Exercise Carbon Dioxide Retention in Chronic Obstructive Pulmonary Disease
A Case for Ventilation/Perfusion Mismatch Combined with Hyperinflation

In health and, more often than not, even in moderate to severe chronic airway obstruction, arterial $\text{PCO}_2$ in the resting awake state is usually guarded within very narrow limits. This precise control is attributable to the vigilance of sensitive chemoreceptors, a respiratory musculature with huge reserves for force development and increasing tidal volume, and the linear shape of the carbon dioxide (CO$_2$) dissociation curve that allows for ventilationary correction of increased $\text{Pa}_\text{CO}_2$ even in the face of nonuniform ventilation/perfusion ($\dot{V}$A/$\dot{Q}$) distribution. In chronic obstructive pulmonary disease (COPD), this precise control of $\text{Pa}_\text{CO}_2$ is not always prevalent in other physiologic states, such as sleep (1) and exercise (2).

In this issue of AJRCCM, O’Donnell and associates (pp. 663–668) remind us that severe CO$_2$ retention often occurs during exercise in severe COPD, even when it is not present at rest (3). These authors identified patients with COPD who did and did not retain significant amounts of CO$_2$ (more than 5 torr above resting levels) during heavy intensity exercise and used a correlational approach to identify potential independent causative factors. Most of the routine resting airway function measurements, including $\text{Pa}_\text{CO}_2$, were not predictive of the increase in $\text{Pa}_\text{CO}_2$ with exercise. Rather, a key predictor was the degree of $\dot{V}$A/$\dot{Q}$ nonuniformity, as determined at rest by the increases in $\text{Pa}_\text{CO}_2$ and the dead space-to-tidal volume ratio, achieved in acute hyperoxia. It followed then that in the face of an increased demand for CO$_2$ elimination with exercise, these patients with $\dot{V}$A/$\dot{Q}$ nonuniformity required a greater overall ventilatory response. Accordingly, they experienced significant expiratory flow limitation, hyperinflation, tidal volume and ventilatory limitation, and CO$_2$ retention at a lower work rate and CO$_2$ production than did nonretainers. Although the combination of $\dot{V}$A/$\dot{Q}$ maldistribution and mechanical constraint has been implicated as causes of chronic CO$_2$ retention in COPD at rest—even in the face of high ventilatory drive (4, 5)—the importance of hyperinflation has not been previously emphasized at rest or in exercise. Expiratory flow limitation and hyperinflation in exercise have also been implicated as major determinants of dyspnea, diaphragm force output, and exercise performance in patients with varying types of increased airway resistance (6–8). Sufficient evidence has now accumulated to recommend that inspiratory capacity and tidal flow-volume loops be carefully measured during routine clinical exercise testing.

There are analogies in healthy persons to the ventilatory limitation experienced in these exercising patients with COPD. For example, older nonsmoking fit subjects with normal age-related loss of lung elastic recoil have a high dead space-to-tidal volume ratio and undergo significant expiratory flow limitation at a lower minute ventilation during exercise than do younger subjects. Thus, although older subjects maintain an isocapnic hyperpneic response to exercise similar to that in the younger subjects, they must produce a greater overall ventilation at a higher end-expiratory lung volume and therefore experience shorter inspiratory muscle length and increased elastic work at any given exercise work rate. Even in young adults, expiratory flow limitation is sometimes achieved at the extraordinarily high work rates achieved in very fit subjects during heavy and maximum exercise; although this does not cause absolute CO$_2$ retention (greater than the resting value) in these fit subjects, it limits the degree of compensatory hyperventilation normally experienced in less fit healthy subjects during heavy intensity exercise (9–11).

It is important to emphasize that these mechanisms of ventilatory limitation and CO$_2$ retention during exercise in COPD are proposed solely on the basis of statistical correlation. None of the key independent correlations in the study of O’Donnell and coworkers, although significant, account for more than 40% of the total variance in the amount of CO$_2$ retention during exercise, although it does appear as though a combination of the resting end-expiratory lung volume plus its further change with exercise will enhance the prediction of exercise CO$_2$ retention. Furthermore, correlational analysis only considers the variables that were measured, and important potential determinants of the ventilatory response, which were not determined in this study, include individual variations in central respiratory motor output and in the force output of the respiratory muscles during exercise. Both of these important determinants of the ventilatory response would likely be affected, and to a varying extent among individuals, in the presence of hyperinflation combined with the potent stimuli that drive exercise hyperpnea (8).

