Critical Care

REVIEW

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# Pathophysiology and clinical implications of the veno-arterial $PCO_2$ gap

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**Abstract**

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## Introduction

The persisting high mortality of circulatory shock highlights the need to search for sensitive early biomarkers to assess tissue perfusion and cellular oxygenation, which could provide important prognostic information and help guide resuscitation efforts. Although blood lactate and venous oxygen saturation ($SvO_2$) are commonly used in this perspective, their usefulness remains hampered by several limitations. The veno-arterial difference in the partial pressure of carbon dioxide (Pv-a$CO_2$ gap) has been increasingly recognized as a reliable tool to evaluate tissue perfusion and as a marker of poor outcome during circulatory shock, and it should therefore be part of an integrated clinical evaluation. In this chapter, we present the physiological and pathophysiological determinants of the Pv-a$CO_2$ gap and review its implications in the clinical assessment of circulatory shock.

## Physiological aspects of $CO_2$ production and transport

Under aerobic conditions, $CO_2$ is produced at the mitochondrial level as a by-product of substrate oxidation (pyruvate and citric acid cycle intermediates) (Fig. 1). The relationship between the amount of oxygen consumed ($VO_2$) and $CO_2$ produced ($VCO_2$) during aerobic metabolism is termed the respiratory quotient ($RQ = VCO_2/VO_2$), and differs according to the main type of oxidized substrate (glucose, RQ = 1; proteins, RQ = 0.8; lipids, RQ = 0.7). Under anaerobic conditions, protons ($H^+$) resulting from lactic acid production and ATP hydrolysis may generate $CO_2$ following buffering by bicarbonates ($HCO_3^-$), leading to the formation of so-called "anaerobic $CO_2$" [1]. Once formed, $CO_2$ diffuses within the surrounding environment and capillary blood, to be transported to the lungs for elimination. In blood, $CO_2$ transport is partitioned into three distinct fractions [2]:

1. Dissolved $CO_2$ fraction, which is in equilibrium with the partial pressure of $CO_2$ ($PCO_2$), according to Henry's law of gas solubility: $V_{gas} = S_{gas} \times (P_{gas}/P_{atm})$, where $V_{gas}$ is the volume of dissolved gas (in ml/ml), $S_{gas}$ is the Henry's constant of gas solubility (0.52 ml/ml for $CO_2$ at 37 °C), and $P_{atm}$ the atmospheric pressure. Thus, in arterial blood with a $PaCO_2$ of 40 mmHg (at sea level, 37 °C), dissolved $CO_2 = [0.52 \times (40/760)] = 27$ ml/l, which is about 5% of the total $CO_2$ (note that, in mmol/l, Henry's constant for $CO_2 = 0.03$ mmol/l/mmHg; also note that the conversion factor from mmol to ml $CO_2$ is ~ 22.3).
2. Bicarbonate ($HCO_3^-$). $CO_2$ in blood readily diffuses within red blood cells (RBCs), where it combines with $H_2O$ to form carbonic acid ($H_2CO_3$), a reac-

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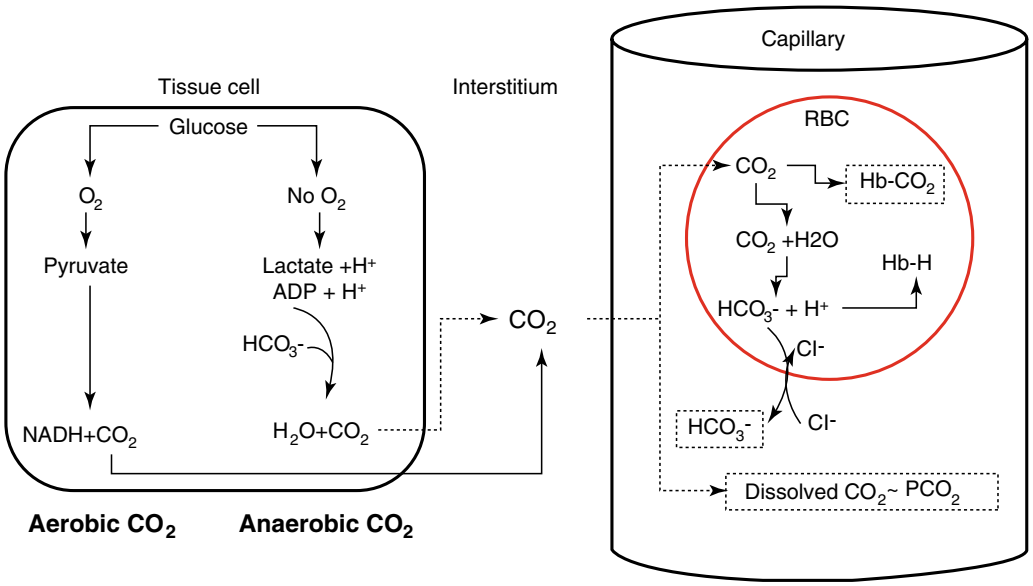


