The PCO_2 Gaps

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Learning Objectives

Carbon dioxide is a catabolic product generated during the Krebs cycle under normoxic condition. As a final product of cellular respiration, carbon dioxide-derived variables could be potentially used to monitor tissue perfusion and to detect the appearance of anaerobic metabolism during shock states.

In this chapter we will analyze some physiological aspects, prognostic value, clinical meaning, and possible clinical applications of the venous-to-arterial carbon dioxide difference (Pv-aCO_2) and the venous-arterial carbon dioxide to arterial-venous oxygen content difference ratio (Cv-aCO_2/Ca-vO_2) during shock states.

16.1 Introduction

Shock is a life-threatening condition in which the circulatory system is unable to deliver sufficient oxygen to maintain the metabolic demand of tissues, resulting in cellular dysfunction [1]. Thus, early recognition of tissue hypoperfusion and its reversion are pivotal factors in limiting progression to multiorgan dysfunction and death [2]. Current techniques for monitoring tissue perfusion have largely focused on systemic blood flow and the balance between oxygen demand and supply to the tissues [3, 4]. In fact, early hemodynamic optimization using resuscitation bundles targeting central venous oxygen saturation ($ScvO_2$) and macro hemodynamics were initially related with significant reduction of mortality in septic shock [5]. However, the usefulness of oxygen-derived parameters has been strongly questioned [6], and recent studies have failed to demonstrate its clinical benefits [7–9]. In fact, $ScvO_2$ is often normal or near normal at ICU admission [10], and attaining normal macro hemodynamics and global oxygen-derived parameters do not rule out the presence or persistence of tissue hypoxia. In this context, other variables such as carbon dioxide (CO_2)-derived parameters might provide valuable information about macro and micro hemodynamics during early phases of shock, even when oxygen variables seem to have been corrected [11–15]. Importantly, CO_2 variations occur faster than changes in lactate levels, which make attractive the CO_2 parameters as monitoring tool during early stages of resuscitation.

In this chapter we will analyze the physiological principles, prognostic value, clinical significance, and potential clinical applications of the venous-to-arterial carbon dioxide difference (Pv-aCO_2) and the venous-arterial carbon dioxide to arterial-venous oxygen content difference ratio (Cv-aCO_2/Ca-vO_2) during shock states.

16.2 Physiological Background

16.2.1 Aerobic Carbon Dioxide Production

Carbon dioxide (CO_2) is a terminal metabolic product generated under normoxic conditions during the Krebs cycle. Total CO_2 production (VCO_2) is directly related to the global oxygen consumption (VO_2) by the relation, $VCO_2 = RQ \times VO_2$, where RQ represents the respiratory quotient. This RQ reflects the ratio of moles of CO_2 generated per mole of oxygen consumed at the tissue level, and it will vary from 0.6 to 1.0 according to the metabolic conditions and the predominant energetic substrate consumed. Consequently, aerobic VCO_2 will increase either during increased oxidative metabolism (i.e., with simultaneous VO_2 increase) or when at constant VO_2; dietary regimen is substituted by a high

carbohydrate intake [16]. Under aerobic resting conditions, RQ will never be >1.0 since CO_2 production should not surpass that amount of O_2 consumed. However, during exhaustive muscular activity or during certain pathological situations, anaerobic CO_2 generation could account for VCO_2/VO_2 ratios >1.0. However, regardless of the mechanism increasing aerobic VCO_2, Pv-aCO_2 will increase only when compensatory increase in cardiac output is not sufficient to clear the CO_2 produced by tissues.

16.2.2 Anaerobic Carbon Dioxide Production

When tissue hypoxia occurs, aerobic VCO_2 decreases, while anaerobic VCO_2 turns on. Increased anaerobic VCO_2 is the final consequence of proton [H^+] buffering by cytosolic and plasmatic bicarbonate (HCO_3^-). The "gross H^+ release" observed during hypoxia results from the sum of all cellular reactions liberating H^+ (e.g., the ATPase, hexokinase [HK], phosphofructokinase [PFK], and glyceraldehyde-3-phosphate dehydrogenase [G_3PDH] reactions), which are counterbalanced by metabolic reactions consuming H^+ (e.g., the creatine kinase [CK], AMP deaminase [AMPDase], pyruvate kinase [PK], and lactate dehydrogenase [LDH] reactions). Consequently, the difference between the "gross H^+ release" and the chemical reactions consuming H^+ (i.e., the "metabolic buffering") will result in the "net H^+ release," which ultimately will be regulated by the intra- and extracellular structural buffering (e.g., amino acids) and the bicarbonate buffering system [17]. This later is the main responsible for the anaerobic VCO_2 increase, when HCO_3^- captures the H^+ excess to become H_2CO_3 and subsequently dissociate in CO_2 and H_2O. An additional source of anaerobic VCO_2 results from anaerobic decarboxylation of some substrates such as α-ketoglutarate and oxaloacetate which occurred during intermediate metabolism, but its contribution to the total VCO_2 is quite small [18].

Despite its biochemical importance, clinical demonstration of anaerobic CO_2 increase might be very difficult because total VCO_2 decreases under hypoxic conditions and 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.

16.2.3 CO_2 Transport in Blood

Carbon dioxide excretion is a passive phenomenon in which CO_2 is transferred down an electrochemical gradient from cells to the environment. The efficiency of this transport is a function of convention (blood flow) and capacity of the carrier (blood content). Fortunately, evolution has led to transport large quantities of CO_2 in blood without large variations in blood flow. Carbon dioxide is approximately 20–30 times more soluble than oxygen, whereby dissolved CO_2 plays a key role in its total transport. As a lipophilic molecule, CO_2 rapidly diffuses through the lipid bilayer of cells and erythrocytes to be hydrated and finally converted into HCO_3^- and H^+. Thus, in general, blood carries both CO_2 and its related compounds in five forms:

1. Dissolved CO_2: $[CO_2]_{DIS}$ follows Henry's law, which establishes that, at constant temperature, any gas dissolves in a liquid phase proportionally to its partial pressure in the gas phase, adjusted by a solubility factor that differs from one gas to another. Under normal conditions, ~ 5% of the total CO_2 content is transported as $[CO_2]_{DIS}$. Despite its relatively low capacitance in blood, $[CO_2]_{DIS}$ has a critical role in gas transport since it can rapidly cross the vascular endothelium, while other forms of CO_2 must be converted into free CO_2 to enter or leave blood.

