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Review

Use of CO_2-Derived Variables in Cardiac Intensive Care Unit: Pathophysiology and Clinical Implications

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Abstract: Shock is a life-threatening condition, and its timely recognition is essential for adequate management. Pediatric patients with congenital heart disease admitted to a cardiac intensive care unit (CICU) after surgical corrections are particularly at risk of low cardiac output syndrome (LCOS) and shock. Blood lactate levels and venous oxygen saturation ($ScVO_2$) are usually used as shock biomarkers to monitor the efficacy of resuscitation efforts, but they are plagued by some limitations. Carbon dioxide (CO_2)-derived parameters, namely veno-arterial CO_2 difference (ΔCCO_2) and the VCO_2/VO_2 ratio, may represent a potentially valuable addition as sensitive biomarkers to assess tissue perfusion and cellular oxygenation and may represent a valuable addition in shock monitoring. These variables have been mostly studied in the adult population, with a strong association between ΔCCO_2 or VCO_2/VO_2 ratio and mortality. In children, particularly in CICU, few studies looked at these parameters, while they reported promising results on the use of CO_2-derived indices for patients' management after cardiac surgeries. This review focuses on the physiological and pathophysiological determinants of ΔCCO_2 and VCO_2/VO_2 ratio while summarizing the actual state of knowledge on the use of CO_2-derived indices as hemodynamical markers in CICU.

Keywords: CICU; congenital cardiac abnormalities; veno-arterial CO_2 difference; VCO_2/VO_2 ratio; pediatric

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1. Introduction

Shock and low cardiac output syndrome (LCOS) are life-threatening conditions characterized by an inadequacy between oxygen delivery (DO_2) and oxygen consumption (VO_2), leading to cellular dysfunction and end-organ lesions [1]. Timely recognition is crucial for early and aggressive management of such dreadful conditions. Therefore, sensitive biomarkers to assess tissue perfusion and cellular oxygenation are required to guide clinical management and prognosis.

Serum lactate level and central venous oxygen saturation ($ScVO_2$) have been used traditionally as markers of tissue perfusion and adequacy of DO_2 in case of shock. Nonetheless, $ScVO_2$ and lactate have drawbacks that need to be known in order to correctly interpret their values in the intensive care setting. Moreover, if their role as predictors of unfavorable outcomes is undeniable, resuscitation algorithms based either on lactate or $ScVO_2$ failed to demonstrate clear clinical benefits [2–8].

The measurement of SvO_2 (venous oxygen saturation measured in the pulmonary artery) has become a rarity, especially in pediatric patients, as a pulmonary catheter must be placed, which is a complicated and risky procedure. SvO_2 and $ScVO_2$ are closely correlated, provided that the central venous catheter tip is correctly positioned at the junction between the superior venous cava and the right atrium.

$ScVO_2$ use is based on the comparison between the VO_2 and the extraction of oxygen by the tissue, using the Fick formula:

$$VO_2 = \text{Cardiac Output} \times \text{Oxygen Extraction}$$

That is

$$VO_2 = \text{Cardiac Output} \times (CaO_2 - CvO_2)$$

Knowing that $CaO_2 = Hb \times 1.34 \times SpaO_2 + 0.003 \times PaO_2$ and $CvO_2 = Hb \times 1.34 \times ScVO_2 + 0.003 \times PaO_2$

And after rearrangement of the equation, the final formula:

$$ScVO_2 = SpaO_2 - VO_2/[CO \times Hb \times 1.34]$$

A reduction of oxygen delivery (the denominator of the equation) will first lead to an increase in oxygen extraction to maintain the VO_2. As a result, $ScVO_2$ will decrease proportionally to the reduction of DO_2, regardless of the cause that generated the DO_2 reduction, thus providing a global picture of the patient's hemodynamic status. The role of $ScVO_2$ as a marker of both hemodynamic deterioration and clinical response to treatments has been extensively studied in both adult and pediatric ICU patients [9]. Specifically, after pediatric cardiac surgeries, $ScVO_2$ levels have been associated with progressive hemodynamic deterioration and unfavorable clinical outcomes [10,11].

