The Goldilocks Principle, Carbon Dioxide, and Acute Respiratory Distress Syndrome

Too Much, Too Little, or Just Right?

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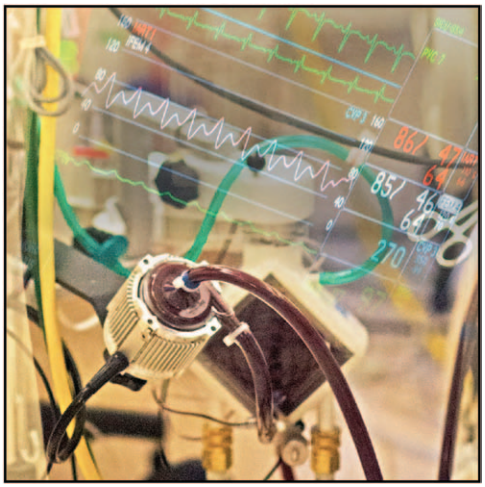
ON the face of it, we have blown hot, then cold when it comes to carbon dioxide. We have tolerated it (permissive hypercapnia), considered adding it (therapeutic hypercapnia), and even at times deliberately or inadvertently decreased it.[1] Advances in extracorporeal therapies, as reported in this month's ANESTHESIOLOGY,[2] mean that if we wish, we can just remove it. Should we?



"New … advances such as reported by Scaravilli et al. [in extracorporeal removal of carbon dioxide] will … move us closer to eventual safe and rational application."

Careful science, rather than caprice, has guided our understanding of the biology of carbon dioxide and the fundamental role it plays in normal physiology, adaptation to, and modulation of disease. Carbon dioxide is essentially a "waste product" of aerobic cellular respiration. Arterial carbon dioxide tension ($Paco_2$) represents the balance between carbon dioxide produced and eliminated. Hypercapnia has been an unavoidable component of lung protection strategies in several key clinical studies over the past four decades. Hickling *et al.*[3,4] first described the concept of "permissive hypercapnia" in two case series, wherein low tidal volume, pressure-limited mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) led to substantial elevations in $Paco_2$ and a mortality that was significantly lower than that predicted by Apache II scores. Comparable findings had been reported a decade before, whereby lowering tidal volumes in status asthmaticus[5] and in neonatal pulmonary hypertension[6] was associated with improved survival. Eventually, two pivotal large randomized controlled trials indicated that low tidal volume mechanical ventilation improves survival in patients with ARDS.[7,8] In all these studies, the relative contribution of lung-protective ventilation or an increase in $Paco_2$ could not be ascertained, although a *post hoc* analysis of one revealed an association between hypercapnia and improved survival.[9]

In parallel with this clinical evolution, several laboratory studies attested to the clear benefit of induced hypercapnia in some circumstances, distinct from tidal volume reduction. In models of lung injury, sepsis and ischemia–reperfusion, hypercapnia has beneficial anti-inflammatory and organ-protective effects.[10] Buffering of hypercapnic acidosis diminishes this benefit,[11] whereas hypocapnia worsens organ injury.[12] Arising from these observations, Laffey and Kavanagh[13] introduced the term "therapeutic hypercapnia," proposing the intentional use of hypercapnic acidosis in select patient populations.

However, just as a pinch of salt can bring out the flavor in food where a fistful will ruin it, excess carbon dioxide has the potential for harm: hypercapnic acidosis has important off-target deleterious effects that limit its use in selected patients (*i.e.*, raised intracranial pressure and pulmonary hypertension), for prolonged periods (increased risk of infection) and at high dose (mitochondrial effects).[14] So there are two sides to the hypercapnia story with the potential for benefit and the risk of harm. Key questions remain around the correct means to achieve hypercapnia to optimize benefit/minimize harm and around dosing and duration. And although the answers to these questions are not straightforward, evidence is emerging that even lower tidal volumes and plateau pressures beyond those investigated heretofore may have incremental survival benefit.[15] Extracorporeal carbon dioxide removal ($ECCO_2R$) is necessary to consistently achieve such low tidal volumes and prevent prolonged and potentially deleterious elevations in carbon dioxide.