2. Carbonic acid: [H_2CO_3] results from the reaction between CO_2 and H_2O. At the pH of most physiological fluids, H_2CO_3 instantly dissociates into H^+ and HCO_3^-. Hence, [H_2CO_3] represents only the 1/400 part of [CO_2], whereby this is not quantitatively important for total CO_2 carriage.
3. Bicarbonate: [HCO_3^-] can form in three ways – by dissociation of H_2CO_3 into H^+ and HCO_3^-, by direct combination of CO_2 and OH^- (a reaction catalyzed by the carbonic anhydrase), and by combination of carbonate (CO_3^{2-}) and H^+. In arterial blood, HCO_3^- accounts for ~ 90% of the total CO_2 content. Thus, CO_2 combines with water (H_2O) to form carbonic acid (H_2CO_3), and this dissociates into HCO_3^- and hydrogen ion: $CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$. Carbonic anhydrase catalyzes almost instantaneously this first reaction mainly in red blood cells (RBC) and pulmonary capillary endothelial cells, while the uncatalyzed second reaction occurs at a much slower rate. When H_2CO_3 dissociates within RBC into H^+ and HCO_3^-, H^+ is buffered by hemoglobin, while the excess HCO_3^- is transported out of RBC into the plasma by an electrically neutral bicarbonate-chloride exchanger (Fig. 16.1).
4. Carbonate: [CO_3^{2-}] is mainly formed from the dissociation of bicarbonate: $HCO_3^- \rightarrow CO_3^{2-} + H^+$. Thus, [$CO_3^{2-}$] is ~ 1/1000 as high as HCO_3^- at pH 7.40. Consequently, CO_3^{2-} is not quantitatively important for CO_2 transport.
5. Carbamino compounds: uncharged amino groups of proteins can reversibly bind to both H^+ and CO_2. By far, the most important carbamino compound is the carbamino hemoglobin (Hb-NH-COO^-), which forms rapidly and reversibly as CO_2 reacts with free amino group on hemoglobin. Carbamino compounds account for ~ 5% of the total CO_2 content in arterial blood.

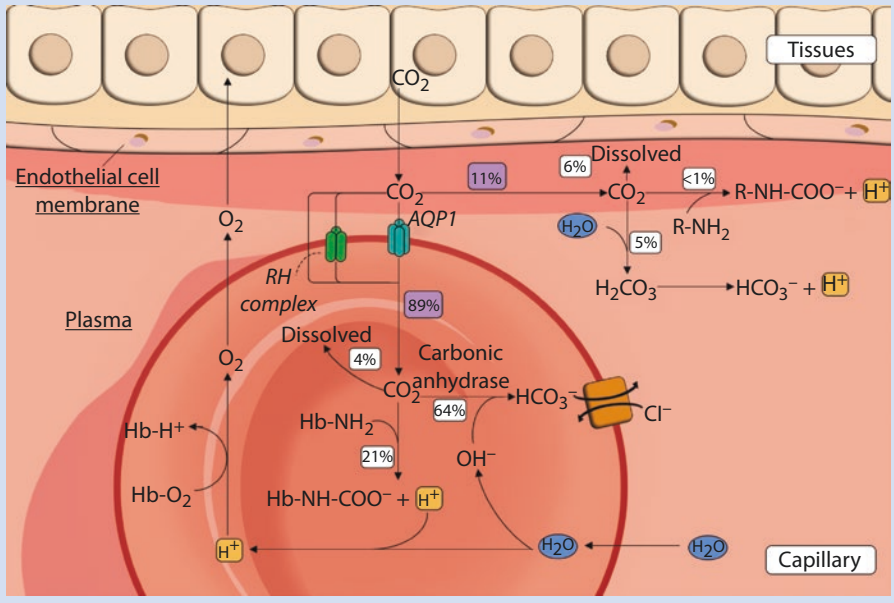

Fig. 16.1 Intracellular and extracellular events of CO_2 carriage in blood

The total CO_2 content (CCO_2) in arterial blood is ~ 48 mL of CO_2 gas/dL measured at standard temperature and pressure/dry (STPD), corresponding to a $PaCO_2$ of 40 mmHg. From that 48 mL/dL, ~ 90% corresponds to HCO_3^-, while carbamino compound contributes with ~ 5%. As blood flows along the microcirculatory bed, it picks up ~ 4 mL/dL of CO_2, so that the total CCO_2 in mixed-venous blood will rise to ~ 52 mL/dL. From that incremental CCO_2, about 10% corresponds to dissolved CO_2, ~ 69% to HCO_3^-, and ~ 21% to carbamino compounds. Accordingly, dissolved CO_2 and carbamino compounds are far more important for carrying incremental CO_2 to the lungs as a result of their contribution to the total increase in CO_2 in venous blood. In as much as oxidative metabolism occurs and Krebs cycle maintains its function, mitochondria generates CO_2, which diffuses out of the cells through the extracellular space, across the capillary endothelium, and into the blood plasma. Near 11% of incremental CO_2 remains in blood plasma throughout its way to the lungs, while ~ 89% enters red blood cells, at least initially. The aforesaid ~ 11% of plasma incremental CO_2 will in turn be transported as dissolved CO_2 (~ 6%, considering a hematocrit of 40%), as HCO_3^- (~ 6%) and small quantities as carbamino compounds. The remaining ~ 89% of incremental CO_2 enters red blood cells through two "gas channels": the aquaporin 1 and the Rh complex. This intra-RBC CO_2 will be transported as dissolved cytosolic CO_2 (~ 4%), while ~ 21% of such increment will be transported as carbamino compounds of Hb (i.e., the CO_2 linked to hemoglobin). Intra-RBC carbamino compounds are far more important than those formed in plasma because hemoglobin concentration in RBC is significantly higher (~ 33 gr/dL) than that represented by albumin, globulins, and other plasma proteins (~ 7 gr/dL total plasma proteins). Furthermore, the affinity of CO_2 for hemoglobin far surpasses that for major plasma proteins. In addition, the affinity of hemoglobin for H^+ and CO_2 will be modified as long as O_2 concentrations vary when blood enters tissue microcirculation or returns to the lungs. The remaining incremental CO_2 in RBC will be represented by HCO_3^- (~ 64%) because of the carbonic anhydrase activity accelerating the conversion of CO_2 into HCO_3^-. In absence of such enzymatic activity, HCO_3^- would hardly be synthesized inside RBCs during the short transit time of RBCs along the capillary bed. Furthermore, the Cl-HCO_3 exchanger AE1 (anion exchanger 1) carries the newly synthesized HCO_3^- out of the cell, promoting further HCO_3^- generation. Figure 16.1 resumes the combined intra-RBC and plasmatic events of CO_2 transportation.

