.0 under aerobic conditions. According to the Fick equation, VCO_2 and VO_2 are directly proportional to the cardiac output and their respective venous-to-arterial and arterial-to-venous content differences, respectively. Thus, the quotient between the venous-to-arterial CO_2 content difference (Cv-aCO_2) and the arterial-to-venous O_2 content difference (Ca-vO_2), i.e., the Cv-aCO_2/Ca-vO_2 ratio, should reflect in some extend the VCO_2/VO_2 fraction, independently of flow variations (since cardiac output is present at both numerator and denominator components of the formula).

The potential clinical use of the Cv-aCO_2/Ca-vO_2 ratio

Although hyperlactatemia has been traditionally used as a marker of anaerobic metabolism, lactate levels might frequently increase by causes different to tissue hypoxia (23). Indeed, high lactate levels can result from increased glycolytic activity, abnormal pyruvate metabolism and altered metabolic lactate reuptake (24-26). Thus, interpretation of hyperlactatemia during the resuscitation and post resuscitation periods of septic shock is not straightforward. In this sense, the use of combined CO_2 and O_2-derived parameters could theoretically help to identify, in some extend, the persistence or reversion of anaerobic metabolism.

Using CO_2 partial pressures (pCO_2) instead of CO_2 contents (CCO_2), Mekontso-Dessap *et al.* (27) demonstrated a good agreement between the Pv-aCO_2/Ca-vO_2 ratio (as surrogate of the Cv-aCO_2/Ca-vO_2 ratio) and lactate levels ≥2.0 mmol/L (accepting it as indicator of anaerobic metabolism). Nevertheless, far beyond a simple agreement, the Cv-aCO_2/Ca-vO_2 ratio might provide

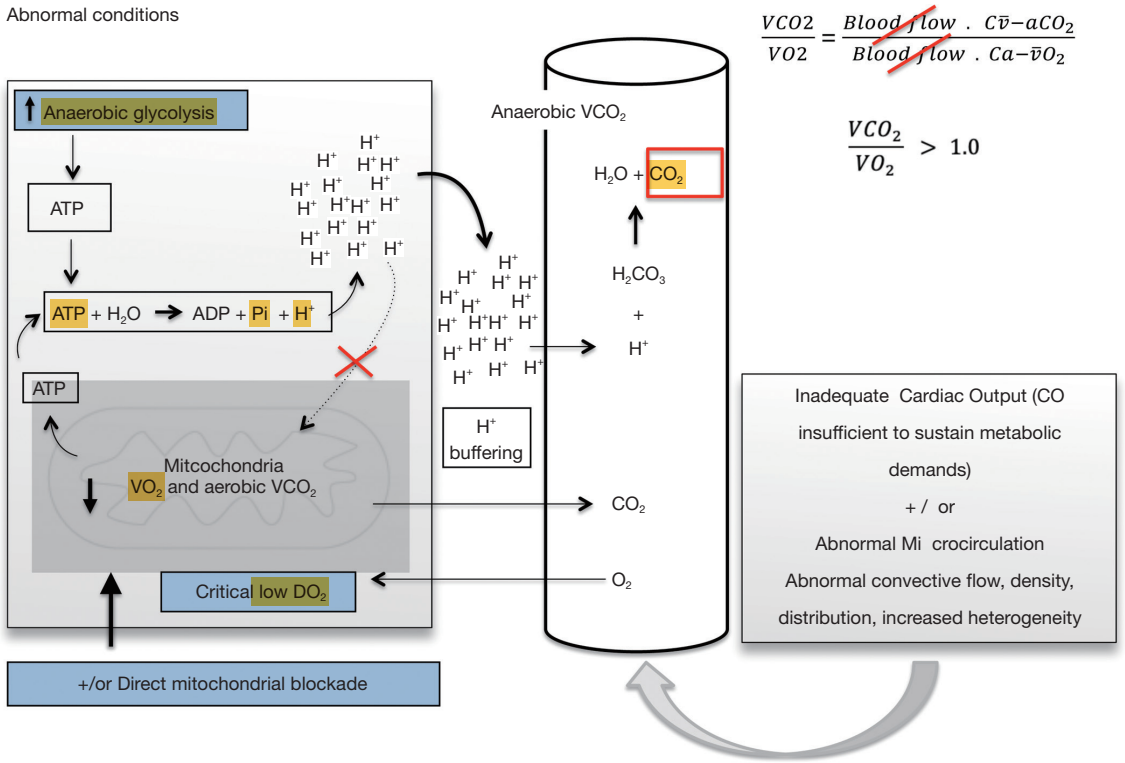

Figure 2 Abnormal conditions. When macro hemodynamics and/or microcirculatory blood distribution are inadequate or when mitochondrial machinery is blocked, the H+ generated during the ATP hydrolysis are not recycled during the oxidative phosphorylation. Thus, the excess of H+ will cross the cell membrane to finally be buffered by the HCO_3- system and thus, to be transformed into CO_2 and H_2O. This leads to increase VCO_2/VO_2 fraction and its surrogate, the Cv-aCO_2/Ca-vO_2 ratio. To minimize the influence of Haldane effect, CO_2 contents should be calculated instead of CO_2 partial pressures (for details, see at the text).

additional information to that offered by lactate levels. A recent study (28) suggested that combination of persistent hyperlactatemia and Cv-aCO_2/Ca-vO_2 ratios >1.0 is related with more severe multiorgan dysfunction and higher mortality rates in patients with septic shock. Remarkably, patients attaining normalization of lactate levels but with Cv-aCO_2/Ca-vO_2 ratios >1.0 depicted similar clinical outcomes than those with persistent hyperlactatemia but with normal Cv-aCO_2/Ca-vO_2 ratios. Nevertheless, this study did not elucidate whether Cv-aCO_2/Ca-vO_2 ratios >1.0 might anticipate increases in lactate levels.

Subsequent studies corroborated the prognostic value of the Pv-aCO_2/Ca-vO_2 ratio in sepsis and septic shock (29,30). Importantly, an increased Pv-aCO_2/Ca-vO_2 ratio was related with delayed lactate clearance (29,30), which suggests that Cv-aCO_2/Ca-vO_2 ratio could anticipate lactate variations. Other studies showed that combined hyperlactatemia and high Cv-aCO_2/Ca-vO_2 ratio (or its equivalent, the Pv-aCO_2/Ca-vO_2 ratio) could identify ongoing supply dependency of O_2 consumption (i.e., VO_2/DO_2 dependency) (31,32). In agreement with this concept, oxygen consumption (VO_2) was increased after a fluid load only in patients with acute circulatory failure and an abnormal Pv-aCO_2/Ca-vO_2 ratio at the baseline (31,32).

An experimental model of septic shock secondary to peritonitis demonstrated that regional mesenteric Cv-aCO_2/Ca-vO_2 ratio tracks the instauration and reversion of anaerobic metabolism following the variations in microcirculatory blood flow distribution at jejunal mucosa and serosa and also tracking the variations in mesenteric lactate levels (33). Hence, anaerobic metabolism reflected by increases in Cv-aCO_2/Ca-vO_2 ratio can be reversed by improvement of O_2 distribution at microcirculatory level, at least during very early stages of septic shock (33).

Combined CO_2 and O_2-derived variables might add prognostic information to that provided by lactate

levels during early stages of shock. In fact, Cv-aCO_2/Ca-vO_2 ratio reacts faster than lactate levels to short-term hemodynamic changes, which makes it an attractive variable to be monitored and, although difficult to be calculated, its interpretation is easier, with values >1.0 suggesting ongoing anaerobic metabolism. Thus, an increased lactate accompanied by a Cv-aCO_2/Ca-vO_2 ratio >1.0 might suggest "ongoing" tissue hypoxia, whereby clinicians should be encouraged to optimize macro and micro hemodynamics. Conversely, increased lactate levels accompanied by Cv-aCO_2/Ca-vO_2 ratios ≤1.0 could suggest that such lactate increase results from slow lactate clearance more than from ongoing tissue hypoxia, whereby additional resuscitation efforts should be discouraged. Nevertheless, such hypothesis must be tested in prospective clinical trials before to translate into the clinical practice.

The Haldane effect, the CO_2 dissociation curves and the criticism about the Cv-aCO_2/Ca-vO_2 ratio as a marker of anaerobic metabolism

The phenomenon whereby hemoglobin increases or decreases its affinity for CO_2 according to variations in its oxygenated or deoxygenated state is known as Haldane effect. Thus, when blood enters systemic capillaries and releases O_2, the CO_2-carrying capacity rises so that blood picks up extra CO_2. Conversely, as blood enters pulmonary capillaries and binds O_2, the CO_2-carrying capacity falls, thus facilitating pulmonary elimination of CO_2.

According to the Haldane effect, the total CO_2 content (CCO_2) rises at a given pCO_2 as O_2 hemoglobin saturation falls, thus indicating a non-linear relationship between pCO_2 and CCO_2. Likewise, changes in tissue oxygen extraction, pH, tissue VCO_2, and hemoglobin concentration can also influence the relationships between pCO_2 and CCO_2, making difficult the interpretation of the venous-to-arterial pCO_2 difference. In addition, depending on baseline SvO_2, the Haldane effect may increase or decrease Pv-aCO_2 in response to the same changes in blood flow or metabolism (34).

