Hyperinflation, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease

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Expiratory flow limitation is the pathophysiologic hallmark of chronic obstructive pulmonary disease (COPD), but dyspnea (breathlessness) is its most prominent and distressing symptom. Acute dynamic lung hyperinflation, which refers to the temporary increase in operating lung volumes above their resting value, is a key mechanical consequence of expiratory flow limitation, and has serious mechanical and sensory repercussions. It is associated with excessive loading and functional weakness of inspiratory muscles, and with restriction of normal VT expansion during exercise. There is a strong correlation between the intensity of dyspnea at a standardized point during exercise, the end-expiratory lung volume, and the ratio of inspiratory effort to volume displacement (i.e., esophageal pressure relative to maximum: VT as a % of predicted VC). This increased effort–displacement ratio in COPD crudely reflects the neuromechanical dissociation of the respiratory system that arises as a result of hyperinflation. The corollary of this is that any intervention that reduces end-expiratory lung volume will improve effort–displacement ratios and alleviate dyspnea. In flow-limited patients, bronchodilators act by improving dynamic airway function, thus enhancing lung emptying and reducing lung hyperinflation. Long-acting bronchodilators have recently been shown to reduce hyperinflation during both rest and exercise in moderate to severe COPD. This lung deflation allows greater VT expansion for a given inspiratory effort during exercise with consequent improvement in dyspnea and exercise endurance.

Keywords: chronic pulmonary obstructive disease; fatigue; respiratory mechanics; work of breathing

The pathophysiologic hallmark of chronic obstructive pulmonary disease (COPD) is expiratory flow limitation, whereas the most common symptom is dyspnea (the perception of respiratory discomfort). Expiratory flow limitation arises because of the combined effects of reduced elastic lung recoil and increased airways resistance. Dyspnea is the primary symptom limiting exercise in patients with more advanced disease, and often leads to avoidance of activity, with consequent skeletal muscle deconditioning. The relationship between the physiologic impairment—as traditionally measured by FEV₁—and the characteristic symptoms of COPD, however, is not straightforward. In this review, the evidence that lung hyperinflation provides a mechanistic link between expiratory flow limitation and dyspnea is examined, with a view to explaining how bronchodilators relieve symptoms.

NEGATIVE CONSEQUENCES OF DYNAMIC HYPERINFLATION

Lung hyperinflation, defined as an abnormal increase in the volume of air remaining in the lungs at the end of spontaneous expiration, is present in COPD because of the effects of increased lung compliance as a result of the permanently destructive changes of emphysema and expiratory flow limitation. Although there are no formal epidemiologic studies, clinical experience suggests that hyperinflation develops slowly and insidiously over many years, similar to the decline in FEV₁. Consequently, patients may not perceive the negative results of hyperinflation until the disease is quite advanced, mainly because the respiratory system adapts to the mechanical disadvantages caused by hyperinflation. For instance, the chest wall reconfigures to accommodate the over-distended lungs, and the diaphragm partially preserves its ability to generate pressure during resting breathing despite its shortened operating length (1–3). However, these compensatory mechanisms quickly become overwhelmed when ventilation rate is acutely increased, for example, during exercise. A patient with severe COPD, faced with a flight of stairs, may only be able to climb four or five steps before experiencing intolerable dyspnea and has to stop.

As expected, the relationship between dyspnea intensity (measured using the modified Borg scale) and VO₂ (a measure of oxygen demand) during a symptom-limited incremental cycle ergometry test is notably different between patients with COPD and normal subjects (Figure 1) (4). We, and others, have shown that patients with COPD started to experience dyspnea at a much lower VO₂ than healthy subjects. Furthermore, they experienced severe dyspnea (Borg score, ≥ 5) and had to stop exercising at a much lower peak symptom-limited VO₂ than did healthy subjects, who, in comparison, had not yet attained noticeable levels of respiratory difficulty (Borg score, < 0.5).

This difference in the sensory experience of exertional dyspnea in patients with COPD compared with normal subjects is accompanied by changes in ventilatory mechanics. Compared with normal subjects, patients with COPD have a heightened ventilatory response to exercise (Figure 2), reflecting greater ventilation–perfusion abnormalities (high fixed physiologic deadspace). In general, the breathing pattern in COPD is more rapid and shallow at any given ventilation compared with the breathing pattern in health (Figure 3) (4).

