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Lung hyperinflation in COPD: applying physiology to clinical practice

Denis E. O'Donnell*, Katherine A. Webb and J. Alberto Neder

Abstract

In chronic obstructive pulmonary disease (COPD), worsening expiratory flow limitation together with alteration in the elastic properties of the lung are associated with progressive lung hyperinflation and gradual decline in the resting inspiratory capacity over time. Dynamic hyperinflation (DH) refers to the variable increase in end-expiratory lung volume (EELV) above the relaxation volume (V_R) of the respiratory system that occurs when expiratory flow limitation is amplified (e.g., during bronchoconstriction and acute exacerbations) or when ventilation is increased in the setting of expiratory flow limitation. During exercise, the combined factors of worsening expiratory flow limitation, increasing respiratory neural drive and breathing pattern alterations dictate the pattern and extent of DH. Acute-on-chronic hyperinflation increases the intrinsic loads on the inspiratory muscles which become functionally weakened. The combined effects of compromised respiratory and integrated cardio-circulatory function due to lung hyperinflation contribute to exercise limitation. In COPD, the resting inspiratory capacity, which indirectly reflects the extent of lung hyperinflation, dictates the limits of tidal volume expansion and thus, peak ventilatory capacity during activity. Moreover, the growing disparity between increased respiratory neural drive and the blunted respiratory muscular/mechanical response due to lung hyperinflation is mechanistically linked to dyspnea during exercise in COPD. From a clinical standpoint, measurement of lung hyperinflation is integral to the assessment of physiological impairment in individuals with COPD and can effectively be targeted for treatment. Moreover, it is now well established that lung volume reduction (deflation) provides a solid mechanistic rationale for observed improvements in dyspnea and exercise tolerance in patients with COPD following bronchodilator therapy.

Keywords: Dyspnea, COPD, Lung volumes, Bronchodilators, Exercise

Introduction

Expiratory flow limitation (EFL) is generally regarded as the pathophysiological hallmark of COPD [1]. Lung hyperinflation is a related phenomenon that is of equal clinical importance but less often considered [2]. Measures of resting lung hyperinflation have been shown to be predictive of respiratory and all-cause mortality and are needed to comprehensively characterize physiological impairment in individual COPD patients [3, 4]. Dynamic lung hyperinflation (DH) refers to the variable increase in end-expiratory lung volume (EELV) above the relaxation volume (V_R) of the respiratory system [1]. DH occurs when EFL is acutely worsened during bronchospasm or exacerbation, often in the setting of increased ventilation ($\dot{V}E$) due to increased chemostimulation and respiratory neural drive [5]. Depending on the extent of resting lung hyperinflation, further DH when the respiratory system is stressed can have important negative consequences for the function of both the respiratory and cardio-circulatory systems [6]. Moreover, acute DH is increasingly implicated as a major cause of dyspnea – the dominant symptom in patients with chronic airway diseases [7]. In this concise review we will attempt to: a) clarify definitions of lung hyperinflation; b) review causative mechanisms; c) consider its natural progression and negative clinical consequences, particularly concerning its role in exercise limitation and dyspnea causation in COPD; and d) summarize the clinical benefits of pharmacological lung volume reduction.

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Hyperinflation: definitions and determinants

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 is consistent with *thoracic hyperinflation*. An increase in plethysmographic functional residual capacity (FRC) above either ULN or 120 % of predicted is termed *lung hyperinflation*. An increase in plethysmographic RV exceeding either ULN or 120 % of predicted is termed *pulmonary gas trapping*, also expressed by an increase in the RV/TLC ratio above the ULN. It should be acknowledged, however, that single-breath inert gas dilution techniques underestimate TLC (e.g., "alveolar volume" during lung diffusing capacity measurements), a phenomenon that increases in tandem with COPD severity [8]. Conversely, body plethysmography may overestimate thoracic gas volume in patients with severe and very severe COPD due to incomplete equilibration of mouth and alveolar pressures, heterogeneity of alveolar pressure swings during the panting maneuver, and excessive compliance of the extrathoracic airway [9]. This error is minimized by ensuring that panting frequency is maintained around 1 Hz.

Total lung capacity

TLC is the greatest volume of gas in the lungs after maximal voluntary inspiration. It depends on the static balance between the outward forces generated by inspiratory muscles during a maximal inspiratory effort and the inward elastic forces of the chest wall and lung (Fig. 1). At TLC, these two sets of forces are equal and opposite in sign. The increase in TLC in COPD usually reflects the increased lung compliance due to emphysema [10, 11] as thoracic compliance decreases with senescence [12–14].

Functional residual capacity at rest

FRC or the lung volume at the end of quiet expiration during tidal breathing (i.e., EELV) is increased in COPD compared with health [15]. The term EELV is used interchangeably with FRC in the current review. It should be noted that FRC is not always synonymous with the static equilibrium volume of the relaxed respiratory system; V_r is the volume at which the elastic recoil pressures of lung and relaxed chest wall are equal and opposite in sign (Fig. 1) [10, 11]. Active or passive mechanisms often operate to make FRC different from V_r both in health and in COPD. For example, in healthy younger subjects during exercise, activation of expiratory muscles commonly drives FRC below the V_r [16].

