Ventilatory Inefficiency and Exertional Dyspnea in Early Chronic Obstructive Pulmonary Disease

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Abstract

Exertional dyspnea is present across the spectrum of chronic obstructive pulmonary disease (COPD) severity. However, without realizing it themselves, patients may decrease daily physical activity to avoid distressing respiratory sensations. Dyspnea also may be associated with deconditioning. Cardiopulmonary exercise testing can uncover exertional dyspnea and its physiological determinants in patients with preserved or only mildly reduced FEV_1. Dyspnea in mild COPD can largely be explained by increased "wasted" ventilation in the physiological dead space, which heightens the drive to breathe and worsens the inspiratory mechanical constraints. During incremental exercise testing, this is readily identified as an excessive ventilation-to-metabolic demand, that is, a high ventilation ($\dot{V}_E$) to carbon dioxide output ($\dot{V}_{CO_2}$) relationship. Linking increases in $\dot{V}_E/\dot{V}_{CO_2}$ to exertional dyspnea may provide objective evidence that a patient's poor exercise tolerance is not just a consequence of deconditioning. This information should prompt a proactive therapeutic approach to increase the available ventilatory reserve by, for example, giving inhaled bronchodilators. Considering that the structural determinants of ventilatory inefficiency (early emphysema, ventilation–perfusion mismatching, and microvascular disease) may progress despite only modest changes in FEV_1, serial $\dot{V}_E/\dot{V}_{CO_2}$ measurements might also prove valuable to track disease progression in these symptomatic patients.

Keywords: ventilation; exercise; chronic obstructive pulmonary disease; cardiopulmonary exercise test

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Activity-related dyspnea is present across the spectrum of functional impairment in patients with chronic obstructive pulmonary disease (COPD) (1). There is emerging evidence that exertional dyspnea is present from the early stages of the disease (2). Most patients with mild COPD, however, often adapt their life style to avoid the distressing consequences of exertional dyspnea (3–5). Accordingly, there is a renewed interest in establishing reliable physiological correlates of exertional dyspnea in this fast-growing patient subpopulation (6).

Graded progressive cardiopulmonary exercise testing provides a unique opportunity to relate exertional dyspnea to its key physiological determinants in COPD (7). In the early stages of the disease, for instance, pronounced detraining makes it difficult to portion out the contribution of peripheral muscular versus "respiratory" factors in limiting exercise tolerance. As the disease evolves, exertional dyspnea varies widely for a given level of resting functional impairment in patients who often present with multiple causes of exercise intolerance (1). Linking patients' out-of-proportion dyspnea to specific pulmonary function abnormalities raises the consideration that the symptom may be related to obstructive physiology. This could be valuable to identify treatment targets for symptom control (8).

In this context, excessive exercise ventilation (ventilatory inefficiency) due to high "wasted" ventilation in the physiological dead space is a key correlate of breathlessness in COPD (as reviewed in Reference 7). This is particularly true in mild COPD, where the pulmonary-mechanical abnormalities are not severe enough to limit patients' ability to increase ventilation (1–3). This relationship forms the basis for a clinical interpretation of the complex interrelationships between ventilation, pulmonary-mechanical constraints, and exertional dyspnea in smokers and patients with COPD with largely preserved FEV_1.

Discussion of ventilatory inefficiency in patients with more advanced COPD has recently been reviewed (9).

Potential Mechanisms of Exertional Dyspnea in COPD

Dyspnea during exercise ultimately reflects a disparity between the increased need to breathe and the diminished ability to meet that demand. Such an imbalance increases the awareness of this largely subconscious act (8, 10, 11). Increased inspiratory effort in patients with COPD may trigger affective consequences, such as anxiety or panic (12). It has been proposed that there are two fundamental mechanisms of exertional dyspnea in COPD: (*1*) a "quantitative" mechanism in which ventilation is excessive for the metabolic demand, and (*2*) a "qualitative" mechanism in which ventilation mechanics are abnormal (13).