Admittedly, Pv-aCO_2/Ca-vO_2 could be equivalent to the Cv-aCO_2/Ca-vO_2 ratio when PCO_2, pH, and SvO_2 approximate to normality, which occurs in many cases. Nevertheless, during low pCO_2 and SvO_2 conditions, Cv-aCO_2 might profoundly differ from Pv-aCO_2. Indeed, clinical observations during very early stages of resuscitation of septic shock suggest that persistence of a high Cv-aCO_2/Ca-vO_2 ratio is related to unfavorable clinical outcomes but not its equivalent, the Pv-aCO_2/Ca-vO_2 ratio (28). Thus, although the influence of the Haldane effect is negligible at low Pv-aCO_2, the disagreement of Cv-aCO_2 and Pv-aCO_2 increases at higher Pv-aCO_2 values (28).

Some authors have proposed that high Pcv-aCO_2/Ca-vO_2 ratio does not reflect anaerobic metabolism and obeys mainly to variations in hemoglobin levels (35), according to observations based on the analysis of expired gases by indirect calorimetry. Nevertheless, under non-steady-state conditions such as during shock states, RQ is easily influenced by a number of physiologic events that can alter the agreement between measurements of RQ by indirect calorimetry (RQic) and the true metabolic activity. Thus, the high solubility of CO_2 in tissues and blood, and the variations in pulmonary ventilation/perfusion (V/Q) relationships might lead to momentary discordant results between RQic and the true RQ, until a new stead- state is attained (36). Consequently, the relationship between venous-arterial CO_2 to arterial-venous O_2 differences and anaerobic metabolism should not be rejected based just on measurements of VCO_2 by RQic. Similarly, attributing high Pv-aCO_2/Ca-vO_2 ratios just to variations in hemoglobin levels could be physiologically misleading, since at very low hemoglobin values, small errors in hemoglobin measurements will amplify the error of calculation of Pv-aCO_2/Ca-vO_2 or Cv-aCO_2/Ca-vO_2 values.

Conclusions

Physiological determinants of combined CO_2 and O_2-derived variables are quite complex. Theoretically, the Cv-aCO_2/Ca-vO_2 ratio is independent of systemic blood flow variations and it should approach the RQ or at least, it should approximates cell respiration state. Although venous-arterial CO_2 to arterial-venous O_2 differences have demonstrated to predict fluid responsiveness in terms of VO_2, to anticipate slowly lactate clearance and to be related with clinical outcomes, its potential application in the clinical practice needs to be confirmed.

Acknowledgments

Centro de Investigaciones clínicas, Fundación Valle del Lili. Cali, Colombia.

Footnote

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Review Article

Venous-to-arterial pCO_2 difference in high-risk surgical patients

Pierre Huette[1], Omar Ellouze[2], Osama Abou-Arab[1], Pierre-Grégoire Guinot[2]

[1]Anaesthesiology and Critical Care Department, Cardiothoracic ICU, Amiens University Hospital, Amiens, France; [2]Anaesthesiology and Critical Care Department, Cardiovascular ICU, Dijon University Hospital, Dijon, France

Contributions: (I) Conception and design: All authors; (II) Administrative support: PG Guinot, P Huette; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: PG Guinot, O Ellouze, P Huette; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Pierre-Grégoire Guinot. Anesthesiology and Critical Care Department, Dijon University Hospital, 2 Bd Maréchal de Lattre of Tassigny, Dijon, France. Email: pierregregoire.guinot@chu-dijon.fr.

Abstract: Alteration of tissue perfusion is a main contributor to organ dysfunction in high-risk surgical patients. The difference between venous carbon dioxide and arterial carbon dioxide pressure (pCO_2 gap) has been described as a parameter reflecting tissue hypoperfusion in critically ill patients who are insufficiently resuscitated. The pCO_2 gap/$CavO_2$ ratio has also been described as an indicator of the respiratory quotient, thus the relationship between DO_2 and VO_2. Most of the knowledge about the pCO_2 gap and the pCO_2 gap/$CavO_2$ ratio has come from studies in the literature on animal models or intensive care unit (ICU) patients. To date, publications pertaining to the operative setting are sparse. In the present review, we will first discuss the physiological background of the pCO_2 gap and CO_2-O_2 derived parameters used in the operating room. Few studies have focused on the clinical relevance of the pCO_2 gap in high-risk non-cardiac surgical patients. Prospective observational studies with a small sample size and retrospective studies have shown that the pCO_2 gap may be a useful complementary tool to identify patients who remain insufficiently optimized hemodynamically. In a few studies, a high pCO_2 gap was associated with postoperative complications following non-cardiac high-risk surgery. Results of observational studies conducted in patients undergoing cardiac surgery are contradictory. We focused on the divergence between non-cardiac surgery, cardiac surgery, and septic critically ill patients. When analyzing the literature, we can find some explanations for the discrepancies in the published results between cardiac and non-cardiac surgery. Finally, we will discuss the clinical utility of the pCO_2 gap in high-risk surgical patients.

Keywords: Venous-to-arterial pCO_2 difference; high-risk surgery; postoperative complications; cardiopulmonary bypass

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Introduction

Individualized hemodynamic optimization during high-risk surgery is an essential key to patient care. Several studies have demonstrated that such strategies improve the postoperative course by reducing morbidity and mortality. Hemodynamic optimization is a preventive strategy aiming to adapt oxygen delivery (DO_2) to oxygen consumption (VO_2) to avoid tissue hypoperfusion during surgery (1). This strategy is based on optimization of blood pressure (fluid and/or vasopressor), cardiac output (CO) (fluid and/or inotrope), and perfusion parameters such as central venous oxygen saturation ($ScVO_2$) or arterial lactate. Nevertheless, normalizing systemic hemodynamic parameters and $ScVO_2$ does not guarantee adequate tissue perfusion, and a substantial number of patients still progress to multiple organ failure and death. Although blood lactate concentration was initially described as a surrogate marker of tissue hypoperfusion, an elevated lactate value may be associated with adrenergic stimulation and surgical stress (2).

Recently, the difference between venous carbon dioxide and arterial carbon dioxide pressure (pCO_2 gap) has been described as a parameter reflecting tissue hypoperfusion in critically ill patients who are insufficiently resuscitated (3). Similarly, the pCO_2 gap/$CavO_2$ ratio has been described as an indicator of the respiratory quotient, thus the relationship between DO_2 and VO_2 (4). Most of the knowledge about the pCO_2 gap and the pCO_2 gap/$CavO_2$ ratio comes from studies in the literature on animal models or intensive care unit (ICU) patients (5). These parameters have been demonstrated to be associated with several variables of tissue perfusion, and most importantly with outcomes (mortality, morbidity). To date, publications pertaining to the operative setting have been sparse.

The purpose of the present review is to discuss clinical evidence of the usefulness of the pCO_2 gap and CO_2-O_2 derived parameters in the operating room. We will then discuss the results according to the type of surgery (cardiac *vs.* non-cardiac) and propose clinical use.

Physiological background

According to the Fick equation, CO_2 elimination (VCO_2) equals the product of the difference between venous blood CO_2 content ($CvCO_2$), arterial blood CO_2 content ($CaCO_2$), and CO [$VCO_2 = CO \times (CvCO_2 - CaCO_2)$]. Because there is a linear association between CO_2 content and CO_2 pressure, the pCO_2 gap may be expressed as: pCO_2 gap = K * VCO_2/CO. Therefore, the pCO_2 gap could be associated with CO_2 generation and CO. As CO_2 is much more soluble than O_2, it represents a very sensitive marker of tissue hypoxia (6). Since the pCO_2 gap depends on CO and VCO_2, it represents an indicator of the capacity of venous blood to eliminate CO_2 generated by peripheral tissues, and thus the adequacy of blood flow during shock states. Interestingly, an inverse curvilinear relationship between the pCO_2 gap and CO has been described, highlighting the importance of blood flow on venous CO_2 accumulation (7,8).

Several studies on septic shock have found that an increase in CO with fluid expansion is associated with a decrease in the pCO_2 gap compared to increased CO (9). For a constant production of CO_2, the increase in CO is coupled with an increased arterial blood volume having a low CO_2 content passing through the tissue, producing a washout effect and lowering the venous CO_2 content. Another factor in the lowering of the pCO_2 gap is the effect of blood pH on the relationship between pCO_2 and total blood CO_2 content. This relationship is shifted to the right, with a pH decrease resulting in an increased pCO_2 gap for the same value of $CvCO_2$. Consequently, an increase in CO will be associated with lower pCO_2 gap if the tissue acid production is decreased by the improvement in oxygen supply (10). Finally, the mechanisms implicated in the elevation of the pCO_2 gap during shock states are not completely understood, and interpretation of the pCO_2 gap could sometimes be difficult.