In healthy subjects, end-expiratory lung volume (EELV) and inspiratory capacity (IC) are maintained throughout exercise. During exercise, both the rate and depth (VT) of respiration are normally increased to accommodate the increased metabolic demand. In COPD, the rate of lung emptying, which is dictated by the product of compliance and resistance (i.e., time constant), is often substantially delayed. In many patients, the expiratory time available during spontaneous resting breathing is insufficient to allow EELV to decrease to its relaxation volume, resulting in lung overinflation. This situation is aggravated further as expiratory time shortens during exercise, resulting in further increases in EELV. This phenomenon has been termed “air trapping,” or dynamic hyperinflation, and refers to the temporary and variable increase in EELV above its baseline value. During exercise, the change in EELV (from rest to peak) in a large population averaged 0.4 L, with considerable variation in the range (5). Changes in EELV are reflected by changes in IC, as total lung capacity (TLC) remains unchanged during exercise.
Figure 1. Relationship between dyspnea intensity (measured using the modified Borg scale) and $\dot{V}O_2$ during a symptom-limited incremental cycle ergometry test in patients with chronic airflow limitation (CAL; closed circles) and in normal subjects (open circles). Patients with CAL experienced severe dyspnea (Borg score, $\geq 5$) and had to stop exercising at a much lower $\dot{V}O_2$ than normal subjects, who, in comparison, had not yet attained noticeable levels of respiratory difficulty (Borg score, $< 0.5$). *$p = 0.001$, significantly steeper slope in patients with CAL compared with normal subjects. Reprinted by permission from Reference 4.

Although $V_t$ is comparable between groups at rest, it comprises a larger proportion of IC in patients with COPD compared with normal subjects. Because of hyperinflation during the increased demands of exercise, $V_t$ can only increase marginally in patients with COPD, and reaches a plateau (Figures 3 and 4). At this point, further increases in ventilation can only be achieved by increasing breathing frequency, which unfortunately rebounds to cause greater hyperinflation in a vicious cycle.

In addition, hyperinflation markedly increases the tidal inspiratory pressure or effort (expressed as a percentage of maximal inspiratory pressure [Pimax]) required to generate an increase in $V_t$ (expressed as a percentage of the VC) in patients with COPD compared with normal subjects (Figure 4) (4). This is because the relationship between pleural pressure and lung volume during a static maneuver from TLC to RV is sigmoidal rather than linear (Figure 5). In healthy subjects, breathing at rest and during exercise takes part in the central linear portion of the pressure–volume relationship, which means that relatively small changes in tidal pressure will produce comparatively large changes in $V_t$. In younger individuals, EELV actually declines (IC increases) as expiratory muscles are recruited during exercise, thus conveying a distinct mechanical advantage (Figure 5). In COPD, $V_t$ must “cycle” close to the TLC on the steep portion of the pressure–volume curve, where higher pressures are required for any given volume expansion. At end-expiration in health, the chest wall recoil is outwardly directed and, therefore, assists the inspiratory muscles in thoracic displacement. When $V_t$ is positioned close to TLC in COPD, the inspiratory muscles must contend with the increased lung elastic recoil pressure at end-expiration. In addition, at end-expiration, the chest wall, in contrast to health, is inwardly directed in an expiratory direction, opposing the action of the inspiratory muscles. Combined inward recoil of the lung and chest wall at end-expiration essentially leads to an inspiratory threshold load on the inspiratory muscles, which must be overcome before expired flow is reversed. This threshold load can be substantial during exercise in COPD. Consequently, increasingly higher fractional tidal inspiratory pressures
Figure 5. The static sigmoidal pressure–volume relationship of the respiratory system is shown in healthy subjects (A) and in patients with COPD (B). Superimposed are the tidal pressure–volume loops at rest (smaller loops) and during exercise (larger loops). In normal subjects, breathing at rest and during exercise (as inspiratory capacity [IC] increases) takes part in the central linear portion of the pressure–volume relationship, which means that relatively small changes in tidal pressure will produce comparatively large changes in Vt. In patients with COPD, however, as IC declines during exercise, Vt “cycles” at the upper nonlinear extreme of the pressure–volume relationship. This means that increasingly high tidal pressures must be generated for any given Vt expansion.

(or effort) must be generated for any given Vt expansion. Breathing at the upper part of the pressure–volume curve weakens the inspiratory muscles, which are not designed to function near TLC, and undoubtedly contributes to both the intensity and the quality of dyspnea.

