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Looking for CO_2: Exploring the Novel Finding of Low Respiratory Quotient After Cardiac Arrest

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Research over decades has explored oxygen consumption (VO_2) during critical illness, and whether altering oxygen metabolism affects clinical outcomes. Clinicians and researchers have long wanted to know why, despite adequate blood pressure and oxygen saturation, critically ill patients so often develop lactic acidosis and how this marker of anaerobic metabolism is associated with multi-organ failure. Difficulty with accurately measuring oxygen metabolism in the intensive care setting has limited mechanistic research in this area.

Multiple mechanisms, including inadequate oxygen delivery and impaired oxygen extraction, may decrease VO_2. In early studies, increasing oxygen delivery through augmentation of cardiac output seemed to improve both VO_2 and survival in septic and high-risk surgical patients, suggesting oxygen delivery was the limiting factor.[1,2] However, VO_2 only rose in response to increases in O_2 delivery in a subset of patients. When the increased oxygen delivery did not increase VO_2 mortality was extremely high.[3] These studies suggest that cytopathic hypoxia (decreased oxygen extraction despite adequate oxygen delivery), rather than decreased oxygen delivery, is a central problem in many critically ill patients.[4] Mitochondrial injury and the consequent breakdown in aerobic metabolism are major drivers of cytopathic hypoxia and occur commonly in severe sepsis and in the ischemia-reperfusion injury following resuscitation from cardiac arrest.

Whether from impaired oxygen delivery or cytopathic hypoxia, lower VO_2 is associated with increased mortality in sepsis[2,3] and after cardiac arrest.[5,6] The details of exactly how cardiac arrest and resuscitation alter cellular metabolism remain unclear. Whole animal laboratory models may provide a platform to study these mechanisms.

In the current issue of the *Journal of the American Heart Association (JAHA)*, Shinozaki and colleagues present a rat model used to compare VO_2, carbon dioxide production (VCO_2) and the respiratory quotient (RQ) after asphyxial cardiac arrest and resuscitation with the same calculations made in rats undergoing a sham surgery.[7] This model has been used widely since the 1980s.[8] While the rat model of cardiopulmonary resuscitation is less easily extrapolated to human cardiopulmonary resuscitation than larger animal models, the rat model reliably exhibits many features of post-cardiac arrest physiology that are common to multiple mammals and humans. For example, the rats recovering from asphyxial cardiac arrest display increases in systemic inflammation,[9] myocardial depression[10] and a stress-like catabolic state,[11] as well as temperature-sensitive primary[12] and secondary brain injury.[13] Therefore, it is reasonable to consider whether physiological findings in the rat asphyxial model may occur in humans.

The study by Shinozaki and colleagues[7] required precise accounting for gas exchange to estimate components of global metabolism, and the investigators meticulously describe the techniques for ensuring that measurements were accurate. For many reasons, it is challenging to obtain accurate measurements of VO_2 and VCO_2 in critically ill patients with devices that use breath-by-breath measurements (as most clinically available devices do). First, such devices must detect the difference between inhaled and exhaled oxygen concentration, which is a small percentage change when patients receive a high concentration of supplementary oxygen. Even a small percentage error in measurement therefore can lead to inaccurate data. Second, higher respiratory rates challenge the processing speed of the gas analyzing sensors. In addition, oxygen concentrations can also vary based on humidity and temperature in the ventilator circuit. Finally, patient factors such as ventilator dyssynchrony can further cloud measurements further.

Shinozaki and colleagues[7] considered all these factors in designing their device. Gases were sampled from the ventilator circuit. To avoid the problem of calculating differences in inspiratory and expiratory oxygen concentration

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despite a rapid respiratory rate, which is even more of an issue in small animals, they sampled gas continuously for several minutes from the inspiratory arm for several minutes, then switched to sampling from the expiratory arm. All inspired and expired gas volumes and content were measured. In the rat model, endotracheal intubation uses uncuffed catheters, raising speculation that there might be a leak around the tubes. However, expired gas volumes matched the inspired volumes provided, ruling out the presence of a leak. In fact, the rat airway is deep and long relative to its mouth, and no significant tidal volume passes around the tube. Experimentalists experienced with the rat will recognize that airway pressures required to force air around the tube are usually high enough to cause barotrauma first, and that tube occlusion from airway secretions is usually rapidly fatal during long-term support. Both of those facts make airway leak an unlikely source of error.

