Dynamic Lung Hyperinflation and its Clinical Implication in COPD

Denis E. O’Donnell, MD, FRCP(I), FRCP(C)

Summary

Static lung hyperinflation is defined as the elevation of end-expiratory lung volume above its predicted value, with no increase in end-expiratory alveolar pressure, which remains equal to atmospheric pressure. Dynamic hyperinflation is the transient increase of this volume above the relaxation volume. In patients with COPD, dynamic hyperinflation is mainly determined by the mechanical properties of the respiratory system. Its measurement relies on plethysmography and, during exercise, inspiratory capacity. During exercise, dynamic hyperinflation attenuates expiratory flow limitation but increases the inspiratory loading and induces functional weakness of the diaphragm. It also has haemodynamic consequences and results in more rapid, shallow breathing and progressive reduction in dynamic lung compliance. These events explain exercise intolerance. Several approaches may help combat dynamic hyperinflation and its deleterious clinical effects: bronchodilators, hyperoxia, helium-oxygen mixtures, lung volume reduction surgery…

Keywords: Expiratory flow limitation • Hyperinflation • Exercise tolerance • COPD • Asthma.
In the early nineteenth century, William Stokes, the famous Irish physician, made the following observation in a patient with Laennec’s emphysema whom he asked to undertake brief voluntary hyperventilation, “the repetition of the inspiratory effort caused such an accumulation of air in the diseased portion of the lungs, so as ultimately to nearly prevent their further expansion”[1].

Stokes, without the benefit of physiological measurement, deduced that his patients’ rapid thoracic over-inflation was the consequence of “difficulty in expiration”. Almost two centuries later, there is renewed interest in the phenomenon of dynamic lung hyperinflation (DH) and its clinical consequences, particularly in patients with COPD.

Mechanisms of dynamic hyperinflation

Static lung hyperinflation during resting spontaneous breathing in COPD refers to the increase in end expiratory lung volume (EELV) above the predicted normal value. This resetting of the respiratory system’s relaxation volume to a higher level occurs in the setting of permanent parenchymal destruction of emphysema, which increases lung compliance. In the presence of expiratory flow limitation, EELV is also dynamically determined and varies with the time constant for emptying (the product of resistance and compliance) of the respiratory system, the inspired tidal volume, and the expiratory time available. DH therefore refers to this temporary and variable increase in EELV above the “static” value. In flow-limited patients, EELV is a continuous dynamic variable, which can fluctuate widely depending on the prevailing level of expiratory flow limitation and breathing pattern. The bulk of the evidence suggests that DH in flow-limited patients is primarily a passive phenomenon: as ventilation (and inspired tidal volume) increases and expiratory duration diminishes, there is simply insufficient time to allow EELV to decline to its baseline resting value. Inspiration begins before expiration is complete and DH is the result.

In asthma, it has been suggested that DH may be the result of active braking by the ribcage muscles during expiration but there is no evidence that this occurs in COPD[2-4]. It has also been postulated that DH during induced bronchoconstriction in asthma may be reflexly modulated by afferent sensory feedback from vagal airway mechanosensors activated by dynamic airway compression during expiration [5]. In this situation, mechanosensors perturbed by airway compression, would prematurely stimulate inspiratory muscle activation before expiration is complete with consequent increase in EELV. Induced dynamic airway compression in COPD at rest has been shown to consistently have a tachypneic influence on breathing and it is intriguing to speculate that airway mechanoreceptor afferent input may similarly influence the control of EELV during exercise [6, 7].

DH has been shown to occur in diverse clinical situations in patients with obstructive lung disease, whose respiratory systems have slow time constants for emptying. Significant DH has been recorded during: (1) mechanical ventilation in patients with asthma and COPD [8], (2) metacholine induced bronchoconstriction in asthma [5], (3) exacerbations of COPD [9, 10], (4) metronome-paced hyperventilation in COPD [11], and (5) during the increased ventilation of weight bearing or cycle exercise in patients with COPD and cystic fibrosis [12, 13].