The ratio between the pCO_2 gap and the arterial-venous oxygen difference (pCO_2 gap/$CavO_2$ ratio) has also been described (11,12). Under situations of tissue hypoxia, we can observe that a decreased VO_2 is associated with decreased aerobic CO_2 generation, whereas anaerobic CO_2 generation can still arise. Knowing that the VCO_2 is being reduced less than the VO_2, we can observe a rise in the VCO_2/VO_2 ratio (i.e., the respiratory quotient). Studies have demonstrated that the pCO_2 gap/$CavO_2$ ratio can be used as an indicator of the presence of overall tissue hypoxia in critically ill patients (13). Mekontso-Dessap and colleagues demonstrated, in a retrospective ICU cohort, that the pCO_2 gap/$CavO_2$ ratio may be a substitute for the respiratory quotient and blood lactate. The pCO_2 gap/$CavO_2$ ratio was able to predict the presence of hyperlactatemia (4). Subsequently, Monnet and colleagues demonstrated that this ratio was able to predict an increase in VO_2 following fluid expansion in ICU patients. The pCO_2 gap/$CavO_2$ ratio was able to better predict the presence of VO_2/DO_2 dependency phenomenon than blood lactate and $ScVO_2$ (14). In 2013, Vallet and colleagues proposed an interpretation of different shock states based on the analysis of blood lactate and O_2-CO_2 derived parameters (15) (*Table 1*).

Clinical relevance of the pCO_2 gap in high-risk non-cardiac surgical patients

Several observational studies have been conducted in patients undergoing non-cardiac surgery. A prospective study on 51 elective neurosurgical patients evaluated the correlation between the pCO_2 gap and CO. The authors demonstrated a close inverse correlation between CO and the pCO_2 gap for both central and mixed venous gas samples. They concluded that the pCO_2 gap could represent a useful parameter for CO assessment, and could be utilized in a neurosurgical practice involving postural changers (16). These authors did not evaluate outcomes. Futier and colleagues (17) conduced a retrospective study on 70 patients undergoing major abdominal surgery with an individualized goal-directed fluid replacement therapy. The

Table 1 Shock type according to lactate and O_2-CO_2 derived parameters (15)

Shock type	Lactate	O_2 extraction	$ScVO_2$	pCO_2 gap
Cardiogenic or hypovolemic	High	High	Low	High
Anemic or hypoxemic	High	High	Low	Low
Distributive	High	Low	High	High
Cytopathic	High	Low	High	Low

pCO_2 gap was measured every hour until the end of the surgery. Of the 70 patients, 34% developed postoperative septic complications. The authors demonstrate that high $ScvO_2$ was not associated with postoperative complications, and that the pCO_2 gap was the only parameter associated with complications (17). During the course of the surgery, the pCO_2 gap was larger in patients with complications (7.8±2 *vs.* 5.6±2 mmHg, P<0.05) than in patients without complications. In addition, a pCO_2 gap value >5 mmHg was able to predict postoperative complications with an area under the ROC curve (AUC) of 0.785 (95% CI: 0.74 to 0.83, P<0.05) (17). In patients with normal $ScVO_2$, the pCO_2 gap may be a useful complementary tool to identify patients who remain insufficiently optimized hemodynamically. Robin and colleagues later performed a prospective observational study in 115 high-risk non-cardiac surgery patients (mostly abdominal surgery) (18). The pCO_2 gap was evaluated at admission to ICU, immediately after surgery. Seventy-eight patients (68%) developed postoperative complications. The pCO_2 gap was significantly higher at ICU admission in patients who suffered from complications (8.7±2.8 *vs.* 5.1±2.6 mmHg, P<0.001). The pCO_2 gap predicted the occurrence of postoperative complications, with an AUC of 0.86 (95% CI: 0.77 to 0.95) and a cut off value of 5.8 mmHg. Moreover, the pCO_2 gap has a higher ability to predict postoperative complications than arterial lactate. Taking together the results of their studies, the authors concluded that "*the PCO_2 gap might be a useful and complementary tool to detect persistent tissue hypoperfusion that could be included as an additional step in the algorithms of early goal-directed therapy protocols*" (18).

Apart from a retrospective study on 66 patients undergoing abdominal surgery, Silva and colleagues demonstrated an association between the pCO_2 gap and mortality (19). A pCO_2 gap of over 5 mmHg was predictive of mortality, with an AUC of 0.73 (95% CI: 0.61 to 0.84, P<0.05) (19). Recently, in a multicenter prospective observational study in non-cardiac surgery, our group demonstrated that the pCO_2 gap and the pCO_2 gap/$CavO_2$ ratio were associated with the postoperative course (20). In summary, there is evidence supporting the association between the pCO_2 gap, the pCO_2 gap/$CavO_2$ ratio, and postoperative morbidity and mortality. To date, no study has assessed the ability of hemodynamic protocols based on the pCO_2 gap measurement to decrease postoperative complications.

Clinical relevance of the pCO_2 gap in high-risk cardiac surgical patients

A study performed in the 90's by Cavaliere and colleagues evaluated the pCO_2 gap in 30 patients in the early postoperative hours following cardiac surgery (21). Of the 30 patients, 21 (70%) developed postoperative complications. The pCO_2 gap was significantly higher at ICU admission in patients who suffered from complications (9±2 *vs.* 5±1 mmHg, P<0.001). By using a multiple linear regression analysis, the authors demonstrated that the pCO_2 gap was associated to the body temperature, the $paCO_2$ and the arterial mixed venous O_2 content difference. The pCO_2 gap was not associated to CO nor blood lactate (21). Based on the assumption that $ScvO_2$ remains challenging as a tool to identify patients with adequate circulatory status, Habicher and colleagues performed a study in cardiac surgical patients with normal $ScVO_2$ (22). The authors hypothesized that the pCO_2 gap could serve as an additional parameter to evaluate the adequacy of tissue perfusion. A retrospective data analysis on 60 patients was performed. The patients had a $ScvO_2$ ≥70% and were divided into 2 groups: the high-pCO_2 gap group (≥8 mmHg) and the low-pCO_2 gap group (<8 mmHg) (22). Patients with a high pCO_2 gap had worse postoperative courses, with higher lactate levels and worse splanchnic functions. These findings were associated with need for longer mechanical ventilation and longer ICU stays. In 2016, a retrospective study that included 220 consecutive patients after elective cardiac surgery evaluated

the association between the pCO_2 gap and postoperative complications (23). The pCO_2 gap was considered normal for a value less than 6 mmHg. The SOFA score and the mortality rate were higher in the low pCO_2 gap group than in the high pCO_2 gap group. Moreover, the pCO_2 gap had a low ability to predict outcomes (23). Guinot and colleagues subsequently evaluated the association between the pCO_2 gap during the ICU course following cardiac surgery and postoperative morbidity and mortality (24). Three hundred thirty-nine patients were enrolled in this prospective observational study. The pCO_2 gap was not predictive of the development of major complications. Moreover, the pCO_2 gap was poorly correlated with tissue perfusion parameters, and arterial lactate clearance (24).

Du and colleagues conducted an observational retrospective study to establish whether the pCO_2 gap/$CavO_2$ ratio could predict the hemodynamic response to resuscitation (25). Seventy-two patients undergoing cardiac surgery were analyzed. VO_2 responders were defined by an increased VO_2 of over 10%. The ratio appeared to be a reliable marker of overall anaerobic metabolism that predicted VO_2 response. Abou-Arab and colleagues later analyzed the ability of the pCO_2 gap/$CavO_2$ ratio to predict an increase in VO_2 upon fluid challenge in cardiac surgical patients (26). One hundred ten patients, consecutively admitted to a cardiothoracic ICU and in whom fluid expansion was performed, were included. VO_2 responders were defined as patients showing more than 15% increase in VO_2. Arterial pressure, CO, and arterial and venous blood gas levels were measured before and immediately after the fluid challenge. CO_2-O_2 derived variables were not predictive of VO_2 changes following fluid challenge in this specific population (26). Only $ScVO_2$ was poorly predictive of VO_2 changes. The pCO_2 gap/$CavO_2$ ratio was not associate to arterial lactate. Interestingly, the authors observed a decrease in the pCO_2 gap only in non-VO_2 responder patients, suggesting a different pattern of microcirculatory alteration following cardiac surgery than in sepsis.

In summary, association between the pCO_2 gap, pCO_2 gap/$CavO_2$ ratio, postoperative course and anaerobic metabolism is unclear in cardiac surgical area. Small and retrospective studies demonstrated positive results whereas larger cohort demonstrated negative results.

Divergence between non-cardiac surgery, cardiac surgery, and septic critically ill patients

When analyzing the literature, some explanations can be found regarding discrepancies in the published results. The most important is probably the type of surgery (21,27). Cardiac surgery with cardiopulmonary bypass is a specific physiologic situation that may be associated with factors altering the relationship between CO_2-O_2 derived content and pressure, VCO_2, DO_2, VO_2, and tissue perfusion. On the contrary, non-cardiac major surgery is often abdominal surgery which may be more similar to the macro- and micro-circulatory disturbance observed in ICU patients (19). Ruokonen and colleagues have already studied the ability of the pCO_2 gap to assess tissue perfusion in cardiac surgery patients by using a control group of abdominal surgery patients (27). According to this author, a pCO_2 gap rise is frequent after cardiac surgery and better reflects an alteration of systemic and regional perfusion compared to tissue hypoxia (26). In this way, some studies did not demonstrate any association between the pCO_2 gap, pCO_2 gap/$CavO_2$ ratio, arterial lactate and VO_2 (21,26).