In the quantitative mechanism, increased chemostimulation of central and peripheral chemoreceptors may arise from any combination of increased ventilation of dead space or poorly perfused areas, hypoxemia, and early metabolic acidosis from deconditioning or coexistent cardiocirculatory abnormalities (7–11). In fact, Bauerle and coworkers provided seminal evidence that variability in ventilatory response is an important determinant of exercise tolerance in COPD (14, 15).

In the qualitative mechanism, as ventilation increases, the expiratory time may become insufficient to allow the lungs to fully empty. This occurs in the presence of expiratory flow limitation and results in hyperinflation, which worsens with exercise. This increases the work needed to inflate the lungs because the forces that oppose lung distension become higher at greater lung volumes and lower dynamic compliance. More work is needed to initiate an inspiration because the air trapped in the preceding expiration did not allow the system to return to its relaxed position. Thus, the respiratory muscles need to overcome an intrinsic positive end-expiratory pressure before a sufficient negative pressure is reached and inspiratory airflow ensues. The inspiratory muscles, however, are ill-prepared to generate such high pressures, as they no longer operate in their "ideal" length for force generation. Thus, increased efferent drive to the muscles of breathing in COPD is ultimately the consequence of high chemostimulation and excessive mechanical loading (7–11).

Ventilatory Inefficiency as Measured By $\dot{V}E/\dot{V}CO_2$

Pulmonary ventilation ($\dot{V}E$) is largely driven by carbon dioxide output ($\dot{V}CO_2$) during exercise (16). The $\dot{V}E/\dot{V}CO_2$ relationship expresses the efficiency of ventilation in removing CO_2 produced by the body. The greater the ventilation for a given $\dot{V}CO_2$ (high $\dot{V}E/\dot{V}CO_2$) the worse the ventilatory efficiency (17).

The ventilation that does not reach the alveoli is the dead space ventilation (V_D) and the fraction of tidal volume (V_T) not contributing to gas exchange is reflected in V_D/V_T. The greater the V_D/V_T, the higher the $\dot{V}E/\dot{V}CO_2$ and the greater the ventilatory inefficiency (18). Ventilation further increases if the subject regulates arterial CO_2 at a low value, as more ventilation is needed to maintain a low than a high arterial CO_2. The $\dot{V}E/\dot{V}CO_2$ increases as a function of age, probably as a consequence of the combined effects of higher V_D, caused by "emphysema of aging" and increased ventilation–perfusion mismatching and lower V_T caused by lower thoracic compliance (Figure 1) (19–21).

At the beginning of exercise, $\dot{V}E/\dot{V}CO_2$ decreases with decreasing V_D/V_T. The $\dot{V}E/\dot{V}CO_2$ nadir typically is reached just before ventilation starts to increase in compensation for lactic acidosis (17). Thus, the $\dot{V}E/\dot{V}CO_2$ nadir and the $\dot{V}E/\dot{V}CO_2$ at the lactate threshold are almost indistinguishable in normal subjects (22). The $\dot{V}E/\dot{V}CO_2$ nadir has been found to be highly reproducible in normal subjects (22) and in patients with COPD (23). In fact, the nadir is the most commonly reported index of ventilatory inefficiency in