The primary finding of Shinozaki and colleagues[7] was that VO_2 increased out of proportion to the observed increase in VCO_2, leading to lower-than-expected RQs in the post-cardiac arrest animals. The RQ in rats and all mammals depends on the fuels being consumed during metabolism, and normally ranges from 0.7 (with chiefly lipid fuel) to 1.0 (with predominantly carbohydrate fuel). In this study, rats had RQs as low as 0.6, which is not consistent with any common fuel. One small study in humans after cardiac arrest observed RQs <0.7,[6] but other studies evaluating oxygen metabolism after cardiac arrest did not.[14,15] However, Oshima et al[14] excluded RQ values below 0.7 since they concluded that these were outside of the normal physiologic range and thus might not be valid. Because they excluded as many as 50% of all recorded measurements in some patients, RQ <0.7 may have been common. Holzinger and colleagues[15] did not report criteria for excluding measurements, but their earliest measurements were 12 hours after the target temperature of 33°C was reached. This later time period may not be comparable to the timing of measurements used in the current animal study or other human studies. These studies are consistent with the scenario in which RQ is low in the initial post-arrest period and returns to normal levels at some later point.

Shinozaki et al propose that the unusually low RQs are attributable to non-mitochondrial respiration, leading to less CO_2 production per unit of O_2 used. High levels of oxidative stress occur in both sepsis and the ischemia-reperfusion injury after cardiac arrest and resuscitation.[16,17] Non-mitochondrial respiration via nicotinamide adenine dinucleotide phosphate oxidases causes free-radical production. While these pathways are small contributors to VO_2 in healthy cells, it is possible that they represent a larger component of metabolism in critical illness. For example, mitochondrial respiration decreases while non-mitochondrial respiration is maintained in septic hepatocytes compared with controls.[16] This results in non-mitochondrial respiration accounting for a higher percentage of total cellular VO_2, lowering the ratio of CO_2 produced to O_2 consumed, and thus lowering the RQ. Kantrow and colleagues also found that while intact hepatocytes in sepsis had lower VO_2, isolated septic hepatocyte mitochondria had higher VO_2. This may reflect the fact that while many mitochondria are injured, lowering total cellular VO_2, the remaining healthy mitochondria compensate with a more rapid metabolic rate.

An alternative explanation for the low observed RQs after cardiac arrest is ketosis. RQs <0.7 occur during ketosis, most commonly in the context of starvation. When healthy subjects fast for several days, the metabolic substrate of the brain shifts rapidly from glucose to beta-hydroxybutyrate and acetoacetate. Relying on these ketones for energy allows the brain to sustain itself much more efficiently.[18] Like starvation, cardiac arrest deprives the cells of the brain and other organs of glucose and oxygen, and ATP levels fall dramatically. Switching over to ketone metabolism may be an adaptive response to maintain ATP production while minimalizing oxygen free radical production. Supporting this hypothesis, rats fed a ketogenic diet have less neuronal damage after induced cardiac arrest and resuscitation than do rats fed a regular diet.[19] Priming with a ketogenic diet also decreases infarct size in rats subjected to focal brain ischemia.[20] We are not aware of any data on ketone levels in post-arrest humans.

Work on oxygen metabolism in critical illness and in cardiac arrest in particular is still in its infancy. It is technically challenging to accurately measure VO_2 and VCO_2 in these settings, and there are many challenges to conducting clinical trials in fragile and dynamic patients. If accurate measurements can be obtained, however, bedside monitoring of VO_2, VCO_2, and RQ in post-arrest patients can reflect the state of aerobic cellular metabolism and mitochondrial function in real time. These parameters are both potential prognostic indicators and targets of treatment. The work by Shinozaki and colleagues[7] is painstakingly done and well thought out. The investigators have done everything possible to minimize the chance of measurement error and they present a truly novel finding. Subsequent experiments can address whether the altered VO_2, VCO_2, and RQ relate to human recovery from cardiac arrest and explore the mechanisms behind the phenomena. This animal model will provide one useful platform for this work.

Disclosures

None.

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