However, several limitations of $ScVO_2$ should be mentioned, and its interpretation comes with some caveats. In fact, low $ScVO_2$ values indicate a global imbalance between DO_2 and VO_2 without giving any further information regarding the individual components of these two elements, such as arterial oxygen saturation, hemoglobin, and CO. Moreover, during the early phase of resuscitation, the increase in DO_2 may lead to an increase in VO_2, which could result in a transitory decrease in $ScvO_2$ levels. In a situation of shock, a mismatch between DO_2 and capillary perfusion may lead to a misleadingly normal $ScVO_2$ resulting from oxygen extraction impairment [9,12,13].

Serum lactate is a key metabolic parameter that could be related to both hypoperfusion and hypoxia [14]. It is produced in all human cells as part of intracellular glucose metabolism. In patients with shock, DO_2 could be insufficient to meet cellular metabolism demands. As a consequence, the absence of aerobic mitochondrial metabolism leads to an over-production of lactate from the intracellular excess pyruvate.

As lactate level is a marker of hypoperfusion, serum lactate's peak level, as well as lactate clearance, are strongly associated with patient outcomes in both adult and pediatric critically ill patients [1,6,15,16]. In patients admitted to the pediatric cardiac intensive care unit (CICU), increased blood lactate level has been associated with significant morbidity and mortality [17,18]. However, both the production and the clearance of lactate can be impacted by several factors, which limit its interpretation. Lactate production can be increased by alternative mechanisms frequently encountered in intensive care, such as hyperglycemia or beta-receptor stimulation [19–22]. Both hyperglycemia and the adrenergic stimulation of beta-2 receptors will lead to excess pyruvate production at the mitochondrial level [20,23–25]. Part of this excess pyruvate will be diverted to lactate production. Reduced lactate clearance, as well as washout phenomena' (temporary increase in serum lactate level once sufficient capillary blood flow has been reestablished), can impact serum lactate level even in the absence of tissue hypoxia.

Given the aforementioned limitations in the interpretations of conventional tissue oxygenation markers, supplementary tools to assess the hemodynamic status of critically ill patients are needed [26,27]. Carbon dioxide (CO_2)-derived parameters may represent a potentially valuable addition to serum lactate level and $ScVO_2$ when it comes to the evaluation of tissue perfusion and hypoxia, as underlined by the recent recommendation on hemodynamic monitoring adult experts when lack of data prevented pediatric experts from giving such recommendations [28,29]. The simplicity of CO_2-derived parameters

measurement at the bedside makes them an attractive tool to guide resuscitation in the clinical setting.

The purpose of this review is to describe currently available CO_2-derived parameters and their physiological underpinnings, as well as their potential clinical applications in CICU.

2. CO_2 Metabolism

CO_2 is produced by cellular metabolism (VCO_2) under both aerobic and anaerobic conditions. Under aerobic metabolism, CO_2 is produced by the mitochondrial metabolism as a by-product of substrate oxidation. In the case of anaerobic metabolism, CO_2 is also produced by bicarbonate buffering of H^+ derived from lactic acid production and ATP hydrolysis. Carbon dioxide diffuses from the intracellular to the extracellular compartment. Once in the blood, CO_2 transportation occurs in three forms: dissolved, as bicarbonate after the reaction of CO_2 with H_2O in red blood cells, and finally, as carbamino compounds within circulating proteins, particularly hemoglobin. The dissolved fraction of CO_2 is in equilibrium with the partial pressure of CO_2 (PCO_2) according to Henry's law of gas solubility, depending on the gas solubility, the atmospheric pressure, and P CO_2 itself. The majority of CO_2 is transported in the blood as bicarbonate. As CO_2 diffuses nearly freely in red blood cells, it reacts with H_2O to form carbonic acid (H_2CO_3). In turn, H_2CO_3 will dissociate to form both bicarbonate (HCO_3^-) and H^+. Eventually, H^+ will be buffered by hemoglobin, and HCO_3^- exits the red blood cell. A small proportion of CO_2 is transported as carbamino compounds that are linked to proteins, particularly to hemoglobin.

The proportion of diluted CO_2, bicarbonate, and protein bounded CO_2 varies between the arterial and venous compartments. In arterial blood, bicarbonate accounts for 90% of total CO_2 content, while 5% is dissolved and 5% is bound to proteins. In venous blood, only 70% of the total CO_2 content corresponds to bicarbonate, while 10% is dissolved, and a carbamino compound contributes 20%. The total content of CO_2 (CCO_2) in the blood under physiological conditions equals the dissolved CO_2 + the bicarbonate (HCO_3) + the CO_2 linked to hemoglobin (R-NH_2-CO_2).