**Fig. 1** Physiology of $CO_2$ production and transport. In cells, $CO_2$ is produced (in mitochondria) as a byproduct of substrate oxidation. Under anaerobic conditions, $CO_2$ is generated in small amounts, as the results of $HCO_3^-$ buffering of protons released by lactic acid and the hydrolysis of ATP. $CO_2$ diffuses into the interstitial tissues and then into capillaries, where it is transported as dissolved $CO_2$ in plasma (in equilibrium with the $PCO_2$), bound to hemoglobin as carbamino-hemoglobin ($HbCO_2$) in red blood cells (RBC), and as $HCO_3^-$, following the reaction of $CO_2$ with $H_2O$ within RBC, a reaction catalyzed by carbonic anhydrase to form $HCO_3^-$ and $H^+$. $HCO_3^-$ exits the RBC in exchange with chloride anions ($Cl^-$), whereas protons are buffered by hemoglobin, forming HbH

tion catalyzed by the enzyme carbonic anhydrase. In turn, $H_2CO_3$ dissociates to form $HCO_3^-$ and $H^+$. While $H^+$ is buffered by hemoglobin (formation of HbH), $HCO_3^-$exits the RBC in exchange for a chloride anion ($Cl^-$) via a $HCO_3^-$-$Cl^-$ transporter (erythrocyte chloride shift or Hamburger effect). Thus, the $HCO_3^-$ concentration increases in venous blood whereas the $Cl^-$ concentration diminishes. $CO_2$ transport as $HCO_3^-$ (RBC and plasma fraction) represents about 90% of the total $CO_2$ content in arterial blood (this proportion is lower in venous blood due to the Haldane effect). Taking into account a normal hematocrit of 0.45, the $CO_2$ content under the form of $HCO_3^-$ (in whole blood) is ~435 ml/l.

3. Formation of carbamino compounds within hemoglobin: part of the $CO_2$ within the RBC combines with free amino (R-$NH_2$) groups within hemoglobin to form carbamino-hemoglobin (R-$NH_2$-$CO_2$). This reaction is enhanced when hemoglobin carries less oxygen, implying that more $CO_2$ is transported as (R-$NH_2$-$CO_2$) when the $PO_2$ decreases, which is the basis of the Haldane effect described below. $CO_2$ transport under the form of (R-$NH_2$-$CO_2$) represents about 5% of the total $CO_2$ content in arterial blood (~1.1 mmol/L≈25 ml/l).

In summary, the total $CO_2$ content of blood under physiological conditions equals:

$$[\text{Dissolved}\,CO_2] + \left[HCO_3^-\right] + [R - NH_2 - CO_2]$$

which is ≈490 ml/l in arterial blood and ≈535 ml/l in mixed venous blood, hence a veno-arterial difference of approximately 45 ml/l. A more precise calculation of the $CO_2$ content of blood can obtained by the Douglas equation, but this is too complex to be calculated at the bedside [3].

#### The $CO_2$ dissociation curve ($PCO_2$-$CCO_2$ relationship)

As is the case for oxygen, a relationship exists between the $PCO_2$ and the $CO_2$ content ($CCO_2$) of blood (Fig. 2). However, in contrast to the sigmoid shape of the $O_2$ dissociation curve, the $CO_2$ dissociation curve is slightly curvilinear, indicating a proportional increase in $CCO_2$ over a wide range of $PCO_2$. In the physiological range, the relationship between $CCO_2$ and $PCO_2$ can therefore be resolved by the equation:

$$PCO_2 = k \times CCO_2 \quad (1)$$

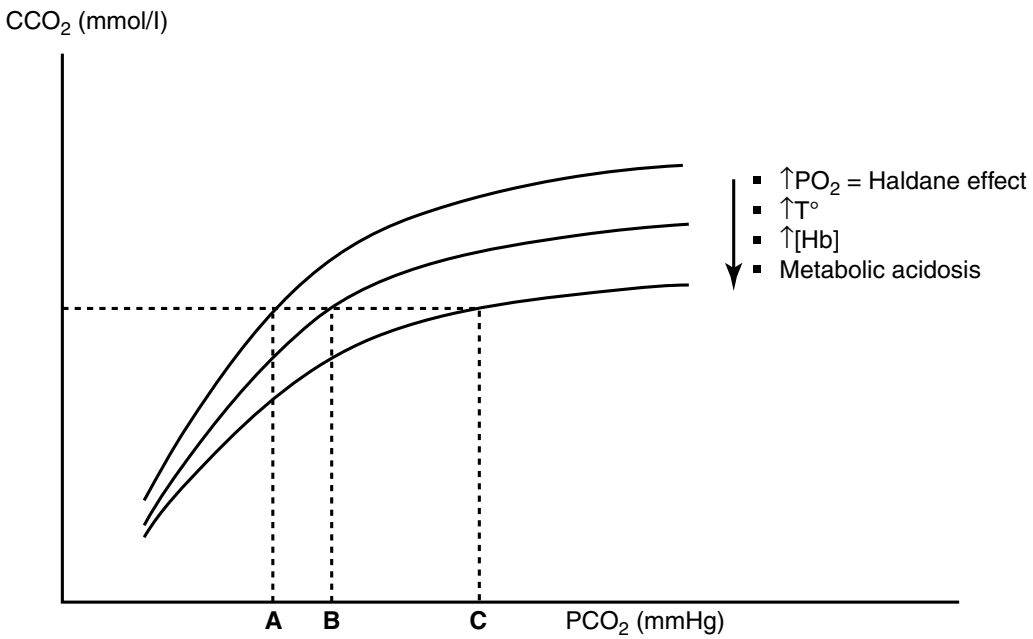


**Fig. 2** The $CO_2$ dissociation curve. A curvilinear relationship exists between $CO_2$ partial pressure ($PCO_2$) and $CO_2$ content ($CCO_2$), so that $PCO_2 = k \times CCO_2$. At low values of $PCO_2$, the slope of the relationship is steeper, implying a smaller increase of $PCO_2$ at any $CCO_2$ than at high values of $PCO_2$, where the slope of the relationship flattens. The position of the relationship is modified by various factors. A rightward and downward shift of the curve, corresponding to an increase of the k coefficient is produced by high $PaO_2$ (Haldane effect), elevated temperatures, high hemoglobin concentrations and metabolic acidosis. A rightward shift of the curves implies that, for a same $CCO_2$, the $PCO_2$ increases, as indicated by the points A, B and C

Important information provided by the $PCO_2$-$CCO_2$ relationship is the shift produced at different values of oxygen saturation of hemoglobin ($HbO_2$). Indeed, as hemoglobin gets saturated with $O_2$, it can carry less $CO_2$ as carbaminoHb, and inversely. This behavior is known as the Haldane effect, which implies that for a same $PCO_2$, $CCO_2$ is higher at lower $HbO_2$ saturation. In other words, this means that as the k constant in the relationship above decreases, the $PCO_2$-$CCO_2$ curve is shifted to the left. The consequence of this effect is that, in tissues, more $CO_2$ is loaded by Hb as it releases $O_2$, allowing $PCO_2$ to increase only moderately (from 40 to 46 mmHg), in spite of a marked increase in $CCO_2$ due to the tissue production of $CO_2$. Without the Haldane effect, the venous $PCO_2$ would increase significantly more for a similar increase in $CO_2$ content.

The curvilinearity of the $CO_2$ dissociation curve indicates that $CCO_2$ increases more steeply at low values of $PCO_2$ and is more flat at high $PCO_2$ values. It is also noticeable that the curve can be displaced by a certain number of factors: In conditions of metabolic acidosis, the reduction in $HCO_3^-$ due to $H^+$ buffering reduces the formation of carbamino ($R\text{-}NH_2\text{-}CO_2$) compounds inside hemoglobin [4]. As a result, for a given $CCO_2$, the $PCO_2$ must increase, which means an increase in the *k* constant, and a rightward shit of the relationship. The opposite occurs under conditions of metabolic alkalosis. Other factors influencing the curve are the hematocrit and temperature. At increasing hematocrit, there is a decrease in plasma space with a reduction of $HCO_3^-$ and a decrease in $CO_2$ content at any value of $PCO_2$, with a shift to the right of the curve. At increasing temperatures, the reduced $CO_2$ solubility also shifts the relationship to the right [4]. These considerations imply, therefore, that $PvCO_2$ may vary at constant total venous $CCO_2$ according to the particular conditions ($HbO_2$ saturation [i.e., the Haldane effect], arterial pH, temperature and hematocrit).

## The Pv-a$CO_2$ gap: pathophysiology and clinical implications

A discussed earlier, the $CCO_2$ in the venous side of the circulation is determined by the aerobic production of $CO_2$ in tissues, influenced by the metabolic rate and the respiratory quotient, and may also increase via non-aerobic production of $CO_2$. The generation of $CO_2$ de facto increases the $CCO_2$ on the venous side of the circulation, implying an obligatory difference between arterial and venous $CCO_2$, termed the veno-arterial

difference in $CCO_2$, or veno-arterial $CCO_2$ gap: va-$CCO_2$ gap = (venous - arterial) $CCO_2$ [1].