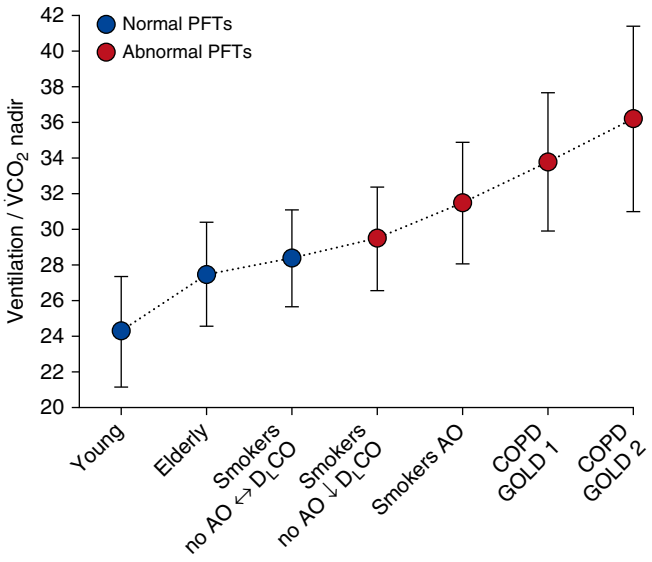

Figure 1. Average effect of senescence (19–21), chronic smoking (34–37), mild chronic obstructive pulmonary disease (COPD) (38–44), and moderate COPD (45–47) on $\dot{V}E/\dot{V}CO_2$, a metric of exercise ventilatory inefficiency. The modulating influence of airflow obstruction (AO) (35, 36) and decrements (*downward arrow*) in lung diffusing capacity for carbon monoxide (D_{LCO}) (37) in smokers are also shown. Values are mean ± SD as obtained from each data source. GOLD = Global Initiative for Chronic Obstructive Lung Disease; PFT = resting pulmonary function test.

COPD (9). Reviews on ventilatory inefficiency and $\dot{V}_E$-$\dot{V}_{CO_2}$ slope and intercept have recently been published (9, 24).

Ventilatory Inefficiency and Dyspnea in Smokers

At times, smokers may present with pulmonary gas exchange abnormalities that precede airflow obstruction on resting spirometry (25, 26). The structural bases for this might involve microvascular destruction (27, 28), localized emphysema and air trapping (29, 30), and ventilation–perfusion distribution abnormalities (31–33) in different combinations. To address whether these abnormalities might worsen under the stress of exercise and if they were related to ventilatory efficiency, Elbehairy and coworkers studied a group of symptomatic smokers without spirometric evidence of airflow obstruction and preserved FEV_1 (34). Although smokers had greater exertional dyspnea and lower exercise tolerance than the healthy control subjects, the $\dot{V}_E/\dot{V}_{CO_2}$ nadir did not differ between the groups. The authors commented, however, that there was considerable variability in the $\dot{V}_E/\dot{V}_{CO_2}$ nadir in smokers, and the $\dot{V}_E/\dot{V}_{CO_2}$ nadir did correlate inversely with peak $\dot{V}_{O_2}$.

Soumagne and colleagues (35) went further by looking at potential mechanisms of exercise intolerance in asymptomatic smokers with airway obstruction. The authors found that the $\dot{V}_E/\dot{V}_{CO_2}$ nadir was increased in these subjects and those with mild COPD compared with healthy nonsmokers. Of note, dyspnea ratings as a function of ventilation were higher in smokers than in healthy control subjects, suggesting that increased ventilation *per se* was not the main cause of their symptoms. In their study, smokers had greater decrements in inspiratory capacity during exercise (dynamic hyperinflation).

Elbehairy and colleagues (36) and Walter Barbosa and colleagues (37) recently confirmed the presence of increased $\dot{V}_E/\dot{V}_{CO_2}$ nadirs in smokers. Elbehairy and colleagues found that $\dot{V}_E/\dot{V}_{CO_2}$ nadir correlated inversely with resting diffusing capacity of the

