Venoarterial Partial Pressure of Carbon Dioxide Difference: Let's Trend It!

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INTRODUCTION

Acute circulatory failure is common in the intensive care unit and it remains a significant cause of mortality, emphasizing the need for early assessment of tissue perfusion and cellular oxygenation. Commonly studied markers or resuscitation targets such as central venous pressure, serum lactates, and central venous oxygen saturation ($ScvO_2$) have gone out of favor and have their limitations like other traditional parameters (e.g., urine output, blood pressure, etc.).[1] Despite this, these are still potential and valuable tools for assessing the patient's circulatory status.[2] The venoarterial difference in the partial pressure of carbon dioxide ($P_{v-a}CO_2$ or ΔPCO_2) is simply called the PCO_2 gap. It has emerged as a valuable tool for evaluating tissue perfusion and predicting outcomes during circulatory shock.[3] The PCO_2 gap is inversely proportional to the cardiac output and has a good correlation with the change in cardiac index in a patient with acute circulatory failure.[4] A high PCO_2 gap identifies patients who benefit from increasing cardiac output and has become an integral part of routine assessment in any patient with acute circulatory failure.[2] Recent studies have shown that a high PCO_2 gap indicates inadequate resuscitation despite having normal $ScvO_2$.[5–7] Moreover, persistent elevation in the PCO_2 gap during resuscitation is associated with poor outcomes such as increased organ failures, and mortality.[6,8–10] So, the PCO_2 gap appears to be a better tool than traditional markers (serum lactate and urine output) for assessing resuscitation efficacy and is useful even in the early stages of tissue hypoperfusion, unlike serum lactates. In this context, it may be useful to serially measure and monitor the PCO_2 gap to optimize circulatory status.

In this issue of *the Indian Journal of Critical Care Medicine*, the authors serially measured the PCO_2 gap at baseline [time of first reading taken after intensive care unit (ICU) admission], 6 hours (T6), 12 hours (T12), and 24 hours (T24) after resuscitation in 110 adult patients with acute circulatory failure.[11] The authors compared the PCO_2 gap with lactates, urine output, and cardiac index (measured by transthoracic echocardiography). The patients were divided into low PCO_2 gap (≤6 mm Hg) and high PCO_2 gap (>6 mm Hg) groups after 6 hours of resuscitation and the outcomes were studied between both groups. The primary outcome was ICU mortality and the secondary outcome was the length of stay (LOS), the need for renal replacement therapy (RRT), etc. The study population included predominantly patients with distributive and hypovolemia shock, almost all were on vasopressor infusion, and 59% were mechanically ventilated. The authors found a significant decline in the serial PCO_2 gap over time which was associated with

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a concurrent decline in serum lactate, an increase in urine output, and an increase in cardiac index at time intervals of T6, T12, and T24 only in the low PCO_2 group and not in high PCO_2 group. Moreover, they found increased LOS and increased need for RRT in patients with persistently high pCO_2 gaps for 24 hours. The overall mortality rate was 26.5% in the entire cohort with higher mortality in the high PCO_2 group (89.6% vs 10.3%). The PCO_2 gap at 6 hours and 12 hours had a moderate ability to discriminate survivors and nonsurvivors with the area under the receiver operating characteristic curve (AUROC) of 0.775 and 0.771, respectively. So, this study shows the importance of serially monitoring the PCO_2 gap which has a good association with improvement in cardiac index, urine output, and serum lactate like in previous studies.[5,10]

PARTIAL PRESSURE OF CARBON DIOXIDE GAP AND ITS DETERMINANTS

The objective for increasing cardiac output with fluids in fluid-responsive patients with shock is to improve oxygen delivery and it is assumed that it, in turn, increases oxygen utilization by the tissues, which is the desired goal. When there is low blood flow to tissues, the tissue extracts more oxygen and the mixed venous oxygen saturation will be low reflecting tissue hypoxia. Understanding the physiological and pathophysiological determinants of the PCO_2 gap is crucial to apply at the bedside. In normalcy, there exists a balance between the carbon dioxide (CO_2) produced by the tissues and eliminated through the lungs which is estimated by the difference between the mixed venous content ($CvCO_2$) and the arterial content ($CaCO_2$) of CO_2, that is, $C_{v-a}CO_2$, the venoarterial difference in CO_2 content (Fig. 1). At the bedside, the CO_2 content is replaced by the corresponding partial pressure of CO_2 due to the linear relationship

