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Rethinking Alveolar Ventilation and CO_2 Removal

"Yea, all things live forever, though at times they sleep and are forgotten."
H. Rider Haggard, She: A History of Adventure, 1887

I recall my mentor and coauthor (M.R.P.) sharing a personal story from the 1970s. He had heard that Drs. Ted Kolobow and Luciano Gattinoni had performed an extracorporeal carbon dioxide removal ($ECCO_2R$) experiment in sheep. They showed that pulmonary ventilation progressively decreased until breathing ceased as CO_2 removal with $ECCO_2R$ approached metabolic CO_2 production (1). This innovative work confirmed important principles of respiratory drive and was groundbreaking enough for my mentor (a young man at the time) to travel from Johns Hopkins in Baltimore to the National Heart Institute in Bethesda and see it for himself. Fast forward to the 21st century, and it is hard to imagine my fellows showing such avid interest in CO_2. In fact, clinicians today appear to have a greater interest in oxygen physiology. This state of affairs is entirely understandable; noninvasive bedside monitoring provides us with regular information on oxygen status, whereas acquisition of information on CO_2 status generally demands more commitment.

The current pandemic has exposed the impact of our knowledge imbalance in this regard, because the mysterious "happy hypoxia" reported in patients with coronavirus disease (COVID-19) (2) is not nearly so mysterious when one considers the role of CO_2 in determining respiratory drive (3). Along similar lines, patients with end-stage chronic obstructive pulmonary disease are not so much limited by hypoxia but by dyspnea from hypercapnia caused by impaired alveolar ventilation (4). Under these circumstances, respiratory dialysis with $ECCO_2R$ can increase CO_2 removal, but removing only the CO_2 dissolved in blood cannot permit long off-dialysis survival because stopping $ECCO_2R$ will cause CO_2 concentrations to immediately rise. This therapeutic approach seems doomed to failure unless the CO_2 removed is not only that stored in the blood and interstitium but from the entire body.

Relative to this concept, in this issue of the *Journal*, Giosa and colleagues (pp. 318–327) report the findings of a physiology study exploring CO_2 kinetics, whole-body stores, and the impact of ventilation and $ECCO_2R$ on both (5). Using a porcine model, they measured exhaled CO_2 and $\dot{V}_{O_2}$ as they altered V_E and $ECCO_2R$. Armed with this information, they were able to use the respiratory quotient to determine metabolic $\dot{V}_{CO_2}$ ($\dot{V}m_{CO_2}$). Here lies a potential limitation of the work because it was necessary to make certain assumptions for $\dot{V}m_{CO_2}$ calculations as the experiment progressed. The animals were subjected to different ventilatory conditions for 48 hours, and the difference between exhaled CO_2 and metabolically produced CO_2 was used to determine changes that had occurred in CO_2 stores. Animals were either hyperventilated or hypoventilated. After 24 hours, some of the hypoventilated animals received $ECCO_2R$ to supplement alveolar ventilation, and some had ventilation returned to baseline. A key observation of their work was that CO_2 changes occurred in two phases, as follows: a fast phase in which P_{CO_2} rapidly changed in blood, followed by a slow phase, which was revealed as a failure of measured P_{CO_2} to reach equilibrium even after 24 or 48 hours. So, how do we interpret these two phases?

Perhaps the simplest data to understand is the fast phase, in which blood and interstitial fluid quickly load or unload their CO_2 stores. Assuming relatively constant metabolism, conventional wisdom accepts that measured P_{CO_2} reaches a new equilibrium within 45 minutes of ventilatory changes (6). A quick glance at the kinetics reported by Giosa and colleagues supports this; changes in ventilation (or $ECCO_2R$) are followed by a rapid change in P_{CO_2} that plateaus within 15 minutes and changes little between 15 and 60 minutes. However, by continuing experimental conditions for 24 or 48 hours, the authors showed that P_{CO_2} steadily increases or decreases at 0.002–0.003 mm Hg/minute depending on whether hypoventilation or hyperventilation is continued.

Importantly, during prolonged hypoventilation, the volume of CO_2 slowly accumulating in the body exceeded the amount present (or stored) in the blood and interstitium. Similarly, during hyperventilation, the volume of expired CO_2 exceeded that which can be explained by the sum of the metabolically produced CO_2

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plus the amount from the blood and interstitium. It is already known that the body stores CO_2 in the tissues, and this study shows that over 80% of the body's CO_2 stores cannot be accounted for by the blood and interstitium, similar to findings reported almost a century ago (7, 8). This consistency alleviates our anxiety over the authors' assumptions for calculating $\dot{V}m_{CO_2}$.

Detailed physiology experiments conducted between the 1930s and 1970s suggest the body stores CO_2 in tissues such as brain, kidney, muscle, fat, and bone (9–11). It has been hypothesized that the rate at which these various tissues store CO_2 depends on the speed it enters the tissues and the rate it is converted to bicarbonate; the latter is probably determined by cytosolic concentrations of carbonic anhydrase (10). Some tissues have very low carbonic anhydrase concentrations, and in certain muscle fibers, it is absent altogether (12). The question is, how does this validation of CO_2 storage and kinetics affect 21st century clinicians?

First, recognition that the majority of CO_2 is stored in a slow compartment helps us understand why P_{CO_2} equilibrium is often not achieved in animal studies and clinical trials of $ECCO_2R$ (13, 14). Second, as the authors highlighted, it provides a plausible rationale for intermittent CO_2 dialysis in patients with chronic respiratory failure, especially because $ECCO_2R$ unloads the slow CO_2 store more efficiently than ventilation, presumably because $ECCO_2R$ can exceed alveolar ventilation. However, this observation might be an artifact of experimental design because the cardiac output was higher in animals receiving hypoventilation, which is likely explained by lower intrathoracic pressures and increased sympathetic tone allowing better venous return to the right ventricle. Third, the presence of a large slow CO_2 tissue compartment enhances our understanding of how nocturnal noninvasive ventilatory support improves daytime P_{CO_2} values in patients with chronic respiratory failure (15). Therefore, by refocusing on longer-term kinetics of CO_2 balance, Giosa and colleagues have helped us better understand the therapeutic implications of CO_2 removing maneuvers, such as noninvasive ventilatory support and $ECCO_2R$. ■

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