LUNG HYPERINFLATION IN COPD: What the Clinician Needs to Know

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ABSTRACT

Lung hyperinflation, chronic dyspnea and reduced exercise capacity are inextricably linked and are independent predictors of increased mortality in COPD. It is no surprise, therefore, that a major goal of management is to reduce lung hyperinflation in the hope of improving dyspnea, exercise tolerance and related long term patient-centered outcomes. The negative effects of lung hyperinflation on respiratory muscle and cardio-circulatory function are now well established and the negative effects of acute dynamic hyperinflation during exacerbations and physical activity are increasingly recognized. Additional evidence of the importance of lung hyperinflation comes from multiple studies which have examined the clinical benefits of therapeutic interventions that reduce the effect of lung hyperinflation. The current review summarizes the causes and clinical consequences of lung hyperinflation and provides a strong rationale for its therapeutic reversal.

INTRODUCTION

While expiratory flow limitation (EFL) is generally regarded as the pathophysiological hallmark of COPD, lung hyperinflation is a related and equally important manifestation of the disease that deserves our attention. Measures of resting lung hyperinflation have been shown to be predictive of respiratory and all-cause mortality in COPD population studies (1,2). There is good evidence that lung hyperinflation is closely linked to the degree of breathlessness (dyspnea) experienced by patients with COPD during exacerbations or physical activity (3-5). Moreover, therapeutic reversal of lung hyperinflation has been shown to effectively improve dyspnea and exercise tolerance (6-10). In this brief review we will: clarify definitions of lung hyperinflation; review causative mechanisms; outline its negative consequences during exacerbations and exercise, and finally; review the benefits of therapeutic lung volume deflation.

HYPERINFLATION AT REST

Definitions and Determinants
There is currently no consensus on the definition of lung hyperinflation. For the purpose of this review, an increase in total lung capacity (TLC) (preferably measured by body plethysmography) exceeding either the upper limit of normal (ULN) or an empiric 120% of predicted, suggests the presence of thoracic hyperinflation. An increase in functional residual capacity (FRC) above either ULN or 120% of predicted is termed lung
hyperinflation. An increase in RV exceeding either ULN or 120% of predicted is termed pulmonary gas trapping, also expressed by an increase in the RV/TLC ratio.

**Functional Residual Capacity (FRC)**
The lung volume at the end of quiet expiration during tidal breathing [i.e., FRC or end-expiratory lung volume (EELV)] is generally increased in COPD compared with healthy individuals. The term EELV is used interchangeably with FRC in the current review. FRC is not always synonymous with the static equilibrium volume of the relaxed respiratory system [relaxation volume (V_r)] – the volume at which the elastic recoil pressures of lung and relaxed chest wall are equal and opposite in sign (11-14) (Figure 1).

![Diagram showing resting lung volumes in COPD and age-matched normal individuals](image)

Figure 1. The bar graphs show resting lung volumes in COPD and in age-matched healthy normal individuals. Pressure-volume (P-V) curves of the respiratory system are shown with tidal P-V curves during rest (filled area) and exercise (open area). In COPD, because of resting and dynamic hyperinflation (a further increased EELV), exercise tidal volume encroaches on the upper, alinear extreme of the respiratory system’s P-V curve where there is increased elastic loading. In COPD, inspiratory reserve volume (IRV) is diminished and the ability to further expand tidal volume is reduced. Abbreviations: EELV=end-expiratory lung volume; ERV=expiratory reserve volume; IC=inspiratory capacity; IRV=inspiratory reserve volume; RV=residual volume; TLC=total lung capacity; ∆IC=change in IC during exercise from that at rest; ∆P=change in pleural pressure during a tidal breath while exercising; ∆V=change in respired volume during a tidal breath while exercising (i.e., tidal volume).

Traditionally, increase in FRC in COPD refers to the increase in V_r due to loss of lung recoil (e.g., with emphysema) which resets the balance of forces between the lung
and chest wall (11-14). EELV is also influenced by body position and body mass: for example, it decreases when adopting a supine position or in the presence of obesity (15,16).