The content of CO_2 (CCO_2) is dependent on several variables and can be precisely calculated. According to the Douglas formula [30], the CCO_2 could be determined using the content of CO_2 in the plasma, the blood pH, and temperature:

$$\text{Plasma } CCO_2 = 2.226 \times S \times \text{plasma } PCO_2 \times (1 + 10^{pH\text{-}pK'})$$

$$S = 0.0307 + [0.00057 \times (37 - \text{Temp})] + [0.00002 \times (37 - \text{Temp})^2]$$

$$pK' = 6.086 + [0.042 \times (7.4 - pH)] + [(38 - \text{Temp}) \times (0.00472 + (0.00139 \times (7.4 - pH))]$$

For the final calculation, the hemoglobin level, the saturation in oxygenation, and the total amount of CO_2 in the plasma are used:

$$CCO_2 = \text{Plasma } CCO_2 \times [1 - [0.0289 \times [Hb]/[[3.352 - 0.456 \times SpO_2] \times [8.142 - pH]]]$$

The complete formula for the calculation of CCO_2 gives the opportunity to appreciate the complexity of factors that are impacting the transport and content of CO_2. However, despite its accuracy, this formula is extremely difficult to use at the bedside due to its computational complexity. Importantly, CO_2 partial pressure (PCO_2) is easier to obtain at the bedside, and a relationship exists between both CCO_2 and PCO_2 [31,32]. This relationship can be defined by the following equation $PCO_2 = k \times CCO_2$, where k is a constant. This relationship follows a curvilinear curve with a near-linear relationship only in physiological PCO_2 [31–33]. This nearly linear relation window has permitted the use of PCO_2 in place of CCO_2 in multiple clinical studies and expert opinion reports [26,28,34–37].

However, outside those ranges, it could be recommended to use CCO_2 as the PCO_2 will mostly divert significantly from the PCO_2. The curvilinear relationship is directly impacted by the complex interaction of numerous variables such as the blood pH and temperature, the dissolved CO_2, the CO_2 bound to hemoglobin, and the CO_2 as bicarbonate, as it is suggested by the multiple variables incorporated in the complete calculation of CCO_2. The relationship between both CCO_2 and pCO_2 could be shifted by four factors: PO_2, plasma pH and temperature, as well as hemoglobin levels. Those factors impact the *k* constant, with *k* increasing in case of a rise in PO_2, acidosis, temperature, and hemoglobin level. Of special importance is the impact of oxygen on the content of CO_2 through the Haldane effect. The Haldane effect describes the ability of hemoglobin to carry, at any PCO_2, increased amounts of CO_2 in the deoxygenated state compared to the oxygenated state [38]. Consequently, as blood enters the systemic microcirculation and releases O_2, the CO_2-carrying capacity increases so that the blood may remove the excess CO_2. On the contrary, as blood enters the pulmonary circulation and binds O_2, the CO_2-carrying capacity decreases, thus facilitating CO_2 removal from the lungs. In light of all the factors impacting the relationship between CCO_2 and PCO_2, we would argue for preferentially using CCO_2 or, in case the PCO_2 is used, it seems crucial that the clinicians understand the limitations of such approximation [38–40].

3. Relation between CO_2 and Cardiac Output

3.1. Macrocirculation and Cardiac Output

Circulating CO_2 is slightly higher in the venous compartment as a result of aerobic production of CO_2 in tissues and alveolar elimination, thus creating a CO_2 gradient between the venous and the arterial compartments. This difference will also be present under anaerobic circumstances due to the non-aerobic production of CO_2. The increase in CO_2 on the venous side will create an obligatory difference between the arterial and the venous blood, which could be estimated using the Fick equation.

In accordance with the Fick principle, the production of CO_2 (VCO_2) could be described as follows:

$$VCO_2 = \text{Cardiac Output (CO)} \times \Delta CCO_2$$

where ΔCCO_2 is the difference in CCO_2 between the venous and arterial compartments ($CvCO_2$-$CaCO_2$).

As mentioned above, PCO_2 and CCO_2 show a near-linear relationship at physiological ranges. Consequently, PCO_2 values may be regarded as surrogate measures for CCO_2 at the bedside.

A modified Fick equation can be obtained by substituting PCO_2 with CCO_2:

$$\Delta PCO_2 = (k \times VCO_2)/CO$$

This equation shows the inversely proportional relationship between CO and ΔPCO_2 (Figure 1).