An increase in FRC measured at rest has both static and dynamic determinants in COPD [17]. Traditionally, an increase in "static" FRC refers to an increase in V_r due to loss of lung recoil which resets the balance of forces between the lung and chest wall [10, 11]. Accordingly, the static V_r is higher than that of predicted normal and FRC is increased in COPD compared with health [1, 6, 15]. In this circumstance the higher V_r means that the alveolar pressure at end-expiration remains atmospheric. Interestingly, resting FRC is also dynamically determined in the setting of EFL and varies with the breathing pattern. For instance, a tachypneic breathing pattern and/or a high inspiratory-to-expiratory time ratio will shorten the time available for adequate lung emptying [17]. Thus, mouth pressure at EELV is positive - a phenomenon termed intrinsic positive end-expiratory pressure (PEEPi) [18]. EELV during spontaneous breathing in flow-limited patients is a continuous dynamic variable

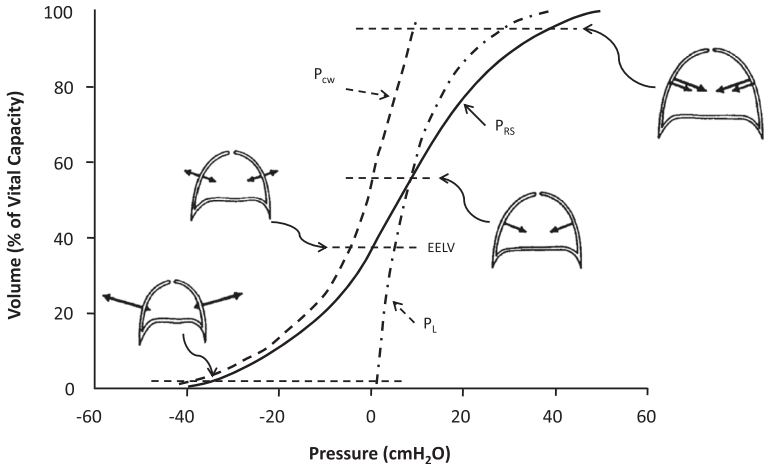

Fig. 1 Quasistatic V–P curves of lung (P_L), chest wall (P_{cw}), and total respiratory system (P_{rs}) during relaxation in a sitting position. The static forces of lung and chest wall are indicated by the arrows in the drawings. P_L increases its curvature with increasing lung volume, whereas the opposite is true for the P_{cw}. The fall in the compliance of the respiratory system at high lung volumes is therefore mainly due to the decrease in compliance of the lung, whereas at low lung volume it reflects the decreased compliance of the chest wall. The volume corresponding to each drawing is indicated by the horizontal broken lines. (From: [95])

[19, 20]. DH can therefore occur when [21]: a) $\dot{V}E$ or breathing frequency are abruptly increased (e.g., voluntarily, during anxiety/panic attacks, acute hypoxemia, physical activity or during metronome pacing);; or b) EFL is suddenly worsened (e.g., increased bronchospasm or during exacerbation) [22–24].

Lung hyperinflation at rest is also influenced by body position and by body mass: for example, EELV decreases when adopting a supine position [11] or with obesity [25, 26]. In this respect, FRC has been shown to decrease exponentially with increasing body mass index (BMI), with the largest changes occurring with BMI in the overweight to mild obesity range [25].

Inspiratory capacity

Inspiratory capacity (IC) is defined as the maximal volume of air that can be inspired after a quiet expiration to EELV. The resting IC (or IC/TLC ratio) [3] is also used as an indirect measure of lung hyperinflation when TLC is stable [27, 28]. Resting IC progressively declines as airway obstruction worsens in COPD (Fig. 2) [29]. Measurement of IC is motivation-dependent and is influenced by static strength of the inspiratory muscles and EELV [28]. The IC represents the operating limits for tidal volume (V_T) expansion during exercise in patients with EFL and influences breathing pattern and peak ventilatory capacity (see below). The IC is diminished in the presence of significant inspiratory muscle weakness [30]. Patients with a resting IC of less than 80 % predicted are thought to have significant EFL during resting breathing and are at greater risk for developing DH during exercise [22, 31].

The natural history of lung hyperinflation

Insufficient data from longitudinal studies are available to precisely chart the natural history of lung hyperinflation in COPD. Clinical experience indicates this is an insidious process that occurs over decades. It is acknowledged that such factors as genetic susceptibility, burden of tobacco smoke, frequency and severity of exacerbations, and pathophysiological phenotype collectively dictate the rate of progression of hyperinflation. A 4-year trial documented a mean rate of decline in pre-bronchodilator IC of 34–50 mL/year in patients with moderate to very severe COPD [32]. In that study, patients with the lowest baseline IC were those with the greatest rates of exacerbation and death [32]. A cross-sectional study in 2265 patients found progressive increases in pulmonary gas trapping and lung hyperinflation (measured by RV and FRC) and a corresponding decline of IC across the continuum of COPD severity [25]. Lung volume increases were shown to occur even in the earliest stages of COPD (i.e., GOLD grade 1) and increased with severity of airway obstruction [25, 29, 33, 34].

Review

Hyperinflation across the continuum of COPD

Small studies in mild COPD have reported increased static lung compliance, and quantitative computed tomography (CT) scans have shown emphysema and gas trapping [35–37]. Gas trapping, as assessed by expiratory CT scans, can exist in the absence of structural emphysema and is believed to indirectly reflect small airway dysfunction in mild COPD [35]. The presence of lung hyperinflation assessed by quantitative CT scans was found to predict a rapid annual decline in FEV_1 in smokers with a normal FEV_1 [36]. Corbin and coworkers [37], in a 4-year longitudinal study of smokers with