The relationship between CO_2-O_2 derived content and pressure depends on several parameters that can be altered in the operating theatre, specifically in cardiac surgery. Of these parameters, body temperature, alveolar ventilation, and hemodilution may be of importance. Van der Linden and colleague have demonstrated an increase in the pCO_2 gap during acute hemorrhaging in anesthetized dogs. Hemorrhage was associated with a progressive increase in venous pCO_2, with a corresponding widening of the pCO_2 gap which was correlated with a blood lactate change (28). Nevertheless, hemodilution was demonstrated to have more complex effects on CO_2-O_2 derived variables than hemorrhage (29,30). During mechanical ventilation, alveolar ventilation may be associated with pCO_2 changes. Mallat and colleagues and Morel and colleagues demonstrated similar results when analyzing the pCO_2 gap during rising alveolar ventilation (31,32). Both studies demonstrated that rising alveolar ventilation is associated with an increased pCO_2 gap. These changes were related to changes in VO_2, systemic vasoconstriction, and variations in the PCO_2/CO_2 content relationship (31,32). By altering the metabolism and the PCO_2/CO_2 content relationship, body temperature can alter the adequacy of the pCO_2 gap. Utoh and colleagues demonstrated, in cardiac surgical patients, that the two main factors associated with high pCO_2 gap values were the duration of cardiopulmonary bypass surgery and the minimum rectal temperature. Cardiac surgery was shown to be associated with changes in metabolic rate, CO, and VO_2 (15,21). Such alterations can occur throughout first postoperative hours.

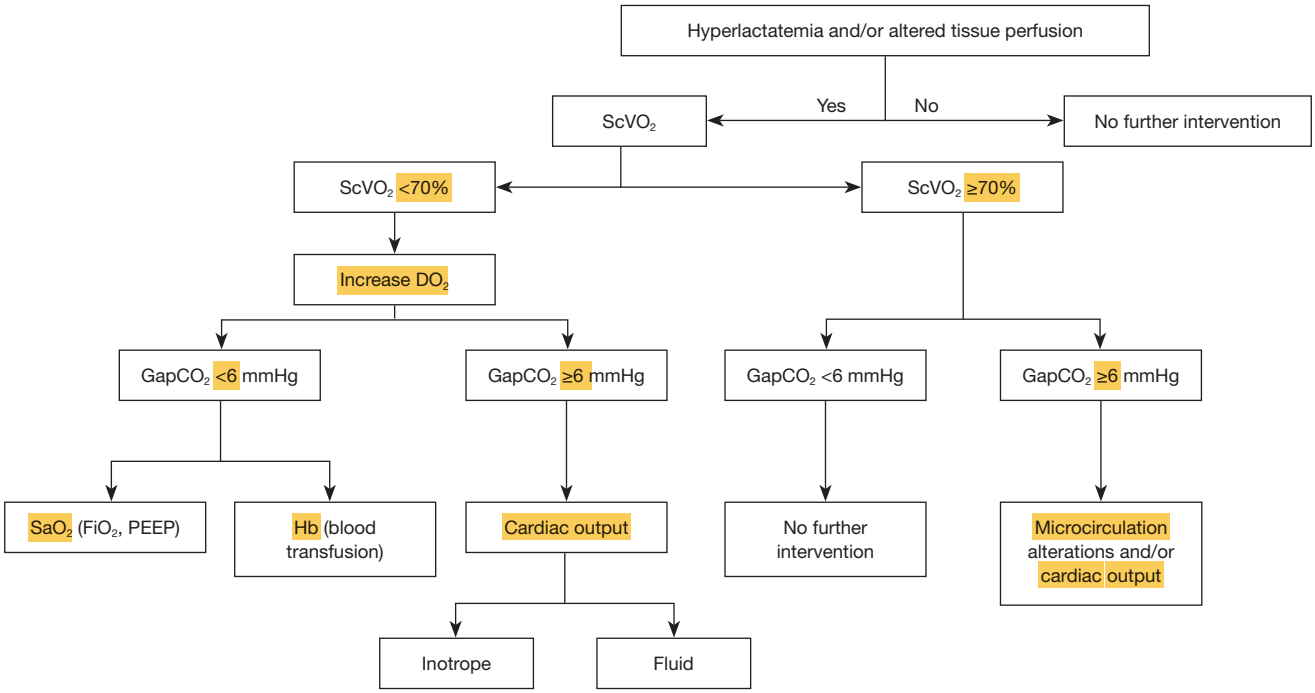

Figure 1 Proposed algorithm to guide hemodynamic treatment in high-risk surgical patients. $ScVO_2$, central venous oxygen saturation; PEEP, positive end-expiratory pressure.

The extent of microcirculation alterations caused by sepsis, surgery, and cardiopulmonary bypass may differ (33,34). Sepsis is normally associated with impaired microcirculatory regulation, decreased functional capillary index, absent/intermittent capillary flow, increased heterogeneity in the perfusion index, arteriovenous shunting, and cellular hypoxia (35). On the contrary, cardiopulmonary bypass is associated with many reversible alterations in microcirculation, including a decrease in microvascular perfusion, increased heterogeneity in the perfusion index and red blood cell velocity, and arteriovenous shunting (33,36). These changes are associated with alterations in the arteriovenous oxygen difference, VO_2, and CO_2 and O_2 diffusion (37). During major abdominal surgery, the microvascular perfusion is not altered, and it is not associated with postoperative complications (38). Nevertheless, an impaired microvascular flow can appear during the postoperative period when patients suffer from complications (38). These changes are similar to those observed in sepsis (39).

Use of the pCO_2 gap in high-risk surgical patients

One has to keep in mind that a high pCO_2 gap may not necessarily indicate an alteration in tissue perfusion or a low flow state. Moreover, studies have demonstrated that a normal pCO_2 gap does not preclude the presence of tissue hypoxia, and thus has poor sensitivity to detect tissue hypoxia (8,40). In patients with low CO and a normal arterial lactate value, the pCO_2 gap was demonstrated to be increased (7). Keeping in mind these limitations and the fact that, to date, no randomized study using the pCO_2 gap has been published, the pCO_2 gap may be interpreted according to the type of surgery (cardiac *vs.* non-cardiac), medical situation (e.g., sepsis, haemorrhage, cardiogenic), and macro- and micro-hemodynamic parameters (e.g., CO, arterial lactate, $ScVO_2$). The pCO_2 gap may be considered as a parameter reflecting the ability of blood flow to remove the total CO_2 produced by tissue rather than a marker of tissue dysoxia. Based on these interpretations, several authors have proposed algorithms. Among them, an algorithm based on the lactate value may be useful in the choice of therapeutic treatment for acute circulatory failure (*Figure 1*).

Conclusions

The pCO_2 gap can be considered as a marker of CO

adequacy for the overall metabolic demand that has been associated with the postoperative course in non-cardiac major surgery. The pCO_2 gap may not always be a marker of tissue hypoxia. During hemodynamic treatment, the interpretation of the pCO_2 gap may help physicians to understand which variables can be optimized. In cardiac surgery, results are inconsistent because of many factors altering the pCO_2 gap interpretation. In surgical patients without any sign/parameter of tissue hypoperfusion, manipulating the pCO_2 gap may be done with caution.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Review Article

Transcutaneous PCO_2 monitoring in critically ill patients: update and perspectives

Arnaud Mari[1], Hélène Nougue[2,3,4], Joaquim Mateo[2,3,4], Benoît Vallet[5], Fabrice Vallée[2,3,4,6]

[1]Intensive Care Unit, Hôpital Yves Le Foll, Saint-Brieuc, France; [2]Department of Anesthesiology and Critical Care, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]UMR-S942, Hôpital Lariboisière, Paris, France; [4]University of Paris Diderot, Paris, France; [5]EA2694 University of Lille, Lille, France; [6]MEDISIM, Inria Paris-Saclay, Palaiseau, France

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Correspondence to: Arnaud Mari, MD. Intensive Care Unit, Hôpital Yves Le Foll, Saint-Brieuc, France. Email: arnaud.mari@ch-stbrieuc.fr.

Abstract: The physiology of venous and tissue CO_2 monitoring has a long and well-established physiological background, leading to the technological development of different tissue capnometric devices, such as transcutaneous capnometry monitoring (TCM). To outline briefly, measuring transcutaneous PCO_2 ($tcPCO_2$) depends on at least three main phenomena: (I) the production of CO_2 by tissues (VCO_2), (II) the removal of CO_2 from the tissues by perfusion (wash-out phenomenon), and (III) the reference value of CO_2 at tissue inlet represented by arterial CO_2 content (approximated by arterial PCO_2, or $artPCO_2$). For this reason, there are, at present, roughly two clinical uses for $tcPCO_2$ measurement: a respiratory approach where $tcPCO_2$ is likely to estimate and non-invasively track $artPCO_2$; and a hemodynamic under-estimate use where $tcPCO_2$ can reflect tissue perfusion, summarized by a so-called "tc-art PCO_2 gap". Recent research shows that these two uses are not incompatible and could be combined. The spectrum of indications and validation studies in ICUs is summarized in this review to give a survey of the potential applications of TCM in critically ill patients, focusing mainly on its potential (micro)circulatory monitoring contribution. We strongly believe that the greatest benefit of measuring $tcPCO_2$ is not to only to estimate $artPCO_2$, but also to quantify the gap between these two values, which can then help clinicians continuously and noninvasively assess both respiratory and hemodynamic failures in critically ill patients.