Measurement of dynamic hyperinflation

Body plethysmography remains the gold standard for the measurement of EELV and yields reproducible results in patients with expiratory flow limitation, provided panting frequency is regulated to less than 1 Hz [14, 15]. Serial plethysmographic measurements have been used to measure acute increases in EELV during chemical bronchoprovocation in asthma and during recovery from exacerbations in COPD [9, 10, 16]. Under these conditions total lung capacity (TLC) appears to remain essentially unaltered: therefore, changes in spirometric inspiratory capacity (IC) should reliably reflect changes in EELV.

A variety of methods have been used to track changes in EELV during the high ventilation of exercise in health and in patients with COPD. These include volume dilution techniques, body plethysmography (adapted for exercise), and more recently, optoelectronic plethysmography (OP) [17, 18]. We can reasonably conclude from the results of various studies that have employed these methods, that TLC remains largely unaltered in the majority of patients with moderate to severe COPD during cycle exercise [18, 19].

Recently, IC measurements have been shown to be highly reproducible during cycle exercise, even in the setting of multi-centre clinical trials [20, 21]. There is good evidence that even breathless patients with severe COPD are capable of maximal electrical activation of their diaphragms during maximal inspiratory effort to TLC [22, 23]. Moreover, a number of studies have confirmed that peak inspiratory trans-pulmonary pressures during IC measurement at the end of exhaustive exercise in patients with COPD were similar to the resting pre-exercise value [24, 25]. The preservation of the ability to generate peak inspiratory pressures throughout exercise in the face of progressive truncation of the IC provides a strong endorsement of the utility of this method of tracking DH.

It seems unlikely that TLC could dynamically increase during exercise in patients with moderate to severe COPD: the high energetic cost of sustaining TLC increments in such mechanically compromised individuals would soon outweigh any potential benefits related to attenuation of expiratory flow limitation. However, it is conceivable (but unproven), that in...
early COPD, simultaneous increases in TLC and EELV during exercise could help to preserve IC, thus allowing ventilation to increase to meet the higher demand imposed by ventilation-perfusion inequalities.

It follows therefore that we can safely conclude that changes in IC accurately reflect changes in EELV during exercise, provided that patients are motivated to make maximal inspiratory efforts during the measurement and that they are not afflicted with concomitant inspiratory muscle weakness. The IC measurement gives us only indirect information about changes in absolute lung volumes but nevertheless provides important mechanical information, irrespective of possible minor shifts in absolute TLC that may occur. The IC represents the limits for tidal volume expansion in patients with expiratory flow limitation and indicates the proximity of the operating lung volume to TLC and the upper alinear extreme of the respiratory system’s pressure-volume relationship. When measurements of IC is coupled with those of dynamic inspiratory reserve volume (IC – tidal volume), further valuable information is provided about prevailing mechanical constraints on ventilation.

### Patterns of Magnitude of DH during Exercise in COPD

Numerous small studies employing serial pneumotachographic IC measurements during incremental cycle exercise have determined that the rest-to-peak change in EELV in patients with moderate to severe COPD averaged 0.3–0.6 L, but with wide variation in the range [12, 25, 26]. In more recent larger population studies in over 500 patients with moderate-to-severe COPD (FEV1 40% predicted, EELV 170% predicted), the change in EELV during cycle ergometry averaged 0.4 L, representing a reduction in IC at peak exercise by ~20% of the resting value (Fig. 1) [12, 21, 27]. Similar reductions of IC have also been recorded following walking without a mouthpiece in place [28].

The pattern of change in EELV during exercise is quite variable. In patients with a similar FEV1, those with a lower diffusion capacity for carbon monoxide, greater small airways dysfunction, and higher exercise ventilation, tended to have immediate DH early in exercise, whereas those with a less emphysematous clinical profile showed later and more slowly progressive DH throughout exercise [12].