1. $VCO_2 = CO \times CvCO_2 - CaCO_2 \rightarrow CO = VCO_2/CvCO_2 - CaCO_2$ ....(1)
2. $\Delta PCO_2 = k \times \Delta CCO_2$ (physiological limits) .... (2)
3. $CO = VCO_2 . k/\Delta PCO_2 \rightarrow PCO_2$ gap $= VCO_2 k/CO$ .... (3)

$$RQ = \frac{VCO_2}{VO_2} = \frac{C_{v-a}CO_2 \times CO}{C_{a-v}O_2 \times CO} = \frac{C_{v-a}CO_2}{C_{a-v}O_2} = \frac{PCO_2 \text{ gap}}{C_{a-v}O_2}$$
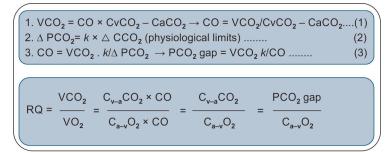
Fig. 1: The PCO_2 gap and its determinants. Equation 1 is based on the modified Fick's equation for cardiac output with CO_2 as an indicator. Equation 2 is the relationship between the partial pressure of CO_2 and the content of CO_2, which is linear in physiological limits. Equation 3 replaces the content of CO_2 with partial pressure of CO_2; so, Equation 1 can be rewritten as Equation 3. PCO_2, partial pressure of CO_2; VCO_2, volume of carbondioxide produced, VO_2, volume of oxygen consumed, ΔCCO_2, venoarterial diferrence in the content of carbondioxide, Cv-aCO_2, venoarterial diferrence in the content of carbondioxide, Ca-vO_2, arteriovenous difference in the content of oxygen, RQ, respiratory quotient and others; CO, cardiac output; $CvCO_2$, venous CO_2 content; $CaCO_2$, arterial CO_2 content; ΔPCO_2, Pv-aCO_2 or PCO_2 gap, venoarterial partial pressure of carbon dioxide difference (various of ways of writing the same); ΔCCO_2, the venoarterial difference in the content of CO_2; k, constant (affected by metabolic acidosis, hemoglobin, arterial oxygen saturation)

between the two within physiological limits. The difference in venous and arterial partial pressure of CO_2, $PvCO_2$-$PaCO_2$ ($P_{v-a}CO_2$) represented as PCO_2 gap replaces the $C_{v-a}CO_2$. So, in clinical practice, the PCO_2 gap is an estimate of the difference between venous and arterial CO_2 content ($C_{v-a}CO_2$) (Fig. 1).

When there is low blood flow, CO_2 produced will be stagnant at the venous side (venous stagnation) compared to the arterial side, causing more difference in PCO_2 gap (>6 mm Hg). The PCO_2 gap increases only in cases of tissue hypoxia if it is due to low blood flow and is not related to hypoxic hypoxia.[12,13] So, a high PCO_2 gap (>6 mm Hg) is an indicator of tissue hypoperfusion, and improving the cardiac output is a potential therapeutic option. Beware of confounding factors that may affect the PCO_2 gap before interpreting. Assuming the sampling technique is correct, there is no atmosphere gas, or excessive fluids in the blood sample, and no faulty analyzer, a high PCO_2 gap can still happen due to acute hyperoxia, acute hyperventilation, metabolic acidosis, and hyperthermia.[14] Consider these conditions especially when you have a high PCO_2 gap in patients with no clinical signs of shock and with $ScvO_2$ < 70% and normal serum lactates.

Expanding the role of the PCO_2 gap, we could even know about the VO_2/DO_2 relationship (oxygen consumption and oxygen delivery), the anaerobic metabolism and oxygen consumption by using the ratio PCO_2 gap/$(C_{a-v}O_2)$, that is, PCO_2 gap over arteriovenous oxygen content. When there is tissue hypoxia related to low blood flow there will be less oxygen utilization by the tissues and in turn low aerobic CO_2 production but on the other hand, there will be increased production of anaerobic CO_2. The net CO_2 will be relatively lower in comparison to when there is no contribution from anaerobic metabolism.[3] So, when we know the amount of oxygen utilized, we can estimate the amount of aerobic CO_2 produced as VCO_2 is equal to VO_2 (VCO_2/VO_2 – the amount of CO_2 produced/amount of O_2 utilized, that is, VO_2/DO_2 balance,). The VCO_2/VO_2 is represented by $(C_{v-a}CO_2)/(C_{a-v}O_2)$, that is, the venoarterial difference in the CO_2 content ($C_{v-a}CO_2$) over arteriovenous difference in the oxygen content. Since there is a good correlation of $C_{v-a}CO_2$ with the PCO_2 gap, the equation is rewritten as PCO_2 gap/$(C_{a-v}O_2)$, The PCO_2 gap replaces CO_2 content (Fig. 1). So, for a given oxygen utilization, an increase in the ratio happens only when there is increased CO_2 production which happens through the anaerobic pathway. The PCO_2 gap that is relatively greater than the $C_{a-v}O_2$ can suggest the presence of anaerobic CO_2 production and thus can detect tissue hypoxia and anaerobic metabolism.