The ability of ΔCCO_2 and ΔPCO_2 to monitor CO is unique and of primary importance. In shocked patients, the measurement of CO is a key element in the evaluation of the hemodynamic status of the patient as well as for the assessment of the appropriateness of the implementation of therapeutic measures. Although measuring CO in PICU patients is theoretically possible, the methods currently available are burdened by some limitations, which make their use in clinical practice sometimes difficult [41].

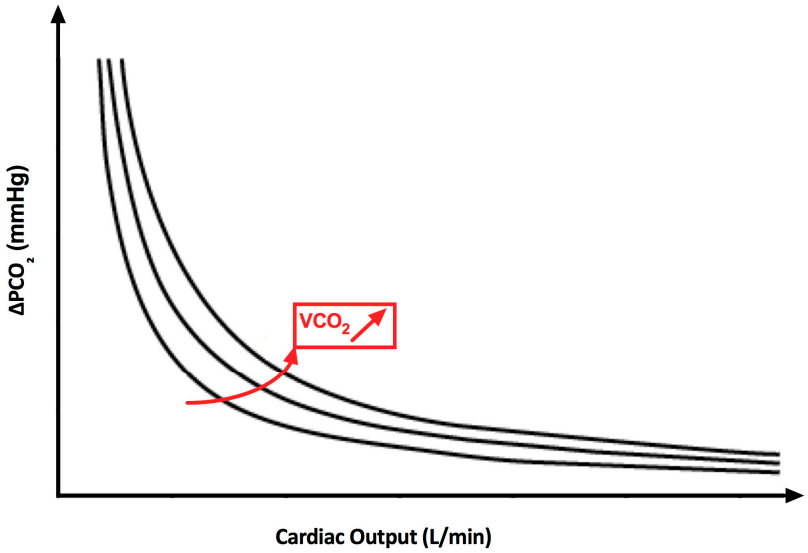

Figure 1. Relation between cardiac output and ΔPCO_2. Inverse relation between cardiac output and ΔPCO_2. Reduction of cardiac output is associated with an increase in ΔPCO_2, initially slow, which become exponential at very low cardiac output. Modification of CO_2 production (VCO_2) shift the curves to the right and upward.

The gold standard of CO estimation is cardiac echocardiography through the measurement of the left ventricular outflow tract (LVOT) diameter and the aortic velocity time integral [42]. Nonetheless, the correct implementation of cardiac echography and its interpretation requires highly specialized training, and it may be difficult to perform in patients with congenital cardiac malformations. Other methods using Doppler technologies are available, such as Ultrasound Cardiac Output Monitor (USCOM™, Sydney, NSW, Australia) or transesophageal Doppler [43–45]. These devices have some drawbacks as they use pre-established LVOT diameters, and the comparison of CO values with thermodilution methods has yielded conflicting results [45]. Thermodilution methods use the change in temperature of the circulating blood after a cold saline bolus to estimate blood flow. Using either a pulmonary catheter or a femoral catheter, CO could be precisely monitored. Some catheters, such as the PICCO™ device, can continuously monitor CO. However, despite very promising data on the applicability and validity of the CO measure devices, the invasiveness and relative difficulties of use probably limit their use in the setting of clinical trials [46–49]. A more recent tool for CO measurement is represented by electrical bioimpedance. This technology is based on the detection of electrical resistance changes in electrical resistance at the level of the thorax skin caused by cardiac stroke volume. The reliability of this method is still under scrutiny [50]. Again, the presence of a congenital cardiac anomaly and intracardiac shunts further complicate the interpretation of CO measurements and represents an important limitation of the aforementioned techniques.

The fact that ΔPCO_2 and ΔCCO_2 only depend on CO under stable VO_2 conditions makes its use in the ICU setting a reliable way to estimate the adequacy of CO with respect to tissue metabolic demand [51]. The relationship between ΔPCO_2 and CO has been studied in previous reports. A progressive decrease in ΔPCO_2 in parallel to an increase in CO in patients receiving escalating doses of dobutamine has been described [52,53]. Moreover, experimental models show that ΔPCO_2 remains stable under hypoxic conditions, and low DO_2 provides a normal and stable CO [54]. It is important to underline that, despite previous reports, ΔPCO_2 does not change in the case of cellular hypoxia [55–57]. In fact, the stagnation of CO_2 in tissues caused by the absence of sufficient blood flow but not hypoxia was responsible for the increase in ΔPCO_2 in patients after cardiac arrest [58]. Clinicians might therefore disentangle low CO (low $ScVO_2$ and elevated ΔPCO_2) from cellular hypoxia in the presence of normal CO (low $ScVO_2$ and normal ΔPCO_2) [31,59].

