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CLINICAL REVIEW

The Clinical Importance of Dynamic Lung Hyperinflation in COPD

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ABSTRACT

Lung hyperinflation commonly accompanies expiratory flow-limitation in patients with Chronic Obstructive Pulmonary Disease (COPD) and contributes importantly to dyspnea and activity limitation. It is not surprising, therefore, that lung hyperinflation has become an important therapeutic target in symptomatic COPD patients. There is increasing evidence that acute dynamic increases in lung hyperinflation, under conditions of worsening expiratory flow-limitation and increased ventilatory demand (or both) can seriously stress cardiopulmonary reserves, particularly in patients with more advanced disease. Our understanding of the physiological mechanisms of dynamic lung hyperinflation during both physical activity and exacerbations in COPD continues to grow, together with an appreciation of its serious negative mechanical and sensory consequences. In this review, we will discuss the basic pathophysiology of COPD during rest, exercise and exacerbation so as to better understand how this can be pharmacologically manipulated for the patient's benefit. Finally, we will review current concepts of the mechanisms of symptom relief and improved exercise endurance following pharmacological lung volume reduction.

DETECTION, MEASUREMENT AND DEFINITIONS OF LUNG HYPERINFLATION

Lung hyperinflation is present *when gas volume in the lungs, or in a region of the lung, is increased compared with the predicted value*. Thoracic hyperinflation in patients with Chronic Obstructive Pulmonary Disease (COPD) can be detected by physical examination, particularly if it is severe. Recognized clinical features of severe hyperinflation include the inward motion of the lower lateral rib cage during inspiration, as originally described by Stokes (1), and paradoxical inward motion of the anterior abdominal wall in synchrony with inspiratory flow (2, 3). However, hyperinflation in its earlier stages is often underes-

timated, even after assiduous clinical assessment. Lung hyperinflation can be detected by a variety of radiographic techniques (4–8). The methodology for radiographic lung volume measurement (taken at total lung capacity) is not standardized and is rarely used in clinical practice for quantitative purposes. Future refinements in high-resolution computed tomography (HRCT) scanning promise to facilitate identification of regional distribution patterns of air space distention and lung volume quantification in COPD patients.

Body plethysmography remains the gold standard for the measurement of end-expiratory lung volume (EELV) and has been shown to be reliable. The term EELV is used interchangeably with the conventional term function residual capacity (FRC). Inert gas dilution techniques are also used extensively to measure hyperinflation, but may underestimate absolute lung volumes because of the effect of non-communicating airways. Conventionally, lung hyperinflation is said to exist when the total lung capacity (TLC) is greater than 120% of the predicted value and/or when the other volume compartments [i.e., EELV and residual volume (RV)] are above the upper limits of natural variability. In practice, values for these volume compartments exceeding 120% to 130% of the normal predicted value are deemed to be potentially clinically important, but these “cut-offs” remain arbitrary. No standardized stratification system currently exists

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for assessment of severity of hyperinflation. In the absence of any consensus on the definition or severity of lung hyperinflation, our practice when using the term is to specify the volume compartment referred to (i.e., TLC, EELV, RV), the method used in measurement, and to express the value as a percent of predicted normal (9, 10).

The natural history of the development of lung hyperinflation in COPD patients is unknown but clinical experience tells us that this is an insidious process that occurs over decades. It would appear that, in general, closing volume and RV are the first volume components to increase, reflecting increased airway closure. EELV increases thereafter, reflecting the effects of worsening expiratory flow-limitation and alteration in static lung mechanics. Eventually, TLC increases as lung compliance increases. However, longitudinal studies in large COPD populations are required to definitively chart the time course of change in the various volume compartments. There is preliminary evidence that significant increases in EELV may be present in patients with early stages of COPD, where severity is defined by stratification systems based on the measurement of forced expired volume in one second (FEV₁) (11). The existence of lung hyperinflation in patients with so-called early or mild disease, may have important clinical implications with respect to impairment and disability and this requires further study.

SPIROMETRIC ESTIMATIONS OF LUNG HYPERINFLATION

Indirect, spirometrically derived assessments of lung hyperinflation [i.e., vital capacity (VC) and inspiratory capacity (IC), which reflect RV and EELV, respectively] are more difficult to interpret, particularly in the absence of simultaneous plethysmographic EELV measurements. Slow or timed vital capacity (SVC) is less prone to measurement artifact in COPD than the forced vital capacity (FVC) and, therefore, provides a better estimation of the efficacy of lung emptying (12). The IC is *the maximal volume of air that can be inhaled after a spontaneous expiration to EELV*. A reduced resting IC can indicate the presence of lung hyperinflation in the setting of expiratory flow-limitation (13). The resting IC represents the operating limits for tidal volume expansion during the increased ventilation of exercise and can predict the peak symptom-limited oxygen uptake (V'O₂) in patients with resting expiratory flow-limitation (14, 15). Moreover, a severely reduced IC/TLC ratio (i.e., <25%) has recently been shown to be an independent predictor of poor survival in COPD (16). The smaller the IC in flow-limited patients, the closer the operating tidal volume is to TLC and the upper reaches of the respiratory system's flattened pressure-volume relationship. In this respect, the IC is a crude surrogate for the extent of elastic loading of the respiratory muscles. However, the IC remains remarkably preserved in some patients with severe lung hyperinflation, since TLC and EELV can rise in parallel (17–20). Clearly, in this circumstance, and in the setting of concomitant mechanical restriction or significant inspiratory muscle weakness, the IC alone is not a reliable marker of lung hyperinflation.