Keywords: Transcutaneous capnometry; carbon dioxide monitoring; intensive care; microcirculation; shock

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Introduction

The measurement of oxygen (O_2) and carbon dioxide (CO_2) gas tension via a transcutaneous route which could non-invasively assess arterial blood gas pressures ($artPO_2$ and $artPCO_2$, respectively) was developed in the 1980s (1). For transcutaneous capnometry (measuring transcutaneous carbon dioxide gas pressure, $tcPCO_2$), sensors are based on chemical electrodes, which Dr. Severinghaus adapted for use in blood gas analysis (2-4). In respiratory failure, the evaluation of adequacy of alveolar ventilation with $artPCO_2$ remains a routine challenge. With consideration of some technical or device-related cautions, relevant interpretation of $tcPCO_2$ measurement is plausible, and can lead to reliable $artPCO_2$ estimation with transcutaneous capnometry monitoring (TCM) while limiting blood gas analysis and arterial puncture (5). Importantly, $tcPCO_2$ is also by nature and physiology a circulatory variable which is dependent on systemic and local cutaneous perfusion conditions. During circulatory failure, decoupling between $artPCO_2$ and $tcPCO_2$ occurs, leading to tissue hypercarbia unrelated to arterial PCO_2 (6-8). Interestingly, this mismatch, with

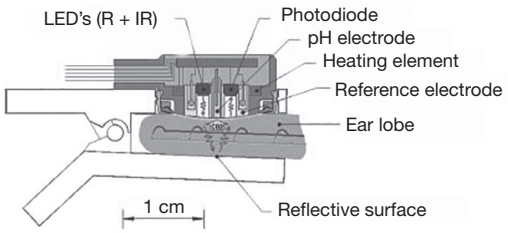

Figure 1 A transcutaneous PCO_2 sensor at the ear lobe using Stow-Severinghaus technology, from Eberhard *et al.* (2,9).

a strong physiological and clinical background, offers potential perspectives for peripheral tissue perfusion monitoring in the critically ill patient (9). Although this approach has been investigated since the 1980s, adherence remains low in daily clinical practice. Updated technology and recent clinical reports of innovative modifications including measurement at low temperature (37 ℃) and/or with thermal challenge (electrode heated from 37 ℃ to 42 ℃) have yielded promising results that may provide crucial support for the use of this tool in the field of peripheral tissue perfusion monitoring (1,10,11).

The body of indications and validation studies in ICUs are summarized in this review to give a panorama of potential applications of TCM in critically ill patients.

$tcPCO_2$ technology

Dr. Severinghaus was the first to describe the measurement of PCO_2 on human skin surfaces (3). Transcutaneous measurement of PCO_2 is based on the phenomenon of CO_2 gas diffusing very easily throughout the body tissue and skin, and can thus be detected by a sensor on the skin surface. CO_2 is measured by determining the pH of an electrolyte solution separated from the skin by a highly permeable membrane. A change in the pH is then proportional to the logarithm of PCO_2 change (*Figure 1*). By heating the skin, vasodilation with local hyperemia is produced which increases the diffusion of CO_2 and increases the delivery of arterial blood to the dermal capillary area beneath the sensor. Most of the time, the sensor is heated between 42 ℃ and 44 ℃ to create the "arterialization" of the tissue (by small arteriole and capillary dilatation) leading to an increase of arterial contribution in the signal. Overall, transcutaneous PCO_2 measurements correlate fairly well with the corresponding arterial PCO_2 values, even after applying a correcting algorithm to take into consideration the physico-chemical modifications after elevating the temperature of the sensor (2).

This electrochemical method has proven to be accurate and reliable but requires an *ex vivo* "calibration period" before placing the sensor on the skin, and a subsequent *in vivo* "equilibration period" to obtain a stable value. It should be noted that the position of the sensor at the earlobe shortens this equilibration time due to its rich vascularization and thus decreases the time response and analytic inertia during acute changes. This technical limitation has hindered the development and use of $tcPCO_2$ monitoring as a surrogate of $artPCO_2$ in current practice (1). A technology based on obtaining $tcPCO_2$ by infrared light is currently being developed to try to increase the ease and reactivity of bedside measurement (2).

$tcPCO_2$ monitoring: physiological overview

Physiology of tissue and cutaneous carbon dioxide monitoring has a long and well-established physiological background, which has been the foundation for the development of different mucosal and cutaneous capnometric devices, extensively described in recent quality reviews (1,6,9). At its core, the measurement of $tcPCO_2$ is dependent on three main phenomena:

(I) The production of CO_2 by the tissues (VCO_2);
(II) The removal of CO_2 from the tissues by perfusion (so-called "washout-out" phenomenon);
(III) The reference value of CO_2 at tissue inlet represented by arterial CO_2 content ($CaCO_2$).

For this reason, there are, at present, roughly two clinical uses for $tcPCO_2$ measurement: a respiratory use where $tcPCO_2$ is likely to non-invasively estimate and track $artPCO_2$, and a hemodynamic use where $tcPCO_2$ could reflect tissue perfusion by an evaluation of the difference between $tcPCO_2$ and $artPCO_2$, so-called "gap CO_2". The simplified physiology of TCM and the main clinical scenario reflecting these two indications are schematically illustrated in *Figure 2* (respiratory use *Figure 2A,B*, hemodynamic use *Figure 2C,D,E,F*). Additionally, we have depicted three frequent and relevant clinical issues and described them according to whether the monitoring of $tcPCO_2$ is performed with a sensor at 37 ℃ or a heated sensor at 42 ℃ to 44 ℃ (11,12). The three clinical hemodynamic situations are the following:

(I) A stable circulatory state with almost preserved tissue perfusion conditions, when $tcPCO_2$ can be interpreted as an $artPCO_2$ surrogate;

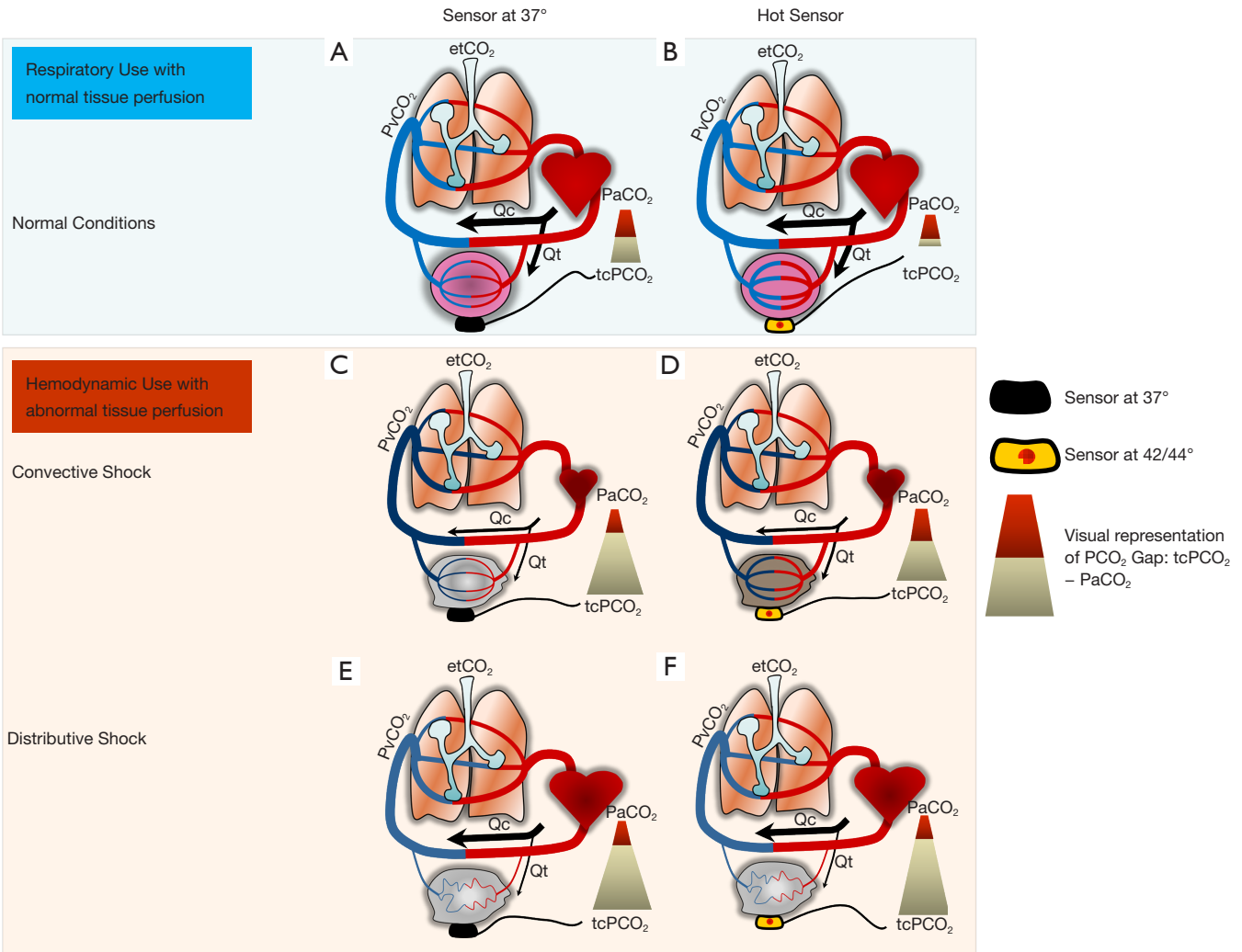

Figure 2 Pathophysiological patterns describing transcutaneous capnometry during respiratory and hemodynamic issues, resumed in schematic vignettes or panels (n=6). See text for extensive description and commentary. Qc, cardiac output; Qt, regional or tissue flow; Pa CO_2 or $artPCO_2$, arterial CO_2 tension; $PvCO_2$ or $cvPCO_2$, central-venous CO_2 tension; $tcPCO_2$, transcutaneous CO_2 tension; $etCO_2$, end-tidal CO_2 tension.