Thus, unlike $ScVO_2$, ΔPCO_2 might play an important role as a further easy-to-use bedside tool to monitor CO regardless of the presence of hypoxemia.

3.2. Microcirculation and the Microhemodynamic

If $ScVO_2$ can be helpful in assessing global hemodynamics with some caveats, it is not suitable for the evaluation of microcirculatory imbalances. Indeed, $ScVO_2$ may exert normal values in case of microcirculation derangements because of a lower oxygen extraction [9,12,13]. In a state of shock, the increased heterogeneity of blood flow (that is, well-perfused vessels in close vicinity to non-perfused capillaries) along with a reduction in the functional capillary density may lead to an increase in ΔCCO_2 regardless of CO [60].

Hypo-perfused areas will accumulate CO_2 under anaerobic circumstances. The excess CO_2 will then diffuse across well-perfused capillaries, and the ΔCCO_2 will increase. The association between abnormal ΔPCO_2 with altered microcirculatory blood flow has been demonstrated in septic shock patients [61–64]. ΔPCO_2 should be regarded as a potential tool for the evaluation of microcirculatory perfusion abnormalities, even in the absence of low CO. Under such circumstances, the increase in CO might improve tissue perfusion [36,65–67].

3.3. Clinical Use of ΔCCO_2 and ΔPCO_2

In adult patients with septic shock, both ΔCCO_2 and ΔPCO_2 are associated with patient mortality [36,65,66,68]. The correlation between ΔCCO_2 and ΔPCO_2 with CO, along with the detection of microcirculation anomalies, could be the main reasons for such findings. Higher ΔPCO_2 levels are also associated with both post-operative complications after cardiac surgery and mortality in general ICU patients [69–72]. Moreover, higher ΔPCO_2 might indicate microcirculatory derangements and predict patient mortality in adult patients on ECMO [73]. A recent meta-analysis confirmed the association between higher ΔPCO_2 and increased mortality in shocked ICU patients [74]. Importantly, ΔPCO_2 plays no role as a marker of tissular hypoxia but rather as a marker of adequacy between CO_2 production and CO. In fact, high-flow shocks should result in a decrease rather than an increase in ΔPCO_2.

Several treatment algorithms based on the combined use of serum lactate, $ScVO_2$, and ΔPCO_2 as a marker of insufficient CO have been proposed [26,31,32]. Most of those algorithms suggest the use of ΔPCO_2 with a cut-off value of 6 mmHg (0.8 kPa). Higher values will mostly indicate that CO is not able to meet global metabolic demands. In case of shock, a high ΔPCO_2 could prompt clinicians to increase CO (fluid bolus and/or inotropes). In the absence of shock, a high ΔPCO_2 might indicate a state of high oxygen demand and CO_2 production. A normal ΔPCO_2 might also indicate that CO is correct, while other determinants of oxygen delivery (SpO_2, hemoglobin) should possibly be improved in the presence of anaerobic metabolism (increased lactate and/or VCO_2/VO_2 ratio). Many of the available algorithms propose the use of both $ScVO_2$ and ΔPCO_2 to help clinicians to identify anemia, hypoxemia, or low CO as possible causes of tissue hypoxia. To our knowledge, though, none of those algorithms have been clinically validated.

Studies in the pediatric population are scarce and showed promising but conflicting results. A recent pediatric study in children with septic shock failed to detect a clear association between higher ΔPCO_2 and CO measures [75].

Most of the studies on ΔPCO_2 have been conducted in the CICU setting. A study from Furqan et al. suggests a possible association between higher ΔPCO_2 and low $ScVO_2$ after pediatric cardiac surgeries [76]. In this study, normal $ScVO_2$ was sometimes accompanied by increased ΔPCO_2. Unfortunately, the association of normal $ScVO_2$ and low ΔPCO_2 with clinical outcomes was not explored.