16.2.4 The CO_2 Dissociation Curve

The carriage of total CO_2 will depend on PCO_2, plasma pH, and PO_2 [19, 20]. The CO_2 dissociation curve is characterized by a near-linear relationship within the physiological ranges of PCO_2 and PO_2 values (Fig. 16.2, panel a). Moreover, at any PCO_2, the total CO_2 content rises as PO_2 falls. As a result, as blood enters the systemic microcirculation and releases O_2, the CO_2-carrying capacity increases, so that blood may remove the extra CO_2. Conversely, as blood enters the pulmonary capillaries and binds O_2, the CO_2-carrying capacity decreases, and blood loses the capacity to transport the extra CO_2. Because of the CO_2 dissociation curve slope, PCO_2 must increase from 40 mmHg in arterial blood to only 46 mmHg in mixed-venous blood to increase the total CO_2 content by ~ 4 mL/dL (i.e., from 48 to 52 mL of CO_2 gas/dL), which is required to remove the CO_2 generated by aerobic mitochondrial functioning.

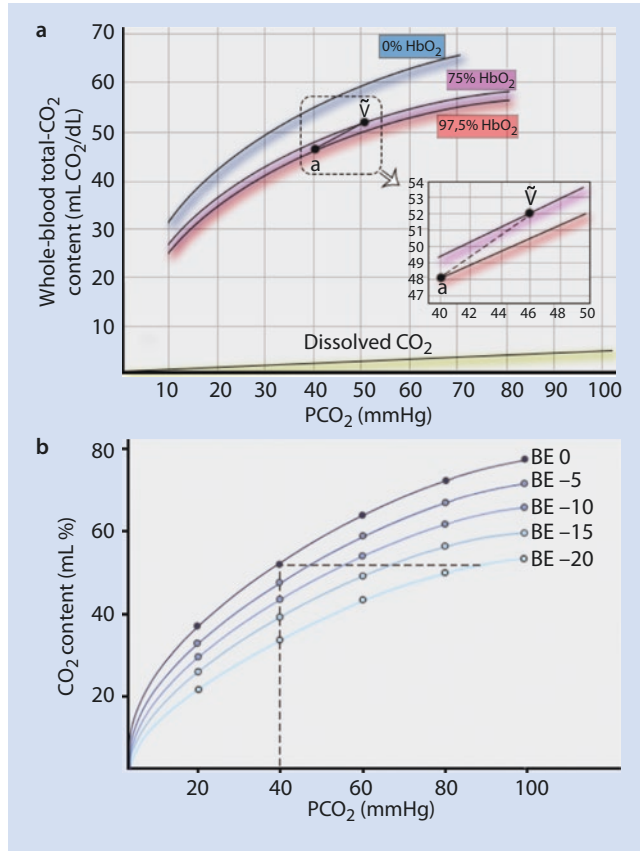

Fig. 16.2 Carbon dioxide dissociation curve. Panel **a** Relationships between whole-blood total CO_2 content (CCO_2) and blood CO_2 pressures (PCO_2) according to SpO_2 variations (Haldane effect). Panel **b** Influence of H^+ load on whole-blood total CO_2 content (CCO_2) and blood CO_2 pressures (PCO_2)

16.3 The Venous-to-Arterial Carbon Dioxide Difference ($Pv\text{-}aCO_2$)

16.3.1 $Pv\text{-}aCO_2$ and Its Relationship with Cardiac Output

The venous-to-arterial carbon dioxide difference ($Pv\text{-}aCO_2$) refers to the gradient of partial pressures exerted by the dissolved CO_2 on the mixed or central venous and the arterial blood. Overall, $Pv\text{-}aCO_2$ depends on the total carbon dioxide (CO_2) production, cardiac output, the complex relationship between CO_2 partial pressures and CO_2 blood contents, and, probably, the microcirculatory blood flow distribution.

The Fick equation indicates that CO_2 excretion, i.e., the equivalent to CO_2 production (VCO_2) at steady state, should equal the product of cardiac output (CO) and the venous-to-arterial CO_2 difference:

$$\dot{V}CO_2 = CO \times \left(CvCO_2 - CaCO_2\right)$$

As mentioned above, CCO_2 and PCO_2 maintain a relatively linear relationship at usual physiological ranges. Thus, PCO_2 values have been suggested as a surrogate for CCO_2 when assessing the venous-to-arterial CO_2 difference at the bedside [20–23]. As a result, a modified Fick equation can be obtained by substituting PCO_2 for CCO_2:

$$\Delta PCO_2 = k\left(\dot{V}CO_2 / CO\right)$$

where *k* is a pseudo-linear coefficient assumed to be constant during physiological conditions [22]. However, under severe hypoxic conditions, the *k* factor may rise up to sixfold as metabolic acidosis increases, causing shifts in the curvilinear relation between CCO_2 and PCO_2 (Fig. 16.2, panel b). Thus, the *k* factor increases as VCO_2 decreases, but the resultant effect on Pv-aCO_2 will depend on the cardiac output and probably on the microcirculatory blood flow distribution.