Studies have shown that this ratio, PCO_2 gap/$(Ca$-$vO_2)$ > 1.4, can be utilized to identify anaerobic metabolism and the higher values are associated with adverse outcomes despite normal lactate.[9,15] It predicts lactate clearance, and also oxygen consumption after increasing oxygen delivery to tissues.[16,17] These emphasize the importance of measuring and guiding the resuscitation with PCO_2 gap and oxygen-derived parameters. Nevertheless, PCO_2 gap/$C_{a-v}O_2$ ratio targeted resuscitation did not show improved outcomes compared to $ScvO_2$ targeted resuscitation in randomized controlled trials.[18] However, there was reduced use of fluids, blood products, and vasopressors in the PCO_2 gap/$C_{a-v}O_2$ ratio group which was nonsignificant.

PARTIAL PRESSURE OF CARBON DIOXIDE GAP AT THE BEDSIDE—LET'S MEASURE, SERIALLY TREND, AND INTEGRATE

Measuring the PCO_2 gap along with other hemodynamic parameters is a valuable addition and is suggested in all patients with acute circulatory failure.[19] It is measured by simultaneously taking blood samples from the artery and pulmonary artery (mixed venous) or a central vein (superior vena cava).

Why to Measure?

Recent studies have shown that either normal or higher values of $ScvO_2$ do not rule out inadequate oxygen delivery but, in contrast, a higher PCO_2 gap is a good predictor of low cardiac output and is associated with adverse outcomes.[10] A high PCO_2 gap identifies inadequate resuscitation despite the normalization of macrohemodynamic parameters. A recent study showed a good correlation between the PCO_2 gap with microcirculation abnormalities measured using a side stream dark-field device in the sublingual microcirculation.[20] A higher PCO_2 gap was associated with progressively lower percentages of small perfused vessels (PPV), lower functional capillary density, and higher heterogeneity of microvascular blood flow.[20] The changes in PCO_2 gap and microcirculation parameters correlated well, both improved with resuscitation. So, a higher PCO_2 gap identifies patients with low tissue perfusion, and abnormal microcirculation despite resuscitation and normal traditional targets. Moreover, the ratio

of PCO_2 gap over Ca-vO_2 identifies anaerobic metabolism and identifies patients who will improve oxygen consumption after improving tissue oxygen delivery, as shown by Monnet et al. the oxygen consumption increased after giving fluids in fluid-responsive patients only when the ratio was high.[17]

Why to Measure Trends?

With ongoing resuscitation, normalization of the PCO_2 gap with the serial measurements indicates improving macro as well as microcirculation which in turn is associated with improving organ functions. No change in the higher PCO_2 gap with resuscitative measures indicates that the intensity of measures is not good enough to bring the change and the physician can consider increasing the dose of the intervention or changing the intervention.[2] Also, persistent elevation in the PCO_2 gap during resuscitation is associated with poor outcomes such as increased organ failures and mortality.[6,8–11] The changes are quick, happen within minutes compared to hours for lactate clearance and are a potential dynamic parameter to monitor. Let us serially monitor the PCO_2 gap but the frequency of measurement of the PCO_2 gap, and use along with oxygenation parameters should be at individual physician discretion until further studies are done.

How to Integrate?

The first step is to identify the presence of shock, traditionally identified by clinical examination, low blood pressure, and elevated serum lactates. Choosing the therapy, and monitoring ongoing resuscitation are vital steps in managing a patient with shock. Measuring the ScvO_2 along with the PCO_2 gap helps to choose therapy, that is, when there is a high ScvO_2 (>70%) and high PCO_2 gap (>6 mm Hg) try to improve cardiac output but when there is a high ScvO_2 (>80%) and low PACO_2 gap (<6 mm Hg) the patient may not benefit from hemodynamic optimization.[2] Similarly, the PCO_2 gap/C$_{a-v}O_2$ ratio with hyperlactatemia and their trends give us a clue about anaerobic metabolism.

CONCLUSION

Monitoring the PCO_2 gap provides valuable insights into tissue perfusion and resuscitation effectiveness, especially when traditional markers may fall short and it is important to serially monitor it along with oxygen-derived parameters. It is time for us to measure and follow the trends of the PCO_2 gap and more importantly, to integrate it with other available hemodynamic parameters.

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