The tissue $VCO_2$ does not accumulate under normal conditions, being washed out by the blood flowing across the tissue and eliminated by the lungs. Accordingly, any reduction in tissue blood flow (stagnant condition) will result in an accumulation of tissue $CO_2$, implying an increase in the va-$CCO_2$ gap, in accordance with Fick's principle:

$$VCO_{2tissue} = \left[\left(\text{Blood flow}_{tissue} \times \left(va - CCO_2\,gap_{tissue}\right)\right)\right]$$

At the systemic level, the relationship is:

$$VCO_2 = \left[\left(\text{Cardiac output} \times \left(va - CCO_2\,gap\right)\right)\right]$$

According to the equation ($PCO_2 = k \times CCO_2$), the Fick equation for $CO_2$ can be rewritten as:

$$k \times VCO_2 = [\text{Cardiac output} \times (Pv - PaCO_2)]$$

and

$$(Pv - PaCO_2) = [(k \times VCO_2)/\text{Cardiac output}]$$

Therefore, the Pv-a$CO_2$ gap represents a very good surrogate indicator of the adequacy of cardiac output and tissue perfusion under a given condition of $CO_2$ production. The normal Pv-a$CO_2$ gap is comprised between 2 and 6 mmHg [5], and many studies assessing Pv-a$CO_2$ gap in clinical conditions used a cut-off value of 6 mmHg above which the gap is considered abnormally elevated. Although the venous $PCO_2$ should ideally be obtained in a mixed venous blood sampling, good agreement between central and mixed venous $PCO_2$ values has been reported [6]. Therefore, both central and mixed venous $PCO_2$ can be used for the calculation of the va-$CO_2$ gap, as long as the variables are not interchanged during treatment in a given patient.

### The inverse relationship between cardiac output and the Pv-a$CO_2$ gap

The inverse relationship between cardiac output and the Pv-a$CO_2$ gap (Fig. 3) has been repeatedly demonstrated in both experimental [7] and clinical [8] settings. It is noteworthy that this relationship is not linear, but curvilinear (Fig. 3). At very low cardiac output, the (Pv-a$CO_2$ gap) indeed increases more rapidly. This large increase in Pv-a$CO_2$ gap is primarily due to the flattened relation between $CCO_2$ and $PCO_2$ at high values of $CCO_2$ in conditions of tissue hypercarbia [5], and this is further magnified if tissue metabolic acidosis develops, due to the rightward shift of the $PCO_2$-$CCO_2$ relationship in acidic conditions (increased $k$ coefficient, see above). Also, venous accumulation of $CO_2$ will increase as a consequence of low pulmonary perfusion and $CO_2$ elimination, further widening the gap [9]. In contrast, the increase in Pv-a$CO_2$ in very low flow states with conditions of $VO_2$-oxygen delivery ($DO_2$) dependence will be attenuated by the mandatory reduction in aerobic $VCO_2$. Such a decrease in $VCO_2$ results in a leftward shift of the cardiac output/Pv-a$CO_2$ gap relationship, as shown in Fig. 3 [5].

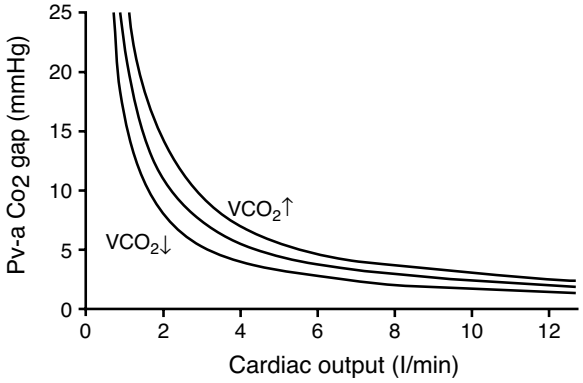


**Fig. 3** The inverse relationship between cardiac output and the Pva-$CO_2$ gap. A reduction in cardiac output is associated with a progressive increase in the Pva-$CO_2$ gap, which becomes exponential at very low cardiac output values, because of the flat slope of the $CO_2$ dissociation curve in conditions of tissue hypercarbia. The relationship is displaced to the right at higher $CO_2$ production ($VCO_2$)