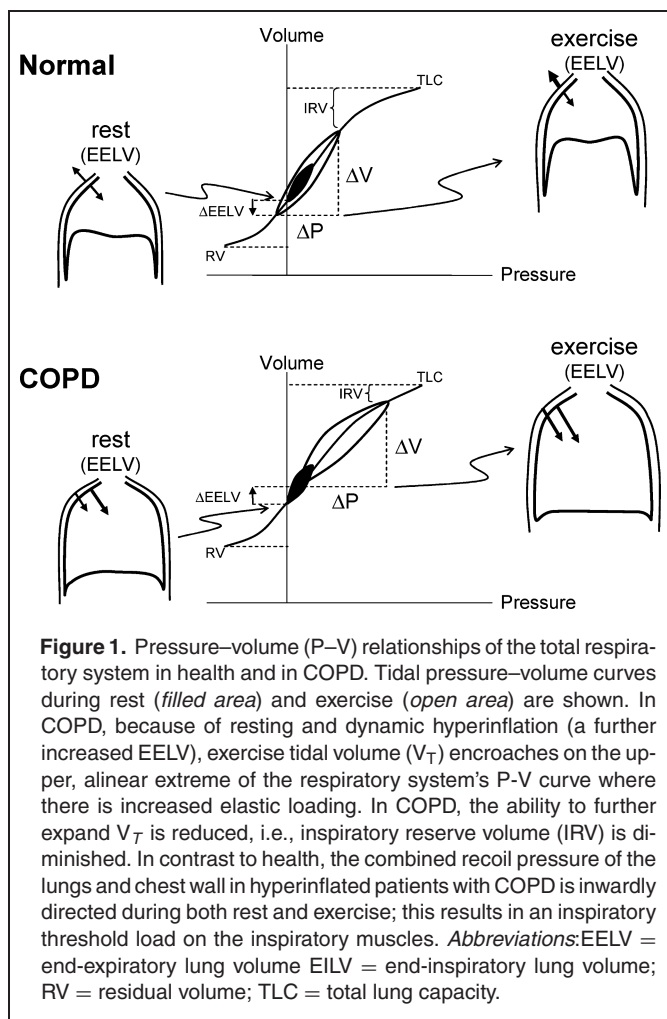
PATHOPHYSIOLOGY OF COPD: MECHANISMS OF LUNG HYPERINFLATION

Expiratory flow-limitation is the pathophysiological hallmark of COPD and arises because of the dual effects of permanent parenchymal destruction (emphysema) and airway dysfunction. The latter reflects the effects of small airway inflammation (mucosal edema, airway remodeling/fibrosis and mucous impaction) and possibly increased cholinergic airway smooth muscle tone. Emphysema results in reduced lung elastic recoil pressure which leads to a reduced driving pressure for expiratory flow through narrowed and poorly supported airways in which airflow resistance is significantly increased. Expiratory flow-limitation is said to be present *when the expiratory flows generated during spontaneous tidal breathing represent the maximal possible flow rates that can be generated at that operating lung volume* (21). Under conditions of expiratory flow-limitation, expiratory flow rates are independent of expiratory muscle effort and are determined by the static lung recoil pressure and the resistance of the airways upstream from the flow-limiting segment (21, 22).

In health, the relaxation volume (V_r) of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of chest wall. With advancing age, changes in the connective tissue matrix of the lung result in a reduction of the lung elastic recoil pressure, and the equilibrium point (where the net elastic recoil of the total respiratory system is zero) therefore occurs at a higher lung volume than in youth (23). In COPD, the increased compliance of the lung, as a result of destructive emphysema, leads to a resetting of the respiratory system's relaxation volume to a higher level than in age-matched healthy individuals (24) [Figure 1]. This has been termed "static" lung hyperinflation.

While in health the EELV during relaxed resting breathing corresponds with the actual equilibrium position of the respiratory system, this is often not the case in COPD (24). During spontaneous resting breathing in patients with expiratory flow-limitation, EELV is also "dynamically" determined and is maintained at a level above the statically-determined relaxation volume of the respiratory system. In flow-limited patients, the mechanical time-constant for lung emptying (i.e., *the product of compliance and resistance*, "τ") is increased in many alveolar units, but the expiratory time available (as dictated by the respiratory control centers) is often insufficient to allow EELV to decline to its normal relaxation volume, and gas accumulation and retention (often termed "air trapping") results. In other words, lung emptying during expiration becomes incomplete because it is interrupted by the next inspiration and EELV therefore exceeds the natural relaxation volume of the respiratory system. EELV in COPD is a continuous dynamic variable that varies with the extent of expiratory flow-limitation and the degree of time-constant abnormalities, as well as the breathing pattern, as expressed by the following equation (25):

$$\text{EELV} - V_r = \frac{V_T}{e^{T_E/\tau_{rs}} - 1} \quad [1]$$



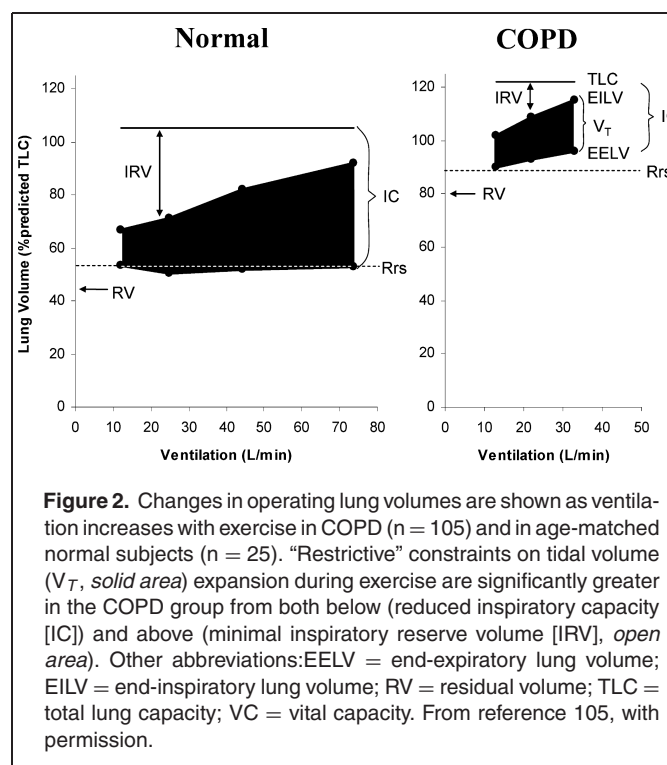
where V_r = relaxation volume, T_E = expiratory time, τ_{rs} = time constant for emptying of the respiratory system, V_T = tidal volume, and base $e = 2.718282$.

In patients with expiratory flow-limitation and acute diffuse bronchoconstriction, severe lung hyperinflation is best explained by dynamic rather than static mechanisms (12, 26–29). The role of other potential contributors to lung hyperinflation such as re-setting of the passive elastic properties of the chest wall or active inspiratory muscle and laryngeal braking during expiration remains uncertain in COPD (30–32).

DYNAMIC HYPERINFLATION DURING EXERCISE

Acute “dynamic” lung hyperinflation (DH) is defined as a temporary and variable increase in EELV above its baseline value. Under any condition of increased ventilation in flow-limited patients with COPD (i.e., exercise, voluntary hyperventilation, anxiety, transient hypoxemia), inspiratory tidal volume increases and expiratory time diminishes further as breathing frequency increases above the baseline value, causing fur-

ther acute-on-chronic DH (14, 33–36). It has been established for some time that DH occurs in flow-limited patients under conditions of increased ventilatory demand during exercise (37–40) [Figure 2]. The rate and magnitude of DH during exercise is generally measured in the laboratory setting by serial IC measurements (17–20). Changes in EELV during exercise can also be tracked by newer methods such as optoelectronic plethysmography or respiratory inductance plethysmography but their use is currently confined to the research setting (41, 42). Since TLC does not change during activity (39, 43), the change (reduction) in IC reflects the inverse change (increase) in dynamic EELV, or the extent of DH. This simple method has been shown to be reliable and recent multi-centre clinical trials have confirmed its reproducibility and responsiveness (17, 18). In several studies conducted in over 500 patients with moderate-to-severe COPD, the change in EELV during cycle ergometry averaged 0.4 L, representing a reduction in IC by ~20 % of the resting value, but with wide variation in the range (14, 19, 20) [Figure 3]. Over 80% of this population sample showed increases in EELV from rest to peak exercise, confirming the presence of significant DH (14, 19, 20). The minority of patients who showed little reduction in IC with exercise demonstrated the most severe resting lung hyperinflation (14). The rate of rise of DH was steeper in patients with the most severe expiratory flow-limitation (as estimated by the FEV_1/FVC ratio), the lowest diffusing capacity for carbon monoxide and the highest ventilatory demand (reflecting greater ventilation-perfusion abnormalities), and generally reached a maximal value early in exercise (14).