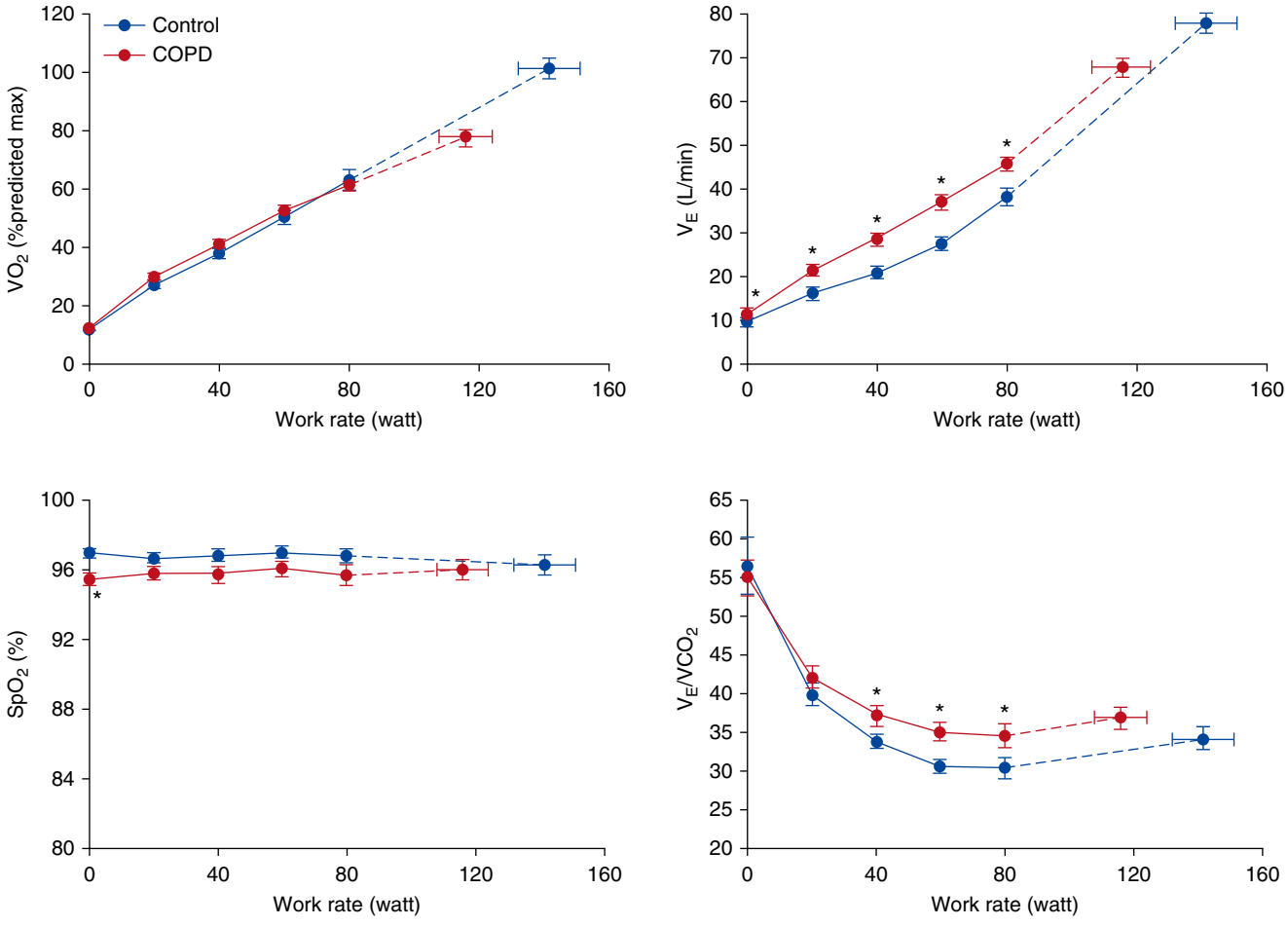

Figure 2. Lower $\dot{V}_{O_2}$ and peak work rate in mild chronic obstructive pulmonary disease (COPD) compared with control subjects (*upper left panel*) was associated with increased $\dot{V}_E$ at a given work rate (*upper right panel*). Increased $\dot{V}_E/\dot{V}_{CO_2}$ (ventilatory inefficiency) in mild COPD (*lower right panel*) was not consequence of higher hypoxic drive, as O_2 saturation by pulse oximetry (Sp_{O_2}) did not differ between patients and control subjects (*lower left panel*). *$P < 0.05$: patients versus control subjects. Reprinted by permission from Reference 38.