According to the modified Fick equation, Pv-aCO_2 and cardiac output keep an inverse curvilinear relationship in which rises in Pv-aCO_2 follow progressive reductions in cardiac output, especially in its lower values. As a result, under stable conditions of both VO_2 and VCO_2, the Pv-aCO_2 progressively increases in response to reductions in cardiac output due to the CO_2-stagnation phenomenon in which the delayed transit time of red blood cells leads to higher addition of CO_2 per unit of blood flowing through efferent microvessels. Early observations during cardiac arrest in both animal and human models clearly revealed a link between slowing (or stopping) blood flow and venous CO_2 accumulation [24, 25]. Similarly, experimental models of hemorrhage, hypovolemia, and obstructive shock demonstrated this inverse relationship between Pv-aCO_2 and cardiac output, thus highlighting the importance of blood flow stagnation on venous CO_2 accumulation [26–29]. Nevertheless, Pv-aCO_2 increases were originally interpreted as a reflection of tissue dysoxia since critical oxygen delivery values appeared to be consistent with the point at which venous CO_2 starts to increase [26, 27]. In a canine experimental model of cardiac tamponade using the Dill nomogram, Schlichtig and Bowles [30] suggested the appearance of anaerobic VCO_2 below critical DO_2, thus suggesting the link between dysoxia and tissue CO_2 accumulation. However, experimental models in which progressive flow decrements are used to achieve critical oxygen delivery (DO_2) with subsequent decrease in oxygen consumption (VO_2) may yield confusing results given the impossibility to distinguish tissue hypoperfusion from tissue dysoxia [31]. To solve this problem, Vallet et al. [32] designed an experiment to measure Pv-aCO_2 changes in canine hind limb preparations isolated from systemic circulation and connected to a roller pump-membrane oxygenator circuit. Comparable decreases in DO_2 were produced by two different mechanisms of tissue hypoxia: one group underwent progressive decrease in blood flow by slowing the roller pump velocity (ischemic hypoxia), while the other group underwent progressive decrease in arterial PO_2 by manipulating the inspired O_2 fraction (hypoxic hypoxia) but preserving flow velocity. Both groups experienced similar declines in DO_2 and VO_2, suggesting similar degrees of tissue dysoxia. However, the regional hind limb Pv-aCO_2 remained constant during hypoxic hypoxia, while it showed a more than twofold increase during ischemic hypoxia. Accordingly, the authors concluded that blood flow is the major determinant of Pv-aCO_2, and therefore, the absence of an increased Pv-aCO_2 does not preclude the presence of tissue dysoxia. Assessing a similar hypothesis, Nevière et al. [33] compared the effects of a reduced inspired oxygen fraction (hypoxic hypoxia) vs. decreased blood flow (ischemic hypoxia) on the gut mucosal-to-arterial CO_2 difference (Pmtis-aCO_2). Pmtis-aCO_2 increased up to 60 mmHg during ischemic hypoxia, while it remained almost constant over a wide range of DO_2 values during hypoxic hypoxia. Interestingly, Pmtis-aCO_2 slightly increased when extremely low FiO_2 values were used. The authors concluded that the increase in Pmtis-aCO_2 is mainly explained by blood flow alterations, although they admitted that an increased intramucosal PCO_2 in very severe hypoxic hypoxia conditions might indicate some local CO_2 generation. Nevertheless, the fact that DO_2/VO_2 dependency was attained earlier than increases in Pmtis-aCO_2 during hypoxic hypoxia conditions implies that Pmtis-aCO_2 should not be used as a marker of tissue dysoxia.

Similarly, in a hemorrhagic model of hypoxia without hypoperfusion in which progressive blood loss was replaced by isovolemic doses of dextran, Pv-aCO_2 showed no increases when blood flow was restituted, hence confirming the leading role of blood flow on increased venous CO_2 [34].

Thus, increases in Pv-aCO_2 are closely related to cardiac output changes during non-inflammatory conditions. Nevertheless, the concordance observed between cardiac output and Pv-aCO_2 during septic shock is weak [14, 35–37], which suggests that other mechanisms might be involved.

16.3.2 Pv-aCO_2 and Microcirculatory Blood Flow Alterations

Microcirculatory dysfunction in septic shock is a generalized phenomenon characterized by decreased functional capillary density (FCD) associated with increased heterogeneity of blood flow involving areas with well-perfused vessels in close vicinity to non-perfused capillaries [38, 39]. In normal conditions, the heterogeneity of microvascular blood flow is negligible [40], and the matching of perfusion to metabolism usually improves during hypoxic or low-flow states [41]. However, increases in heterogeneity of the microcirculatory blood flow with the subsequent reduction of FCD could be responsible for the abnormal oxygen extraction capacity occurring in sepsis [42, 43]. In fact, the heterogeneous flow cessation of individual capillaries could be an important factor determining the phenomenon of oxygen supply dependence during the most severe cases of septic shock [42, 44]. Importantly, microcirculatory alterations may occur even when global oxygen parameters appear to be adequate, and it seems to trigger the development of multiple organ dysfunction [45]. Furthermore, such microcirculatory derangements are stronger determinants of clinical outcomes than global hemodynamic parameters, with progressive increase in the risk of death in quartiles representing the most severe disturbances [46].

The link between microcirculatory alterations and tissue CO_2 accumulation in septic shock was proposed by Creteur et al. [47] by simultaneous evaluations of sublingual microcirculation, sublingual tissue CO_2, and gastric mucosal CO_2 during the infusion of a low fixed dose of dobutamine. They observed increases in cardiac output and SvO_2, while sublingual-to-arterial CO_2 difference (Psl-aCO_2) significantly decreased (from 40 ± 15 to 17 ± 8 mmHg). The proportion of well-perfused small vessels was inversely related with Psl-aCO_2 ($R^2 = 0.80$, $p < 0.01$), indicating that increases in the proportion of well-perfused capillaries paralleled inverse variations in tissue CO_2 pressure. Similarly, Nevière and colleagues [48] found that dobutamine-induced changes in gastric microvascular blood flow were well reflected by the changes in gastric mucosal-to-arterial CO_2 differences (Pgtis-aCO_2), thus supporting the leading role of microvascular blood flow on gastric-tissue CO_2 accumulation.

Recent observations have also suggested a close relationship between microcirculatory blood flow alterations and Pv-aCO_2 during the early stages of septic shock [11]. Particularly, the increased heterogeneity of microcirculatory blood flow and decreased functional capillary densities were well related with progressive increases of Pv-aCO_2. Interestingly, variations in cardiac output were not well correlated with changes in microcirculatory blood flow parameters, although admittedly, higher Pv-aCO_2 values were generally observed at lower cardiac output values.

During tissue hypoxia, total VCO_2 decreases despite some anaerobic CO_2 generation. However, venous CCO_2 will increase as macro blood flow decreases or microvascular blood flow turns more heterogeneous. In fact, considering a constant VCO_2, venous CO_2 will increase even at apparent "normal" cardiac output values when microcirculatory blood flow becomes heterogeneous and capillary densities fall (Fig. 16.3). In this manner, monitoring PCO_2 gaps may provide important information about microcirculatory blood flow alterations even in patients with apparently normalized cardiac output and oxygen-derived parameters.