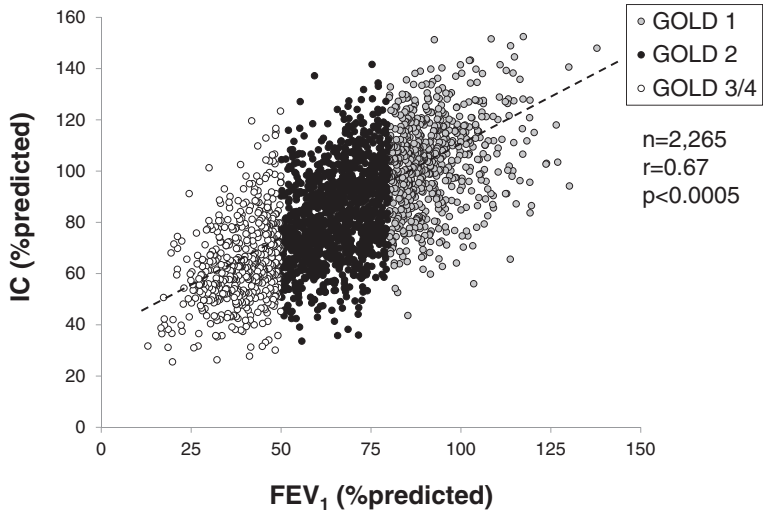

Fig. 2 Inspiratory capacity (IC) decreased linearly as forced expired volume in 1 s (FEV_1) worsened ($r = 0.67$, $p < 0.0005$) in a group of 2265 individuals with airway obstruction. (Constructed with data from: [96])

chronic bronchitis, reported a progressive increase in lung compliance. Interestingly, these investigators reported that increases in TLC in milder COPD led to a preserved slow vital capacity (VC) and IC in the setting of increased RV and FRC, respectively [37]. Although there is considerable heterogeneity in FRC and RV across GOLD grades, many patients in each GOLD category have values that are above the predicted normal range [25]. From cross-sectional studies, it would appear that RV and FRC increase exponentially as airway obstruction worsens [25].

Physiological adaptations to chronic lung hyperinflation

In the presence of lung hyperinflation, functional muscle weakness is mitigated, to some extent, by long term adaptations such as shortening of diaphragmatic sarcomeres and reduction in sarcomere number which cause a leftward shift of the length-tension relationship; thus improving the ability of the muscles to generate force at higher lung volumes [11, 38]. In patients with chronic lung hyperinflation, adaptive alterations in muscle fiber composition (an increase in the relative proportion of slow-twitch, fatigue resistant, type I fibers) and oxidative capacity (an increase in mitochondrial concentration and efficiency of the electron transport chain) are believed to preserve the functional strength of the overburdened diaphragm and make it more resistant to fatigue [39, 40]. In this regard, Similowski et al. [41] demonstrated that the reduction in the pressure-generating capacity of the inspiratory muscles of stable COPD patients was related to lung hyperinflation, but that diaphragmatic function in such patients was similar to normal subjects when measurements were compared at the same lung volume. Despite these impressive temporal adaptations, the presence of severe lung hyperinflation means that IC and ventilatory reserve in COPD is diminished and the ability to increase V_T and $\dot{V}E$ is greatly limited when the demand suddenly rises (e.g., with exercise or exacerbation).

Consequences of lung hyperinflation at rest

Respiratory muscle function

A mild increase in EELV at rest might be advantageous as it improves airway conductance and attenuates expiratory flow limitation to a variable degree. However, lung hyperinflation in moderate to severe COPD places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers, thereby compromising its force generating capacity [42]. Lung hyperinflation also affects the capacity of the parasternal intercostals and scalenes to shorten with potential negative consequences [43].

Known mechanisms of compromised diaphragmatic function secondary to hyperinflation can be summarized as follows [44, 45]:

a) worsening of the length-tension relationship,
b) decrease in the zone of apposition,
c) decrease in the curvature,
d) change in the mechanical arrangement of costal and crural components, and
e) increase in the elastic recoil of the thoracic cage.

Lung hyperinflation decreases the resting length of the diaphragm and, less so, the rib cage muscles. The shortening of the diaphragm is due to a decrease in the length of its zone of apposition, which causes a decrease in its pressure generating capacity [43, 44]. The change in fiber orientation with lung hyperinflation decreases the ability of the diaphragm to generate force, and this muscle has an expiratory rather than inspiratory action on the rib cage [39, 40, 44, 45].

When EELV represents approximately 70 % of predicted TLC, thoracic elastic recoil is directed inward (i.e., increased) so that the inspiratory muscles have to work, not only against PEEPi and the elastic recoil of the lungs, but also against the elastic recoil of the thoracic cage (Fig. 1) [11]. The net effect is a pronounced increase in the work and oxygen (O_2) cost of breathing at rest in patients with severe COPD [46].

Lung hyperinflation and central hemodynamics

Severe hyperinflation, as defined as an IC/TLC ratio <25 %, has been shown to be associated with increased cardiovascular mortality [3], impaired left ventricular (LV) filling [47], and reduced exercise tolerance [6, 48]. Severe lung hyperinflation has been linked to a reduced intra-thoracic blood volume and reduced LV end-diastolic volume as assessed by magnetic resonance imaging (MRI) [49]. Barr et al. reported that in a large population-based sample of smokers and non-smokers, a 10 % increase in the percentage of emphysema (measured by CT) correlated with reductions in LV diastolic volume, stroke volume and cardiac output, as estimated by MRI [47]. Lung hyperinflation has also the potential to impair cardiac function by increasing pulmonary vascular resistance [50]. Increased intrathoracic pressure swings linked to the increased mechanical loading of hyperinflation may result in increased LV afterload as a result of the increased LV transmural pressure gradient (Fig. 3) [51]. Reductions in venous return, right and left ventricular volumes, and LV stroke volume are additional consequences of the altered intra-thoracic pressure gradients [6, 15].