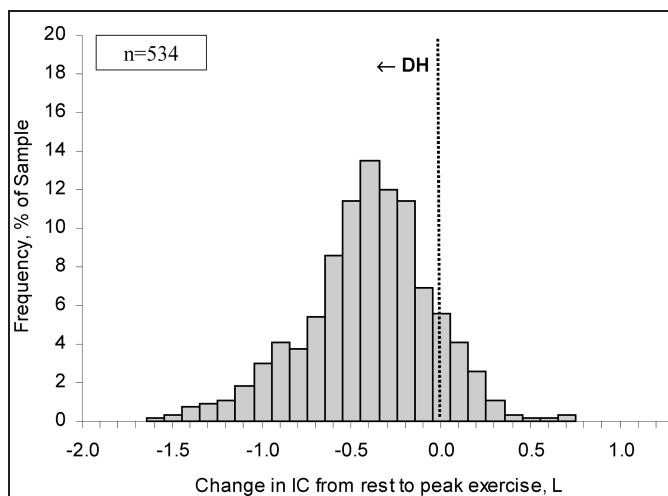


Figure 3. The distribution of the extent of change in inspiratory capacity (IC) during exercise is shown in moderate-to-severe COPD (n=534). A reduction (negative change) in IC reflects dynamic hyperinflation (DH) during exercise. Each bar width corresponds to a change in IC range of 0.10 L. The majority of patients with COPD experienced significant DH during exercise. Graphs represent cumulative data from references 14, 19 and 20.

CONSEQUENCES OF ACUTE DYNAMIC HYPERINFLATION

The insidious development of flow-limitation and hyperinflation over many years allows for several adaptive mechanisms to come into play to preserve the functional strength of the overburdened inspiratory muscles, particularly the diaphragm (44). A number of studies have shown several structural adaptations to chronic intrinsic mechanical loading, which include: (1) reduction in sarcomere length, which improves the ability of the muscle to generate force at higher lung volumes (45); (2) an increase in the relative proportion of Type I fibres, which are slow-twitch and fatigue resistant (46, 47); and (3) an increase in mitochondrial concentration and efficiency of the electron transport chain, which improves oxidative capacity (45). It is believed that the function of intercostal and sternomastoid muscles is less disadvantaged than that of the diaphragm in the presence of severe lung hyperinflation (26, 48). However, despite this temporal adaptation, the presence of severe hyperinflation means that the ability to increase ventilation, when this demand arises, is greatly limited in COPD.

The negative effects of acute DH during exercise are now well established (49):

- (1) DH results in sudden increases in the elastic and threshold loads on the inspiratory muscles as tidal volume is forced to operate at the upper, alinear extreme of the respiratory system's pressure-volume relation, thus increasing the work and oxygen cost of breathing. In moderate-to-severe COPD, the inspiratory threshold load (ITL) at the peak of exercise, which reflects the force that the inspiratory muscles must generate to initiate inspiratory flow, can be considerable.

Thus, the ITL reflects the force that the inspiratory muscles must generate to counterbalance the inward (expiratory) recoil of the lung and chest wall at end-expiration (50).

- (2) DH results in functional inspiratory muscle weakness by maximally shortening the muscle fibers in the diaphragm (51). The combination of excessive mechanical loading and increased velocity of shortening of the inspiratory muscles can predispose them to fatigue.
- (3) DH reduces the ability of tidal volume to expand appropriately during exercise and this leads to early mechanical limitation of ventilation (52).
- (4) In some patients, this mechanical constraint on tidal volume expansion, in the setting of severe ventilation-perfusion abnormalities (i.e., high fixed physiological dead space), leads to carbon dioxide retention and arterial oxygen desaturation during exercise (52).
- (5) Finally, DH adversely affects dynamic cardiac function by contributing to pulmonary hypertension, by reducing right ventricular pre-load (reduced venous return) and, in some cases, by increasing left ventricular afterload (53–55). All of the above factors are clearly interdependent and contribute in a complex, integrated manner to dyspnea and exercise limitation in COPD.

DYNAMIC HYPERINFLATION AND EXERTIONAL DYSPNEA

A recent mechanistic study in our laboratory has determined that DH early in exercise allows flow-limited patients to increase ventilation while minimizing respiratory discomfort (56). Thus, as a result of this early DH, the airways are maximally stretched at the higher lung volumes (close to TLC) and expiratory flow-limitation is attenuated allowing patients to maximize expiratory flow rates. Thus, patients with severe COPD could abruptly increase ventilation commensurate with increased metabolic demand, to approximately 40 L/min and generate tidal inspiratory pressures exceeding 40% of the maximal possible pressure generation while experiencing minimal increases in dyspnea (modified Borg dyspnea ratings 1–2). However, this advantage of DH was quickly negated when tidal volume expanded to reach a critically low inspiratory reserve volume (IRV) of approximately 0.5 L (or 10% predicted TLC) below TLC [Figure 4]. At this “threshold,” tidal volume becomes fixed on the upper less compliant extreme of the respiratory system's sigmoid-shaped pressure-volume relation, where there is increased elastic loading of the inspiratory muscles. At this operating volume, the diaphragm muscle fibers are maximally shortened and the increased breathing frequency leads to increased velocity of shortening and significant reductions in dynamic lung compliance. After reaching this minimal IRV, dyspnea (described as unsatisfied inspiration) soon rose to intolerable levels and reflected the widening disparity between inspiratory effort (reaching near maximal central neural drive) and the simultaneous tidal volume response, which becomes essentially fixed, i.e., increased effort/displacement ratio (14, 56). Dyspnea intensity correlated

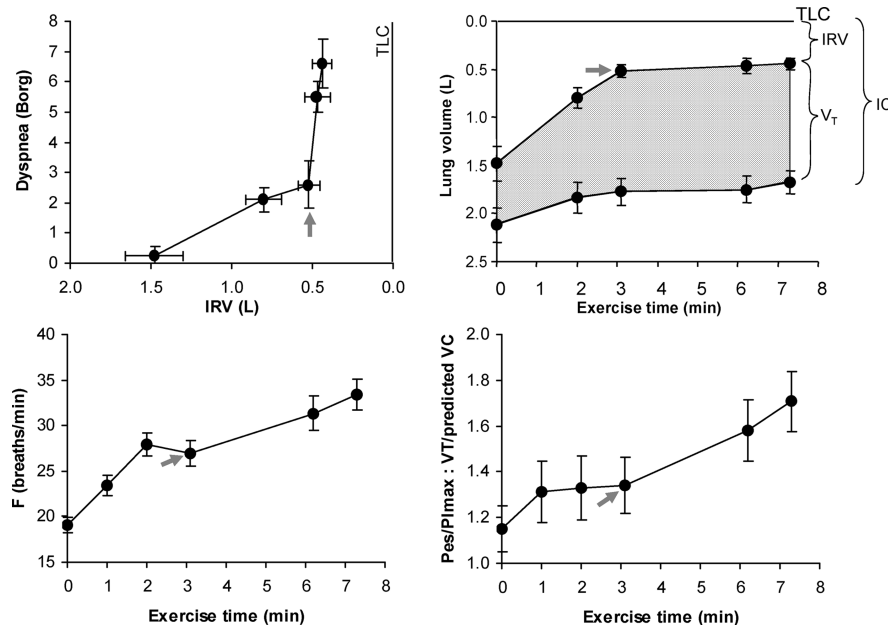


Figure 4. The mechanical threshold of dyspnea is indicated by the abrupt rise in dyspnea after a critical “minimal” inspiratory reserve volume (IRV) is reached which prevents further expansion of tidal volume (V_T) during exercise. Beyond this dyspnea/IRV inflection point during exercise, dyspnea intensity, breathing frequency (F), and the ratio of respiratory effort (Pes/Plmax) to tidal volume displacement [VT standardized as a % of predicted vital capacity (VC)] ratio all continue to rise. Arrows indicate the dyspnea/IRV inflection point. Values are expressed as means $\pm$ SEM. IC = inspiratory capacity. Modified from reference 56, with permission.

well with the increase in this effort/displacement ratio during exercise in COPD (14, 56).