### Pv-a$CO_2$ gap and tissue dysoxia

In addition to tracking changes in cardiac output and tissue perfusion, the Pv-a$CO_2$ gap can increase through an augmentation of $VCO_2$ [8]. Under *aerobic* conditions, that is in the absence of any clinical sign of shock or increased blood lactate, such an increase reflects an increased metabolic demand or an increase in RQ (glucidic diet), or both. Physiologically, an increased metabolic rate is generally coupled with an increase in cardiac output, but such adaptation may not occur in critically ill patients with inadequate cardiovascular reserves, which may result in an increased Pv-a$CO_2$ gap. Interventions should here be targeted first to reduce the metabolic demand. Persistence of an increased Pv-a$CO_2$ gap should not necessarily prompt therapies to increase cardiac output, given the risk associated with deliberate increase in cardiac output in the absence of tissue dysoxia [10]. However, it is noteworthy that an increased Pv-a$CO_2$ gap immediately after surgery in high risk patients, independent of their hemodynamic condition, $SvO_2$ and lactate, has been associated with significantly more complications [11]. This suggests that a high Pv-a$CO_2$ gap could track insufficient resuscitation and might represent a goal

for hemodynamic optimization in such patients, but this issue is controversial and remains to be proven [9].

Under *anaerobic* conditions, the question as to whether the Pv-a$CO_2$ gap can be used as a marker of tissue dysoxia, by detecting increased anaerobic $VCO_2$ from $H^+$ buffering, has attracted much attention. An advantage of Pv-a$CO_2$ gap in this sense would be its ability to rapidly track changes in $CO_2$ formation, hence providing sensitive, rapid and continuous detection of ongoing anaerobiosis. This would contrast from usual markers of tissue dysoxia, such as $SvO_2$ or lactate. Indeed, $SvO_2$ can be unreliable in conditions of reduced oxygen extraction and hyperdynamic circulation (sepsis) [12]. The disadvantage of lactate is its lack of specificity as a marker of dysoxia (type A vs type B hyperlactatemia), and its relatively slow clearance kinetics dependent on liver perfusion and function [13], which limits its utility to rapidly track changes in tissue oxygenation [9].

#### *The Pv-a$CO_2$ gap in stagnant dysoxia*

In essence, tissue dysoxia is classically attributed to stagnant, hypoxic, anemic and cytopathic mechanisms. As a sensitive marker of reduced cardiac output, an increased Pv-a$CO_2$ gap is a reliable indicator of stagnant dysoxia. Importantly, the major gap noted under very low flow conditions (see earlier) has been associated with a global reduction in $VCO_2$ ($VO_2$-$DO_2$ dependence), implying that any increase in anaerobic $VCO_2$ could not offset the depressed aerobic $VCO_2$ [7]. Therefore, the increased Pv-a$CO_2$ gap depends entirely on the stagnant accumulation of tissue $CO_2$, but not on increased anaerobic $VCO_2$ in low flow conditions [1, 14].

#### *The Pv-a$CO_2$ gap in hypoxic or anemic dysoxia*

To address the role of the Pv-a$CO_2$ gap to detect hypoxic dysoxia, Vallet et al. reduced $DO_2$ below the critical threshold in an isolated dog hindlimb model, by reducing blood flow or by decreasing $PO_2$ [15]. Both conditions similarly reduced $VO_2$ and $O_2$ extraction, but the Pv-a$CO_2$ gap increased exclusively in the ischemic, but not hypoxic condition, implying that stagnant, but not hypoxic dysoxia was the responsible mechanism [15]. Comparable results were obtained by Nevière et al. in the intestinal mucosa of pigs, following the systemic reduction in $DO_2$ to similar levels either by reduction of cardiac output or arterial $PO_2$ [16]. With respect to anemic dysoxia, similar conclusions were obtained in sheep hemorrhage models, in which no increase in Pv-a$CO_2$ gap was detected under conditions of $VO_2$/$DO_2$ dependency due to reduced hemoglobin concentration [17], unless there was a concomitant reduction in cardiac output [18]. Hence, significant hypoxic or anemic dysoxia occurs in the absence of any Pv-a$CO_2$ gap increase.

#### *The Pv-a$CO_2$ gap in cytopathic dysoxia*

An acquired intrinsic abnormality of tissue $O_2$ extraction and cellular $O_2$ utilization, primarily related to mitochondrial impairment, defines the concept of cytopathic hypoxia, and the resulting cellular bioenergetic failure could represent an important mechanism of organ dysfunction in sepsis [19]. Mitochondrial defects have been demonstrated in several tissues obtained from animals in various models of sepsis, and limited data also exist on altered mitochondrial metabolism in human biopsy samples or circulating blood cells [20]. The detection of cytopathic hypoxia, however, is still not feasible at the bedside, although new techniques such as the measurement of mitochondrial $O_2$ tension using protoporphyrin IX-Triplet State Lifetime Technique (PpIX-TSLT) are currently being developed [21]. Furthermore, impaired $O_2$ extraction in sepsis does not necessary imply cytopathic hypoxia, as it may be related to impaired microcirculation.