DH during exacerbations of COPD

The mechanisms of DH are broadly similar during induced bronchoconstriction in asthma and during acute exacerbations in patients with COPD (AECOPD). However, patients with COPD, especially those with more severe airway obstruction, are more likely to have significant

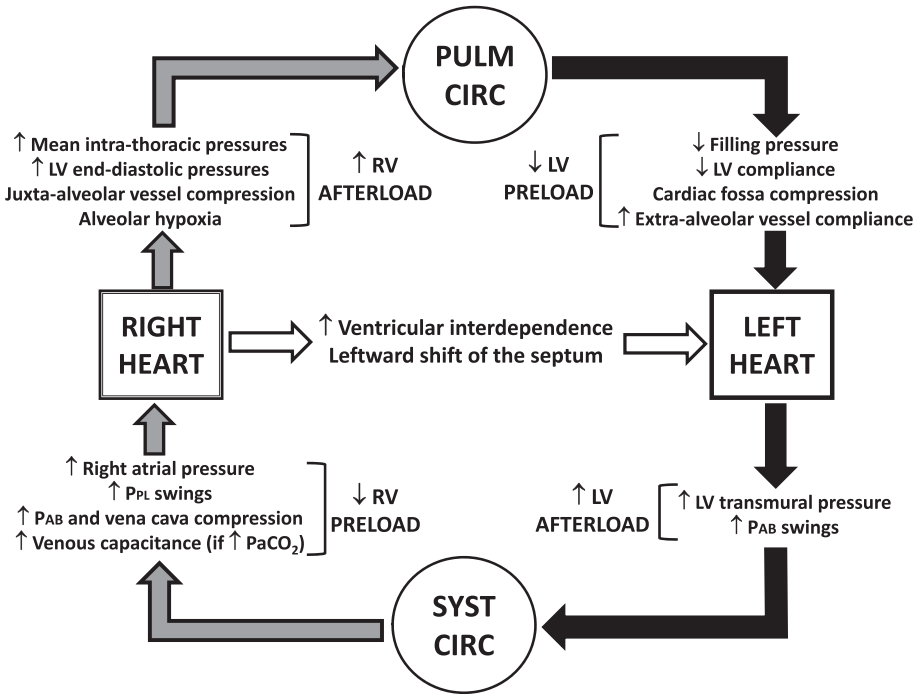

Fig. 3 A schematic diagram showing the potential deleterious effects of lung hyperinflation on cardio-pulmonary interactions in patients with COPD. These interactions may vary according to phase alignment between the respiratory and cardiac cycles. There are also important modulating effects of volemic status, sympathetic nervous system activation, ventilation-related vagal reflexes and comorbidities (e.g., pulmonary hypertension and chronic heart failure) which are not depicted. *Abbreviations*: Circ, circulation; LV, left ventricular; Pab, abdominal pressure; $PaCO_2$, partial pressure of arterial carbon dioxide; Ppl, pleural pressure; Pulm, pulmonary; Syst, systemic; RV, right ventricular. (From: [15])

baseline abnormalities of both lung mechanics and pulmonary gas exchange [5] (Fig. 4). Thus, the consequences of acute-on-chronic lung hyperinflation in such individuals may be serious and even life-threatening. During AECOPD, airway resistance is abruptly increased due to a combination of bronchospasm, mucosal edema and sputum inspissation; which worsens expiratory flow limitation and compromises effective lung emptying [5]. The increased respiratory neural drive (RND), secondary to attendant ventilation-perfusion abnormalities in the face of increasing lung hyperinflation, means that patients tend to adopt a rapid, shallow breathing pattern during an exacerbation. This further limits the time available for lung emptying, thus promoting greater DH in a vicious cycle. Moreover, subjective fear, anxiety or overt panic related to distressing dyspnea, with attendant increased sympathetic nervous system activation, also powerfully influence breathing pattern to worsen DH and perceived respiratory discomfort [5].

During AECOPD, the respiratory muscles already burdened by increased resistive loading become subjected to increased elastic loading, decreased dynamic lung compliance and functional muscle weakness. Intrapulmonary pressures are positive at the end of expiration (i.e., increased $PEEP_i$) [52, 53]. $PEEP_i$ essentially acts as an inspiratory threshold load and may be as high as 6–9 cm H_2O during quiet breathing at rest in clinically stable patients with severe resting lung hyperinflation. The short-term clinical consequences of acute DH in individual patients during AECOPD will depend on the baseline IC; those with the most severe resting lung hyperinflation (i.e., lowest IC) can expect the most negative clinical outcomes. During acute-on-chronic hyperinflation, PEEPi may rise precipitously and, together with the increased elastic (related to breathing at a less compliant part the pressure-volume relationship) (Fig. 1) and resistive work, collectively increase the overall work and O_2 cost of breathing with development of fatigue or frank respiratory failure [53]. During AECOPD, the mechanical output of the flow-limited and hyperinflated respiratory system may not increase in proportion to increasing respiratory neural drive, resulting in critical neuromechanical dissociation of the respiratory system which may explain the worsening dyspnea [5, 6]. In fact, dyspnea and functional indices of hyperinflation have been found to improve in parallel in the recovery phase of acute AECOPD [54]. The major goal in AECOPD is lung deflation by intensive bronchodilator therapy to restore neuromechanical coupling and relieve dyspnea. Non-invasive mechanical ventilation with continuous positive airway pressure or bi-level support can also effectively counterbalance the

