The Unappreciated Role of Carbon Dioxide in Ventilation/Perfusion Matching

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Ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$) matching is fundamental to efficient gas exchange, and its disruption or augmentation in disease, during surgery, and with certain drugs is important in the practice of anesthesiology, pulmonology, and critical care medicine. The role of hypoxic pulmonary vasoconstriction is very well known to most physicians and is considered primarily responsible for the effective matching of regional ventilation and perfusion. Hypoxic pulmonary vasoconstriction diverts blood flow from poorly or nonventilated lung regions to better ventilated areas and was first demonstrated in the late 1940s in animals and humans.[1] While hypoxic pulmonary vasoconstriction is due to the decrease in alveolar oxygen occurring in underventilated units and initiating vasoconstriction, an increase in carbon dioxide also occurs concurrently and is equally potent in this regard, as von Euler and Liljestrand[2] recognized in their seminal study. Although hypercapnia clearly magnifies the strength of hypoxic pulmonary vasoconstriction, hypercapnic vasoconstriction occurs in the normoxic healthy lung as well,[3] where the evidence for any role of hypoxic pulmonary vasoconstriction has been questioned.[4] Given the importance of matching regional perfusion to ventilation, it should not be surprising that nature and evolution have endowed the lungs with more than one mechanism to accomplish it.

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Far less appreciated, however, in regional $\dot{V}_A/\dot{Q}$ regulation, is the ability of the lungs to also respond to changes in local perfusion by appropriately diverting ventilation from poorly perfused regions toward better perfused areas, as shown elegantly in the current issue of Anesthesiology by Langer *et al.*[5] The authors show in the anesthetized pig that temporary occlusion of lobar blood flow by inflation of a balloon-tipped 5-F Swan-Ganz pulmonary artery catheter in the left inferior pulmonary artery (subserving roughly a third of the lungs) for 30 min generates far less dead space and less arterial hypercapnia than would be predicted by the volume of lung with interrupted perfusion. They observed only a small increase in dead space assessed by the Bohr-Enghoff equation from 37 to 43% and an increase in $Paco_2$ of just 2 mmHg at a fixed level of minute ventilation. Respiratory system compliance fell from 24.4 to 22.8 ml/cm H_2O, with the greatest reduction occurring in the left hemithorax. Utilizing quantitative computed tomographic imaging, they demonstrated a significant reduction in density of the nonperfused lung area due both to a reduction in tissue density and an increase in air volume. These findings are consistent with a significant diversion of ventilation from the less compliant left lower lobe. Studies dating back to the 1950s using different means of assessing acute ventilation changes after cessation of blood flow established a figure of 30 to 50% reduction of ventilation with cessation of blood flow to a lobe or lung.[6] This is comparable to the amount of blood flow diversion from a nonventilated (shunt) region by hypoxic pulmonary vasoconstriction,[7] and for both oxygen and carbon dioxide, the magnitude of diversion is greater the smaller the volume of lung involved.

Shifts in ventilation after perturbations in perfusion result from the change in regional alveolar carbon dioxide, which, like alveolar oxygen, is determined by the ratio of local alveolar ventilation and perfusion. As blood flow decreases or is interrupted, carbon dioxide delivery into

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that region is diminished or eliminated, and alveolar carbon dioxide decreases. The reduction in alveolar carbon dioxide causes hypocapnic bronchoconstriction as well as a decrease in parenchymal compliance (sometimes termed hypocapnic pneumoconstriction).[6,8] Both reduce regional ventilation for the same peak and static airway (end-inspiratory) pressures. The shift in blood flow to elsewhere in the lung initiates compensatory hypercapnic bronchodilation and hypercapnic pneumodilation in these regions to accommodate greater ventilation. The effects of changes in carbon dioxide on airway smooth muscle and parenchymal contractile elements are largely the result of changes in pH, the speed of which is greatly enhanced by the catalysis of lung tissue carbonic anhydrase.[9,10] Findings supporting the dominant role of carbon dioxide in initiating these responses include (1) prevention of ventilation redistribution if alveolar carbon dioxide is maintained by addition of inspired carbon dioxide,[6] and (2) inhibition of carbonic anhydrase, which reduces the rate of ventilatory diversion by slowing the speed at which the carbon dioxide–mediated pH change occurs.[10]

While the findings of Langer *et al.* at 30 min have little bearing on the clinical relevance of temporarily wedging a pulmonary artery catheter to obtain estimates of left atrial pressure since that maneuver requires less than 30 s to accomplish, their results are of interest for both normal physiology and in clinical situations involving any duration of regional blood flow disruption. We have shown by inhaled krypton nuclide scanning and the multiple inert gas elimination technique that the response is quite fast with a half time of 75 s and completion by 5 min,[10] very similar to the speed of hypoxic pulmonary vasoconstriction.[1] The kinetics of these responses to oxygen and carbon dioxide provide a means by which the lungs can rapidly respond to fluctuations in regional blood flow or ventilation that occur either spontaneously as frequently as every 20 min or shorter[11] or because of external factors that alter blood flow and ventilation distribution such as changes in body position. In situations involving longer durations of regional blood flow restriction (*e.g.*, pulmonary thromboembolism or other processes decreasing regional arterial or venous blood flow), the response decreases the magnitude of dead space creation. As a result, the associated wasted ventilation and arterial hypercapnia, as well as the need to increase minute ventilation to reestablish better alveolar ventilation, are minimized. In a pig model of acute thromboembolism, we found there were significant compensatory ventilation shifts out of embolized regions to nonembolized regions within 30 min, and of the same magnitude as suggested by balloon occlusion.[12] Ultimately, with sustained cessation of perfusion over days, atelectasis (the ultimate ventilation redistribution) develops as surfactant production decreases (another carbon dioxide–dependent process), and compliance is profoundly reduced.[13,14]

This work reminds us that preservation of $\dot{V}_A/\dot{Q}$ matching is complex, and befitting an important defense, it relies on multiple mechanisms involving responses to changes in both regional alveolar oxygen and carbon dioxide. Much of the emphasis in the teaching and understanding of gas exchange physiology is oxycentric, and carbon dioxide is often neglected and understudied. Since carbon dioxide acts on both the regulation of regional ventilation and perfusion, while oxygen lacks any significant effect on control of local ventilation, a strong argument can be made that carbon dioxide may be more important than oxygen in $\dot{V}_A/\dot{Q}$ regulation. In addition, the multiple effects of carbon dioxide on perfusion, airway resistance, and parenchymal compliance have a dose-response relationship over the entire range of alveolar carbon dioxide in healthy and diseased lungs, in contrast to hypoxic pulmonary vasoconstriction, which only becomes measurable when P_{AO_2} decreases to less than 70 to 80 mmHg. Greater understanding of the mechanisms and signaling pathways by which carbon dioxide acts, especially effects mediated by its downstream signaling, should not involve imposing hypercapnia and might be therapeutically useful in managing patients with chronic lung diseases or acute lung injury.

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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