Theoretically, the increased anaerobic $CO_2$ generation in conditions of cytopathic hypoxia could result in increased anaerobic $VCO_2$ leading to an increased Pv-a$CO_2$ gap. This assumption has been evaluated in a porcine model of high dose metformin intoxication, which induces mitochondrial defects comparable to cyanide poisoning [22]. As expected, treated pigs exhibited reduced $VO_2$ and marked lactic acidosis, in spite of preserved systemic $DO_2$. However, although $VCO_2$ decreased less than $VO_2$, suggesting some anaerobic $VCO_2$, no significant increase in Pv-a$CO_2$ gap was noted. In a human case report of massive metformin intoxication, Waldauf et al. also reported no elevation in Pv-a$CO_2$ gap despite major lactic acidosis and reduced aerobic $VO_2$, as detected by increased $SvO_2$ [23]. Therefore, although data are very limited, cytopathic dysoxia related to impaired mitochondrial respiration appears not to widen the Pv-a$CO_2$ gap.

### The Pv-a$CO_2$ gap in sepsis

Ongoing tissue dysoxia with persistent lactic acidosis is a hallmark of sepsis, and associated with a poor prognosis. Although a hyperdynamic circulation is characteristic of sepsis, many septic patients may have a cardiac output that is insufficient to meet metabolic demands, because of persistent hypovolemia or concomitant myocardial dysfunction. An increased Pv-a$CO_2$ gap has been reported in patients with lower cardiac output in sepsis, consistent with the ability of the Pv-a$CO_2$ gap to detect stagnant dysoxia, also in the context of sepsis [24]. In

such conditions, an increase in cardiac output correlates with a parallel decrease in Pv-a$CO_2$ gap [25]. Importantly, as reported by Vallee et al. [26], the Pv-a$CO_2$ gap is able to detect persistently low cardiac output even in patients with a normal $SvO_2$. Such a high Pv-a$CO_2$ gap during the early resuscitation of septic shock has been correlated with more organ dysfunction and worse outcomes [27].

Many septic patients display persistent lactic acidosis in spite of an elevated cardiac output and normal or even increased $SvO_2$. This implies that mechanisms unrelated to macrohemodynamics sustain tissue dysoxia in this setting, i.e., a loss of so-called hemodynamic coherence, with significant negative impact on outcome [28]. Impaired microcirculatory perfusion is indeed a prototypical perturbation in experimental [29] and human sepsis [30], which may impair tissue oxygenation. Such microcirculatory derangements result in tissue $CO_2$ accumulation, which can be tracked, for example, by sublingual capnometry, as shown by Creteur et al. [31]. Accordingly, in a prospective observational study including 75 patients with septic shock, Ospina-Tascon et al. found a significant correlation between Pv-a$CO_2$ gap and microcirculatory alterations. These were independent of systemic hemodynamic status and persisted even after correction for the Haldane effect [32], indicating that the Pv-a$CO_2$ gap may be a useful tool to assess impaired microcirculation in sepsis [33]. Furthermore, Creteur et al. reported that increasing cardiac output with dobutamine in patients with impaired microcirculation resulted in a decreased regional $PCO_2$ gap (sublingual and gastric mucosal) that was associated with a significant increase in well-perfused capillaries [31].

In summary, an elevated (>6 mmHg) Pv-a$CO_2$ gap in sepsis detects stagnant dysoxia, whether related to a low cardiac output or a derangement in microcirculatory blood flow, and this holds true even in the presence of a normal or elevated $SvO_2$. As such, a high Pv-a$CO_2$ gap might prompt a trial to improve tissue blood flow by increasing cardiac output [34].

Finally, many septic patients with an elevated cardiac output exhibit a normal Pv-a$CO_2$ gap, resulting from elevated $CO_2$ washout by increased tissue blood flow. Many of these patients still display signs of ongoing dysoxia with lactic acidosis and organ dysfunction. Whether this pattern reflects cytopathic dysoxia or regional microcirculatory alterations not tracked by Pv-a$CO_2$ gap elevation remains to be established.

