The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation.


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**THE MAJOR LIMITATION TO EXERCISE PERFORMANCE IN COPD IS DYNAMIC HYPERINFLATION**

The inability to engage in sustained physical activity is a common feature of chronic obstructive pulmonary disease (COPD) and contributes importantly to the perception of poor health status. Given the vast pathophysiological heterogeneity of this disease, the concomitant effects of aging on physical performance, and the existence in many serious comorbidities, the mechanisms of exercise intolerance are necessarily complex and multifactorial. Recognized contributory factors to exercise limitation include critical dynamic physiological impairment of the ventilatory, cardiovascular, metabolic, and locomotor muscle systems in highly variable combinations. In practice, intolerable exertional symptoms limit exercise performance even before physiological maxima are reached: in more advanced COPD, perceived respiratory difficulty (dyspnea) is usually the proximate limiting symptom (10, 12).

Expiratory flow-limitation (EFL) and lung hyperinflation that are only partially reversible to bronchodilator therapy are pathophysiological hallmarks of COPD. Static lung hyperinflation refers to the resetting of the respiratory system’s relaxation volume to a higher level as a result of the increased static lung compliance of emphysema. When EFL is present during resting spontaneous breathing, end-expiratory lung volume (EELV) is also dynamically determined and varies with the mechanical time constant for emptying (the product of resistance and compliance) of the respiratory system, the inspired tidal volume, and the expiratory time available.

Breathing at higher lung volumes increases airway conductance at rest in flow-limited patients with COPD. Moreover, the insidious development of thoracic hyperinflation over decades is associated with several adaptations that remarkably preserve the force-generating capacity of the diaphragm (27).

The existence of significant lung hyperinflation at rest means that the patients’ ability to increase ventilation when the situation demands it (e.g., exercise) is seriously curtailed. During exercise, the combination of increased ventilatory requirements (mainly secondary to increased ventilation/perfusion mismatching) and abnormal dynamic ventilatory mechanics stresses the already diminished cardiopulmonary reserves of patients with COPD. Reduced peak oxygen uptake has been found to correlate well with the low resting inspiratory capacity (IC; reflecting increased EELV) in patients with demonstrable resting EFL, confirming that mechanical factors contribute importantly to exercise limitation (5, 17, 25).

The temporary and variable increase in EELV above the “static” value that occurs when ventilation is acutely increased is termed dynamic pulmonary hyperinflation (DH; Fig. 2). DH

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**Fig. 2.** Dyspnea intensity, operating lung volumes, breathing pattern, and the effort displacement ratio are shown during incremental exercise in patients with COPD and in age-matched healthy individuals (Normal). Dyspnea intensity is greater and breathing pattern is relatively rapid and shallow in COPD compared with health. In COPD, tidal volume (VT) takes up a larger proportion of the reduced inspiratory capacity (IC) at any given ventilation—mechanical constraints on tidal volume expansion are additionally compounded because of dynamic hyperinflation during exercise. In COPD compared with health, tidal inspiratory pressure swings expressed as a fraction of their maximal force-generating capacity (P inspiratory – P expiratory) are greater and the VT response expressed as a fraction of the predicted vital capacity (VC) is reduced, i.e., the effort-displacement ratio is increased. TLC, total lung capacity; F, breathing frequency. Values are shown as means of data from Ref. 12.
occurs during exercise in flow-limited patients despite active recruitment of expiratory muscles (12, 15). Pneumotachographic IC measurements are reliable (16, 31) and changes accurately reflect changes in EELV during exercise as total lung capacity (TLC) remains unaltered (28, 31). Significant DH (by ~0.5 l) has recently been documented in symptomatic patients with early COPD (GOLD stage I) and was associated with reduced peak oxygen uptake (19). In recent studies in 430 patients with moderate to severe COPD (FEV1.0 40% predicted), IC at peak exercise was reduced by an average of 20% of the already reduced resting value (10, 14). Fifteen percent of COPD patients did not significantly decrease IC during incremental or constant work rate cycle exercise. These included: 1) patients with milder COPD (the minority) who increased or maintained IC during exercise and 2) patients with severe resting lung hyperinflation who could not decrease IC any further.

In a recent mechanical study, DH early in exercise (by attenuating EFL) permitted acute increases in submaximal ventilation (to ~30 l/min) and concomitant inspiratory effort (to ~40% maximum) without provoking significant breathing discomfort (Borg ratings ~2 “slight”; Ref. 15).

However, as end-inspiratory lung volume expanded to reach a minimal inspiratory reserve volume (IRV) of ~0.4 liters below TLC, the inspiratory muscles become functionally weakened and burdened with significant increases in elastic and inspiratory threshold loading (i.e., auto-PEEP effect). When the minimal IRV was reached, dyspnea subsequently escalated to intolerable levels at a point where their inspiratory and expiratory muscles used ~50 and 10% of their maximal possible force generating capacity, respectively.