We found three studies looking at the possible association between increased ΔPCO_2 and unfavorable outcomes in the immediate post-operative period in children after cardiac surgery has been recently studied (Table 1) [35,77,78]. Two articles reported an association between higher ΔPCO_2 and poor outcome, defined as a composite variable including

death, cardiac arrest, ECMO requirement, unplanned surgical reinterventions, and elevated inotropic score [35,78]. On the contrary, Akamatsu et al. could not find such an association [77]. Differences in the study population, as well as the use of the PCO_2 variable used in the analysis (continuous vs. dichotomous), might explain these conflicting results. Although encouraging, current literature on the relation between CO_2-derived parameters and clinical outcomes in ICU is not yet conclusive. As ΔPCO_2 is directly linked to the CO, a more immediate and precise outcome, such as the duration of inotrope/vasopressor support or the need for mechanical circulatory support, may be more suited.

Table 1. Pediatric study looking ΔCO_2 as a tool in resuscitation.

	Insom et al. [78] Cardiol Young 2021	**Rhodes et al. [35] PCCM 2017**	**Akamatsu et al. [77] PCCM 2017**
N patients	40 patients	139 patients	114 patients
Age (days/months)	Median 215 days (range 3–5600)	Median 12 days (IQR 6–38)	Median 15.5 months (IQR 7–34)
Population	CICU	CICU	CICU
Outcome measured	Composite outcome – VIS > 15 – CICU LOS > 5 days	Composite outcome: – IS > 15 – Mortality – Cardiac arrest – ECMO within 48 h – Reintervention	– Mecanical ventilation duration – Mortality
ΔPCO_2 measured (mmHg)	Median 9 mmHg (range 1–25)	Median 5.9 mmHg (IQR 3.8–9.2)	Not reported ΔPCO_2 analyzed as a dichotomous variable >6 mmHg or <6 mmHg
Association ΔPCO_2-outcome	Significant association OR 1.13 (95% CI 1.01–1.35)	Significant association – composite outcome OR 1.3 (95% CI 1.1–1.45) – Mortality OR 1.2 (95% CI 1.07–1.31)	No significant association
Commentary	Higher values of ΔPCO_2 are associated with more complex clinical course.	Underline role for ΔPCO_2 monitoring in CICU Suggest an association between ΔPCO_2 and outcome.	Population separated into 2 groups: ΔPCO_2 > 6 mmHg or < 6 mmHg and no difference between both groups.

CICU, cardiac intensive care unit.

3.4. Production of CO_2 and O_2 Consumption (VCO_2/VO_2 Ratio)

Oxygen consumption (VO_2) and CO_2 production (VCO_2) are directly proportional to CO. Under aerobic steady-state conditions, the ratio between VO_2 and VCO_2 (VCO_2/VO_2 ratio) varies between 0.7 and 1, depending on the main metabolic substrate used for oxidative metabolism [79,80]. Under aerobic conditions, VCO_2 should not exceed O_2 availability; therefore, the ratio should not exceed one. However, under anaerobic conditions, during circulatory shock, both VO_2 and VCO_2 are globally reduced. However, due to buffering of cations (H^+) by bicarbonate, a small production of CO_2 remains [81]. This "anaerobic CO_2 production" would result in a relative rise of VCO_2 in comparison to VO_2. As a result, under anaerobic metabolism and dysoxia, the VCO_2/VO_2 ratio will be higher than one [33].

The VCO_2/VO_2 ratio can be calculated at the bedside.

According to the Fick principle:

$$VO_2 = CO \times (CaO_2 - CvO_2)$$

and

$$VCO_2 = CO \times (CvCO_2 - CaCO_2)$$

The ratio is, therefore, equal to $CvCO_2 - CaCO_2/CaO_2 - CvO_2$. As mentioned above, at usual physiologic ranges, $CvCO_2 - CaCO_2$ can be replaced by ΔPCO_2.

It gives the final equation:

$$VCO_2/VO_2 = \Delta PCO_2/CaO_2 - CvO_2$$

ΔPCO_2, CaO_2, and CvO_2 are either directly accessible or easily calculated at bedside (CaO_2 and CvO_2 only need hemoglobin and oxygen saturation for their calculation).

The VCO_2/VO_2 ratio can identify anaerobic metabolism, and it has shown to be closely correlated with lactate levels, the usual dysoxia marker [33,39]. Moreover, the use of the VCO_2/VO_2 ratio might represent a possible alternative to lactate levels in specific situations that are frequently encountered in the ICU setting, such as hyperglycemia or catecholamine-induced hyperlactatemia.