### “Euvolumics”

Aliverti et al. coined the term “euvolumics” to describe a subset of patients (8 out of 20) with moderate to severe COPD who did not increase regional chest wall volume expansion as measured by OP during incremental cycle exercise [17]. These patients, who had better resting spirometry (FEV1, 50 % predicted) than the remainder (FEV1 = 39 % predicted), demonstrated significant reduction in end expiratory abdominal volumes and appeared to have poorer exercise performance than the majority who showed DH during exercise. However, in that study no information was provided on TLC or IRV during exercise, which makes interpretation difficult. Vogiatzis et al. [18] repeated a similar study using OP in 20 patients with COPD (FEV1 35% predicted), and found that, in all patients, end inspiratory chest wall volume encroached on a minimal IRV close to TLC at peak exercise. In that study, different patterns of hyperinflation were evident and those with earlier increases in chest wall volume had a slower recovery of the resting baseline value after exercise termination.

In larger population studies (~500 patients), where DH was assessed using pneumotachographic IC measurements, it was found that ~15% of COPD patients (FEV1, 40% predicted) did not show significant decrease in IC (>2 SD) during incremental or constant work rate cycle exercise [12, 21, 27]. These patients fell into 2 categories: (a) those with milder COPD (the minority) who decreased EELV during exercise and (b) patients with significant resting hyperinflation who reached the mechanical limit (minimal IRV) early in exercise and could not decrease IC any further: there was an inverse correlation between the resting IC (% predicted) and the extent of DH during exercise. From the information that is
currently available, we can conclude that potential adaptations to reduce DH such as prolongation of expiratory time (with shortening of the inspiratory duty cycle) or recruitment of expiratory muscles are not effective in attenuating the rise in dynamic EELV during exercise in the majority of patients with more advanced COPD.

**Consequences of DH During Exercise**

Acute increases in operating lung volumes will stretch the airways and optimize expiratory flow rates, thus attenuating expiratory flow limitation. We have recently reported that in patients with severe COPD, DH early in exercise permits increases in sub-maximal ventilation (to approximately 40 L/min) and concomitant inspiratory effort (to ~40% maximum) without provoking significant breathing discomfort (Borg dyspnea ratings 1 to 2) [29] (Fig. 2). Thus, DH conveys a mechanical advantage at lower exercise levels provided operating lung volumes remain positioned within the linear portion (20 to 80% of the vital capacity) of the respiratory system’s sigmoidal pressure-volume relationship. However, as end inspiratory lung volume expands to reach a minimal inspiratory reserve volume (IRV) of approximately 0.5 L (or 10% predicted TLC) below TLC, the inspiratory muscles become burdened with significant increases in elastic and inspiratory threshold loading (Fig. 2). While it is known that the inspiratory muscles, particularly the diaphragm, undergo remarkable adaptation to chronic thoracic hyperinflation [30], sudden increases in EELV

![Fig. 2](image_url)

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 (VT) during exercise. Beyond this dyspnea/IRV inflection point during exercise, dyspnea intensity, respiratory effort (Pes/PImax), and the ratio of Pes/PImax to tidal volume displacement [VT standardized as a % of predicted vital capacity (VC)] all continued to rise. Arrows indicate the dyspnea/IRV inflection point. Values are expressed as means ± SEM. IC=inspiratory capacity. Modified from reference 29.
during exercise can disrupt length-tension relationships, resulting in functional weakness [22]. Sustained inspiratory muscle loading could, theoretically, predispose to fatigue or mechanical failure, but the evidence for this occurring in COPD is limited [22, 31]. In fact, recent studies have failed to demonstrate inspiratory muscle fatigue at the peak of exhaustive exercise in COPD [32-34].

The breathing pattern becomes more shallow and rapid as DH proceeds. In moderate to severe COPD there is a discernible mechanical ceiling during exercise when tidal volume and IRV reach a plateau value and further increases in ventilation can only be achieved by increasing tachypnea. The greater the resting and dynamic hyperinflation, the lower the ventilation (and work rate) at which the mechanical $V_T$ plateau is discernible [12] (Fig. 3). In extreme cases, the lack of ability to increase $V_T$ further in the setting of severe ventilation-perfusion abnormalities, may lead to alveolar hypoventilation and arterial oxygen desaturation [35].