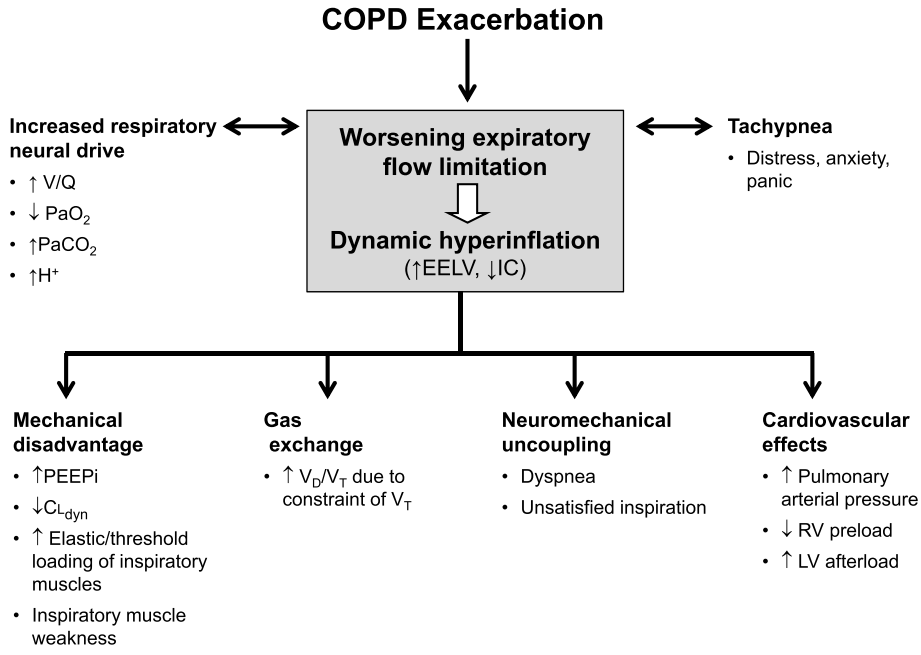

Fig. 4 The negative consequences of dynamic hyperinflation during an acute exacerbation of COPD. Dynamic hyperinflation develops as a consequence of worsening expiratory flow limitation. *Abbrevations*: EELV, end-expiratory lung volume; IC, inspiratory capacity; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; PEEPi, intrinsic positive end-expiratory pressure; CL_{dyn}, dynamic lung compliance; H^+, hydrogen ion concentration; LV, left ventricular RV, right ventricular; V_D/V_T, physiological dead space; V/Q, ventilation/perfusion; V_T, tidal volume

negative effects of increased lung hyperinflation on the inspiratory muscles and provide important dyspnea relief [55].

DH during exercise in COPD

Dynamic increases in EELV are inevitable during exercise in patients with significant EFL in the setting of high ventilatory demand [17]. RND (and ventilatory demand) is often greatly increased in COPD because of the effect of increased wasted ventilation (high ventilation/perfusion ratios) [6, 56–58] and, in some instances, significant arterial hypoxemia and metabolic acidosis secondary to skeletal muscle deconditioning and/or poor O_2 delivery [6, 59]. RND is increased for any given ventilation in COPD compared with healthy controls reflecting the increased intrinsic mechanical loads on the inspiratory muscles and the attendant functional muscle weakness caused by breathing at high lung volumes. In early exercise, mean inspiratory flow rates and tidal volume increase substantially but expiratory time is often too short to allow complete gas emptying resulting in DH. Increases in EELV above resting values by 0.3–0.6 L, on average, have been shown to occur in as many as 85 % of patients with moderate to severe COPD during cycle exercise [21].

In patients with advanced COPD, patterns of DH vary widely but the magnitude of increase in EELV is inversely related to the resting IC. Thus, in patients with a low resting IC due to severe resting 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 [60, 61]. DH during exercise is even present in many individuals with mild airway obstruction (and dominant peripheral airways disease) as a result of the combined effects of higher ventilatory inefficiency and dynamic expiratory flow limitation [34, 62]. DH occurs in the face of vigorous expiratory muscle effort and likely occurs "passively" rather than by active inspiratory muscle braking throughout the respiratory cycle [63]. Guenette et al. found that non-hyperinflators (15 % of the large multicenter group) had similar baseline characteristics compared with FEV_1-matched hyperinflators. These results suggest that dyspnea intensity was related to the constraints on V_T expansion (reduction in IRV) and not the magnitude of acute DH during exercise [64].

Increasing lung hyperinflation as COPD progresses is associated with increasing reduction of the resting IC [29]. During exercise when V_T reaches approximately 70 % of the prevailing IC (or end-inspiratory lung volume reaches ~90 % of the TLC at a minimal IRV), there is an inflection or plateau in the $V_T/\dot{V}E$ relation (Fig. 5) [65].