(II) An overt shock state with low cardiac output or low O_2 delivery called "convective shock", for and corresponding to core pathophysiological patterns of hypovolemic, hemorrhagic or cardiogenic shock;

(III) A "distributive shock" corresponding to a resuscitated septic shock with restored cardiac output but with an alteration of peripheral microperfusion.

Moreover, as warming the skin impacts $tcPCO_2$ value and local cutaneous blood flow, behavior of tissue hypercarbia depends on locally applied electrode temperature (1,2). For this reason, interpretation of $tcPCO_2$ measurements must take into account the temperature level (i.e., normothermia at 37 ℃ *vs.* heated conditions at 42–45 ℃) (11). The authors propose this graphic representation in order to illustrate and clarify these six "clinical and measurement situations" based on robust physiological concepts and the results of their recent work. Each illustration will be developed in more detail in the sections to follow.

$tcPCO_2$ monitoring as a surrogate of $artPCO_2$

TCM to track $artPCO_2$ variations: remind the basics

Cutaneous PCO_2 represents a mixture of venous, capillary, and arterial CO_2 tension values. In normal conditions,

tissue metabolism (VCO_2) is coupled with tissue perfusion. When metabolism increases, all the CO_2 produced is washed out so that the PCO_2 gap between $tcPCO_2$ and $artPCO_2$ ($_{tc\text{-}art}\Delta PCO_2$) remains constant at around 5 mmHg (*Figure 2A*) (8,9). Heating the skin from 37 ℃ to 45 ℃ increases the skin blood flow by three to four times and enhances the contribution of arterial blood flow by opening the precapillary sphincter arterioles (1,3). Also, in preserved circulatory conditions, $tcPCO_2$ with heated electrodes (42–45 ℃) will closely approximate $artPCO_2$, as heat produces the so-called "arterialization" of local blood flow in the cutaneous area where the sensor is applied (*Figure 2B*) (13-15). Two correcting factors are then applied to bring the $tcPCO_2$ value close to the value of $artPCO_2$: (I) a fixed correction is removed from the crude $tcPCO_2$ value, as an "aerobic factor", and, as a consequence, that tissue PCO_2 is always physiologically higher than the arterial PCO_2 regardless of the quality of tissue arterialization (4.5 mmHg/℃); (II) a Severinghaus constant is applied, due to the increase of $tcPCO_2$ responds to the CO_2 production induced by the heat of the sensor, also called the "metabolic constant", ranging from 5 to 10 mmHg depending on the type of device (2).

Summary of the clinical evidence for $tcPCO_2$ as a reliable $artPCO_2$ surrogate

As the main purpose of this issue concerning CO_2-related variables is to focus on hemodynamic management, we will briefly relate and summarize the main clinical data available on TCM for respiratory use.

We can reasonably state that TCM may be useful for non-invasively and continuously estimating actual arterial PCO_2, which can be of critical importance during respiratory pump failure leading to alveolar hypoventilation with hypercapnic issues. This tool could prevent the need to perform iterative blood gas analysis and could help to monitor the course of $artPCO_2$ with populations in whom estimates of $artPCO_2$ may guide therapeutic interventions. Different pathophysiological disorders are likely to promote an increase of $artPCO_2$: low alveolar ventilation (with related respiratory acidosis), increased dead space (anatomic or functional), depressed respiratory drive, or bronchial obstructive diseases as acute exacerbation of chronic obstructive pulmonary disease (COPD), especially whose receiving NIV.

While monitoring $tcPCO_2$ is considered as a valid method in routine respiratory care practice for assessing the adequacy of ventilation (16), and the cumulative data available in the specific setting of critically ill patients appears to be substantial, the precision of the technique as an $artPCO_2$ surrogate is still disputed (3,5). Examination of the aggregated literature suggests that accuracy and reliability appear good with limits of agreement in a narrow range for most ICU patients (inside ±5 mmHg and almost all values inside ±10 mmHg) (1,5). However, this opinion is debated, as other authors claim that confidence may be insufficient, as around 20% of the values of arterial-to-transcutaneousPCO_2 difference are outside the acceptable range of ±7.5 mmHg (15). There are also numerous reports underscoring the underestimation in the highest $artPCO_2$ values along with other authors who consider the TCM unsuitable or disputable for the emergency room or ICU patients (3,17,18).

As it concerns end tidal CO_2 ($EtCO_2$), pragmatically speaking, the relevance of $tcPCO_2$ could be increased with an initial and punctual concomitant arterial blood gas analysis to estimate initial potential gradient, and repeated sequentially so as to not dismiss the distortion with time. Relating to this, Horvath *et al.* reported good concordance during NIV for ARF and that discordance might have decreased with the initial $_{tc\text{-}art}\Delta PCO_2$ estimate to rule out discrepancy (19). Additionally, Rodriguez *et al.* reported good correlation in PCO_2 data changes (transcutaneous and arterial) over a 17-hour period, and only 20% of the samples had minor changes in opposing directions (13).

Nonetheless, Conway *et al.* recently pooled the available literature on the accuracy and precision of TCM to offer the most complete picture about this issue in a review with extensive meta-analysis (whole pooled population: 7,021 paired measurements, 2,817 patients in 73 studies; ICU patients: 16 studies (22% of 73 reviewed studies) with n=2,128 measurements; acute respiratory failure, 14 studies, n=993 paired measurements). In the whole population, they concluded that there are substantial differences between $tcPCO_2$ and $artPCO_2$ depending on the technical aspects (17,20,21), such as location site or temperature of electrode, and advocated the ear lobe as the site and a heated electrode of more than 42 ℃ for the temperature. However, these authors stated that the available literature attests to TCM being an accurate tool to estimate $artPCO_2$ to a clinically acceptable degree in the adult ICU population (22).

Finally, many factors or limitations should be considered when interpreting $tcPCO_2$-observed values as a surrogate of $artPCO_2$. Hasibeder *et al.* reported that $artPCO_2$ and cardiac output values could only explain 66% of the $tcPCO_2$

value variability, suggesting that many other factors were distorting the concordance between transcutaneous and arterial CO_2 in ICUs (23). In our opinion, it would be interesting to further investigate the role of several factors, especially in most hypercapnic critically ill patients with acidosis, to determine the accuracy of $tcPCO_2$ in outlier ICU patients and help in the interpretation of TCM. The most important factors appear to be the technological concerns relating to device performance and differences between monitors (TCM developed by SenTech© or Radiometer©, fiberoptic sensors etc.), location of sensor for measurement, cutaneous adiposity or edema, and of course, disturbed peripheral perfusion by adrenergic tone, drugs, sepsis, shock, fever, etc. However, the respective contribution of each factor may be difficult to capture in ICUs, as outlined by these authors (13).

To conclude this chapter, and in accordance with abundant concordant literature, we advocate the potential use of TCM in ICUs for ventilator management, because of its non-invasiveness, continuous monitoring, and accuracy of the transcutaneous CO_2 sensor technology (2,5,13,15,22,24-26). For the longitudinal use as a trending monitor, we support the application of iterative punctual invasive $artPCO_2$ measurements with blood gas analysis to recalibrate and rescale the difference between arterial and transcutaneous PCO_2 value, or $_{tc\text{-}art}\Delta PCO_2$ gap (13,22). In this way, TCM could perform an interesting sniffing function over time to track artPCO2 elevation during therapeutic procedures such as prolonged NIV. Finally, in the case of suspected altered tissue perfusion or ongoing shock, $tcPCO_2$ signal may be ambiguous and should be interpreted with caution, as detailed in the next section.