**Dynamically-determined Resting EELV**

COPD is associated with heterogeneous pathological derangements of the elastic properties of the lung and the function of conducting airways. A major consequence of the increased compliance and resistance of regional alveolar units in COPD is ineffective gas emptying on expiration: the mechanical time constant (i.e., the product of compliance and resistance) for lung emptying is therefore increased (prolonged) (11-14). The result is that inhalation begins before full exhalation is complete: the available expiratory time is insufficient to allow the respiratory system to return to the predicted $V_r$, (14) Thus, in the presence of significant EFL and uneven mechanical time constants, lung hyperinflation is “dynamically” determined. EELV is therefore a continuous dynamic variable that varies with the prevailing breathing pattern and ventilatory requirements. In this circumstance, the alveolar pressure at end-expiration becomes higher (i.e., more positive) than atmospheric pressure (positive end-expiratory pressure, PEEP) (13).

**Inspiratory Capacity**

Inspiratory capacity (IC) is the maximal volume of air that can be inspired after a quiet expiration to EELV. The resting IC (or IC/TLC ratio) is also an indirect measure of lung hyperinflation. The IC is an important surrogate measurement of respiratory system mechanics as it indicates the operating position of tidal volume ($V_t$) on the respiratory system’s s-shaped pressure-volume relation. The smaller the IC (i.e., the greater the hyperinflation), the closer $V_t$ is positioned to TLC and the “stiff” upper reaches of the respiratory system’s pressure-volume relation where there is increased elastic work for the inspiratory muscles (11-14). Resting IC progressively declines as airway obstruction worsens in COPD (17). The IC, and not the vital capacity, represents the true operating limits for $V_t$ expansion in patients with EFL and therefore importantly influences breathing pattern and peak ventilatory capacity (4).

**Consequences of Resting Lung Hyperinflation**

**Mechanics and respiratory muscle function**

The presence of severe lung hyperinflation and the resultant intrinsic PEEPi means that the inspiratory muscles have to overcome a “threshold” load before inspiratory flow can begin (18-26). The higher EELV also means that the inspiratory muscles – particularly the diaphragm – are working at a mechanical disadvantage. Shortening of the muscle fibers because of hyperinflation leads to functional weakness which means that they are ill-equipped to deal with the added burden of overcoming the elastic/threshold loads due to increased hyperinflation. The net effect of these mechanical abnormalities is a pronounced increase in the work and oxygen ($O_2$) cost of breathing, especially in patients with severe COPD (27). Long term adaptations to lung hyperinflation are
known to develop slowly in COPD (19,28-30). Despite these impressive temporal adaptations, the presence of severe lung hyperinflation means that ventilatory reserve in COPD is diminished and the ability to increase ventilation is greatly limited when demand suddenly rises (e.g., exercise or exacerbation).

**Hyperinflation and Cardio-circulatory Impairment**
Severe hyperinflation at rest has been associated with increased all-cause and respiratory mortality (1) and impaired left ventricular (LV) filling (31-35). Severe lung hyperinflation has recently been linked to reduced intra-thoracic blood volume and reduced LV end-diastolic volume (36). Lung hyperinflation also has the potential to impair cardiac function by increasing pulmonary vascular resistance. Increased intrathoracic pressure swings linked to the increased mechanical work related to hyperinflation may lead to increased LV afterload as a result of the increased LV transmural pressure gradient (Figure 2). Reductions in venous return, right and left ventricular volumes, and LV stroke volume are additional consequences of these altered intra-thoracic pressure gradients.

![Figure 2. Schematic representation of the potential deleterious effects of lung hyperinflation on cardiopulmonary interactions in patients with COPD. Note that most of these interactions may vary according to phase alignment between the respiratory and cardiac cycles. Important modulating effects of volemic status, sympathetic nervous system activation, ventilation-related vagal reflexes](image-url)
and comorbidities (e.g., pulmonary hypertension and chronic heart failure) are not depicted. Abbreviations: Circ = circulation; LV = left ventricular; Pab = abdominal pressure; PaCO2 = partial pressure of arterial carbon dioxide; Ppl = pleural pressure; Pulm = pulmonary; Syst = systemic; RV = right ventricular. From: Langer D, et al. Expert Rev Respir Med 2014; 8(6): 731-749.