RELATIONSHIP BETWEEN NEUROMECHANICAL DISSOCIATION AND DYSPNEA

Dyspnea includes a number of qualitatively distinct sensations that vary in intensity, and differ between patients with COPD and healthy subjects. In a study designed to compare the qualitative aspects of dyspnea in patients with COPD and age-matched healthy subjects, study participants were asked to perform a symptom-limiting exercise test and then describe their sensation of dyspnea using qualitative descriptors (4). Both healthy subjects and patients with COPD chose descriptors of “increased work/effort” and “heaviness” of breathing; however, only patients with COPD consistently chose descriptors denoting “unsatisfied inspiratory effort” (i.e., “can’t get enough air in”), “inspiratory difficulty,” and “shallow breathing.”

The distinctive qualitative sensations of dyspnea in patients with COPD suggest that they receive altered peripheral sensory afferent information from multiple mechanoreceptors in the ventilatory muscles, chest wall, lung, and airways, which indicates to them that the mechanical response of the ventilatory system is insufficient or inappropriate for the effort expended. The sense of heightened effort is believed to be conveyed via corollary discharge relayed from the motor cortex to the sensory cortex in the forebrain. In normal subjects, both at rest and during exercise, there is a harmonious matching of effort to ventilatory output. This is because Vt is positioned on the linear part of the pressure–volume curve (Figures 4 and 5).

In health, inspiratory effort increases as ventilation rises during exercise, but the perception of unsatisfied effort is rarely reported. In contrast, in patients with COPD, there is increasing disparity between effort and ventilatory output (or neuromechanical dissociation) as exercise progresses, because Vt is positioned in the extreme upper nonlinear part of the pressure–volume curve due to dynamic hyperinflation. Although patients with COPD try to meet ventilatory demand by increasing breathing frequency, Vt expansion is constrained by the progressive encroachment of EELV from below and the finite TLC from above. Therefore, they experience intolerable dyspnea very quickly during exercise, as there is “no room to breathe.” This so-called “intolerable dyspnea threshold” seems to be at the level at which the inspiratory reserve volume (i.e., the difference between TLC and EELV) approaches less than 500 ml (Figures 4 and 5) (6).

Increased neural drive has previously been linked to the perception of dyspnea, both in asthma and in COPD (7–9). Accumulating evidence suggests that neuromechanical dissociation due to dynamic hyperinflation is the basis for the inspiratory difficulties experienced by patients with COPD during exercise. For instance, Borg score at a standardized V02 during a symptom-limited incremental cycle ergometry test is strongly correlated with the Pes/PImax:Vt/VC ratio (r = 0.86, p < 0.001) and EELV/TLC (r = 0.69, p < 0.001). The Pes/PImax:Vt/VC ratio was also strongly related to EELV/TLC at a standardized V02 (r = 0.78, p < 0.001).

Figure 6. Correlations between dynamic hyperinflation (end-expiratory lung volume [EELV]/total lung capacity [TLC]), neuromechanical dissociation (esophageal pressure[Pes]/PImax:Vt/VC ratio) and dyspnea (Borg score), at a standardized time during exercise in patients with COPD. Borg score at a standardized V02 during a symptom-limited incremental cycle ergometry test was strongly correlated with the Pes/PImax:Vt/VC ratio (r = 0.86, p < 0.001) and EELV/TLC (r = 0.69, p < 0.001). The Pes/PImax:Vt/VC ratio was also strongly related to EELV/TLC at a standardized V02 (r = 0.78, p < 0.001).

RELIEVING DYSPNEA WITH BRONCHODILATORS

A number of strategies have been shown to reduce hyperinflation in patients with COPD. As mentioned previously, in flow-limited
patients with COPD, the extent of dynamic hyperinflation depends on the prevailing level of ventilation. Therefore, interventions, such as oxygen therapy and exercise rehabilitation, which reduce ventilatory demand, may also reduce the rate of air trapping and dynamic hyperinflation (see article by Casaburi and Porszasz in this issue, pp. 185–189) (13–15). Breathing techniques, such as pursed-lip breathing (16), also help to deflate the lungs. Lung volume reduction surgery is another obvious approach to reducing hyperinflation (17, 18). In addition, continuous positive airway pressure and noninvasive pressure support may counteract the negative effects of hyperinflation on the inspiratory muscles (19, 20). The scope of this review, however, is limited to the role of bronchodilators in reducing air trapping and hyperinflation.