Several studies have shown correlations between the intensity of dyspnea and the change in IC during exercise, suggesting that mechanical factors are contributory (14, 17, 50). The contention that DH contributes importantly to exercise limitation in COPD has been bolstered by studies that have shown that pharmacological and surgical lung volume reduction are associated with consistent improvements in dyspnea and exercise endurance (17, 19, 56–64).

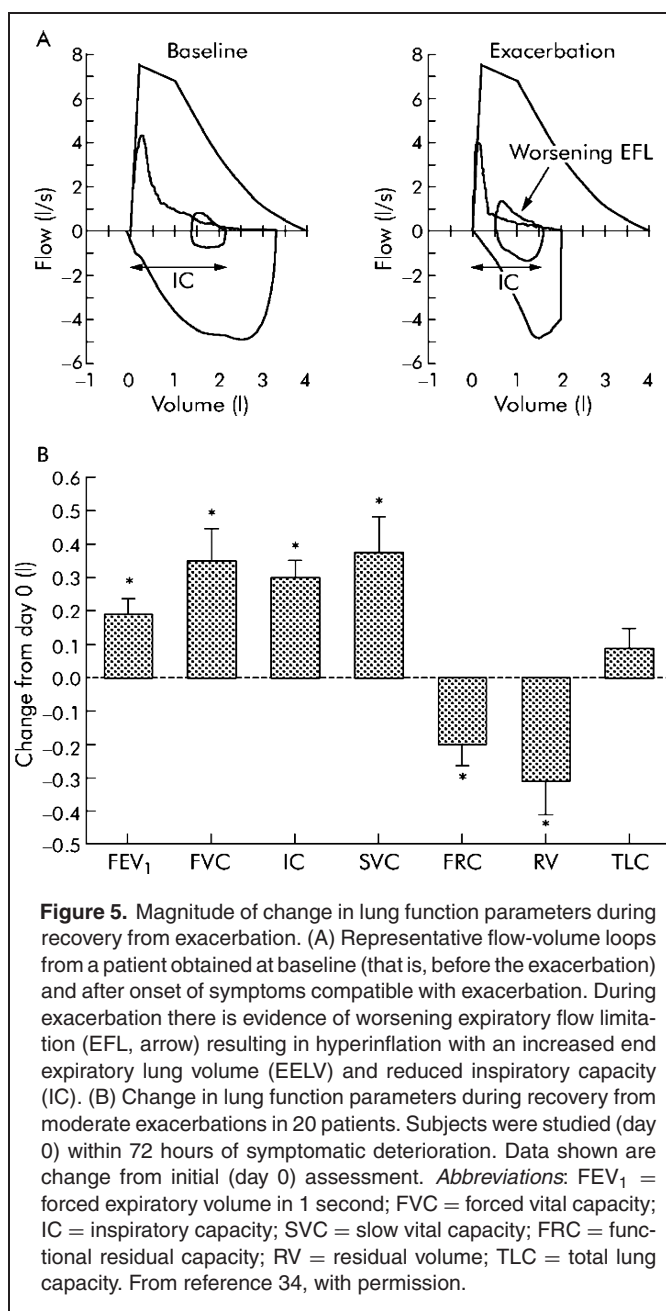
DYNAMIC HYPERINFLATION DURING EXACERBATIONS OF COPD

This topic has recently been reviewed more comprehensively elsewhere (34). During acute exacerbations of COPD, airway resistance is increased (which effects the time-constant of the respiratory system) and ventilatory demand and breathing frequency may also be increased (reflecting increased ventilation-perfusion abnormalities) (65, 66). Together, these result in acute DH, which can stress the cardiopulmonary reserves of patients with more advanced disease and contribute to life-threatening respiratory failure (66). Thus, acute DH results in excessive loading and functional weakness of the inspiratory muscles, which together with hypoxemia, acidosis and compromised cardiac function can culminate in mechanical failure of the respiratory pump (34, 66–68). We and others have recently argued that acute DH in the setting of an exacerbation contributes importantly to their most prominent symptom, i.e., worsening dyspnea (33, 34,

69). The time course of recovery of dyspnea following exacerbations is closely associated with the reduction of DH, as measured by serial IC maneuvers (34). This method of tracking hyperinflation appears to be reliable as TLC does not change significantly during acute exacerbations of COPD [Figure 5]. Further studies are required to determine if IC measurements during acute exacerbations of COPD can be used to evaluate clinical severity, to predict poor outcome and to monitor the course and recovery of the acute illness.

THE EFFECT OF BRONCHODILATOR THERAPY ON LUNG HYPERINFLATION AT REST

All classes of bronchodilators act by relaxing airway smooth muscle tone. Traditionally, improvement in airway function after bronchodilators is assessed by spirometric measurements of maximal expiratory flow rates (9). Improvements in the FEV_1 (beyond the natural variability of the measurement) after inhaled bronchodilators signify reduced resistance in the larger airways, as well as in alveolar units, with rapid time constants for lung emptying. In more advanced COPD (in contrast to asthma), post-bronchodilator increases in FEV_1 mainly occur as a result of lung volume recruitment: the ratio of FEV_1 to FVC is unaltered or actually decreases in response to bronchodilators (19, 20, 57, 70, 71). Measurements of timed vital capacity or forced expiratory volume in 6 seconds (FEV_6) appear to be more sensitive than FVC in detecting enhanced lung emptying after pharmacotherapy (72, 73). Improvement in small airway function is more



difficult to measure, but reduced lung volumes (RV and EELV) as a consequence of reduced airway closure and enhanced gas emptying in alveolar units with slower time constants, provides indirect evidence of a positive effect. Recent studies have shown that substantial reductions (i.e., > 0.5 L) in EELV and improvements in IC (i.e., 10% predicted) can occur after acute short- and long-acting bronchodilator treatment in the presence of only modest improvements in FEV₁ (13, 19, 20, 57, 70, 71, 74, 75) (Table 1).

Long-acting bronchodilators have been shown to be associated with sustained lung volume reduction as measured by “trough” or morning, pre-bronchodilator EELV or IC (19,20,74). Bronchodilator therapy is often associated with small but consistent increases in maximal volume-corrected expiratory

flow rates in the effort-independent mid-volume range where tidal breathing occurs (19, 57). Bronchodilator therapy does not necessarily abolish resting expiratory flow-limitation (especially in more severe disease), but changes the conditions under which it occurs (13). Thus, patients may remain flow-limited but can now accomplish the required alveolar ventilation at a lower operating lung volume and, therefore, at a reduced oxygen cost of breathing. Patients who show expiratory flow-limitation during spontaneous resting breathing (as determined by the negative expiratory pressure technique) and those with more severe resting lung hyperinflation have demonstrated the greatest lung volume reduction with bronchodilators (13, 71, 75).

A recent mechanical study on the mechanisms of dyspnea relief following tiotropium therapy showed that release of cholinergic tone was associated with improved airway conductance at all lung volumes from TLC to RV (56). Static elastic recoil of the lung was unchanged after acutely administered tiotropium and expiratory timing during spontaneous resting breathing was unaffected. Lung deflation, therefore, primarily reflected improvements in the mechanical time constants for lung emptying (i.e., reduced airway resistance). This is in contrast to the situation following lung volume reduction surgery (76), where increased elastic lung recoil pressure appears to be an important mechanism of lung deflation. The main impact of bronchodilator therapy is, therefore, on the *dynamically* determined resting EELV through pharmacologic manipulation of resistance in the airways upstream from the flow-limiting segments (21, 22).