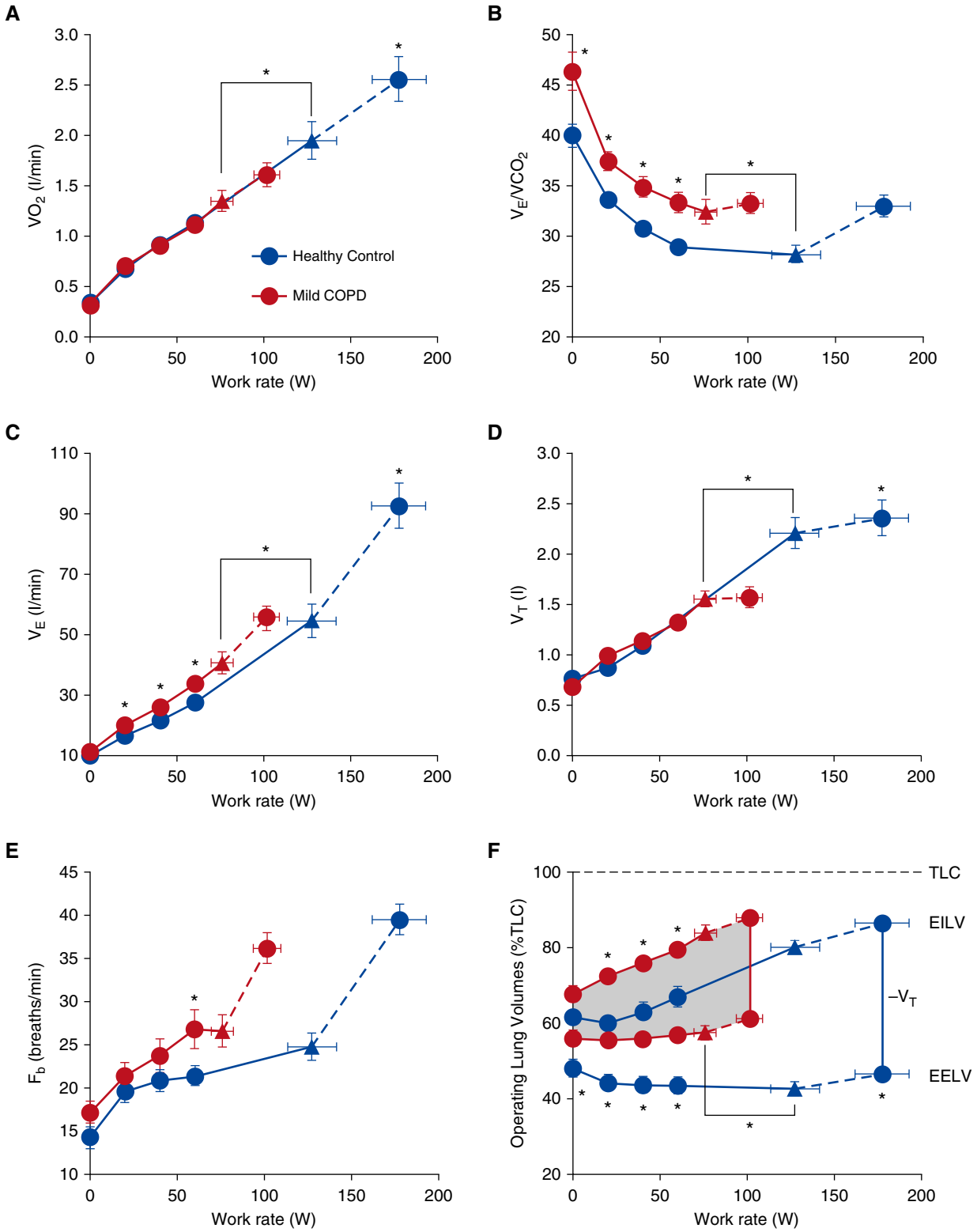

Figure 3. Lower peak oxygen uptake ($\dot{V}O_2$) and work rate in mild chronic obstructive pulmonary disease (COPD) compared with control subjects (*A*) was associated with increased $\dot{V}E/\dot{V}CO_2$ (ventilatory inefficiency) at a given work rate (*B*). Higher $\dot{V}E$ (*C*) was a consequence of faster respiratory rates (F_b) (*E*) but similar submaximal tidal volume (V_T) (*D*). V_T plateaued (*D*) when critical inspiratory constraints were reached at lower exercise intensities in patients (*F*). *$P < 0.05$: patients versus control subjects. Differences at the work rate corresponding to V_T inflection point are highlighted. EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; TLC = total lung capacity. Reprinted by permission from Reference 39.

lung for carbon monoxide (D_{LCO}), which, in turn, correlated with exertional dyspnea and peak oxygen uptake ($\dot{V}O_2$) (36).