Bronchodilators work by improving dynamic airway function, allowing improved lung emptying with each breath. Therefore, the time constant for lung emptying is shortened because airways resistance is diminished. This permits the patient to achieve the required alveolar ventilation during rest and exercise at a lower operating lung volume and, thus, at a lower oxygen cost of breathing. In other words, Vt is positioned at a lower operating lung volume (i.e., EELV is decreased and IC is increased). By deflating the lungs, bronchodilators effectively improve ventilatory muscle performance through greater Vt expansion. Exercise can proceed for a longer duration before the mechanical limitation to ventilation (i.e., critically low inspiratory reserve volume) is reached.

What effect do these improvements in lung mechanics have on dyspnea? We conducted a mechanistic crossover study in 23 patients, in which exertional dyspnea was measured using the modified Borg scale during a constant work-rate cycle ergometry test at 75% of maximal work capacity after a 2-wk treatment with the long-acting β2-agonist salmeterol (50 μg) or placebo (6). Dyspnea intensity at the point of symptom limitation was not different between groups (somewhat severe to severe); however, patients in the salmeterol group exercised for longer before reaching the same degree of dyspnea as patients in the placebo group. The reason for this improvement was that, at rest, as well as throughout exercise, IC was significantly greater and EELV was significantly reduced in the salmeterol group versus the placebo group. This reduction in hyperinflation permitted patients taking salmeterol to significantly increase Vt throughout exercise compared with those on placebo. The increased ability to expand Vt after bronchodilators correlated closely with improved dyspnea ratings at a standardized time during exercise.

In a recent mechanical study on the effects of the long-acting anticholinergic tiotropium (21), relief of exertional dyspnea was closely associated with the improvement in the ratio of expiratory effort to Vt, thus supporting the notion that neuromechanical coupling, as a result of dynamic hyperinflation, forms the basis (at least in part) for the quality and intensity of dyspnea during exercise in COPD.

Accumulating evidence suggests that sustained pharmacologic lung volume reduction with modern-day pharmacotherapy translates into improvements in dyspnea relief and exercise tolerance, as shown in larger-scale clinical trials. For example, a 4-wk treatment with tiotropium has been shown to significantly reduce trough (predose) FRC (a measure of lung hyperinflation) by 0.5 L and peak (postdose) FRC by 0.7 L compared with placebo in 81 patients with severe COPD (22).

Recently, the effects of tiotropium (18 μg once daily) versus placebo on measures of exercise tolerance were compared in 187 patients with severe COPD (23). The results of this 6-wk study showed that tiotropium provided a significant and sustained reduction in air trapping at rest and during exercise, which allowed for greater Vt expansion during exercise. The effects of these improvements in lung volume were reflected by significant increases in exercise tolerance. Furthermore, these improvements in air trapping and exercise tolerance were associated with reductions in exertional dyspnea. At a standardized time point during exercise, for example, Borg dyspnea scores were significantly reduced from baseline in the tiotropium group compared with the placebo group. This allowed patients in the tiotropium group to exercise for longer before their dyspnea became intolerable. These results have been confirmed in a further study (24). The results from these studies on the effects of long-acting bronchodilators support the hypothesis that lung hyperinflation, dyspnea, and exercise intolerance are closely linked in COPD.

**CONCLUSIONS**

Although expiratory flow limitation is the pathophysiologic hallmark of COPD, the main consequence of this is lung hyperinflation. During activity, acute-on-chronic hyperinflation has serious sensory and mechanical consequences. This dynamic hyperinflation likely contributes to both the intensity and the distinct qualitative sensations of dyspnea, particularly the distressing feeling of unsatisfied inspiration. Bronchodilator therapy relieves dyspnea by deflating the lungs, which reduces the elastic load on the inspiratory muscles. This, together with the reduction of resistive work, improves the functional performance of the inspiratory muscles. The attendant increased ability to expand Vt contributes to enhanced neuromechanical coupling of the respiratory system. Sustained pharmacologic volume deflation has the potential to impact positively on the important patient-centered outcomes of dyspnea and activity limitation in the long term.

**Conflict of Interest Statement:** D.E.O. acted as principal investigator for two multinational trials. Queen’s University received $376,137 between 2001 and 2004 for these. An additional single-site, mechanistic study with Dr. O’Donnell (principal investigator) was financed to the amount of $83,260, which was received by Research Services, Queen’s University, Kingston, Ontario, Canada.

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