EFFECT OF BRONCHODILATORS ON DYNAMIC VENTILATORY MECHANICS DURING EXERCISE

Improvements in resting IC have been shown to occur as a result of treatment with all classes of bronchodilators and this indirectly signifies reduced EELV (57–59, 77) (Table 1). A bronchodilator-induced increase in the resting IC (indicating reduced lung hyperinflation), in the order of 0.3 L or ~10% predicted, appears to be clinically meaningful and corresponds with important improvements in exertional dyspnea and exercise endurance measured during constant work rate cycle exercise at 60–75% of the patients pre-determined maximal work rate (19, 20, 57–60, 77). Recent studies in patients with moderate to severe COPD have indicated that combined long-acting anticholinergic and β_2 -agonist bronchodilators have additive effects on airway function. A recent study by van Noord et al. (78) showed that tiotropium (once daily) combined with formoterol (twice daily) was associated with sustained lung volume reduction, as assessed by serial IC measurements over a 24-hour period. The mean 0–24 hour increase in IC after this bronchodilator combination was 0.22 L, with an impressive daytime peak effect of 0.55 L. A recent study confirmed that the fluticasone propionate/salmeterol combination (FSC 250/50) was associated with reduced lung hyperinflation (increased IC) during rest and exercise, and increased cycle exercise endurance time when compared with placebo (60).

Table 1. Bronchodilator-induced changes in spirometric variables and resting lung volumes

Author	Bronchodilator	Dosage and frequency of administration	Baseline FEV ₁ , L (%pr)	Baseline IC L (%pr)	Δ FEV ₁ , L (%)	Δ FVC, L (%)	Δ FEV ₁ /FVC, %	Δ IC, L (%)
O'Donnell et al. <i>Chest</i> 2006	Salmeterol	50 µg bid × 8 wks	1.21 (39.5%)	2.26	+0.17 (14%)	+0.28 (9.9%)	+1%	0.27 (11.9%)
	Salmeterol + fluticasone	250/50 µg bid × 8 wks	1.32 (42.5%)	2.14	+0.24 (18%)	+0.28 (9.5%)	+3%	+0.33 (15.4%)
Peters et al. <i>Thorax</i> 2006	ipratropium + salbutamol	0.5 mg + 2.5 mg (1 dose)	1.16 (43%)	2.01 (72%)	+0.33 (28%)	+0.41 (15.3%)	+3%	+0.33 (16.3%)
Van Noord et al. <i>Chest</i> 2006	Tiotropium	18 µg od × 2 wks	1.05 (38%)	2.18	+0.23 (10%)	0.58 (22.5%)	0%	+0.39 (18%)
	Tiotropium + formoterol	18 µg + 12 µg od <i>times other 2 wks</i>	1.05 (38%)	2.18	+0.38 (36.4%)	+0.79 (30.7%)	+1%	+0.53 (24.3%)
	Tiotropium + formoterol	18 µg od + 12 µg bid × other 2 wks	1.05 (38%)	2.18	+0.39 (37%)	+0.78 (30.3%)	+2%	+0.55 (25.3%)
Maltais et al. <i>Chest</i> 2005	Tiotropium	18 µg od × 6 wks	1.20 (43.1%)	2.1	+0.17 (14%)	+0.36 (13%)	0%	+0.22 (10.5%)
O'Donnell et al. <i>ERJ</i> 2004	Tiotropium	18 µg od × 6 wks	1.25 (42%)	2.19	+0.22 (17.6%)	+0.43 (15.7%)	+1%	+0.24 (11%)
O'Donnell et al. <i>ERJ</i> 2004	Salmeterol	50 µg bid × 2 wks	1.08 (42%)	1.81 (65%)	+0.16 (14.8%)	0.34 (14.6%)	0%	+0.33 (18.8%)
Di Marco et al. <i>ERJ</i> 2003	Salbutamol	200 µg (1 dose)	52%	74%	0.20 (16%)	+0.30 (9.1% pred)	NO SIGNIFICANT CHANGE	+0.22 (11.4%)
	Formoterol	12 µg (1 dose)	52%	74%	0.24 (18.4%)	+0.34 (10.3% pred)	NO SIGNIFICANT CHANGE	+0.33 (16.5%)
	Salmeterol	50 µg (1 dose)	52%	74%	0.17 (13.3%)	+0.26 (8% pred)	NO SIGNIFICANT CHANGE	+0.17 (9%)
	Oxitropium	200 µg (1 dose)	52%	74%	0.07 (6.7%)	+0.13 (4.1% pred)	NO SIGNIFICANT CHANGE	+0.14 (6.5%)
Celli et al. <i>Chest</i> 2003	Tiotropium	18 µg od × 4 wks	1.23 (46%)	2.1	+0.22 (19.6%)	+0.48 (19.5%)	-1.5%	+0.35 (16%)
Newton et al. <i>Chest</i> 2002	Salbutamol	200 µg (1 dose)	52.4% in severe hyperinflated COPD	87.1%	+0.16 (14.9%)	+0.34 (15.6%)	+1%	+0.22 (11.5%)
	Salbutamol	200 µg (1 dose)	78% in moderate hyperinflated COPD	94.9%	+0.15 (11%)	+0.20 (9.1%)	+1%	+0.11 (5.7%)
O'Donnell et al. <i>AJRCCM</i> 1998	ipratropium	500 µg tid. × 3 wks	1.05 (40%)	1.83	+0.17 (16%)	+0.32 (14.3%)	+1.3%	+0.33 (18%)

Baseline values are presented in liters as mean (% predicted), whereas changes (Δ) in all of the variables are shown in liters as mean difference (% from baseline), unless otherwise stated. Abbreviations: wks, weeks; od, once daily; bid, twice daily; tid, three times daily; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity.

A number of studies have shown that bronchodilator therapy, alone and in combination with inhaled corticosteroids, does not alter the rate of dynamic hyperinflation (or air trapping) during exercise (19, 20, 57–61, 77). In fact, the rest to peak exercise reduction in IC may actually increase as a result of the higher levels of ventilation permitted by bronchodilator therapy (19, 20, 57–61, 77). However, because of recruitment of the IC at rest, the dynamic EELV at peak exercise is lower, in absolute terms, than the value obtained at the breakpoint of exercise during the placebo arm of the treatment (19, 20, 57–61, 77). In other words, bronchodilator treatment (compared with placebo) is associated with a parallel downward shift in the EELV over the course of the exercise test [Figure 6].

Improvements in the resting IC (standardized as a % of the predicted normal value) following bronchodilator therapy has been shown to correlate well with:

- (1) improved peak symptom-limited $\dot{V}'O_2$ (15, 59),
- (2) increased peak tidal volume (19, 59),
- (3) reduced dyspnea ratings (17, 19, 56–61), and 4) increased endurance time during constant work-rate cycle exercise testing in moderate-to-severe COPD patients (15, 17, 19, 56–61).