In health, the ratio of tidal inspiratory effort (relative to the maximum) to tidal volume displacement (the effort/displacement ratio) remains essentially unaltered throughout much of exercise, indicating the optimal position of operating lung volumes and breathing pattern are shown as ventilation increases with exercise. Note that in COPD there is a discernible mechanical ceiling during exercise when inspiratory reserve volume and tidal volume reach a plateau value (as indicated by the arrows) and further increases in ventilation can only be achieved by increasing tachypnea. Note also that the greater the resting and dynamic hyperinflation, the lower the ventilation at which the mechanical tidal volume plateau is discernible (arrows).

**Fig. 3.** Example of ventilatory response to exercise in a patient with mild, moderate, severe and very severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease 2006 (GOLD I, GOLD II, GOLD III and GOLD IV, respectively). Dashed lines indicate age-matched normal response established in our laboratory. Changes in operating lung volumes and breathing pattern are shown as ventilation increases with exercise. Note that in COPD there is a discernible mechanical ceiling during exercise when inspiratory reserve volume and tidal volume reach a plateau value (as indicated by the arrows) and further increases in ventilation can only be achieved by increasing tachypnea. Note also that the greater the resting and dynamic hyperinflation, the lower the ventilation at which the mechanical tidal volume plateau is discernible (arrows).
Dynamic Hyperinflation, Dyspnea, and Exercise Intolerance in COPD

Traditional spirometric measurements, such as the FEV₁, correlate poorly with exercise tolerance and exertional dyspnea in COPD [43-47]. Exercise limitation is multifactorial in COPD and it is remarkable that ventilatory factors have consistently emerged, in several studies, to predict pressure excursions during exercise will affect left ventricular transmural pressure gradients and afterload [37-42]. The impact of DH on cardiac output and ventilatory/locomotor muscle competition during exercise needs further study.

Fig. 4.
Pressure-volume (P-V) relationships of the total respiratory system in health and in COPD. Tidal pressure-volume curves during rest (filled area) and exercise (open area) are shown. In COPD, because of resting and dynamic hyperinflation (a further increased EELV), exercise tidal volume (Vₜ) encroaches on the upper, alinear extreme of the respiratory system’s P-V curve where there is increased elastic loading. In COPD, the ability to further expand Vₜ is reduced, i.e., inspiratory reserve volume (IRV) is diminished. In contrast to health, the combined recoil pressure of the lungs and chest wall in hyperinflated patients with COPD is inwardly directed during both rest and exercise; this results in an inspiratory threshold load on the inspiratory muscles. Abbreviations: EELV=end-expiratory lung volume; RV=residual volume; TLC=total lung capacity. From O’Donnell DE, and Webb KA. 2005. Mechanisms of dyspnea in COPD. In Dyspnea: Mechanisms, Measurement, and Management, 2nd edition. Edited by DA Mahler, and DE O’Donnell. Taylor & Francis Group, New York. Lung Biology in Health and Disease Series, Volume 208, Chapter 3, pp. 29-58.
symptom-limited peak oxygen uptake ($V'_O_2$) in patients with moderate to severe COPD. Thus the presence of resting expiratory flow limitation (measured by the negative expiratory pressure technique), reduction in resting IC (<80% predicted) and in dynamic IC during exercise, have all been shown to be associated with lower peak symptom-limited $V'_O_2$ during cycle exercise [12, 48, 49].

Similarly, a number of studies have shown consistent statistical associations between the intensity of dyspnea (measured by Borg ratings) and indices of DH measured during cycle exercise and walking in patients with moderate to severe COPD [12, 25, 26, 28, 49]. The mechanisms by which DH leads to dyspnea are multifactorial and likely include centrally generated sensory signals in the motor cortex related to the increased inspiratory muscular effort required to increase ventilation when the ventilatory muscles are overloaded and functionally weakened [25]. The dominant sensation of unsatisfied inspiration at end exercise in COPD may represent an imbalance between the central neural ventilatory drive (augmented by chemo-stimulation) and the blunted mechanical response (with altered peripheral mechanosensor inputs) imposed by DH. Dyspnea intensity correlates strongly with the increased effort/displacement ratio during exercise, the latter a crude index of neuromechanical dissociation [25, 29].