It is imperative then that these postulated mechanisms for CO$_2$ retention be tested experimentally. For example, in healthy fit subjects, inhalation of low-density helium–oxygen mixture improves the maximum flow-volume loop and reduces tidal expiratory flow limitation and minimizes increases in end-expiratory lung volume during heavy intensity exercise; a helium-oxygen mixture was also shown to augment the tidal volume and hyperventilatory response to both exercise and dead space breathing (10). Furthermore, in COPD


DOI: 10.1164/rccm.2206004
with high dead space-to-tidal volume ratio and CO₂ retention at rest, administration of a chronic ventilatory stimulant was successful in increasing alveolar ventilation sufficiently to reduce PaCO₂ only in those instances where increased ventilatory drive resulted in an increased tidal volume (4). A limited inspiratory reserve volume (even at rest) was likely a key mechanical determinant of these patients’ ventilatory responsiveness to treatment, just as it was during exercise in the study of O’Donnell and coworkers (3). Methods for experimentally reducing flow limitation and/or changing central respiratory motor output or even respiratory muscle maximum force output could similarly be applied to the exercising patient with COPD who has CO₂ retention.

In summary, O’Donnell and associates have used a comprehensive approach and propose some insightful postulates to explain the complex problem of exercise-induced CO₂ retention in COPD. They make a strong case for the importance of Vₐ/Q maldistribution leading to increased ventilatory requirements combined with tidal volume limitation because of flow limitation and hyperinflation, in response to the increased demands for CO₂ elimination imposed by exercise. The findings add to several recent findings in underscoring the critical importance of considering and measuring hyperinflation as a very important mechanical consequence of airway obstruction, especially under conditions of increased ventilatory requirement.

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DOI: 10.1164/rccm.2206001

The Adaptive Response of Smokers to Oxidative Stress
Moving from Culture to Tissue

An efficient antioxidant defense is essential to protect the lung against the continuous threat posed by exogenous and endogenous oxidants. Major airborne sources of oxidants that may cause injury to the lung are cigarette smoke and air pollutants, whereas inflammatory cells may constitute an endogenous source of oxidants. Oxidative stress is considered to be an important element in the pathogenesis of a variety of inflammatory lung diseases, including idiopathic pulmonary fibrosis, acute respiratory distress syndrome, and chronic obstructive pulmonary disease (COPD) (1, 2). The relative contribution of inhaled (exogenous) and inflammatory cell-derived (endogenous) oxidants differs among these conditions. The ability of oxidants to cause direct injury to the epithelium of the lung and to inactivate proteinase inhibitors, and their involvement in mucus hypersecretion, inflammatory gene expression, and neutrophil recruitment has provided a rationale for the development of antioxidants as a treatment for inflammatory lung disease. Current therapeutic strategies to protect the lung against oxidative stress, however, are far from optimal.

Lung tissue has the capacity to mount an adaptive response quickly to oxidative stress by recruitment of antioxidant defenses. Various antioxidant mechanisms are operative in the lung, and include the action of glutathione (GSH), the predominant nonprotein antioxidant in the lung. This tripeptide has been shown to play a key role in the lung’s defense against oxidative stress (3), as demonstrated by studies showing its critical involvement in the regulation of oxidant-induced apoptosis in lung epithelial cells (4). There is a substantial turnover of GSH in the lung, which requires an efficient system to maintain GSH levels. De novo synthesis is an important mechanism to maintain and increase GSH levels in epithelial lining fluid and involves the action of various components, among which γ-glutamylcysteine synthetase (γ-GCS) appears to play a key role as a rate-limiting enzyme (3). In vitro studies have revealed that a variety of mediators, including oxidants and proinflammatory cytokines, is able to increase expression of γ-GCS, usually secondary to depletion of intracellular GSH stores. In contrast, transforming growth factor-β was found to decrease γ-GCS expression (3). This is important because the expression of transforming growth factor-β is increased in various inflammatory lung disorders, including COPD and idiopathic pulmonary fibrosis. γ-GCS is a heterodimer in which the heavy subunit contains the catalytic activity, whereas the light subunit serves as a regulatory chain. Interestingly, expression of