In all of the studies, increased resting IC permitted greater tidal volume expansion with reduced breathing frequency

throughout exercise (17, 19, 20, 56–61). Moreover, in a recent mechanical study, tiotropium was associated with reduced airways resistance and elastic loading of the inspiratory muscles which resulted in a reduced work and oxygen cost of breathing, compared with placebo (56). A reduced inspiratory threshold load, reflecting reduced intrinsic positive end-expiratory pressure (PEEPi), would be expected to enhance neuromechanical coupling of the respiratory system during exercise. Lung volume deflation, by increasing sarcomere fiber length in the diaphragm, may also favorably affect this muscle's force generating capacity, which again would contribute to reduced effort requirements (and central neural drive) for a given tidal volume displacement. Thus, avoidance of “high end” mechanics (where the respiratory system's pressure-volume relation is relatively flat) as a result of bronchodilator-induced reductions in EELV and increases in IRV, should contribute importantly to alleviation of exertional dyspnea and improved exercise performance (19, 57, 70, 71, 74, 75).

IMPROVED VENTILATORY MECHANICS AND DYSPNEA RELIEF

The strongest correlate of improved exercise endurance in a number of bronchodilator trials has been reduced exertional dyspnea intensity (19, 57). Several bronchodilator studies have shown

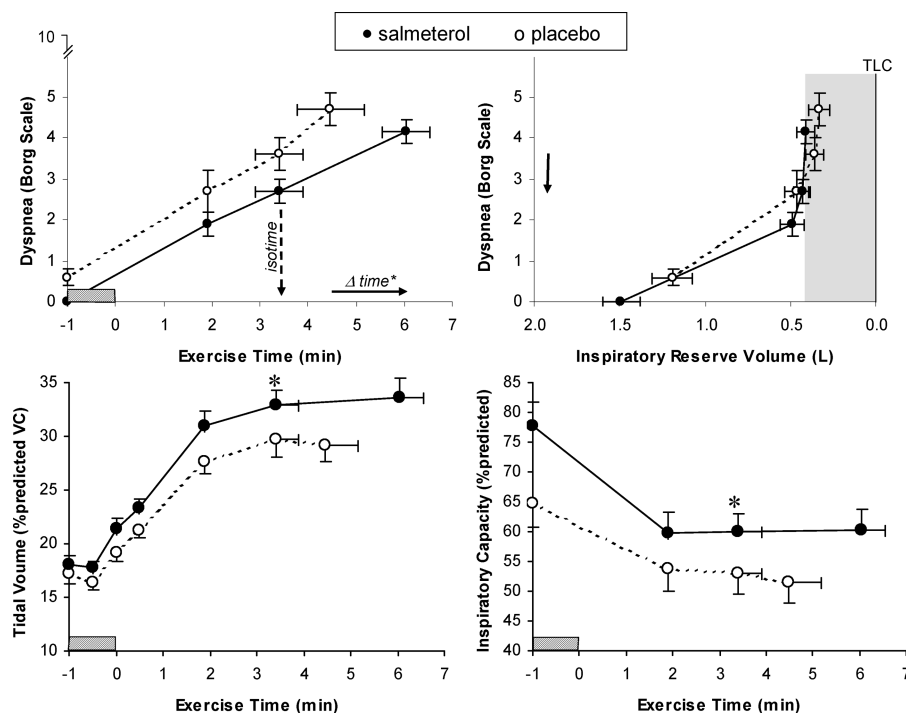


Figure 6. Relationships between Borg ratings of dyspnea intensity and each of exercise time and inspiratory reserve volume (IRV) are shown during constant-load cycle exercise at 75% of each patient's maximum work rate after salmeterol (closed circles, solid lines) and placebo (open circles, dotted lines). Dyspnea-IRV relationships were unchanged after salmeterol, with dyspnea increasing rapidly once a critically reduced IRV (shaded area) was reached which prevented further expansion of tidal volume. At isotime during exercise, measurements of inspiratory capacity and tidal volume increased significantly after salmeterol compared with placebo (* $p < 0.05$). Values are means $\pm$ SEM (points measured at rest, at standardized times during exercise, and at end-exercise). Adapted from reference 59, with permission.

that reduced dyspnea ratings at a standardized exercise time correlated well with reduced operating lung volumes (i.e., reduced EELV and an increased IRV) and improved breathing pattern (i.e., increased tidal volume and reduced breathing frequency) (57, 58, 70, 74) [Figure 6]. The precise neurophysiological mechanisms of dyspnea relief remain speculative. In one study, treatment with the long-acting anticholinergic agent, tiotropium, was associated with consistent reductions in the ratio of respiratory effort to volume displacement throughout exercise, suggesting a more harmonious relation between neural drive and the mechanical response (56) [Figure 7]. Bronchodilator-induced unloading of the ventilatory muscles must mean that less neural activation is required for a given force generation. Reduced motor command output (and central corollary discharge) may be sensed directly as a decrease in perceived inspiratory effort (79–81). Improvement in the performance characteristics of inspiratory muscles secondary to lung deflation would be expected to enhance length-tension appropriateness—the muscle spindles may have an important role in sensing this (80, 82). To the extent that restriction of the normal volume response to the increased neural drive of exercise contributes to perceived respiratory discomfort (83), then the newfound ability to increase tidal volume after bronchodilators may form the basis, at least in part, for reduced dyspnea intensity or for alteration in its quality. Interestingly, in two studies patients selected qualitative descriptors of dyspnea in the “unsatisfied inspiration” cluster less frequently after bronchodilators compared with placebo (56, 59). There are numerous mechanosensors throughout the respiratory system whose afferent inputs project to the cerebral cortex and can convey the sense of improved thoracic motion or volume displacement for a given electrical activation of the muscle (84, 85). Following bronchodilators, altered peripheral sensory inputs from these sources in the lung and chest wall, together with reduced central corollary discharge, culminate in reduced perceived respiratory discomfort during physical exertion in ways that are not yet fully understood. The emerging evidence supports the idea that the beneficial effects of bronchodilators on respiratory sensation in COPD patients are ultimately related to enhanced neuromechanical coupling of the respiratory system as a result of improved dynamic ventilatory mechanics.

OXYGEN BREATHING AND REDUCED DYNAMIC HYPERINFLATION

Since the extent of DH during exercise in flow-limited patients depends on minute ventilation (V'_E), it follows that therapeutic interventions, such as oxygen, that reduce submaximal ventilation should reduce and/or delay the rate of onset of DH and therefore the onset of critical ventilatory constraints that limit exercise. However, the effects of ambulatory oxygen (O_2) on DH, dyspnea and exercise performance in any given individual with symptomatic COPD is difficult to predict (86–90). A reduced rate of DH has been shown to be associated with a hyperoxia-induced reduction of submaximal ventilation (i.e., breathing frequency) during exercise in hypoxemic COPD pa-