3.5. Clinical Use of VCO_2/VO_2 Ratio

The VCO_2/VO_2 ratio has been less studied than ΔCO_2. The princeps study by Mekontso-Dessap et al., carried out nearly 20 years ago, showed the role of the VCO_2/VO_2 ratio as a mortality marker in adult septic shock [66]. More recently, Ospina-Tascon also described the same relation, again in patients with septic shock [39]. Interestingly, even in patients with a normal lactate level, increased VCO_2/VO_2 ratio was strongly associated with a worse outcome. Other reports described the link between the VCO_2/VO_2 ratio and patients' outcome both in septic shock and after cardiac surgery. Interestingly, both Ospina-Tascon et al. and He et al. showed an association between the VCO_2/VO_2 ratio and outcome in shocked patients with normal $ScVO_2$ [39,82]. These findings underline the role of more advanced indices of tissue hypoxia when $ScVO_2$ levels are within normal ranges, possibly signaling low O_2 extraction and/or capillary perfusion disturbances [64,83]. This ratio might provide important prognostic information, especially in case of persistent high values and normalization of lactate levels after initial resuscitation.

The VCO_2/VO_2 ratio has also been described as a possible tool for the prediction of fluid responsiveness. In patients with a hypotensive episode, only those with an elevated VCO_2/VO_2 ratio showed a rapid increase in VO_2 after the fluid challenge [65,84].

As with the ΔCO_2, several algorithms propose the use VCO_2/VO_2 ratio in the initial patient assessment as a sign of tissue dysoxia. As for lactates, an elevated VCO_2/VO_2 ratio > one indicates anaerobic metabolism and should prompt a complete hemodynamic assessment of the patient and the possible implementation of rapid therapeutic measures to restore aerobic metabolism. On the other hand, a VCO_2/VO_2 ratio < one could also point to hyperglycemia or adrenergic stimulation as possible alternative causes of elevated lactate levels. Several cut-off values have been proposed to predict unfavorable outcomes, varying from 1.2 to 1.6 [31,37,85]. Unfortunately, as for the ΔPCO_2, none of those algorithms has been validated in the clinical setting.

To the best of our knowledge, only one study looked at the VCO_2/VO_2 ratio in the pediatric population. Xu et al. studied the impact of elevated increased VCO_2/VO_2 ratio on acute kidney injury after pediatric cardiac surgery [86]. As blood is diverted from the kidneys in the case of shock, the authors suggest that an increased VCO_2/VO_2 ratio might represent a sign of anaerobic metabolism at the kidney level and indicate a possible kidney injury in CICU patients [87]. Despite the lack of clear evidence at the moment, these results suggest that VCO_2/VO_2 ratio may possibly help detect patients at risk of end-organ lesions in the context of anaerobic metabolism.

4. Implications for Research

Future studies are warranted to establish reference values of ΔPCO_2 in CICU and PICU. Currently, reference values are derived from adult patients with septic shock. However, those values may differ significantly in children, especially in the cardiac population after a cardio-pulmonary bypass, where alterations of microcirculation may increase the ΔPCO_2 value without macrohemodynamic disturbances. Our experience confirms current pediatric

literature describing large ΔPCO_2 regardless of clinical outcomes. Multicenter prospective cohort studies are also needed to better define the relationship between ΔPCO_2.and cardiac output in the case of LCOS. The description and validation of the impact of CO_2-derived parameters in patient management, both adult and pediatric patients, are highly needed. Whether the introduction of CO_2-derived parameters into clinical algorithms may improve patients' outcomes is unknown.

5. Conclusions

Despite the many limitations and the lack of robust data, CO_2-derived parameters such as ΔPCO_2 and VCO_2/VO_2 ratio represent valuable markers of hemodynamic derangements from macrocirculation to microcirculation. Moreover, unlike traditional markers of cardiac output, they seem to be reliable in specific situations commonly encountered in the post-cardiac surgery setting, such as hyperglycemia and catecholamine use. Their integration with classical markers of hypoperfusion into treatment algorithms holds the promise of adding substantial information that might help refine the management of patients suffering from shock in the adult and in the pediatric population alike. Further studies are needed to clearly define the role of those attractive tools in guiding resuscitation in the clinical setting.

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