$ECCO_2R$ has an appealing rationale in ARDS and in other causes of acute respiratory failure: in addition to ultraprotective

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ventilation, it can reduce hypercapnia and severe respiratory acidosis and thus avoid the need for endotracheal intubation or even noninvasive ventilation in patients with chronic obstructive pulmonary disease and asthma and facilitate weaning and extubation in intubated patients. Techniques to achieve $ECCO_2R$, where carbon dioxide is effectively "dialyzed" out of the blood using a membrane lung, have existed since the late 1970s, but widespread uptake has been limited due to the paucity of trial data, the demanding technical requirements, and concerns regarding complications. Following the original concept developed by Kolobow *et al.*,[16] several new devices and technical approaches have been recently implemented to perform $ECCO_2R$. Ever-expanding indications have created a clinical need for low blood flow $ECCO_2R$ devices (less than 500 ml/min) that require less invasive cannulation and can regulate blood carbon dioxide independent of alveolar ventilation in patients with acute respiratory failure. The key is that because these approaches use a lower blood flow, smaller cannulas, and less anticoagulation, they have fewer side effects.

In this respect, Scaravilli *et al.*[2] should be congratulated on the results of a study in this issue of Anesthesiology evaluating the effects of $ECCO_2R$ combined with the infusion of lactic acid before the membrane lung in the extracorporeal circuit (a technique they have termed acid load carbon dioxide removal [$ALCO_2R$]). Membrane lungs can only remove dissolved carbon dioxide from blood. This gaseous form represents only a small part of the total blood carbon dioxide content, whereas the majority is chemically combined with water to form bicarbonate ions. The former and the latter are in a chemical equilibrium that can be altered by shifts in acid–base status. Specifically, the lower the pH, the higher the partial pressure of carbon dioxide. By adding lactic acid, the pH and the electrolyte concentration are selectively modulated in specific sections of the extracorporeal circuitry. Blood is regionally acidified, and $Paco_2$ is increased, leading to facilitated membrane lung carbon dioxide removal. Clear advantages over previous applications of $ALCO_2R$ are noteworthy, including the use of hydrochloric acid and sodium hydroxide,[17] attempts that resulted in severe important complications (hemolysis, arrhythmias, pulmonary arterial hypertension, and electrolyte derangements) and a failure to clinically translate. Nevertheless, this $ALCO_2R$ technique, based on the infusion of a metabolizable acid, although effective in increasing the membrane lung carbon dioxide removal and safe regarding inflammation and organ function, has one particular disadvantage: it increases the overall carbon dioxide production and induces a mild metabolic acidosis. Instead of reducing ventilatory requirement, $ALCO_2R$ increased tidal volumes and alveolar ventilation by 7%. In this regard, further refinement of this technique by this group and others may represent further advancement.[18]

Is there sufficient evidence to recommend carbon dioxide removal in ARDS and acute respiratory failure? In our rush to embrace new technologies and innovative solutions, we must remember that $ECCO_2R$ remains an experimental therapy and, like hypercapnia itself, is not without risks. Complications associated with arterial cannulation bedeviled the early use of arteriovenous $ECCO_2R$ systems, including vessel perforation, lower limb ischemia, and compartment syndrome.[19,20] Although the technology has markedly improved, the need for venous cannulation and the use of systemic anticoagulation present a potential for harm. In two recent published cohorts,[21,22] significant bleeding events necessitating blood transfusion were common during $ECCO_2R$, while serious life-threatening events occurred in both these small studies (retroperitoneal bleed after femoral vein catheterization and vessel perforation after femoral vein cannulation), an incidence that may be higher in larger groups of patients. Despite anticoagulation with heparin, the rate of circuit thrombosis and pump failure was also unacceptably high.[22]

New technologies and incremental advances such as those reported by Scaravilli *et al.*[2] will make $ECCO_2R$ simpler, safer, less invasive, and more efficient, requiring lower blood flow rates and smaller access cannulas with reduced anticoagulation requirements and move us closer to eventual safe and rational application. In the meantime, we should be dissuaded from the routine clinical use of $ECCO_2R$ outside of suitably designed clinical studies. More careful science will accurately define the benefits of tidal volume and plateau pressure reduction allowed by the latest generation $ECCO_2R$ devices, separate from the effects of induced hypercapnia, and help us in the quest to get carbon dioxide management just right.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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