**DYNAMIC HYPERINFLATION**

Dynamic lung hyperinflation (DH) refers to the temporary and variable increase in EELV above the resting value in patients with obstructive airways disease (37-39). DH occurs when EFL is acutely increased during bronchospasm or exacerbation, often in a setting of increased ventilation and inspiratory neural drive to the respiratory muscles. Patients with a resting IC of <80% predicted have significant EFL during resting breathing and are at greater risk for developing further gas trapping (dynamic hyperinflation) during exercise or in any situation where ventilation is suddenly increased, e.g., anxiety, hypoxemia, voluntary hyperventilation (40). Depending on the extent of baseline lung hyperinflation, sudden further DH can have serious negative consequences for the function of both the respiratory and cardio-circulatory systems. Moreover, acute DH is increasingly implicated as a major cause of dyspnea – a dominant symptom during exacerbations and physical activity in COPD.

**Dynamic Hyperinflation during Exacerbations of COPD**

The mechanisms of DH are broadly similar during induced bronchoconstriction in asthma and during exacerbations in patients with COPD (5, 41-43). However, patients with COPD, especially those with more severe airway obstruction, are more likely to have significant baseline abnormalities of both lung mechanics and pulmonary gas exchange (5, 42, 43). Thus, the consequences of sudden acute-on-chronic DH in such individuals may be serious and even life-threatening. During an acute exacerbation of COPD (AECOPD), airway resistance is increased due to a combination of bronchospasm, mucosal edema and sputum inspissation; which worsens EFL and compromises effective lung emptying. Furthermore, the acute increase in lung hyperinflation during AECOPD forces patients to adopt a rapid, shallow breathing pattern, which further limits the time available for lung emptying, thus promoting greater DH in a vicious cycle. The attendant increase in inspiratory neural drive to the respiratory muscles not only reflects the response to acute mechanical muscle loading but also increased chemostimulation as a result of amplified ventilation-perfusion abnormalities (e.g., high physiological dead space). Moreover, subjective fear, anxiety or overt panic related to distressing dyspnea, with attendant increased sympathetic system activation, also powerfully influence breathing pattern to worsen DH. Cardio-circulatory function is also compromised (as already described) and this may precipitate LV decompensation in those predisposed. In this context, cardiovascular comorbidity is common in patients with COPD and often compounds the clinical expression and eventual outcome of AECOPD. **(Figure 3)**
During AECOPD, the respiratory muscles are stressed and functionally weakened (5,43,44). PEEPi may rise precipitously and, together with the increased elastic load (related to “high-end” mechanics), increase the overall work and oxygen cost of breathing with development of fatigue or respiratory failure (44) (Figure 3). Thus, the mechanical output of the flow-limited and overinflated respiratory system may not increase in tandem with central neural drive. This progressive disparity has been termed neuromechanical dissociation of the respiratory system which helps explain the worsening dyspnea.

**Figure 3.** Schematic of the negative consequences of dynamic hyperinflation during an acute exacerbation of COPD. Dynamic hyperinflation develops as a consequence of worsening expiratory flow limitation. Abbreviations: EELV= end-expiratory lung volume; IC= inspiratory capacity; PaO₂= arterial oxygen tension; PaCO₂= arterial carbon dioxide tension; PEEPi= intrinsic positive end-expiratory pressure; Cdyn= dynamic compliance of the lung; VD/Vt= physiological dead space; VT= tidal volume; RV= right ventricular; LV= left ventricular. From: O’Donnell DE, Parker CM. Thorax 2006; 61: 354-361.