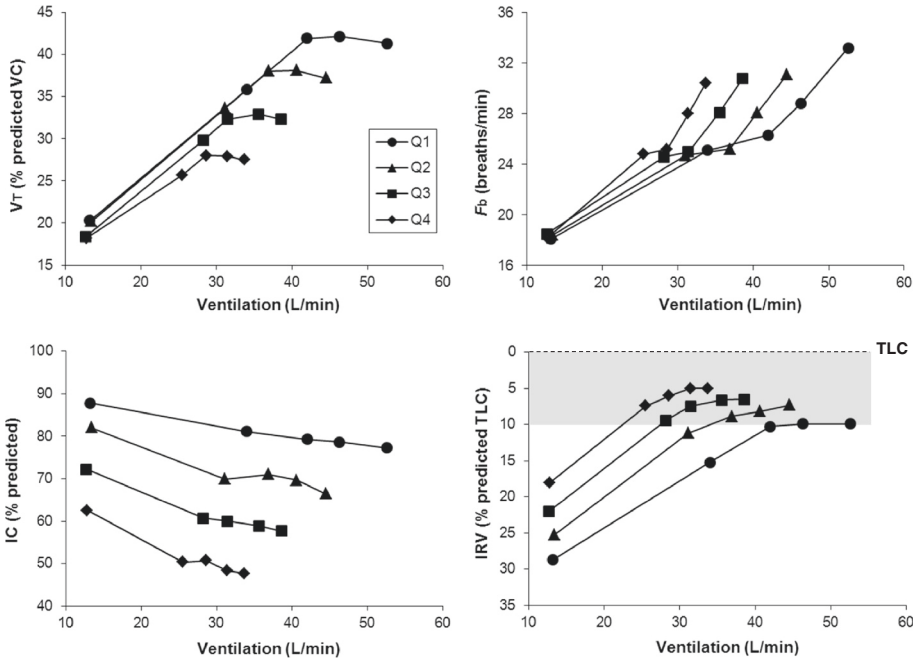

Fig. 5 Tidal volume (V_T), breathing frequency (F_b), dynamic inspiratory capacity (IC) and inspiratory reserve volume (IRV) are shown plotted against minute ventilation ($\dot{V}E$) during constant work rate exercise for each forced expiratory volume in 1 s (FEV_1, expressed as % predicted) quartile (Q). The upper through to lower quartiles (Q1-Q4) represent the mildest to most severe groups, respectively. Note the clear inflection (plateau) in the $V_T/\dot{V}_E$ relationship which coincides with a simultaneous inflection in the IRV. After this point, further increases in $\dot{V}E$ are accomplished by accelerating F_b. Data plotted are mean values at steady-state rest, isotime (i.e., 2 min, 4 min), the $V_T/\dot{V}E$ inflection point and peak exercise. (Modified from: [29])

This critical point represents a mechanical limit where further sustainable increases in $\dot{V}E$ are impossible in the face of near maximal ventilatory drive. The inability to further expand V_T is associated with tachypnea – the only remaining strategy available in response to the increasing ventilatory drive. As explained above, increased breathing frequency results in increased elastic loading due to further DH and the increased velocity of shortening of the inspiratory muscles, with associated functional weakness and decreased dynamic lung compliance. In this setting, RND (indirectly assessed by diaphragm electromyography (EMGdi)) reaches >70 % of the maximal possible value and tidal esophageal pressure swings increase to about 50–60 % of the maximal value [62, 66]. The work and O_2 cost of breathing required to achieve a given increase in $\dot{V}E$ steadily increases to a high percentage of the total O_2 uptake [46]. These collective derangements can predispose to critical inspiratory muscle functional weakness, fatigue or even overt respiratory insufficiency with carbon dioxide (CO_2) retention [21, 67].

Cardio-circulatory consequences of exercise DH

DH adversely affects dynamic cardiac function by contributing to pulmonary hypertension (intra-alveolar vessel compression), by reducing right ventricular pre-load (reduced venous return) and, in some cases, by increasing left ventricular afterload [6, 51]. In the absence of cardiac disease, cardiac output has been found to increase normally as a function of oxygen uptake during submaximal exercise in COPD, although stroke volume is generally smaller and heart rate correspondingly higher than in health [68, 69]. Of note, peak cardiac output reaches a lower maximal value during exercise in COPD, which may be due, in part, to abnormal ventilatory mechanics [6]. There is also evidence that impaired cardiac output response in the rest-to-exercise transition in non-hypoxemic patients with moderate-to-severe COPD is associated with increased muscle deoxygenation thereby suggesting reduced muscle perfusion [59]. Of note, reducing resting hyperinflation with bronchodilators improved muscle oxygenation during exercise [70, 71], a finding related to a faster cardiac output adjustment to exercise [71]. It has also been postulated that competition between the overworked ventilatory muscles and the active peripheral muscles for a reduced cardiac output may compromise blood flow and oxygen delivery to the latter, with negative consequences for exercise performance [72–74]. The impact of DH on cardiac output and ventilatory/locomotor muscle competition during exercise merits further study.

Respiratory mechanical abnormalities and exertional dyspnea

Dyspnea is a common symptom in patients with COPD across the continuum of the disease and is often the proximate cause of exercise limitation. The increase in dyspnea intensity at any given ventilation as COPD severity increases (compared to health), reflects the progressively increasing intrinsic mechanical loading of the respiratory muscles [7, 75]. The rise in dyspnea intensity ratings during exercise correlates strongly with indirect indices of increased respiratory neural drive (central motor command output) such as tidal electromyographic activation of the diaphragm relative to maximum, tidal esophageal pressure swings relative to maximum, and ventilation relative to peak ventilatory capacity [66, 76]. It is postulated that the amplitude of central 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 cortical motor and medullary centers in the brain and the somato-sensory cortex [75, 77].

Dyspnea intensity is more closely correlated with the reduction in IRV during exercise than the change in EELV (i.e., DH) *per se* [62]. The $V_T/\dot{V}E$ inflection corresponds with the IRV/$\dot{V}E$ inflection during exercise and marks the point where V_T expands to reach approximately 70 % of the prevailing IC and dyspnea intensity sharply increases (Fig. 6); it also coincides with the point where the dominant descriptor of dyspnea changes from increased effort to unsatisfied inspiration [33, 63]. The V_T inflection point, therefore, represents the onset of a widening disparity between increasing central neural drive and the mechanical/muscular response of the respiratory system [21, 65]. In advanced COPD, the ratio of respired effort (and presumably neural drive) to V_T increases steeply from rest to peak exercise, reflecting progressive neuromechanical dissociation of the respiratory system [67]. Exertional dyspnea intensity closely correlates with indices of effort-volume displacement dissociation (e.g., the ratio of Pes/PImax to V_T/predicted VC) [65]. The corollary is that effective relief of dyspnea in COPD following bronchodilators [78, 79] or lung volume reduction surgery [80] are largely explained by partial restoration of effort-displacement ratios and reduced neuromechanical dissociation.