Consistent with these findings, Walter Barbosa and colleagues found that smokers without airflow obstruction but with a low D_{LCO} had higher $\dot{V}E/\dot{V}CO_2$ nadir and lower peak $\dot{V}O_2$ than their counterparts with preserved D_{LCO} (37). These two studies point out a role for D_{LCO} in identifying a subgroup of smokers at greater risk of progressing to the symptomatic stages of COPD. Smokers with low D_{LCO} and poor exercise ventilatory efficiency might benefit from closer follow-up for early detection of activity-related breathlessness and its deleterious consequences.

Ventilatory Inefficiency and Dyspnea in Mild COPD

The potential relationship between ventilatory inefficiency and exertional dyspnea in patients with symptomatic COPD with preserved FEV_1 (Global Initiative for Chronic Obstructive Lung Disease stage 1) was first explored by Ofir and colleagues (38). These authors found that ventilation was increased by 30% or more for any given power output throughout exercise in these patients compared with control subjects. This was largely explained by poorer ventilatory efficiency in the former group (Figure 2).

Higher exercise ventilation reduced the instantaneous ventilatory reserves and increased the operating lung volumes. Thus, the best correlates of exertional dyspnea were ventilation expressed as a percentage of the estimated maximal ventilatory capacity (MVC) and inspiratory reserve volume as percentage of total lung capacity, (38) corresponding to the quantitative and qualitative mechanisms mentioned above. Guenette and coworkers (39) subsequently confirmed that higher dyspnea intensity in patients with mild COPD, compared with control subjects, ultimately reflected two negative consequences of ventilatory inefficiency: a higher drive to breathe as indicated by higher ventilation relative to MVC (Figure 3) and increased inspiratory muscle effort (higher diaphragmatic activation by electromyography).

The key role of ventilatory inefficiency in decreasing patients' mechanical-ventilatory