## Use of the Pv-a$CO_2$ gap as a prognostic tool

In sepsis, evidence exists that a Pv-a$CO_2$ gap > 6 mmHg, even after normalization of blood lactate, is predictive of poor outcomes [35–37], which has been highlighted in a recent systematic review of 12 observational studies [38]. Whether this holds true for a broader population of critically ill patients with circulatory shock has been questioned in a recent meta-analysis of 21 studies with a total of 2155 patients from medical, surgical and cardiovascular ICUs [37]. Overall, a high Pv-a$CO_2$ gap was associated with higher lactate levels, lower cardiac output and central venous oxygen saturation ($ScvO_2$), and was significantly correlated with mortality. The latter was however restricted to medical and surgical patients, with no association found for cardiac surgery patients. Since the meta-analysis included only two studies in cardiac surgery, this negative result should be interpreted with caution. Three recent retrospective studies not included in the meta-analysis [39–41] indeed reported a negative impact of high postoperative Pv-a$CO_2$ gap on major complications and mortality after cardiac surgery, although with limited diagnostic performance [41].

Future studies are needed to refine the value of the Pv-a$CO_2$ gap as a prognostic biomarker in cardiac surgery patients, taking into account the low mortality (3.4%) in this population [42].

## Pitfalls in the interpretation of the Pv-a$CO_2$ gap

As already mentioned, several factors may influence the position of the $PCO_2$-$CCO_2$ relationship by influencing the *k* factor of proportionality between both variables (see Fig. 2), which must be taken into account for a proper interpretation of the Pv-a$CO_2$ gap. These include the oxygen saturation of hemoglobin (Haldane effect), metabolic shifts of pH, temperature and hemoglobin concentration. In addition, it is essential to consider possible sources of errors in the measurement of $PCO_2$, including contamination of the samples with fluid or air bubbles, and insufficient precision of the gas analyzer. When comparing successive determinations of Pv-a$CO_2$ gap, it is therefore recommended to consider only variations of at least ± 2 mmHg as real changes [43].

Two additional confounders in the interpretation of the Pv-a$CO_2$ gap require some discussion. The first is hyperoxia. It has been observed that, in patients with circulatory shock, ventilation at 100% inspired oxygen fraction ($FiO_2$) for 5 min increased venous $PCO_2$, and hence the Pv-a$CO_2$ gap, independent of changes in the hemodynamic status [44]. While this observation may be explained by a lower $CO_2$ affinity of hemoglobin due to elevated venous $PO_2$ (Haldane effect) [44], it may also reflect some impairment in microcirculatory blood flow, owing to the vasoconstrictive effects of hyperoxia [45]. The second confounder is acute hyperventilation with respiratory alkalosis. For example, as shown by Mallat et al. in 18 stable septic shock patients [46], an acute decrease in arterial $PCO_2$ from 44 to 34 mmHg produced by transient hyperventilation

(30 min) induced a significant increase in $PCO_2$ gap (absolute 2.2 mmHg, relative + 48.5%). Possible mechanisms include, first, increased aerobic production of $CO_2$ due to stimulated aerobic glycolysis under conditions of cellular alkalosis, and second, a reduction in microcirculatory blood flow due to the acute drop of $CO_2$. Thus, both acute hyperoxia and hypocapnia may be important confounders in the interpretation of an increased Pv-a$CO_2$ gap, which must be taken into account by the clinician.

## Conclusion

The Pv-a$CO_2$ gap is a reliable indicator of impaired tissue perfusion, whether the result of a global reduction in cardiac output or to microcirculatory abnormalities, but it does not track tissue dysoxia, unless related to a stagnant mechanism. Being easily accessible and readily available, the Pva-$CO_2$ gap should be included in the integrated evaluation of the patient in circulatory shock. Several diagnostic algorithms incorporating Pva-$CO_2$ gradients have been proposed, such as those presented in Figs. 4