The corollary of this is that therapeutic interventions that effectively reduce lung hyperinflation should reduce exertional dyspnea and improve exercise endurance in COPD. Reduction in exertional dyspnea at a standardized time during constant work cycle exercise has been shown to correlate well with reduction in the simultaneous operating lung volumes during various pharmacological and surgical volume reduction treatments (see below).

Reducing lung hyperinflation

Bronchodilators

Bronchodilator therapy is the first step in reducing lung hyperinflation in COPD. Modern, long acting bronchodilators have been shown to be associated with sustained 24-hour lung volume reduction [50]. The combination of different bronchodilating agents appears to have additive effects on volume reduction [50, 51]. The physiological consequences of the various bronchodilator agents appear to be similar. Fundamentally, bronchodilators release airway smooth muscle tone, improve airway conductance, and accelerate the time constants for emptying of heterogeneously distributed alveolar units. The increased ability to empty the lungs during spontaneous expiration and forced manoeuvres are reflected by reductions in EELV and residual volume, respectively. Improvements in these resting volumes are associated with increases in IC and vital capacity. In severe COPD these lung volume changes can occur in the presence of little or no increase in FEV$_1$ [21, 27, 52-56]. The improvements in exertional dyspnea and exercise endurance are critically linked to the improvement in the resting IC rather than the rate of DH during exercise [21, 27, 53, 57-61]. Studies have found that rest to peak changes in DH can actually become amplified after bronchodilator compared to placebo, reflecting the increased submaximal and peak ventilation achieved as a result of lung deflation [21, 27, 53, 57-61]. After bronchodilators these patients remain flow limited at the new reduced operating lung volume but the attendant increased sub-maximal ventilation (by 2-5 L/min) will continue to be associated with air trapping. Reduction in absolute lung volumes permits increased tidal volume recruitment throughout exercise and ultimately improves the ratio of inspiratory effort to tidal thoracic displacement (Fig. 5). Improvements in dyspnea following bronchodilator therapy correlated with increases in tidal volume, increases in IC and IRV, and reduction in the effort/displacement ratio [21, 29, 52, 53, 59]. Collectively, recent studies have confirmed that small improvements in resting IC of approximately 0.3 L, or 10% predicted, are consistently associated with improvements in dyspnea and exercise endurance in patients with moderate to severe COPD [21, 27, 53, 57-61]. Bronchodilators of all classes consistently decrease Borg/ventilation slopes during constant work exercise in COPD and reflect reduced mechanical loading of the muscles of breathing [29, 59, 61].

Hyperoxia

Any therapeutic intervention, such as oxygen therapy, that consistently reduces breathing frequency (and ventilation) during exercise in flow-limited patients, should reduce the rate of DH. In the study by Somfay et al. [62], improvements in IRV and endurance time increased as fractional inspired oxygen concentration increased from 21 to 50% with no further improvements thereafter. It is clear that the change in operating lung volumes in response to hyperoxia is quite variable and depends on the extent of expiratory time prolongation induced and underlying disease severity [62-64]. Patients who show reductions in the rate of DH during hyperoxia usually have significantly greater baseline airway obstruction, greater ventilatory constraints during exercise and poorer exercise performance with steeper dyspnea/$V'_O_2$ slopes [61]. Dyspnea relief following hyperoxia is multifactorial and reduction in DH is not obligatory for a positive response. Improvements in cardiovascular performance, peripheral muscle function, and reduced metabolic acidosis are all likely instrumental in improving exercise performance.

Heliox

In a number of recent studies, heliox, which both elevates the fraction of inspired oxygen and replaces nitrogen with a lower density gas (usually 79% Helium and 21%
Oxygen), has been shown to be associated with consistent improvements in dyspnea and exercise performance in patients with severe COPD [65-67]. Heliox decreases airway turbulence and airflow resistance. The net effect is to reduce the time constant for lung emptying, which in turn reduces the rate of DH. The added benefit of reduced neural drive and improved dynamic ventilatory mechanics on exertional dyspnea is also evident when hyperoxia is combined with bronchodilators in patients with severe COPD [61].