**Dynamic Hyperinflation during Exercise in COPD**
Dynamic increase in EELV is inevitable during exercise in patients with significant expiratory flow limitation in the setting of high ventilatory demand (4, 38, 39, 45, 46).
Inspiratory neural drive is often greatly increased during exercise in COPD because of the effect of increased wasted ventilation (high physiological dead space) and, in some instances, the added stimulus of significant arterial hypoxemia and early metabolic acidosis secondary to skeletal muscle deconditioning (44,47-50). In early exercise, mean inspiratory flow rate and \(V_t\) increase substantially but expiratory time is often too short to allow complete gas emptying, resulting in DH (14). Increases in EELV above resting values by 0.3-0.6 L, on average, have been shown to occur in approximately 85% of patients with moderate-to-severe COPD during cycle exercise (4, 38, 39, 45, 46). In patients with COPD, patterns of DH vary widely but the magnitude of increase in EELV is inversely related to the resting IC (4). In patients with a low resting IC due to severe hyperinflation, \(V_t\) quickly expands during exercise (even in the absence of DH) to reach a critical minimal IRV – a true mechanical limit where further increases in ventilation soon become impossible. DH during exercise is even present in many individuals with mild airway obstruction as a result of the combined effects of higher ventilatory inefficiency (wasted ventilation) and dynamic EFL (51-54). DH persists in the face of vigorous expiratory muscle effort (55).

An increase in resting lung hyperinflation with advancing COPD severity is associated with progressive reduction of resting IC (4) (Figure 4). During exercise when \(V_t\) reaches approximately 70% of the prevailing IC (or a minimal inspiratory reserve volume (IRV) of 0.5L), there is an inflection or plateau in the \(V_t\) response (Figure 4). This critical point represents a mechanical limit where further sustainable increases in ventilation are impossible in the face of near maximal respiratory neural drive. The inability to further expand \(V_t\) is associated with tachypnea – the only remaining strategy available in response to the increasing inspiratory neural drive. Increased breathing frequency results in worsening DH, mechanical \(V_t\) constriction, increased velocity of shortening of the inspiratory muscles with associated functional weakness and decreased dynamic lung compliance (50). In this setting, inspiratory neural drive (indirectly assessed by diaphragm electromyography [EMGdi]) reaches >70% of the maximal possible value (51,54). The work and \(O_2\) cost of breathing required to achieve a given increase in ventilation steadily increases to a high percentage of the total oxygen uptake (50). In some individuals, these collective derangements can predispose to critical functional weakness of the inspiratory muscles, fatigue or even overt respiratory failure with carbon dioxide (\(CO_2\)) retention at end-exercise (56-58).
Figure 4. Tidal volume ($V_T$), breathing frequency ($F_b$), dynamic inspiratory capacity (IC) and inspiratory reserve volume (IRV) are shown plotted against minute ventilation during constant work rate exercise for each forced expiratory volume in 1 second (FEV$_1$, expressed as % predicted) quartile (Q). The upper through to lower quartiles (Q1-Q4) represent the mildest to most severe groups, respectively. Note the clear inflection (plateau) in the $V_T$/ventilation relationship which coincides with a simultaneous inflection in the IRV. After this point, further increases in ventilation are accomplished by accelerating $F_b$. Data plotted are mean values at steady-state rest, isotime (i.e., 2 min, 4 min), the $V_T$/ventilation inflection point and peak exercise. Abbreviations: VC= vital capacity; TLC= total lung capacity. From: O’Donnell DE, et al. Chest 2012; 141: 753-762.

DH adversely affects dynamic cardiac function during exercise by contributing to increased pulmonary artery pressures, by reducing right ventricular pre-load (reduced venous return) and, in some cases, by increasing LV afterload (35,59-70). Finally, it has recently been postulated that competition between the overworked ventilatory muscles and the active peripheral muscles for a finite cardiac output may compromise blood flow and oxygen delivery to the latter, with negative consequences for exercise performance (71).
Respiratory mechanical abnormalities and dyspnea
The progressive increase in dyspnea intensity during exercise (at any given ventilation) as COPD severity increases, reflects the progressively increasing intrinsic mechanical loading of the respiratory muscles (72-84) (Figure 5). The rise in dyspnea intensity ratings during exercise correlates strongly with indirect indices of increased inspiratory neural drive (central motor command output) such as inspiratory EMGdi and tidal esophageal pressure swings (both relative to maximum), ventilation relative to peak ventilatory capacity and Vt relative to IC. All of these physiological ratios that correlate with dyspnea intensity are fundamentally measures of demand/capacity imbalance of the respiratory system. It is postulated that the amplitude of inspiratory neural drive (originating from motor cortical and medullary centers in the brain) to the respiratory muscles is sensed via neural inter-connections (i.e., central corollary discharge) between these motor centers in the brain and the somato-sensory cortex (77,85-89).