16.3.3 The Clinical Value of Pv-aCO_2

Pv-aCO_2 changes reflect macro blood flow variations during abnormal noninflammatory conditions such as cardiac arrest, hypovolemic or hemorrhagic shock, and cardiac tamponade [24–28]. However, during septic shock, Pv-aCO_2 could be potentially influenced by microcirculatory blood flow distribution, whereby the relationship between cardiac output and Pv-aCO_2 has not been consistently observed in clinical and experimental studies.

Early observations in septic shock demonstrated that patients with Pv-aCO_2 > 6 mmHg showed lower cardiac output values than those with Pv-aCO_2 ≤ 6 mmHg [36]. Interestingly, positive responders to fluid loads exhibited simultaneous reductions in Pv-aCO_2, although the mathematical agreement between Pv-aCO_2 and cardiac output changes was actually poor (r = 0.42 or R^2 = 0.18, p < 0.001). Likewise, an inverse (although mathematically weak) relationship between cardiac output and Pv-aCO_2 (r = 0.41 or R^2 = 0.17, p < 0.001) was reported by Bakker et al. [35], and although cardiac output and DO_2 were lower in patients with Pv-aCO_2 > 6 mmHg, identical VO_2 was observed in both groups due to the adaptive ERO_2 changes.

A Pv-aCO_2 > 6.0 mmHg in patients with septic shock attaining a $ScvO_2$ > 70% after initial resuscitation has also been related with more severe multiorgan dysfunction [15]. Similarly, Ospina-Tascón et al. [14] showed that the persistence of high Pv-aCO_2 during early resuscitation of septic shock is associated with more severe multiorgan dysfunction and poorer outcomes at day 28. Increases in Pv-aCO_2 were associated with adverse clinical outcomes even when attaining $ScvO_2$ and $ScvO_2$ goals. Furthermore, higher lactate levels and slower lactate recovery were observed in those patients with persistently high Pv-aCO_2 values during the first 6 h of resuscitation. Importantly, PCO_2 gaps obtained from central venous and mixed-venous blood samples exhibited good agreement. However, as also suggested in another recent study in septic shock patients [37], no agreement was observed between Pv-aCO_2 and cardiac output.

Interestingly, although Pv-aCO_2 has been associated with adverse outcomes in septic shock [14, 15, 37, 49, 50] and high-risk surgical procedures [51], its predictive value in cardiac surgery remains controversial [52, 53].

Thus, a high Pv-aCO_2 may identify septic patients who remain inadequately resuscitated despite attaining oxygen metabolism targets, reinforcing the notion about the Pv-aCO_2 as a marker of global perfusion due to its ability to detect blood flow alterations. Nevertheless, a normal Pv-aCO_2 may not detect the presence of tissue hypoxia as elevated cardiac output values could prevent venous CO_2 increases by simple tissue washout.