Bronchodilator therapy

Effects on lung hyperinflation at rest

Bronchodilators reduce airway smooth muscle tone and airway resistance, improve airflow, and accelerate the mechanical time constants for lung emptying [81]. In this way, inhaled bronchodilators favorably alter the dynamically-determined components of resting lung hyperinflation and help deflate the overinflated lung. Bronchodilators of all classes and duration of action have consistently been shown to decrease lung hyperinflation and pulmonary gas trapping, with reciprocal increases in IC and VC in patients with COPD [82, 83].

Since spirometric measurements are simple to perform, changes in IC have often been used to track changes in EELV both at rest and throughout exercise. However, bronchodilator-induced improvements in IC may underestimate the reduction in resting EELV since TLC has been shown to fall by a small amounts (0.1–0.2 L) [84]. As single agents, both classes of inhaled bronchodilators (β_2-agonists and muscarinic antagonists) have been shown to increase the resting IC in patients with COPD by approximately 0.2–0.4 L or 10–15 % (as reviewed in reference [83] and, more recently, in reference [85]). The largest post-bronchodilator improvements in IC are seen in patients with the greatest resting lung hyperinflation (e.g., baseline IC <80 % predicted) [84]. Decreases in lung volume of the

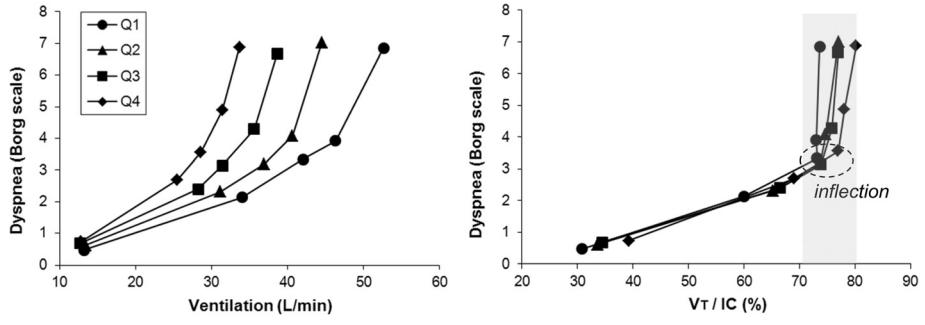

Fig. 6 Relationships between exertional dyspnea intensity and ventilation and the ratio of tidal volume to inspiratory capacity (V_T/IC) are shown during symptom-limited cycle exercise in COPD. There is a progressive increase in the dyspnea/ventilation curve with worsening disease. After the V_T/IC ratio 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 s (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 $V_T/\dot{V}_E$ inflection point and peak exercise. (From: [29])

magnitude seen in response to bronchodilators are associated with reduced intrinsic mechanical loading and increased functional strength of the respiratory muscles [15]. Such mechanical improvements are particularly important in dyspneic patients with more severe COPD who gain the greatest subjective benefit [75].

Improvement in 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). Thus, studies have shown a preserved or decreased FEV_1/FVC ratio in response to all classes of bronchodilators [83]. This pattern of lung volume recruitment is noted particularly in patients with more severe lung hyperinflation [81, 84]. 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 benefits for the patient [81, 84].

The combination of a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) can have additive effects on reducing lung hyperinflation [86, 87]. Van Noord et al. [86] were the first to study the combined effect of two long-acting bronchodilators (tiotropium and formoterol) on IC over a 24-hour period in patients with moderate-to-severe COPD. After the 2-week treatment periods, they confirmed additive effects on lung deflation with significant increases in average daily IC and daytime peak IC with the combination treatment versus tiotropium alone. Importantly, the mechanical benefits were also evident throughout the night. More recent studies have also shown slightly greater improvements in resting lung hyperinflation (increases in IC) with long-acting bronchodilator combinations or fixed-dose dual products such as indacaterol/tiotropium [88] and indacaterol/glycopirronium [89] over tiotropium monotherapy.

Effects on lung hyperinflation during exercise

There has recently been interest in measuring increases in IC as a surrogate measure of lung deflation during exercise in response to bronchodilator treatment in COPD [28, 81]. As mentioned, a post-bronchodilator increase in IC indicates reduced elastic/inspiratory threshold loading of the inspiratory muscles, an important determinant of dyspnea [6]. By increasing resting IC, bronchodilators also increase the available dynamic IRV and thereby delay the onset of critical respiratory-mechanical constraints on V_T expansion (and thereby $\dot{V}E$) during exercise [60, 78, 79, 90, 91]. Thus, throughout exercise, less respiratory muscle effort is required to achieve greater tidal volume expansion: the dissociation between central respiratory drive and the mechanical response of the respiratory system is partially reversed. Improvements in dyspnea and exercise tolerance after bronchodilators are closely related to this release of V_T restriction and enhanced neuromechanical coupling of the respiratory system [65]. Thus, for any given exercise intensity or $\dot{V}E$, patients breathe on the more linear portion of the respiratory system's pressure-volume curve, which delays the onset of neuromechanical dissociation and the attendant dyspnea [60, 78, 79, 90].