$tcPCO_2$ monitoring as a marker of tissue perfusion

Proof of concept and clinical rationale for use of capnometric data (CO_2 derived parameters) in altered tissue perfusion during macrocirculatory or microcirculatory failure have been extensively demonstrated and described (6-8,27-29). These numerous studies clearly demonstrate that the elevation of tissue CO_2 is ubiquitous throughout the body in shock states, and is closely related to tissue perfusion alteration. This paradigm has been evidenced by monitoring tissue PCO_2 at different clinically available sites including the gastric, buccal, sub-lingual, and thus, the skin level. Schematically, the difference between $tcPCO_2$ and $artPCO_2$ ($_{tc\text{-}art}\Delta PCO_2$ gradient) can increase when circulatory failure or occult microcirculatory shock is ongoing. This may be considered a limitation of the arterial PCO_2 estimation technique, and may give an opportunity for hemodynamic assessment in specific clinical situations.

$tcPCO_2$ in low oxygen delivery situations or convective shocks

Behavior of $tcPCO_2$ during macrocirculatory failure leading to low cardiac output and/or low O_2 delivery (DO_2), referred to as "convective shocks" (cardiogenic or hemorrhagic shock), is depicted in (*Figure 2C*) (12). When circulatory failure occurs, $tcPCO_2$ and $artPCO_2$ mismatch and become decoupled as demonstrated in a famous and seminal clinical study from an L.A. team of Tremper and Shoemaker who monitored the kinetics of $tcPCO_2$ during overt shock states (hemorrhage, heart failure, or the operating room) (*Figure 3*) (30). This figure illustrates the hemodynamic nature of $tcPCO_2$ as we can observe that $tcPCO_2$ values mirror the cardiac output time course, and become dramatically decoupled from $artPCO_2$ kinetics in the clinical case condition of low flow states. In this setting, note that the difference between tissue and arterial PCO_2 is more relevant than the absolute value of $tcPCO_2$ to track local tissue PCO_2 balance (and overcome the influence of arterial CO_2 content and thus $artPCO_2$ on $tcPCO_2$). In this framework, high PCO_2 gap values may be suggestive of flow stagnation by low local perfusion. Many clinical reports, along with robust experimental data, support the notion that hemorrhagic or cardiogenic shocks, together with cardiac arrest, lead to a huge increase in tissue hypercarbia. Of note, some recent additional pre-clinical data reinforce this currently still valid finding (29,31).

$tcPCO_2$ in microcirculatory or distributive shock

According to experts, the gold-standard technique for microcirculatory perturbation assessment remains optical direct sublingual microvideoscopy (SDF-OPS or IDF technologies) (32). However, these tools appear cumbersome, require time-consuming offline analysis, and have not yet reached clinical utility despite over a decade of research and technological advance. Also, a system to assess the microcirculation at the point of care seems highly desirable. On the other hand, the clinical signs of peripheral perfusion impairments (skin mottling, refill capillary time, etc.) are meaningful and informative for microcirculatory derangement but may appear late and be

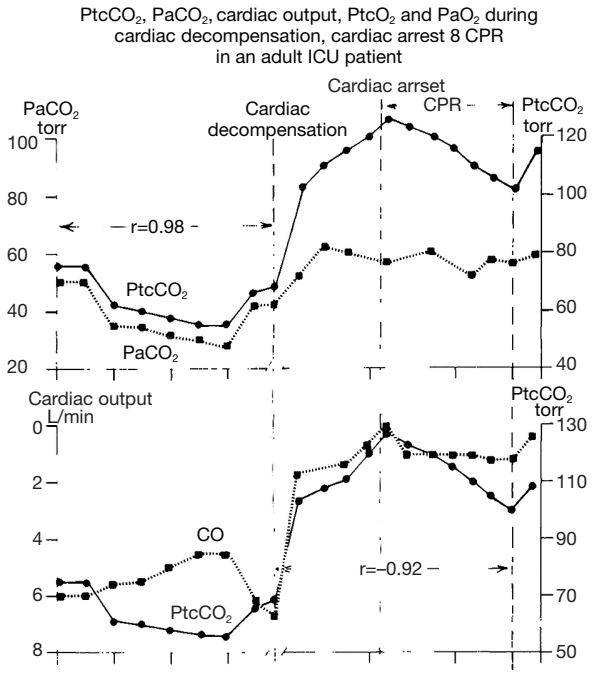

Figure 3 Two-day time course of $PtcCO_2$ and PaO_2, upper section; $PtcCO_2$ and cardiac output (CO plotted inversely i.e., with zero at the top to 8 L/min at the bottom of the scale), lower section. Note during the first day, the close trend of $PtcCO_2$ with $PaCO_2$, while the patient has adequate blood flow (CO >4 L/min). During day 2, the CO drops to below 2 L/min and $PtcCO_2$ rises, and note how $PtcCO_2$ correlates with1/CO (r=–0.92). Also note how $PtcCO_2$ responds to CPR by a decrease of more than 20 torr (upper section). Adapted from (30).

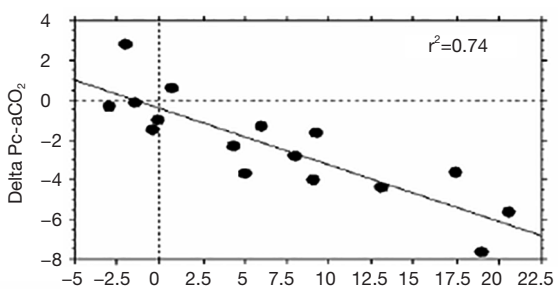

Figure 4 Relation between changes in delta Pc-aCO_2 (as cutaneous-arterial ΔPCO_2) and changes in microcirculatory skin blood flow assessed by laser Doppler flowmetry (delta TPU, variation or tissue perfusion unit, abscissa axis) during 16 fluid challenges. For more details, see (10).

insufficiently sensitive for guiding therapeutics. As outlined by several authors, refined therapeutic tailored management should embrace and target microcirculatory dimensions of shock (33). Tissue capnometry, via gastric or sublingual routes, or more simply with trans-cutaneous monitoring, could aid in this purpose, and offer, as complement, a more sensitive insight than that provided by clinical examination (9-11,27,33).

Gastric tonometry and sublingual capnometry have shown their clinical validity and their relationship to microperfusion, but have not been put into practice at this time due to paradigmatic or technological concerns (6,9). As an alternative, skin monitoring at the earlobe thus seems to be a user-friendly way to monitor tissue CO_2. Indeed, in a previous work, Vallée *et al.* used this device to examine whether cutaneous earlobe $tcPCO_2$ could be used to assess tissue perfusion in septic shock patients. In that study, the sensor was heated at 37 ℃ to limit the impact of arterial PCO_2 on cutaneous PCO_2 due to the arterialization of the blood being minimal compared with when the sensor is warming to 42 ℃ (10). They found that a threshold value of 16 mmHg for the gradient between the earlobe $tcPCO_2$ and arterial PCO_2 reliably discriminated between those patients with septic shock and tissue hypoperfusion from those patients in the control group, with a sensitivity of 83% and a specificity of 90%. Furthermore, it was found that the fluid challenge induced a decrease in the earlobe to-arterial PCO_2 gradient in parallel with the improvement of the microcirculatory blood flow in the earlobe (*Figure 4*). Interestingly, where a significant reduction in earlobe-to-arterial PCO_2 gradient was observed in survivors compared to non-survivors, no significant changes were found with the traditional macrocirculatory parameters (cardiac output and central venous oxygen saturation). Interestingly, these authors confirmed the microcirculatory nature of $tcPCO_2$ signal as demonstrated by the correlation between laser-Doppler flowmetry investigation and $tcPCO_2$ values (*Figure 5*). $tcPCO_2$ at 37 ℃ at the earlobe, therefore, seems to be a plausible tool to continuously and non-invasively estimate tissue perfusion in shock patients in ICUs.

$tcPCO_2$ monitoring with variations of sensor temperature: insights from a heat challenge

We have seen that the $tcPCO_2$ can be monitored at 37 ℃ with a heated sensor. The dynamic change in the

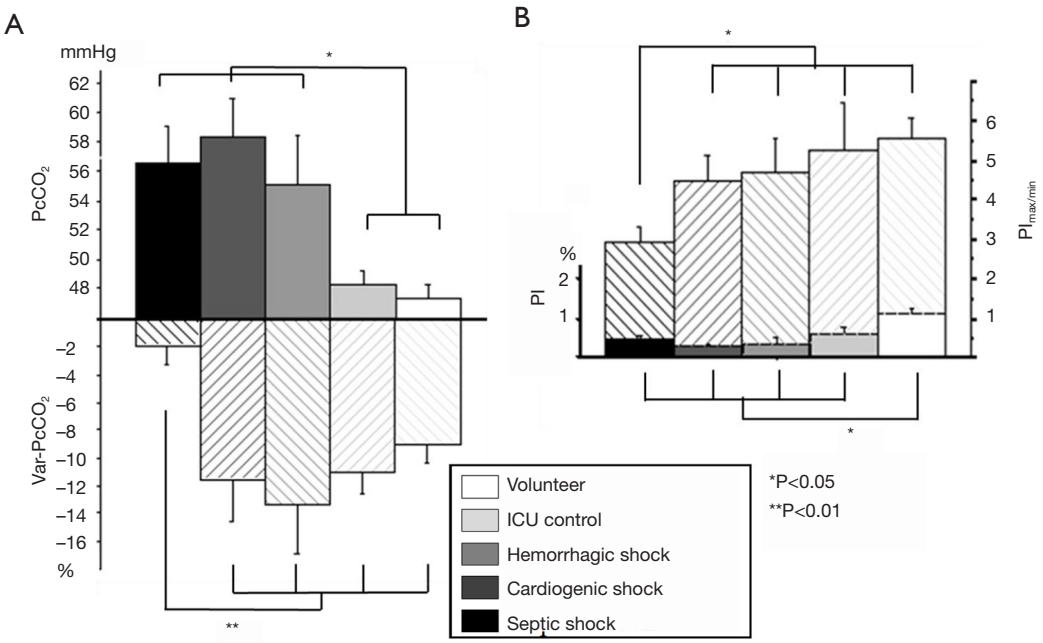

Figure 5 Results of the heating challenge at baseline in the different groups (volunteers, ICU control, hemorrhagic shock, cardiogenic shock, septic shock). (A) Baseline $tcPCO_2$ (or $PcCO_2$) measured at 37 ℃ (solid bars), and tc-art$\Delta PcCO_2$ ($\Delta PcCO_2$) (hashed bars). (B) Baseline plethysmographic perfusion index (PI) measured at 37 ℃ (solid bars) and $PI_{max/min}$ (hashed bars). For more details, see reference (11).