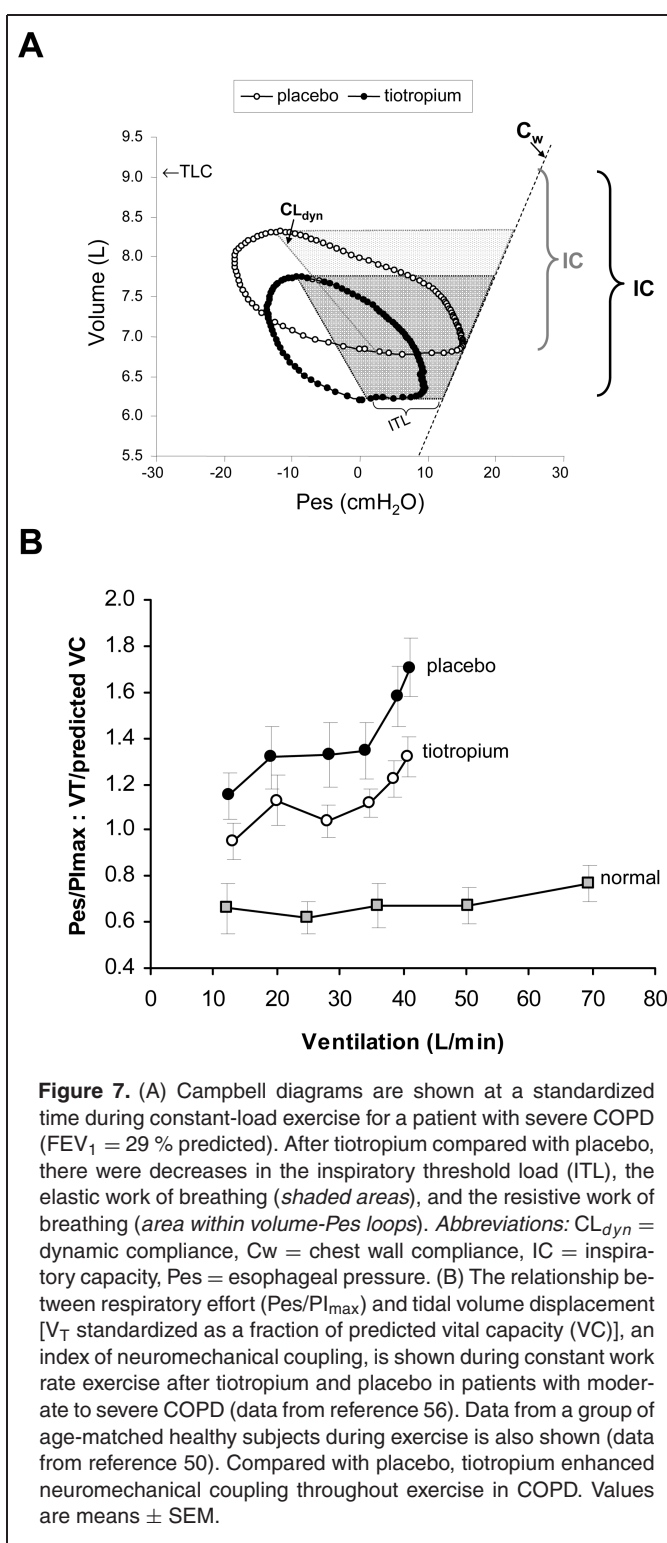


Figure 7. (A) Campbell diagrams are shown at a standardized time during constant-load exercise for a patient with severe COPD ($FEV_1 = 29\%$ predicted). After tiotropium compared with placebo, there were decreases in the inspiratory threshold load (ITL), the elastic work of breathing (shaded areas), and the resistive work of breathing (area within volume-Pes loops). Abbreviations: CL_{dyn} = dynamic compliance, C_w = chest wall compliance, IC = inspiratory capacity, Pes = esophageal pressure. (B) The relationship between respiratory effort (Pes/Pl_{max}) and tidal volume displacement [V_T standardized as a fraction of predicted vital capacity (VC)], an index of neuromechanical coupling, is shown during constant work rate exercise after tiotropium and placebo in patients with moderate to severe COPD (data from reference 56). Data from a group of age-matched healthy subjects during exercise is also shown (data from reference 50). Compared with placebo, tiotropium enhanced neuromechanical coupling throughout exercise in COPD. Values are means $\pm$ SEM.

tients (36). The effects of hyperoxia on the rate of exercise-induced DH in normoxic patients is less pronounced (61, 91). A placebo-controlled, crossover study, where patients with advanced COPD received either 60% oxygen or room air during constant work rate exercise showed that hyperoxia more than doubled the time taken to reach ventilatory limitation compared

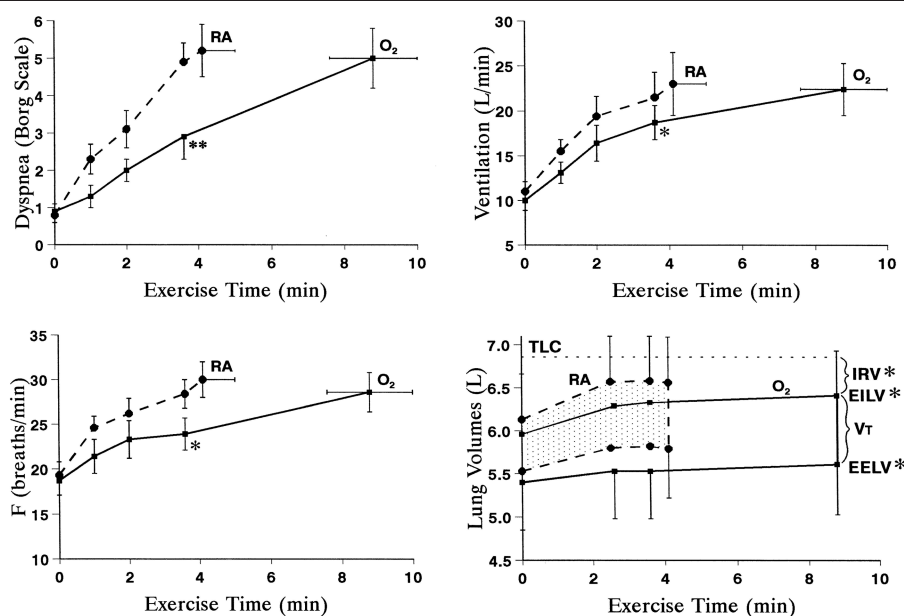


Figure 8. Dyspnea, ventilation, breathing frequency (F), and operating lung volumes plotted against exercise time in patients randomized to breathe either room air (RA) or 60% oxygen. While breathing oxygen, exercise endurance increased significantly in conjunction with significant decreases in dyspnea, ventilation, F, end-expiratory lung volume (EELV, i.e., increased IC) and end inspiratory lung volume (EILV, i.e. increased IRV) at isotime during exercise (* $p < 0.05$, ** $p < 0.01$). From reference 36, with permission.

with when breathing room air (36) [Figure 8]. At a standardized submaximal work rate, V_E decreased by approximately 3 L/min and the IRV increased by 0.3 L during 60% oxygen compared with room air (36). Somfay et al. (92) examined the dose-response relationship between increasing concentrations of supplemental oxygen and dynamic operating lung volumes in 10 patients with advanced normoxic COPD who had clinical characteristics of emphysema (i.e., diffusion lung for carbon monoxide of 40% predicted). In that study, improvements in IRV and endurance time increased as inspired O_2 concentrations increased from 21 to 50%, with no further improvements thereafter. Reductions in dyspnea with supplemental O_2 administration were correlated with changes in EELV ($r = 0.48$, $p = 0.002$) and end-inspiratory lung volume (EILV, $r = 0.43$ and $p = 0.005$) during exercise (92).