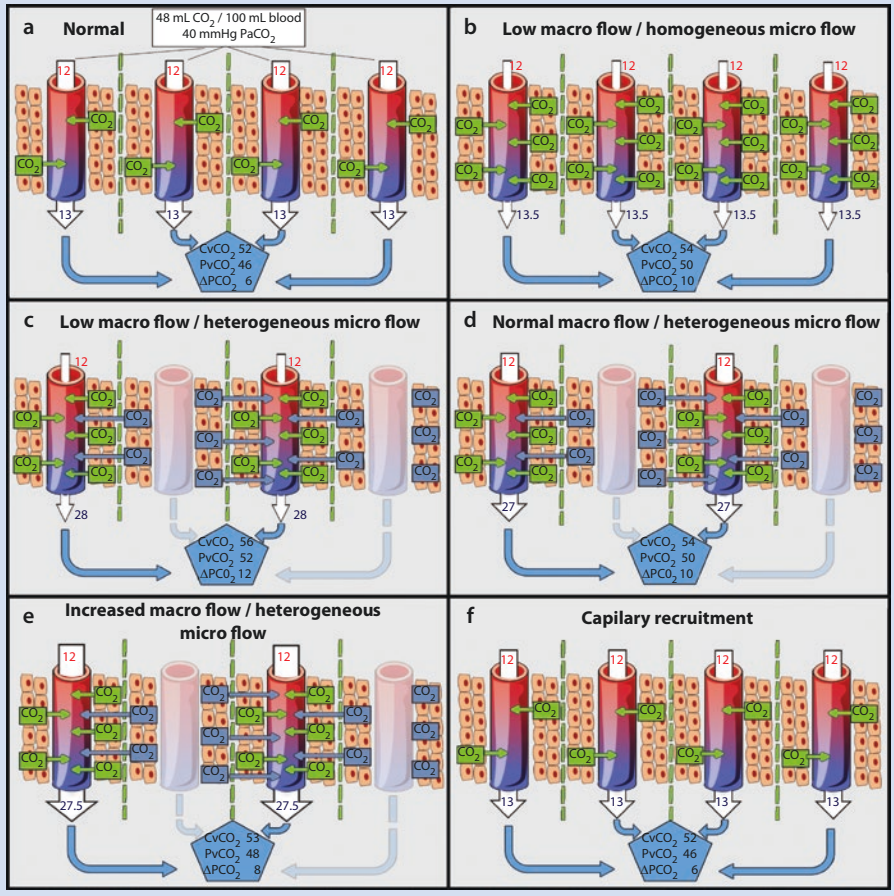

Fig. 16.3 Macro- and microcirculatory blood flow variations and its effects on Pv-aCO_2. Panel **a** Normal conditions of macro and micro blood flow: 48 mL CO_2/dL (or $PvCO_2$ 40 mmHg) are conducted throughout four capillaries with normal continuous convective flow (white arrows throughout capillaries). Venous effluent will come loaded with aerobic-produced CO_2 leading to $CvCO_2$ of 52 mL/dL (or $PvCO_2$ 46 mmHg) generating a Pv-aCO_2 of 6 mmHg. Panel **b** Low cardiac output with homogeneous microvascular blood flow. Delayed transit time of capillary blood (thin white arrows throughout capillaries) will conduct to higher CO_2 loads at the venous effluent even aerobic metabolism is maintained (stagnation phenomenon). Venous effluent will be charged with extra aerobic CO_2 leading to $CvCO_2$ of 54 mL/dL (or $PvCO_2$ 50 mmHg) and Pv-aCO_2 of 10 mmHg. Panel **c** Low cardiac output and heterogeneous microvascular blood flow. Patent capillaries will be loaded with higher amounts of aerobic CO_2 from adjacent cellular groups because of vascular stagnation (thin white arrows throughout open capillaries represent low convective flow). Furthermore, venous effluent will be also loaded with additional CO_2 from distant cellular groups. This additional CO_2 will be in part a product from the reduced aerobic metabolism, and most will proceed from anaerobic CO_2 generation because of the buffering of net H^+ release (see the text for details). Thus, venous effluent will be charged with extra aerobic and anaerobic CO_2 leading to $CvCO_2$ of 56 mL/dL (or $PvCO_2$ 52 mmHg) and Pv-aCO_2 of 12 mmHg. Panel **d** Normal cardiac output and heterogeneous microvascular blood flow. Anaerobic CO_2 will be generated into the blood as a product of buffering of net H^+ release (increased because of O_2 limitation secondary to blood flow misdistribution – see text for details). Despite apparent normal cardiac output, this is not enough to wash out the excess of CO_2. Thus, venous effluent will be charged with extra aerobic and anaerobic CO_2 leading to $CvCO_2$ of 54 mL/dL (or $PvCO_2$ 50 mmHg), and Pv-aCO_2 will remain high (10 mmHg). Panel

16.4 The Venous-Arterial CO_2 to Arterial-Venous O_2 Ratio ($Cv\text{-}aCO_2/Ca\text{-}vO_2$ Ratio)

16.4.1 Physiological Rationale

According to the Fick equation, oxygen consumption (VO_2) and CO_2 production (VCO_2) are directly proportional to the cardiac output and their respective arterial-to-venous and venous-to-arterial content differences. Under aerobic steady-state conditions, VCO_2 approaches VO_2, whereby the mixed venous-to-arterial CO_2 content difference ($Cv\text{-}aCO_2$) approximates to the arterial-to-mixed-venous CO_2 content difference ($Ca\text{-}vO_2$). Accordingly, VCO_2 should not exceed O_2 availability, and, therefore, the VCO_2/VO_2 ratio (i.e., the respiratory quotient (RQ)) should not be >1.0 during such aerobic resting conditions. $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio could be a surrogate of the VCO_2/VO_2 ratio or RQ, and, to some extent, it should be independent of flow variations since, according to the Fick equation, the cardiac output is present in both the numerator and denominator components. A recent subanalysis from an experimental shock model of progressive hemorrhage suggested that the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio is a poor surrogate of anaerobic metabolism during hemodilution [54]. However, other authors have observed simultaneous increases in $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio, the respiratory quotient (measured by indirect calorimetry), and lactate levels during circulatory failure in mechanically ventilated patients [55], thus reinforcing the idea about the link between anaerobic metabolism and increased $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio.

Experimental blockade of mitochondrial O_2 utilization leads to nonsymmetrical reductions in VCO_2 and VO_2 with RQ increase. This asymmetric VCO_2/VO_2 fall could be explained by increased anaerobic CO_2 production derived from the buffering of excess of protons (mainly delivered during ATP hydrolysis) that are not recycled during oxidative phosphorylation as a result of the severely limited O_2 availability (Fig. 16.4). Analogously, under conditions of excessive metabolic demand (such as during exhaustive exercise), total VCO_2 may exceed adaptive increases in VO_2, once the anaerobic threshold is attained [56]. Otherwise, during circulatory shock, a global decrease in VO_2 should be accompanied by a proportional reduction in aerobic VCO_2. However, experimental shock models also demonstrated that VCO_2 could decrease slightly less than the VO_2 fall [28, 57], with the subsequent increase in the VCO_2/VO_2 ratio. Interestingly, this VCO_2/VO_2 ratio returns to normal after shock reversion. The aforementioned then suggests that $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio could identify the presence of anaerobic metabolism.

e Increased cardiac output and heterogeneous microvascular blood flow. An increased macro flow will wash both aerobic and anaerobic CO_2 produced in tissues (thick white arrows throughout open capillaries represent increased convective flow). However, when microvascular blood flow is severely heterogeneous, anaerobic CO_2 will increase in the venous effluent despite apparent high cardiac output values. Thus, venous effluent will be charged with extra aerobic and anaerobic CO_2 leading to $CvCO_2$ of 53 mL/dL (or $PvCO_2$ 48 mmHg) and $Pv\text{-}aCO_2$ of 8 mmHg. Panel **f** Capillary recruitment. Interventions improving microvascular blood flow distribution lead to normalize $Pv\text{-}aCO_2$ that even cardiac output apparently decreases from "high" to "normal" values. Note: green vertical dotted lines represent the limits of the theoretical cylindrical areas dependent from each capillary vessel