temperature may therefore appear as a dynamic test to evaluate tissue perfusion during shock. Heat challenge may be added to track microcirculatory failure and reversibility. This concept of studying the variations of cutaneous capnometry during a heating challenge was recently described (*Figure 6*) (11). The same paradigm has been used in a recent study by the De Backer team with a laser-Doppler flowmetry device, adding external validity for heat or thermal challenge with TCM (34). Schematically, a crude estimate with no heated electrode (standardized normothermia) together with a functional provocative test (as a thermal or heating challenge) could be useful or informative on peripheral perfusion to evaluate tissue hypercarbia related to low flow states or altered microcirculation with loss of "hemodynamic coherence", as recently conceptualized as occurring during sepsis and "microcirculatory shock" (35). For example, in the case of convective shock, without functional microcirculatory damage, the heat challenge will induce vasodilation which can lead to a decrease in $tcPCO_2$ by a recruited flow (or washout phenomenon) (*Figure 2D*). This is conceptually more hazardous in the case of a longstanding distributive shock where the constitutive alteration of the microcirculation (shunt, micro-thrombi, etc.) is not even slightly sensitive to vasodilation induced by the local increase in the temperature of the sensor (*Figure 2F*). Thus, a heat challenge (*Figure 2D*), which is likely to recruit a microvascular contingent with preserved vasoreactivity, could help to confirm hemodynamic coherence (intact macro-microcirculatory coupling) and/or to diagnose the reversibility of local peripheral hypoperfusion and anticipate targeted therapies (11). From this perspective, the combined monitoring of the perfusion index (PI) from the photoplethysmography signal also allows a good reflection of the quality of vasodilation and "arterialization" induced by the local heating of the sensor (*Figure 5*).

$tcPCO_2$ monitoring: personal perspectives and unanswered questions

We promote the graphical conceptual framework depicted in *Figure 2* to describe two possible uses of TCM in ICUs. The first, and most commonly proposed utility, is when TCM is used to estimate $artPCO_2$ for respiratory issues (*Figure 2A,B*); the second is when TCM is used to estimate tissue perfusion in shock states (*Figure 2C,D,E,F*). We believe that these two approaches are not conflicting, but it seems necessary to consider the limitations and specific

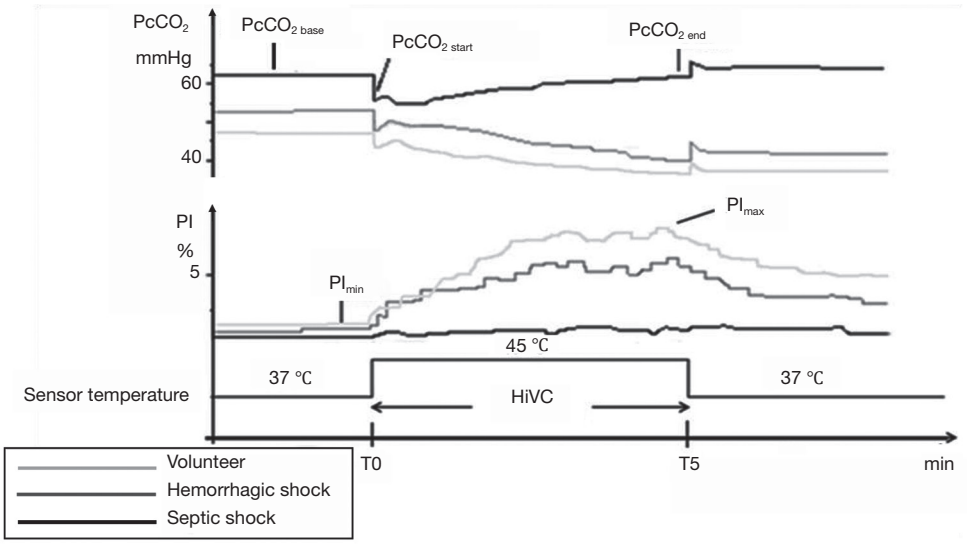

Figure 6 Stereotypical examples of the heating challenge performed in a healthy volunteer (light grey), non- septic shock (hemorrhagic in this example, medium grey), and septic shock patient (black). For more details, see reference (11). $PcCO_2$ or $tcCO_2$, transcutaneous CO_2 tension; PI%, plethysmographic perfusion index.

conditions for each indication. In doing so, we can obtain the appropriate bedside interpretation and receive the maximum benefit from this currently underused, but non-invasive and continuous type of benign monitoring. Indeed, we believe that a dual approach could allow the clinicians to better capture both the respiratory and hemodynamic status of the most severe patients. For example, a patient under respiratory TCM monitoring who exhibits an unexpected increase in $tcPCO_2$ due to *de novo* or early onset shock, may be misinterpreted as a false positive of a presumed related respiratory issue instead of a tissue perfusion abnormality. For this reason, we might advocate the continuous use of the sensor at low temperature (37 ℃) to thereby limit the risk of skin burns, but with regular heating challenges and a coupled and dynamic analysis of all parameters. Indeed, a "normal" 37°-$tcPCO_2$ value would show that there is no patent tissue perfusion disorder (*Figure 2A*), and then the $tcPCO_2$ value at the end of the heating test would reflect a value close to $artPCO_2$ (*Figure 2B*). Conversely, a high value of $tcPCO_2$ would attempt to show abnormalities in tissue perfusion (*Figure 2C,E*), and the heating test would make it possible to monitor the existence of microcirculation dysfunction and its reversibility, which would be strongly related to the prognosis of a patient in shock (*Figure 2D,F*). We believe that these assumptions would allow for a unique and codified interpretation of TCM. Obviously, additional studies dealing with different clinical situations and populations are mandatory to further support our hypotheses and refine our suggested algorithm. There are also many unanswered questions which include the temperature of the sensor in relation to the skin temperature (iso *vs.* normothermia), the thermal variations and kinetics during a heating test, the position at the earlobe as a reflection of the whole peripheral perfusion, and the variability and reproducibility of the $tcPCO_2$ value mainly in specific clinical situations such as acidosis or hyperoxia (2,13,23). Furthermore, it will be necessary to compare TCM with other devices that estimate the microcirculation, and to ultimately test drugs targeting microcirculatory dysfunction. To conclude, as a next step, we suggest integrating values of the $tcPCO_2$ and tc-$artPCO_2$ gap into holistic therapeutic algorithms, and advocate considering systemic and regional CO_2-related parameters for advanced circulatory monitoring, as recently proposed (36,37).

$tcPCO_2$ monitoring: conclusion

Transcutaneous CO_2 monitoring has been developing for many years, and its utility has been proven in at least two different clinical situations in critically ill patients: arterial PCO_2 estimation and tissue perfusion monitoring. Probably because of this ambivalence, which can be confusing for clinicians, this monitoring has been, in our

opinion, underused thus far. However, recent research has shown that these two aforementioned applications are not irreconcilable and could be combined. We believe that estimating arterial PCO_2 and measuring the $tcPCO_2$ gap between arterial-to-tissue CO_2, in normothermia (37 ℃), combined with the provocative perfusion test as a heat challenge (electrode warmed to 42–44 ℃), would help clinicians to continuously and noninvasively capture both respiratory and hemodynamic failures in critically ill patients. Even preliminary, our data on heat challenge as a way to assess microcirculatory shock has shown potential and may stimulate further investigations in this field. For the future, it would be desirable for $tcPCO_2$ sensors to offer refined technological innovation (with automated temperature tests and manipulation of algorithmic constants) in order to popularize the daily use of this device in different clinical settings.

Acknowledgments

None.

Footnote

Conflicts of Interest: A patent application (n° PCT IB2009/006903) is pending on variations of $PcCO_2$ and PI during Heating Challenge. The patent belongs to the Assistance Publique-Hôpitaux de Paris (France). F Vallée and H Nougue received consultant fees from Radiometer. The other authors have no conflicts of interest to declare.

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