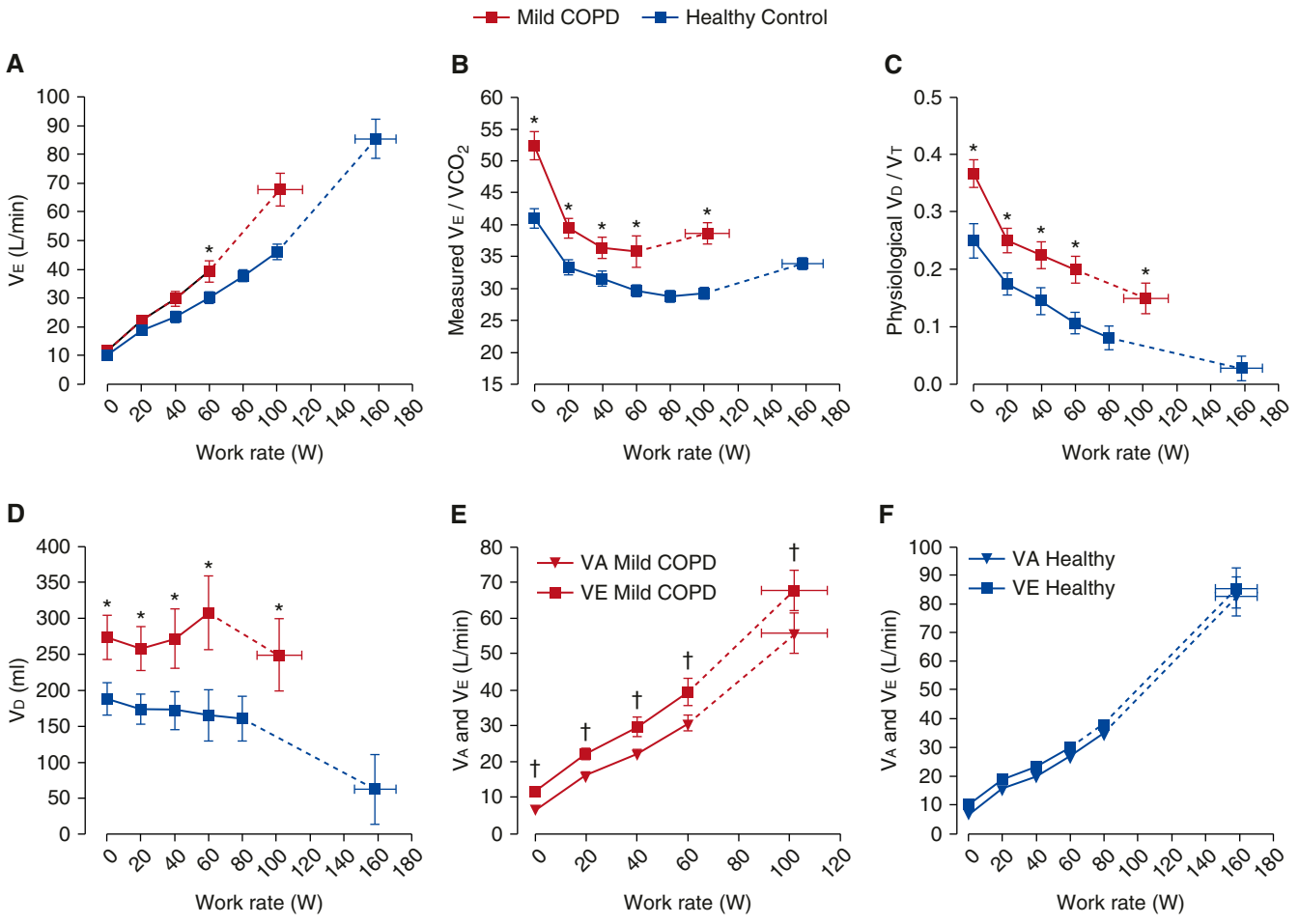

Figure 4. Increased $\dot{V}E$ at a given work rate in mild chronic obstructive pulmonary disease (COPD) compared with control subjects (*A*) was associated with increased $\dot{V}E/\dot{V}CO_2$ throughout exercise (ventilatory inefficiency) (*B*). These abnormalities were consequence of a higher physiological V_D/V_T ratio (*C*) due to a higher V_D (*D*). A higher V_D in patients led to a wider difference between $\dot{V}E$ and alveolar ventilation ($\dot{V}A$) (*E*) compared with controls (*F*). *$P < 0.05$: patients versus control subjects. Reprinted by permission from Reference 41.

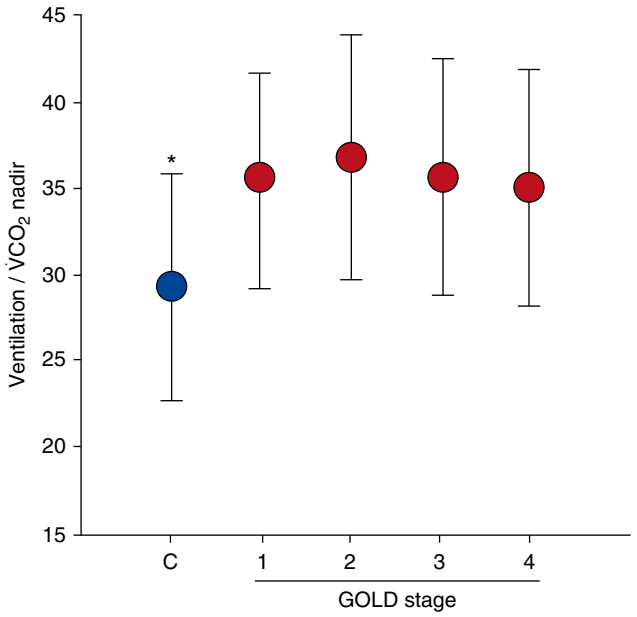

Figure 5. Increased ventilation/$\dot{V}_{CO_2}$ nadir (a metric of ventilatory inefficiency) across the stages of chronic obstructive pulmonary disease severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry stages. *C* represents age- and sex-matched healthy control subjects. *$P < 0.05$: control subjects versus patients (all stages). Adapted by permission from Reference 45.

reserves was demonstrated by Guenette and coworkers in a subgroup of elderly women with mild COPD, who had reduced reserves compared with the men (40). Similarly increased $\dot{V}_E/\dot{V}_{CO_2}$ ratios led women to reach a higher fraction of their MVC at a given work rate compared with men. Moreover, the women reached a critically reduced inspiratory reserve volume over a substantially lower ventilation range. Consequently, they had higher dyspnea scores for any given absolute work rate or ventilation. Thus, this study demonstrated that the mechanical and ventilatory abnormalities of mild COPD have greater sensory implications in elderly women than age-matched men (40).