DH results in restrictive mechanical constraints (see Fig. 2), which in the extreme can lead to alveolar hypoventilation during exercise (13). The smaller the resting IC (and IRV), the lower the ventilation (and work rate) at which a VT plateau is discernible. The consequent tachypnea will result in an increased velocity of shortening of the inspiratory muscles (with further functional weakness; Ref. 24) as well as sharp decreases in dynamic lung compliance. DH, particularly if it is accompanied by excessive expiratory muscle activity, also has the potential to adversely affect cardiocirculatory function, and thus ventilatory/locomotor muscle interactions, during exercise in COPD (1, 23). When impairment of cardiac output (and oxygen transport) is coupled with severely compromised ventilatory muscle function, the development of inspiratory muscle fatigue is possible. However, objective diaphragmatic fatigue has not been consistently demonstrated at the limits of tolerance in COPD (9, 21).

In health, the ratio of tidal inspiratory effort (esophageal pressure relative to the maximum) to VT displacement—the effort-displacement ratio—remains essentially unaltered throughout much of symptom-limited cycle exercise, indicating the optimal position of operating volume on the pressure-volume relationship of the respiratory system (12) (see Fig. 2). By contrast, this ratio increases approximately twofold during exercise in COPD, reflecting “high-end mechanics” and consequent neuromechanical uncoupling of the respiratory system as a result of DH (12, 15). In essence, a situation arises during activity in the patient with COPD where, despite expending the most vigorous inspiratory efforts, very little air enters the lungs with each breath.

Several studies have shown that dyspnea intensity is strongly correlated with indexes of mechanical restriction (reduced dynamic IC and IRV, increased VT/IC ratio) and with increased effort-displacement ratios that rise precipitously when VT expands to reach the minimal IRV (12,15). We postulate that in COPD, a mismatch between central neural drive (sensed via increased central corollary discharge; Ref. 3) and the abnormal “restricted” mechanical response (conveyed by afferent inputs from abundant respiratory mechanosensors) is fundamental to the origin of dyspnea or its major qualitative dimensions (11).

The contention that lung hyperinflation contributes importantly to dyspnea and exercise intolerance in COPD has been bolstered by a number of intervention studies (2, 6–8, 10, 14–16, 18, 20, 22). All classes of bronchodilators act by relaxing airway smooth muscle tone, thereby decreasing the mechanical time constants for emptying in heterogeneously distributed alveolar units. Sustained increases in the resting IC (reflecting lung deflation) in the order of 0.3 liters or ~10–15% predicted (or 15–17% of baseline value) appear to be clinically meaningful (2, 10, 15, 16, 20). Greater IC recruitment (e.g., 0.5 liters) is possible with combined long-acting bronchodilators (31).

In moderate-to-severe COPD patients, improvement in the resting and dynamic IC has been shown to correlate well with: 1) improved peak symptom-limited oxygen uptake and constant work endurance time (4, 14–16, 20), 2) increased peak VT (14, 15, 20), and 3) reduced dyspnea intensity (4, 14, 15, 20). In all of these studies, increased resting IC was linked to a deeper slower breathing pattern during exercise. Moreover, bronchodilator therapy was associated with reduced resistive and elastic/threshold loading of the inspiratory muscles, which resulted in a reduced oxygen cost of breathing compared with placebo (15). Lung volume deflation was also linked to increased ventilatory muscle strength and reduced fractional effort requirements for a given VT displacement (15).

Decreased dyspnea intensity ratings correlate with improved effort-displacement ratios and increased VT during exercise (8, 15). Pharmacological lung volume reduction is associated with minor improvements in cardiac performance during exercise (26, 29). In carefully selected patients, lung volume reduction surgery (LVRS) and bullectomy has similarly been shown to improve operating lung volumes, effort-displacement ratios, exertional dyspnea, and exercise performance (8, 18). Surprisingly, LVRS was not associated with positive short- or long-term effects on cardiac hemodynamics, at least at rest (4). Finally, interventions such as hyperoxia (alone or in combination; Refs. 6, 20) and exercise training (22) have been shown to reduce the rate of DH during exercise (mainly by reducing breathing frequency), thereby contributing to improved dyspnea and exercise endurance.

In conclusion, although activity limitation in COPD is multifactorial, there is now compelling evidence that acute derangements in dynamic ventilatory mechanics contribute importantly. Therapies aimed at partially reversing pulmonary hyperinflation represent the first step in improving dyspnea and exercise capacity, thus facilitating rehabilitation in symptomatic patients with COPD.
REFERENCES


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REBUTTAL FROM ALIVERTI AND MACKLEM

We do not dispute the fact that dynamic hyperinflation and skeletal muscle myopathy are important factors limiting exercise in COPD. We suggest, however, that in the natural history of the disease an insufficient energy supply to respiratory and skeletal muscles to meet demand is the primary limiting factor occurring before dynamic hyperinflation and myopathy. The elegant study by Öfir et al. (4) on exercise performance in GOLD stage 1 patients with COPD supports our hypothesis. Although on average these patients hyperinflated during exercise, this evidently did not limit exercise as the inspiratory reserve volume (IRV) at peak exercise (Wmax) was 0.69 liters (±0.31 SD) compared to an IRV in a well-matched control group of 0.70 liters (±0.37 SD). Furthermore, the decrease in inspiratory capacity (IC) at Wmax had a large standard deviation (mean decrease in IC: −0.54 liters (±0.34 SD); with the 95% confidence limits of ±2 SD, some patients must have increased IC at Wmax or else the data were not normally distributed.