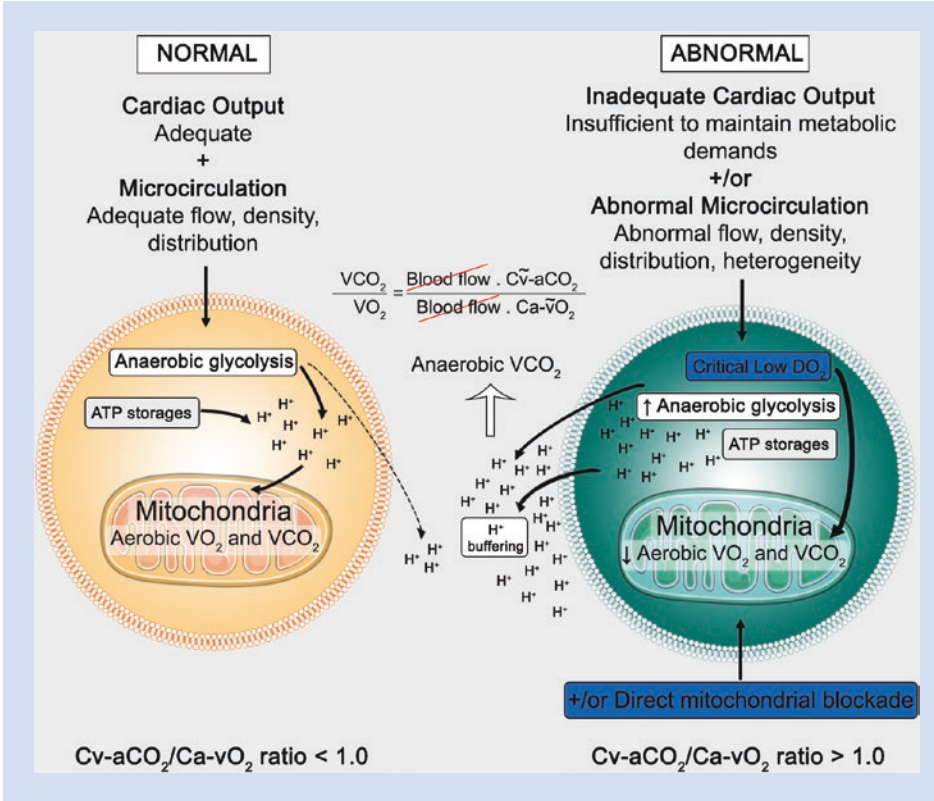

Fig. 16.4 The venous-arterial CO_2 to arterial-venous O_2 ratio (Cv-aCO_2/Ca-vO_2 ratio). Normal aerobic (left side) and anaerobic conditions (right side). Adequate cardiac output and normal microvascular blood flow distribution usually preserve cellular respiration, and Cv-aCO_2/Ca-vO_2 ratio remains ≤1.0. Conversely, inadequate cardiac output, microvascular blood flow misdistribution, and direct mitochondrial blockade decrease VO_2 with subsequent fall in aerobic VCO_2. Cellular metabolism shifts toward anaerobic glycolysis, and H^+ liberated during ATP hydrolysis is not reused in the oxidative phosphorylation. Thus, excess of non-recycled H^+ is buffered by HCO_3^- generating H_2CO_3, which dissociates into CO_2 and H_2O. This anaerobic CO_2 will increase the Cv-aCO_2/Ca-vO_2 ratio

16.4.2 The Cv-aCO_2/Ca-vO_2 Ratio and Its Clinical Implications

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Hyperlactatemia has been traditionally recognized as a marker of anaerobic metabolism secondary to an inadequate oxygen supply to the cells. However, plasma lactate levels may increase by causes other than tissue hypoxia [58]. In fact, high lactate levels can frequently result from increased glycolytic activity, abnormal pyruvate metabolism, or altered metabolic lactate clearance [59–61], which hinder its interpretation during the resuscitation and post-resuscitation periods. Using CO_2 pressures instead of CO_2 contents, Mekontso-Dessap et al. [12] showed 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). However, more important than a simple agreement, the Cv-aCO_2/Ca-vO_2 ratio can provide additional information to that provided by lactate levels. In a recent study, Ospina-Tascón et al. [13] demonstrated that persistent hyperlac-

tatemia combined with a high Cv-aCO_2/Ca-vO_2 ratio was associated with more severe organ dysfunction and worse clinical outcomes in septic shock as compared to those patients with normal lactate levels and a Cv-aCO_2/Ca-vO_2 ratio ≤ 1.0. Intriguingly, patients attaining lactate levels <2.0 mmol/L but with persistently elevated Cv-aCO_2/Ca-vO_2 ratios had similar clinical outcomes than those with persistent hyperlactatemia and normal Cv-aCO_2/Ca-vO_2 ratios. However, whether an increased Cv-aCO_2/Ca-vO_2 ratio can precede increases in lactate levels during septic shock should be confirmed in the future.

Subsequent studies have corroborated the Cv-aCO_2/Ca-vO_2 ratio as a prognostic factor in septic shock [62, 63], while others have suggested that concomitant high Cv-aCO_2/Ca-vO_2 ratios and hyperlactatemia may identify an ongoing VO_2/DO_2 dependence [64, 65]. In agreement with this concept, other authors have demonstrated that VO_2 increases after a fluid load only in patients with acute circulatory failure and an increased pre-fluid Pv-aCO_2/Ca-vO_2 ratio [64, 65]. Furthermore, evidence from experimental septic shock models suggests that improvement of microcirculatory blood flow distribution can reverse the anaerobic metabolism reflected by proportional falls in the Cv-aCO_2/Ca-vO_2 ratio [41].

In conclusion, the Cv-aCO_2/Ca-vO_2 ratio or its equivalent, the Pv-aCO_2/Ca-vO_2 ratio (with the obvious limitations because the Haldane effect), might provide important prognostic information, and it could help to clarify the origin of lactate increases (from aerobic or anaerobic nature) during the early stages of shock. The 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 probably the presence of ongoing anaerobic metabolism.

16.5 The Pv-aCO_2 and the Haldane Effect

The CO_2 binding to hemoglobin will vary according to the oxygenated or deoxygenated state of hemoglobin. This phenomenon known as the Haldane effect allows better loading of CO_2 from tissues to the blood when oxygen moves in the opposite direction, thereby increasing the CO_2-carrying ability of venous blood. Conversely, oxygen moving from alveoli to the capillary blood enhances unloading of CO_2 from hemoglobin, thus facilitating its pulmonary elimination. Therefore, low oxygen saturation values increase the CO_2 content (CCO_2) for a given PCO_2, whereby more CO_2 will be bound to hemoglobin. Changes in tissue oxygen extraction, pH, VCO_2, and hemoglobin concentration can influence Pv-aCO_2 despite a preserved or even increased tissue perfusion. For example, a combination of high blood flow and larger increases in VCO_2 compared with the respective change in oxygen consumption may lead to dissociation of the tissue-to-arterial or venous-to-arterial CO_2 gradients among different vascular beds with different baseline ERO_2 values. In fact, paradoxical increases in mucosal-to-arterial PCO_2 differences can occur during increasing splanchnic blood flow because of changes in venous oxygen saturation effluent, local VCO_2, or both [66].

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 [67]. 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 frequently. However, Cv-aCO_2 is not always represented by Pv-aCO_2, especially during low PCO_2 and SvO_2 conditions. In this regard, a

recent study demonstrated the prognostic value of the $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio in septic shock and the unreliability of its equivalent in terms of partial pressures, the $Pv\text{-}aCO_2/Ca\text{-}vO_2$ ratio [13]. Thus, although at low $Pv\text{-}aCO_2$ values the influence of the Haldane effect is negligible, the dispersion of $Cv\text{-}aCO_2$ vs. $Pv\text{-}aCO_2$ becomes significantly wider at higher $Pv\text{-}aCO_2$ values [13].

