PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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 multiorgan dysfunction and death in critically ill patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3} Oxygen-derived parameters, like ScvO\textsubscript{2}, are affected by metabolic demands and oxygen extraction capabilities making them difficult to interpret.\textsuperscript{4} This warrants exploring for additional markers especially in the setting of a normal or near-normal ScvO\textsubscript{2} levels. Recently, central venous arterial CO\textsubscript{2} partial pressure difference or CO\textsubscript{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.\textsuperscript{5} The CO\textsubscript{2} gap can be affected by changes in tissue microcirculation and high flow states.\textsuperscript{6} In this context, combination of O\textsubscript{2}-derived and CO\textsubscript{2}-derived parameters, such as PcvCO\textsubscript{2}–PaCO\textsubscript{2}, may be useful.

During normoxic conditions, CO\textsubscript{2} is produced by Krebs cycle. The CO\textsubscript{2} production (VCO\textsubscript{2}) is directly related to oxygen consumption (VO\textsubscript{2}) by the equation \(\text{VCO}_2 = \text{RQ} \times \text{VO}_2\), where RQ is the respiratory quotient. During aerobic conditions, VCO\textsubscript{2} never exceeds VO\textsubscript{2}, as the CO\textsubscript{2} production cannot be more than O\textsubscript{2} availability. So, the ratio is always <1. In anaerobic conditions, VO\textsubscript{2} decreases, but VCO\textsubscript{2} increases due to generation from bicarbonate buffering of anaerobically generated protons. Also, the diffusion of CO\textsubscript{2} is 20 times higher than O\textsubscript{2}, so in tissue hypoperfusion, diffusion of CO\textsubscript{2} from tissues to plasma is more than O\textsubscript{2}. Hence, a VCO\textsubscript{2}/VO\textsubscript{2} ratio of >1 can be used as a marker of tissue hypoperfusion.\textsuperscript{7}

According to Fick’s equation, VO\textsubscript{2} and VCO\textsubscript{2} are directly proportional to cardiac output and their respective arterial-to-tissue venous and venous-to-arterial content difference. Therefore, Cv-aCO\textsubscript{2}/Ca-vO\textsubscript{2} reflects VCO\textsubscript{2}/VO\textsubscript{2}, as cardiac output present in both numerator and denominator gets cancelled. In the physiological range, CO\textsubscript{2} tension is linearly related to CO\textsubscript{2} content; hence, Pc-aCO\textsubscript{2} difference is used as a surrogate for difference in Cv-aCO\textsubscript{2}.\textsuperscript{8}

In this issue of IJCCM, Madabhushi et al. reported their study on temporal evolution of the PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{2} ratio and arterial lactate at 0, 6, 12, and 18 hours of resuscitation. They also found that PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{2} ratio and the lactate (\(R = 0.57, p < 0.0001\)).\textsuperscript{9} They also found greater than 1 month survival when PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{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-aCO\textsubscript{2}/Ca-cvO\textsubscript{2} and lactate were lower in survivors than in nonsurvivors. They showed a cutoff value of Pcv-aCO\textsubscript{2}/Ca-vO\textsubscript{2} 0.25 at baseline was predictive of 28-day mortality (sensitivity 58%, specificity 85%, LR+ 3.86, LR-0.49).\textsuperscript{10} Zhou et al. in a retrospective study of 144 patients with septic shock found that Pcv-aCO\textsubscript{2}/Ca-cvO\textsubscript{2} more than 1.4 and lactate were independent predictors of 28-day mortality, and their combination was a better predictor.\textsuperscript{11} In another observational study in 35 patients with septic shock, Pcv-aCO\textsubscript{2}/Ca-cvO\textsubscript{2} of 1.4 was found to be a strong predictor of lactate improvement.\textsuperscript{12}

\textbf{Is PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{2} Ratio the Holy Grail in Shock Resuscitation?}

Before reaching this conclusion, we must consider the following issues. PcvCO\textsubscript{2}–PaCO\textsubscript{2}/CaO\textsubscript{2}–CcvO\textsubscript{2} ratio may be affected by

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factors other than tissue hypoperfusion. Anemia increases PCO₂ for a given CO₂ by shifting CO₂ dissociation curve. Also, anemia due to hemodilution causes decrease in Ca-vO₂ which increases the Pv-aCO₂/Ca-vO₂ ratio independent of anaerobic metabolism.  

Similarly, in the presence of metabolic acidosis and high oxygen concentration, the same PCO₂ is associated with decreased CO₂ content. In these situations, it may be erroneous to use Pv-aCO₂ as a surrogate for Cv-aCO₂.  

The amount of anaerobically produced CO₂ may be low compared to CO₂ produced under anaerobic conditions. Whether such small amounts can increase VO₂, above VO₂ is questionable. Finally, all these markers assess only global and not regional tissue perfusion.

In a randomized controlled trial, Su et al. compared P(v-a) CO₂/C(a-v)O₂-targeted and ScvO₂-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. In a prospective study of 110 postoperative cardiac patients by Abou-Arab et al., P(v-a)CO₂/C(a-v)O₂ ratio was not predictive of VO₂ changes following fluid challenge. In conclusion, the study by Madabhushi et al. adds important information regarding initial resuscitation of patients with shock. Pv-aCO₂/Ca-vO₂ ratio may serve as an added parameter in patients especially those with normal ScvO₂. Whether this should be introduced as a routine practice in shock resuscitation needs further exploration with larger studies.

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**References**