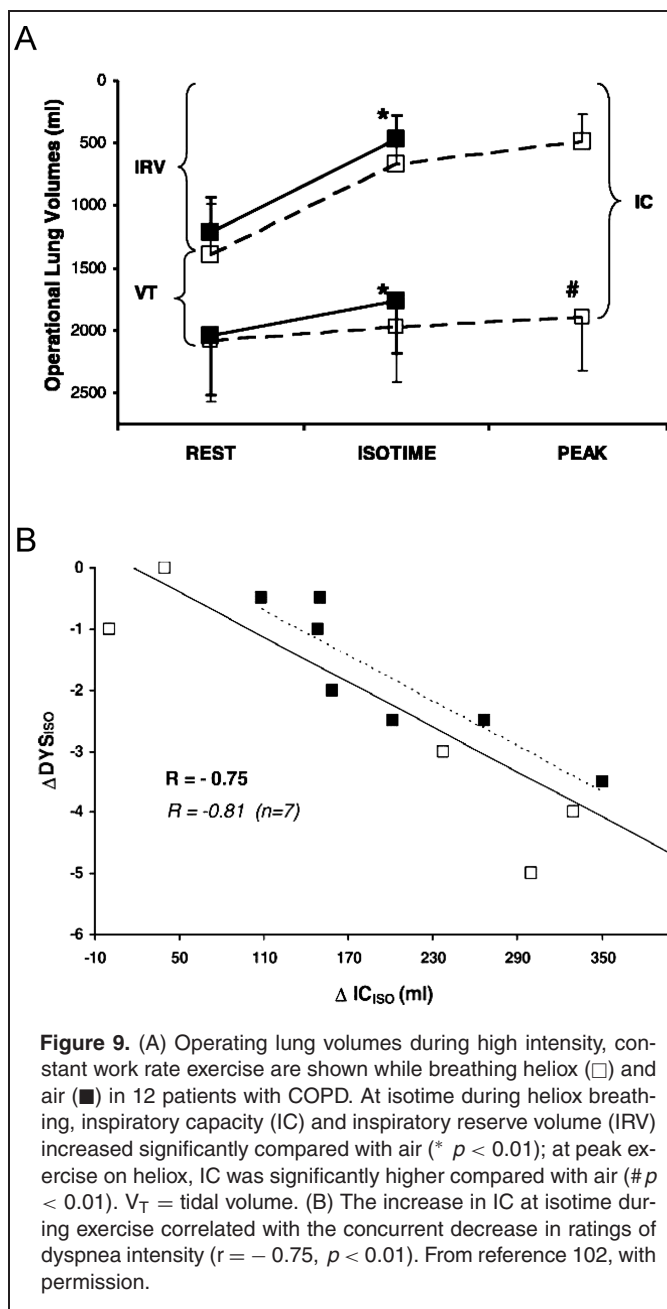
By contrast, we examined the effects of O_2 (60%) in 11 patients with COPD of comparable severity but with mild arterial oxygen desaturation, and found that there were no consistent effects on operating lung volumes throughout exercise (91). In two studies designed to examine the effects of hyperoxia in normoxic patients with COPD (61, 91), T_E prolongation at a standardized time during exercise with hyperoxia averaged only 6% (~ 0.16 s) and 9% (0.11 s), respectively, compared with the room air value. This is in contrast with increases of T_E found in two studies associated with consistent reductions in operating lung volumes: in Somfay's paper (92) and our previous paper in hypoxic patients (36), T_E increased by $\sim 27\%$ (0.39 s) and 23% (0.35 s), respectively. These data suggest that the overall effect of hyperoxia on operating lung volumes in a given individual with COPD likely depends on the net time constant for emptying of the lungs and

the extent of T_E prolongation that accompanies altered neural inputs in response to added oxygen. Patients who reduce DH in response to hyperoxia appear to have significantly greater baseline airway obstruction, greater ventilatory constraints during exercise, and poorer exercise performance with steeper dyspnea/ventilation slopes (61). It follows that such patients should experience greater dyspnea relief in response to even modest reductions in V_E following supplemental O_2 .

It must be remembered that the effects of O_2 administration in COPD are multifactorial and include improvements in peripheral muscle and cardiac function as well as reduced ventilatory drive. A recent study has shown that significant dyspnea relief and improvement in exercise endurance can occur even in the absence of an effect on DH (61).

THE IMPACT OF HELIUM/OXYGEN MIXTURES ON DYNAMIC HYPERINFLATION

The use of helium-oxygen mixtures (usually 79% helium and 21% oxygen, also called heliox) for the treatment of asthma and COPD was introduced in 1935 by Barach (93). Maximum flow rate is determined by airway size and compliance (at the choke point) as well as by physical gas properties (22). During heliox breathing, the density of which is about one third of air, expired flow rate is expected to increase as a result of decreased turbulence within the large airways (94). While Grapé et al. found a significant decrease in pulmonary resistance with heliox, Wouters et al. found no change in total respiratory



resistance (95, 96). Also controversial is the effect of heliox on lung hyperinflation. Grapé et al. (95) found no significant reduction in EELV with heliox, while Swidwa et al. (97) found a substantial fall in EELV. This discrepancy may reflect variation in the response to heliox within the COPD populations studied. Indeed, Meadows et al. (98) found that only half of their COPD patients exhibited an increase of maximal expiratory flows with heliox therapy. Similarly, inconsistent results have been found in mechanically ventilated COPD patients (99, 100).

By contrast, studies conducted in healthy older volunteers during physical exercise documented that the effects of low gas

density are mostly evident at high work loads where expiratory flow limitation can occur during tidal breathing and EELV tends to increase. Under these conditions, breathing heliox allows higher ventilation since it allows tidal volume to increase at the expense of a reduced EELV (101). Recently, Palange et al. (102) reasoned that resistive unloading of the airways during heliox breathing could also be beneficial in COPD patients. They tested this hypothesis in a group of moderate-to-severe COPD patients exercising at 80% of their maximal power output, while breathing either heliox or room air, in random order. Heliox was associated with a two-fold increase in exercise endurance time, with significant increases in maximal expiratory flow rates, tidal volume and ventilation at peak exercise. Operating lung volumes were reduced together with dyspnea ratings at as standardized time [Figure 9]. Interestingly, the increase in endurance time achieved with heliox appears to be superior to that reported in studies using oxygen supplementation alone (36) or single bronchodilation treatments (19). The beneficial effects of heliox on exercise tolerance in COPD has been confirmed in subsequent studies (103,104), where the authors showed that the effects of heliox alone or in combination with supplementary oxygen, are additive in nature but vary with disease severity (104).

SUMMARY

In COPD, lung hyperinflation is associated with expiratory flow-limitation and becomes further amplified under conditions of acutely increased ventilatory demand. Acute-on-chronic dynamic hyperinflation during exercise and exacerbation leads to excessive loading and functional weakness of the inspiratory muscles and can impose a critical mechanical limitation to ventilation. Ultimately, acute dynamic hyperinflation contributes to neuromechanical uncoupling of the respiratory system with attendant respiratory discomfort and activity limitation. Relief of dyspnea and improvement of exercise endurance following bronchodilator therapy is explained, at least in part, by reduced lung hyperinflation, with release of tidal volume restriction and improved neuromechanical coupling. Measurement of lung volumes can therefore provide useful complementary information in clinical trials designed to evaluate bronchodilator efficacy. Other interventions that reduce ventilatory drive or improve airway function, such as oxygen and helium, alone or in combination, have been shown to slow the rate of dynamic hyperinflation during exercise, with positive sensory and mechanical consequences. Collectively, all of these interventions have the potential to augment exercise re-conditioning which, arguably, has the highest impact on the pivotal patient-centered outcomes in the COPD population. It now appears that we have the capability of achieving sustained lung volume reduction by pharmacologic means that is comparable in magnitude (in terms of inspiratory capacity recruitment) to that obtained by lung volume reduction surgery. What remains to be determined is whether long term pharmacological lung volume reduction will favorably alter the natural history of this devastating disease.

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