The simplicity of $Pv\text{-}aCO_2$ measurement makes it an attractive tool to guide resuscitation in the clinical setting. However, $Pv\text{-}aCO_2$ is a physiologically complex measurement that should be interpreted according to a number of physiological variables.

16.6 Interpreting $Pv\text{-}aCO_2$ and $Cv\text{-}aCO_2/Ca\text{-}vO_2$ Ratios in Septic Shock

Tissue-to-arterial and venous-to-arterial CO_2 differences should be considered as markers of tissue perfusion rather than indicators of tissue hypoxia. Concomitance of high $Pv\text{-}aCO_2$ (> 6.0 mmHg) and low SvO_2 levels usually reflects low cardiac output in both inflammatory and noninflammatory conditions. Likewise, normal SvO_2 accompanying persistently increased $Pv\text{-}aCO_2$ suggests the presence of a cardiac output that is insufficient to clear the CO_2 produced by tissues. Alternatively, high $Pv\text{-}aCO_2$ values with normal or even high SvO_2 values coincide with microcirculatory derangements such as decreased functional capillary densities or increased heterogeneity of microvascular blood flow, at least during the early stages of septic shock [11, 45]. In any case, an increased $Pv\text{-}aCO_2$ reflects altered macro or micro blood flow independently of the presence of anaerobic metabolism. Consequently, an elevated $Pv\text{-}aCO_2$ should encourage clinicians to optimize the cardiac output or possibly recruiting microcirculation to improve tissue perfusion, especially when lactate levels are increased and clinical signs of hypoperfusion are present. However, such decisions should take into account the clinical context and information provided by "multimodal" monitoring [68]. Under aerobic conditions, a high $Pv\text{-}aCO_2$ would mean that blood flow is not sufficient even when the cardiac output is in "normal" ranges. In this context, further efforts to increase the cardiac output aimed to prevent the possible onset of tissue hypoxia remain controversial and need to be evaluated in the future.

Under conditions of oxygen supply dependency, increases in cardiac output should be accompanied by rises in VO_2 and, consequently, by increases in aerobic VCO_2, so that $Pv\text{-}aCO_2$ may decrease by a lesser extent after such positive intervention. Thus, minor decreases in $Pv\text{-}aCO_2$ not always mean an ineffective therapeutic intervention. Consequently, in cases of probable oxygen supply dependency, interventions optimizing the cardiac output should probably be maintained until a decrease in $Pv\text{-}aCO_2$ values is obtained. Remarkably, most interventions aimed to increase the cardiac output will increase VCO_2 since vasoactive amines and inotropes positively increase the thermogenic effect [69]. In this regard, $Pv\text{-}aCO_2$ could be used as an index reflecting the VCO_2/cardiac output relationship [29], and consequently, it could help titrate drug therapy [70]. Conversely, a normal $Pv\text{-}aCO_2$ (<6.0 mmHg) suggests that the cardiac output is sufficient to clear the CO_2 produced by tissues and also suggests that the microcirculatory blood flow is adequately distributed. However, whether cardiac output or microcirculation should be manipulated during apparent hypoxic conditions with a $Pv\text{-}aCO_2 < 6.0$ mmHg remains also debatable.

A $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratio > 1.0 could suggest the presence of anaerobic metabolism. Thus, combining lactate levels and $Cv\text{-}aCO_2/Ca\text{-}vO_2$ ratios might provide relevant infor-

mation during the early stages of resuscitation. An increased lactate level accompanied by Cv-aCO_2/Ca-vO_2 ratios >1.0 could suggest "ongoing" anaerobic metabolism; thus clinicians should be encouraged to optimize both macro and micro blood flow parameters. Conversely, increased lactate levels accompanied by Cv-aCO_2/Ca-vO_2 ratios ≤1.0 may could suggest lactate accumulation as a result of cell dysfunction in the presence of aerobic metabolism. In such cases, additional resuscitation maneuvers aimed to increase blood flow should probably be discouraged, although this should be confirmed in clinical trials. Given the faster response in CO_2 variables, a Cv-aCO_2/Ca-vO_2 ratio > 1.0 with normal lactate levels could eventually suggest the onset of anaerobic metabolism, even anticipating the increase in lactate levels. Nevertheless, the complexity of the Cv-aCO_2/Ca-vO_2 ratio merits further research and confirmation in the clinical setting.

Conclusion

Physiology determining venous CO_2 increases is complex. However, Pv-aCO_2 globally reflects blood flow alterations at both macro- and microvascular levels, more than tissue dysoxia. Meanwhile, an elevated Cv-aCO_2/Ca-vO_2 ratio could reflect anaerobic metabolism, and it could add important prognostic information in patients with shock. Despite the physiological bases of such monitoring CO_2-derived variables, its clinical utility during resuscitation in shock remains to be proved in future experimental and clinical studies.

Take-Home Messages

- Pv-aCO_2 is determined by the conjunction of macro- and/or microvascular blood flow, the total CO_2 production (both aerobic and anaerobic), and the complex relationship between CO_2 partial pressures and CO_2 blood contents (Haldane effect).
- Pv-aCO_2 should be considered as a marker of tissue perfusion but not of tissue hypoxia.
- An increased Pv-aCO_2 usually suggest a "low" or "insufficient" cardiac output. However, during severe inflammatory conditions, alterations in functional capillary density and heterogeneity of microvascular blood flow could also account for venous CO_2 accumulation.
- An elevated Pv-aCO_2 should encourage clinicians to optimize the cardiac output, especially when lactate levels are increased and clinical signs of hypoperfusion are present.
- Under aerobic conditions, further efforts to increase the cardiac output in order to prevent the possible onset of tissue hypoxia in the presence of a high Pv-aCO_2 remain controversial.
- An increased venous-arterial carbon dioxide to arterial-venous oxygen content difference ratio (Cv-aCO_2/Ca-vO_2) could reflect the presence of anaerobic metabolism. There is some experimental evidence that high Cv-aCO_2/Ca-vO_2 ratio can be reversed by resuscitation maneuvers, at least during early stages of shock.
- A high Cv-aCO_2/Ca-vO_2 ratio could offer additional prognostic information in septic shock. Whether Cv-aCO_2/Ca-vO_2 ratio could anticipate lactate increase during early stages of shock remains to be elucidated.

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