Figure 5. Relationships between exertional dyspnea intensity and ventilation and the ratio of tidal volume to inspiratory capacity (Vt/IC) are shown during symptom-limited cycle exercise in COPD. There is a
progressive increase in the dyspnea/ventilation curve with worsening disease. After the \( V_t/IC \) ratio plateaus (corresponding to the \( V_t \) inflection point), dyspnea rises steeply to intolerable levels. Quartiles (Q) of COPD severity are based on forced expiratory volume in 1 second (FEV\(_1\)) expressed as percent predicted (ranges: Q1 = 54.5–85.1; Q2 = 43.8–54.1; Q3 = 34.9–43.6; Q4 = 16.5–34.9). Data plotted are mean values at steady-state rest, isotime (i.e., 2 min, 4 min), the \( V_t/\text{ventilation} \) inflection point and peak exercise. From: O’Donnell DE, et al. Chest 2012; 141: 753-762.

Dyspnea intensity is more closely correlated with the reduction in IRV during exercise than the change in EELV (i.e., DH) per se (4,47). The plateau in \( V_t \) corresponds with the IRV inflection during exercise and marks the threshold where dyspnea intensity sharply increases towards intolerable levels at end-exercise (50,75,76,83); it also marks the point where the dominant descriptor of dyspnea selected by patients changes from increased effort to unsatisfied inspiration (83). Thus, the \( V_t \) inflection represents the onset of neuromechanical dissociation.

**REDUCING LUNG HYPERINFLATION**

**Bronchodilator Therapy**

Inhaled bronchodilators reduce airway smooth muscle tone and airway resistance, improve airflow, and accelerate the mechanical time constants for lung emptying. In this way, bronchodilators favorably alter the dynamically-determined EELV, leading to improved lung deflation (6-10,75) (Figure 6).

![Figure 6](image)

*Figure 6.* Typical bronchodilator-induced changes in: (A) maximal and tidal flow-volume loops and (B) lung volumes at rest. With a bronchodilator, maximal expiratory flows increase allowing
inspiratory capacity (IC) to increase and functional residual capacity (FRC) to decrease. TLC = total lung capacity.

Bronchodilators of all classes and duration of action have consistently been shown to decrease measurements of lung hyperinflation (EELV) and pulmonary gas trapping [residual volume (RV)], with reciprocal increases in IC and vital capacity (VC), in patients with COPD. New fixed-dose combinations of long-acting bronchodilators are especially effective for achieving sustained pharmacological lung deflation (Figure 7) (90-92).

![Figure 7](image-url)

**Figure 7.** Changes in function residual capacity (FRC) are shown in response to new long-acting fixed-dose combination bronchodilators. Abbreviations: tio= tiotropium; olo= olodaterol; umec= umeclidinium; vil= vilanterol; ind= indacaterol; glyc= glycopyrronium. Data are from references 90-92.
Since spirometric measurements are simple to perform, changes in IC are often used to track changes in EELV at rest and during exercise in clinical trials, assuming that TLC is unchanged (37,45,93). Subtraction of $V_T$ from IC measured serially during exercise allows us to track changes in dynamic IRV (94). Generally, single agent bronchodilator-induced improvements in resting IC range from 0.2-0.4L or 10-15% of the baseline value (6-10,75). The largest post-bronchodilator improvements in IC are seen in patients with the greatest resting hyperinflation (17,95-97). Decreases in lung volume of this magnitude are associated with reduced intrinsic mechanical loading.

Improvements in spirometry ($FEV_1$) following a bronchodilator, especially in more advanced COPD, commonly indicate lung volume recruitment (increased VC) as a result of reduced pulmonary gas trapping (decreased RV) (6-9,95,96). This pattern of lung volume recruitment is noted particularly in patients with more severe lung hyperinflation. Moreover, a lack of change in $FEV_1$ after bronchodilator treatment does not necessarily reflect a lack of change in lung hyperinflation or associated subjective benefit (6-9,95,96).