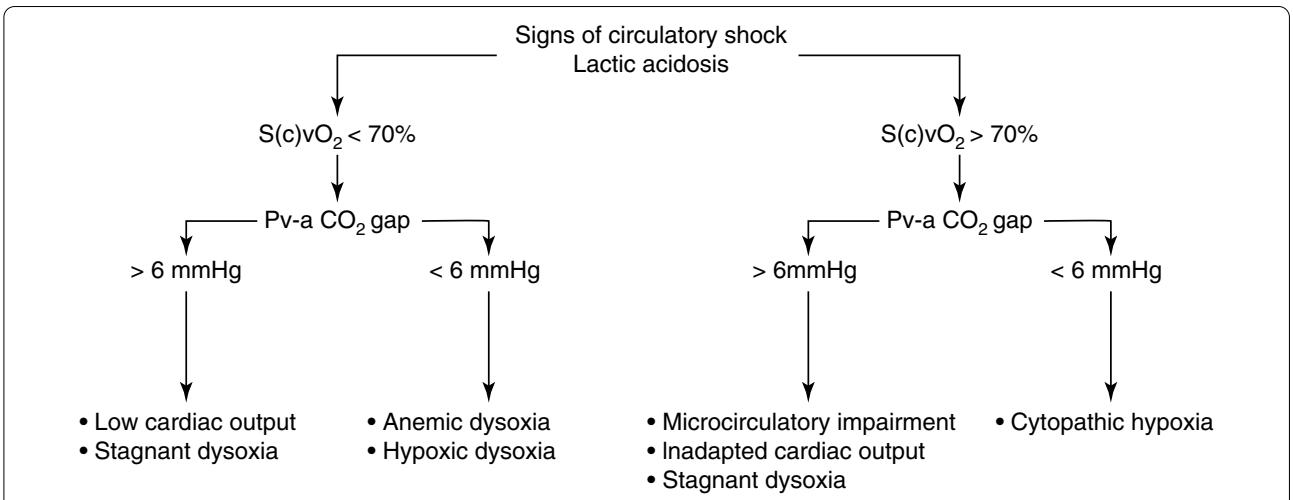


**Fig. 4** Usefulness of the Pva-$CO_2$ gradient under conditions of circulatory shock. Proposed diagnostic algorithm integrating lactate, mixed (central) venous oxygen saturation (S(c)v$O_2$) and the Pva-$CO_2$ gap in patients with circulatory shock

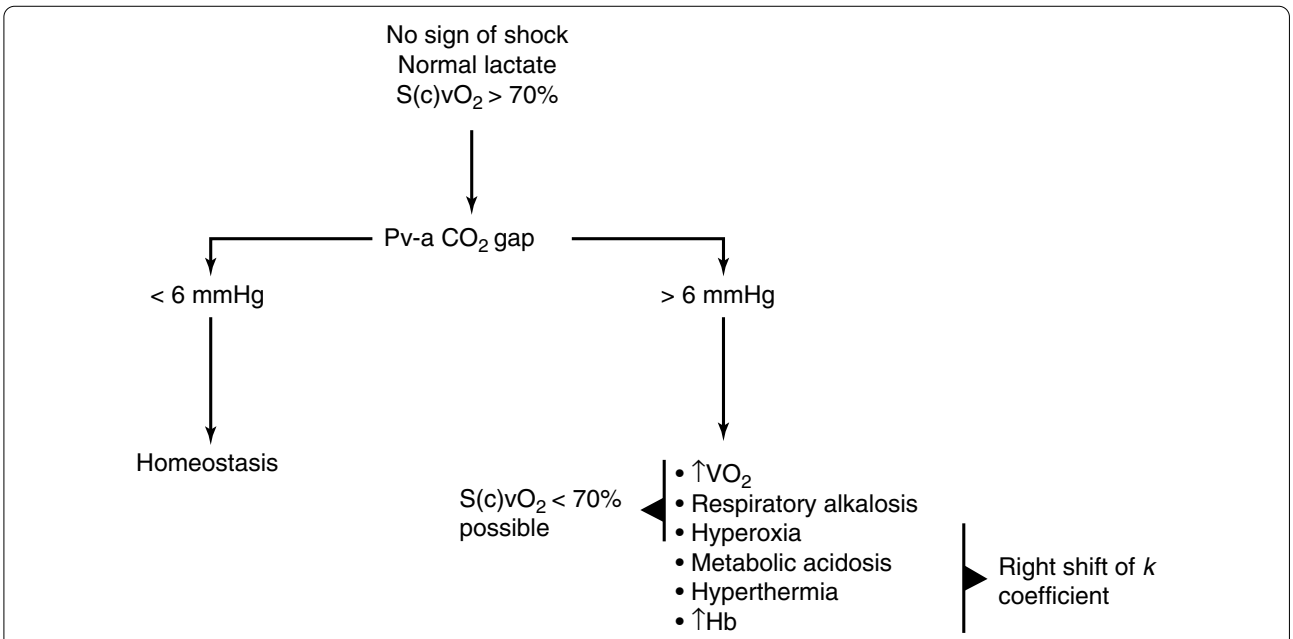


**Fig. 5** The Pva-$CO_2$ gradient in the absence of circulatory shock. Proposed diagnostic algorithm to interpret an elevation in the Pva-$CO_2$ gap in the absence of circulatory shock and with normal blood lactate. *S(c)v$O_2$* mixed (central) venous oxygen saturation

and 5. It remains to be established whether the Pva-$CO_2$ gap should be part of a resuscitation bundle protocol, and whether therapies aimed at normalizing an increased Pva-$CO_2$ gap could improve the dismal prognosis of circulatory shock.

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ZL performed the literature review drew the figures and drafted the manuscript. AS critically reviewed the manuscript. LL critically reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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**Competing interests**
All authors stated they have no conflicts of interest to declare.

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