Another important study by Elbehairy and colleagues (41) shed light on the mechanisms underlying ventilatory inefficiency in mild COPD, defined as having an FEV_1 of 94 ± 10% predicted. By measuring arterial blood gases during exercise, the authors corroborated the notion that increased $\dot{V}_E/\dot{V}_{CO_2}$ in these patients was mainly a consequence of high V_D/V_T ratio (Figure 4). These data provided direct evidence supporting earlier inferences from Chin and colleagues (42) who found an upward displacement of $\dot{V}_E/\dot{V}_{CO_2}$ when V_D was artificially increased in mild COPD (FEV_1 equal to 87 ± 11% predicted). In both studies, a higher V_D/V_T increased the ventilatory requirements at a given work rate, leading to greater $\dot{V}_E$/MVC ratio and greater respiratory mechanical constraints. Of note, Elbehairy and colleagues subsequently found high $\dot{V}_E/\dot{V}_{CO_2}$ nadirs in patients with mild COPD whether or not they had chronic bronchitis (43). They also found a significant correlation between $\dot{V}_E/\dot{V}_{CO_2}$ nadir and $D_{L_{CO}}$ in both groups, a finding recently confirmed by Jones and colleagues (44). This is additional evidence that $D_{L_{CO}}$ can be a useful predictor of ventilatory inefficiency in mild COPD.

A retrospective study by Neder and coauthors of 316 patients with a large range of resting functional impairment (FEV_1 from 148 to 12% predicted) and healthy control subjects confirmed the presence of high $\dot{V}_E/\dot{V}_{CO_2}$ nadir in the subgroup of patients with preserved FEV_1 (Figure 5) (45). Similar to previous investigations, high $\dot{V}_E/\dot{V}_{CO_2}$ nadir was associated with greater exertional dyspnea scores and poorer exercise tolerance. In another study, the same authors found worse ventilation distribution abnormalities in the subgroup of patients with mild COPD with higher $\dot{V}_E/\dot{V}_{CO_2}$ nadir and lower exercise capacity (46). These two independent studies found correlations between $\dot{V}_E/\dot{V}_{CO_2}$ nadir and emphysema severity on high-resolution computed tomography in patients with largely preserved FEV_1 (44, 47). Although these investigations show increased dead space ventilation and ventilatory inefficiency caused by enlarged air spaces in mild COPD, there has been no thorough investigation of the role of early microvascular destruction in increasing wasted ventilation in these patients. These patients often have extensive pulmonary microvascular abnormalities despite preserved FEV_1 (28, 48), which merits further investigation.

Conclusions

Sixty years after the seminal description of the "dyspnea index" (submaximal ventilation/MVC ratio) by Gandevia and Hugh-Jones (49), we now fully recognize the relevance of this concept to exertional dyspnea in the early stages of COPD. When the predations of smoking decrease the efficiency of the lungs as a gas exchanger, susceptible smokers and symptomatic patients with mild COPD ventilate in excess to compensate for the wasted ventilation. Air trapping may increase the operating lung volumes, requiring higher efferent input to overloaded respiratory muscles, leading to the sensation of shortness of breath. A continuum of ventilatory inefficiency may precede the development of COPD and worsen as the disease evolves (Figure 1).

As an effort-independent, easily obtained exercise test parameter, $\dot{V}_E/\dot{V}_{CO_2}$ nadir is an attractive metric of ventilatory inefficiency. Linking increases in $\dot{V}_E/\dot{V}_{CO_2}$ to exertional dyspnea provides objective evidence that exercise intolerance not only is a consequence of chronic inactivity but also is associated with mild COPD. A reduced $D_{L_{CO}}$ has further negative implications. In patients with mild COPD and multiple comorbidities, establishing an association between ventilatory inefficiency and exertional dyspnea might prove valuable to identify objective treatment targets for symptom management. These measures also may be useful to track disease progression. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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