**Surgical lung volume reduction**

Lung volume reduction surgery (LVRS) is undertaken in selected patients with localized heterogeneous emphysema, who have poor exercise performance despite exercise training [68, 69]. As expected, LVRS is associated with post-operative reductions in all lung volumes, as well as improvements in total exercise time, peak VO\textsubscript{2} and peak ventilation [70-74]. Studies have shown that LVRS increases dynamic expiratory flow rates, likely as the result of the combination of volume recruitment (i.e., increased vital capacity) and enhanced static recoil of the lung in expiration [75-78]. The physiological effects of surgical lung volume reduction are broadly similar to pharmacological volume reduction and include: (1) reduced mechanical constraints on tidal volume expansion and reduced breathing frequency for a given ventilation; (2) increased efficiency of CO\textsubscript{2} elimination because of reduced relative physiological deadspace; (3) improved ventilation-perfusion relationships and increased arterial oxygen saturation; (4) reduced ventilatory demand in some patients; and (5) favourable hemodynamic effects. The mechanisms of dyspnea relief are complex [79]. Martinez et al. have shown that reduced Borg ratings of exertional dyspnea following LVRS correlated well with reduced EELV and reduced auto-PEEP [80]. Similarly, Laghi et al. found a close association between improved exertional dyspnea and enhanced neuromuscular coupling of the diaphragm as a result of LVRS [81], and this positive effect appears to persist for at least two years after LVRS [82].

**Future Research Questions**

The natural history of lung hyperinflation in COPD has not been studied and we have yet to understand the factors that influence the time course of change of the various lung volume components. The impact of the various clinical COPD phenotypes (predominant emphysema versus small airway bronchiolitis; localized versus heterogeneous emphysema, etc.) on dynamic ventilatory mechanics, dyspnea, activity limitation and the response to pharmacotherapy has not been adequately studied. We know little about the effects of acute regional DH on lung and chest wall mechanics, ventilatory muscle recruitment patterns, cardiovascular function,

---

**Fig. 5.**

**(A)** Campbell diagrams are shown at a standardized time during constant-load exercise for a patient with severe COPD (FEV\textsubscript{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\textsubscript{dyn}=dynamic compliance, Cw=chest wall compliance, IC=inspiratory capacity, Pes = esophageal pressure. **(B)** The relationship between respiratory effort (Pes/PImax) and tidal volume displacement [VT 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 29). Data from a group of age-matched healthy subjects during exercise is also shown (data from reference 25). Compared with placebo, tiotropium enhanced neuromechanical coupling throughout exercise in COPD. Values are means ± SEM.
cardio-pulmonary interactions, and pulmonary neurosensory reflexes. DH likely importantly influences the interaction between cardiac, ventilatory and locomotor muscles during exercise, but the precise nature of this physiological integration remains unknown.

Acute DH becomes particularly problematic during exacerbations of COPD. The question arises whether acute regional alveolar overdistention modulates the inflammatory response, which could, along with the obvious mechanical stresses, lead to permanent destructive changes within the lung parenchyma and irreversible step increases in resting hyperinflation. It is also uncertain whether more aggressive therapeutic deflation during exacerbations, using interventions such as heliox in conjunction with non-invasive ventilation, may result in better short and long-term clinical outcomes.

There is intense interest in newer non-invasive, endoscopic, volume reduction procedures (one way valves, fenestrations, etc.) designed to improve regional deflation in emphysematous lungs. Clinical trials currently underway will determine their eventual clinical utility. With modern pharmacotherapy we now have the ability to achieve sustained pharmacological volume reduction but know little of the long-term consequences with respect to impact on respiratory muscle function, ventilatory mechanics and cardiovascular function. To the extent that resting lung hyperinflation has been recognized as an independent predictor of survival in COPD, a most intriguing question is: can pharmacological lung deflation now positively influence the natural history of this devastating disease?

References


