EDITORIAL

$PcvCO_2–PaCO_2/CaO_2–CcvO_2$ Ratio: The Holy Grail in Resuscitation!

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Early identification and reversal of tissue hypoperfusion and adequate resuscitation are key factors in prevention of progression to multi-organ dysfunction and death in critically ill patients.[1] Therefore, monitoring of tissue oxygenation and perfusion is an important step in the management of patients with shock. Tissue perfusion can be monitored by clinical evaluation as well as by using biochemical markers. The clinical signs of tissue hypoperfusion are not very sensitive and appear only in later stages.[2] Hence, biomarkers which identify tissue hypoperfusion earlier are crucial for improvement in outcomes. Popular biochemical markers, like lactate, may be unreliable for identification of tissue oxygenation.[3] Oxygen-derived parameters, like $ScvO_2$, are affected by metabolic demands and oxygen extraction capabilities making them difficult to interpret.[4] This warrants exploring for additional markers especially in the setting of a normal or near-normal $ScvO_2$ levels. Recently, central venous arterial CO_2 partial pressure difference or CO_2 gap has been studied as an additional tool to identify global tissue hypoperfusion. A cutoff value of >6 mm Hg suggests insufficient tissue perfusion.[5] The CO_2 gap can be affected by changes in tissue microcirculation and high flow states.[6] In this context, combination of O_2-derived and CO_2-derived parameters, such as $PcvCO_2–PaCO_2$, may be useful.

During normoxic conditions, CO_2 is produced by Krebs cycle. The CO_2 production (VCO_2) is directly related to oxygen consumption (VO_2) by the equation $VCO_2 = RQ \times VO_2$, where RQ is the respiratory quotient. During aerobic conditions, VCO_2 never exceeds VO_2 as the CO_2 production cannot be more than O_2 availability. So, the ratio is always <1. In anaerobic conditions, VO_2 decreases, but VCO_2 increases due to generation from bicarbonate buffering of anaerobically generated protons. Also, the diffusion of CO_2 is 20 times higher than O_2, so in tissue hypoperfusion, diffusion of CO_2 from tissues to plasma is more than O_2. Hence, a VCO_2/VO_2 ratio of >1 can be used as a marker of tissue hypoperfusion.[7]

According to Fick's equation, VO_2 and VCO_2 are directly proportional to cardiac output and their respective arterial-to-venous and venous-to-arterial content difference. Therefore, $Cv\text{-}aCO_2/Ca\text{-}vO_2$ reflects VCO_2/VO_2, as cardiac output present in both numerator and denominator gets cancelled. In the physiological range, CO_2 tension is linearly related to CO_2 content; hence, $Pc\text{-}aCO_2$ difference is used as a surrogate for difference in $Cv\text{-}aCO_2$.[8]

In this issue of IJCCM, Madabhushi et al. reported their study on temporal evolution of the $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio versus serum lactate during resuscitation in septic shock. In their prospective observational study, they analyzed 186 samples from 30 patients. They found a positive correlation between $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio and arterial lactate at 0, 6, 12, and 18 hours of resuscitation. They also found that $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratios were higher among nonsurvivors than survivors and it assumed statistical significance at 24 hours. Similarly, higher lactates were found in nonsurvivors. They also reported that $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio at 24 hours with a value greater than 1.696 mm Hg/mL/dL was predictive of mortality with a sensitivity of 80% and a specificity of 69.2% with an area under-receiver operating curve of 0.8205 (95% CI 0.661–0.979). They performed a Kaplan–Meier survival estimate at 24 hours, and they found that there was difference in survival probability for a $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio of 1.696 and the probability of 28-day survival was 25 and 75% above and below this ratio, respectively ($\chi^2 = 6.00$, $p = 0.0143$). The authors propose that $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio could be used as an end point of hemodynamic resuscitation.

In a retrospective study 20 years ago, Mekontso-Dessap et al. found good correlation between the $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio and the lactate ($R = 0.57$, $p < 0.0001$).[9] They also found greater than 1 month survival when $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio was less than 1.4 (38 ± 10% vs 20 ± 8%, $p < 0.01$). Shaban et al. in a prospective study of 50 patients found that baseline $Cv\text{-}aCO_2/Ca\text{-}cvO_2$ and lactate were lower in survivors than in nonsurvivors. They showed a cutoff value of $Pv\text{-}Aco_2/Ca\text{-}vO_2$ 0.25 at baseline was predictive of 28-day mortality (sensitivity 58%, specificity 85%, LR+ 3.86, LR -0.49).[10] Zhou et al. in a retrospective study of 144 patients with septic shock found that $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ more than 1.4 and lactate were independent predictors of 28-day mortality, and their combination was a better predictor.[11] In another observational study in 35 patients with septic shock, $Pcv\text{-}aCO_2/Ca\text{-}cvO_2$ of 1.4 was found to be a strong predictor of lactate improvement.[12]

Is $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ Ratio the Holy Grail in Shock Resuscitation?

Before reaching this conclusion, we must consider the following issues. $PcvCO_2–PaCO_2/CaO_2–CcvO_2$ ratio may be affected by

factors other than tissue hypoperfusion. Anemia increases PCO_2 for a given CCO_2 by shifting CO_2 dissociation curve. Also, anemia due to hemodilution causes decrease in Ca-vO_2 which increases the Pv-aCO_2/Ca-vO_2 ratio independent of anaerobic metabolism.[13] Similarly, in the presence of metabolic acidosis and high oxygen concentration, the same PCO_2 is associated with decreased CO_2 content. In these situations, it may be erroneous to use Pv-aCO_2 as a surrogate for Cv-aCO_2.[7] The amount of anaerobically produced CO_2 may be low compared to CO_2 produced under anaerobic conditions. Whether such small amounts can increase VCO_2 above VO_2 is questionable.[14] Finally, all these markers assess only global and not regional tissue perfusion.

In a randomized controlled trial, Su et al. compared P(v-a)CO_2/C(a-v)O_2-targeted and $ScvO_2$-targeted therapies in 228 patients with severe sepsis or septic shock, and found no difference in mortality, organ dysfunction, length of ICU stay, or 28-day survival.[15] In a prospective study of 110 postoperative cardiac patients by Abou-Arab et al., P(v-a)CO_2/C(a-v)O_2 ratio was not predictive of VO_2 changes following fluid challenge.[16]

In conclusion, the study by Madabhushi et al. adds important information regarding initial resuscitation of patients with shock. Pv-aCO_2/Ca-vO_2 ratio may serve as an added parameter in patients especially those with normal $ScvO_2$. Whether this should be introduced as a routine practice in shock resuscitation needs further exploration with larger studies.

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