Effects of Bronchodilators during Exercise
Inhaled bronchodilators of every class have been shown to increase IC at standardized exercise work rates/times and at peak exercise (6-10). It is important to understand that bronchodilators mainly increase the resting IC with a parallel downward shift in the IC/work rate slope throughout exercise: the rate of DH is not necessarily changed. Such increases in IC measurements have consistently been associated with improvements in exertional dyspnea and exercise endurance time (by 15-20%) in patients with moderate-to-severe COPD (6-10). Throughout exercise, release of $V_T$ restriction and partial reversal of neuromechanical dissociation is readily measurable (75). Thus, for any given exercise intensity or ventilation, patients breathe on the more linear portion of the respiratory system’s pressure-volume relation. Collectively, these studies provide convincing evidence that after bronchodilator therapy patients are capable of undertaking a demanding physical task with less discomfort for a longer duration. Recently, dual long-acting bronchodilators in a single inhaler have been shown to achieve impressive and sustained pharmacological lung deflation (Figure 7) which should translate into important clinical benefits, particularly in patients with a reduced resting IC (90-92).

Non-pharmacological Lung Volume Reduction
In selected patients with localized destructive emphysema and regional lung hyperinflation, surgical (bullectomy, lung volume reduction surgery) and endoscopic volume reduction are associated with consistent improvements in perceived dyspnea and exercise tolerance (98-105). The underlying mechanisms of improvement are broadly similar to those described above for pharmacological interventions. Finally, any intervention that reduces breathing frequency such as hyperoxia, opiate medication and exercise training has the potential to reduce dynamic hyperinflation (by prolonging
expiratory time), thereby delaying the onset of mechanical limitation and improving dyspnea (106-111).

SUMMARY
In COPD, progressive EFL and alteration in the elastic properties of the lung are associated with the development of progressive lung hyperinflation and decline in the resting IC. Severity of lung hyperinflation is an independent predictor of mortality in COPD. DH occurs when EFL is acutely amplified during episodes of bronchoconstriction and underlies the clinical expression of exacerbations of COPD. Similarly, during exercise in COPD the combined factors of worsening EFL, breathing pattern alterations and increasing respiratory neural drive dictate the pattern and extent of DH. The clinical consequences of DH in a given patient will depend on the baseline mechanical and gas exchange abnormalities. During AECOPD and exercise, further hyperinflation and IC reduction critically restricts VT expansion, mechanically loads and weakens the inspiratory muscles, forces early respiratory mechanical limitation and compromises integrated respiratory and cardio-circulatory function. Additionally, the growing disparity between increased respiratory neural drive and the blunted respiratory muscular/mechanical response is mechanistically linked to perceptions of respiratory discomfort and distress. Accordingly, pharmacological lung volume reduction improves dynamic respiratory mechanics and muscle function. Thus, neuromechanical dissociation is partially reversed and dyspnea is ameliorated.

CLINICAL IMPLICATIONS
Traditional assessments of COPD severity based on forced expiratory flow measurements fail to expose the heterogeneous physiological derangements of the disease. Additional measurement of lung hyperinflation provides important information about the abnormal respiratory mechanics and allows a more comprehensive, individualized characterization of disease severity. Demonstration of pulmonary gas trapping in smokers with relatively preserved FEV₁ can help explain common underlying respiratory symptoms such as activity-related dyspnea. Serial measurements of IC during AECOPD have the potential to track key abnormalities in respiratory mechanics and response to therapy. In clinical trials, exclusive reliance on change in FEV₁ as the primary outcome of interest (favored by regulatory authorities) can lead to significant underestimation of therapeutic efficacy that can be uncovered by simple measurements of IC. As clinicians, we should recognize that lung hyperinflation is an important physiological biomarker that can be successfully targeted for reversal. A reasonable expectation is that sustained therapeutic lung deflation with modern pharmacotherapy will ultimately be linked to long term improvements in morbidity and even mortality in COPD.
REFERENCES