Effects on dyspnea and exercise endurance

Randomized controlled trials have examined the effects of LABA, LAMA and LABA/LAMA combinations on dyspnea intensity ratings during exercise and/or dyspnea related to activities of daily living in patients with moderate-to-severe COPD [78, 79, 90, 92]. Bronchodilator-induced improvements in perceived dyspnea intensity during constant work rate cycle exercise are variable, possibly due to measurement variability in this outcome as well as the modest numbers of patients in many of these studies. Despite variability in improvements in exertional dyspnea, increases in IC at a standardized time near end-exercise (isotime) and in exercise endurance time with long-acting bronchodilators compared with placebo appear to be more consistent (Fig. 7) [83]. Increases in cycle exercise endurance time in response to bronchodilator therapy are in the order of 20 %, on average [83]. Such increases in cycling endurance time are typically within the range that is thought to be clinically important, i.e., about 100 s [93, 94]. It is possible that LABA/LAMA fixed-dose combinations may extend the improvements seen with single agents [89], however, there is currently limited information on exercise responses with dual bronchodilator therapy. It is to be anticipated that the effects of inhaled dual LABA/LAMA bronchodilator agents will be most pronounced in patients with more severe resting lung hyperinflation and troublesome persistent dyspnea.

Conclusions

Summary and clinical relevance

Our understanding of the cause and consequences of lung hyperinflation in patients with COPD has considerably advanced in the last decade. It is now well established that lung hyperinflation and its effects provide a compelling physiological basis for the subjective experience of breathing discomfort during both exacerbations and physical activity in patients with COPD. It is now understood how acute-on-chronic lung hyperinflation in these clinical settings can abruptly undermine the normal functioning of the respiratory and cardio-circulatory systems with consequent negative clinical consequences. The corollary is that partial reversal of lung hyperinflation by pharmacotherapy and other interventions can effectively mitigate such negative effects. Thus, a persuasive case can be made to support the inclusion of indices of lung hyperinflation as

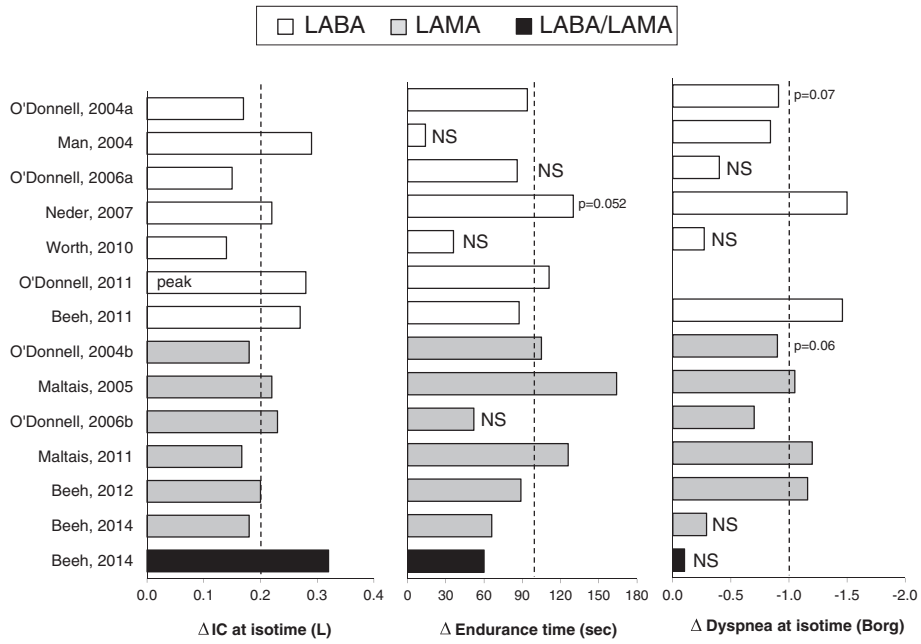

Fig. 7 Improvements in response to long-acting ß$_2$-agonists (LABA), long-acting muscarinic antagonists (LAMA) and LABA/LAMA combinations compared with placebo are shown for exercise measurements of inspiratory capacity (IC) at a standardized time during exercise (isotime), constant-work rate cycle exercise endurance time, and dyspnea intensity ratings at isotime. Treatment differences in these randomized, placebo-controlled studies are statistically significant ($p < 0.05$) unless indicated otherwise (NS, not significant)

valid physiological markers of disease severity that link to important clinical outcomes such as mortality, risk of exacerbation, activity-related dyspnea and exercise intolerance. Ideally, comprehensive characterization of physiological impairment in individual symptomatic patients with COPD should incorporate measures of lung hyperinflation. The exclusive reliance of spirometric forced expiratory flow rates to evaluate efficacy of bronchodilators in clinical trials in the past has led to underestimation of their clinical benefits, particularly in patients with more advanced COPD. In this context, the increasing use of direct or indirect measures of lung hyperinflation in assessment of patients with COPD and their response to pharmacotherapy in clinical and research settings represents a welcome advance.

Abbreviations

AE: Acute exacerbation; COPD: Chronic obstructive pulmonary disease; CT: Computed tomography; DH: Dynamic hyperinflation; EELV: End-expiratory lung volume; EFL: Expiratory flow limitation; FRC: Functional residual capacity; IC: Inspiratory capacity; IRV: Inspiratory reserve volume; LABA: Long-acting β_2-agonist; LAMA: Long-acting antimuscarinic; LV: Left ventricular; MRI: Magnetic resonance imaging; PEEPi: Intrinsic positive end-expiratory pressure; RND: Respiratory neural drive; RV: Residual volume; TLC: Total lung capacity; ULN: Upper limit of normal; $\dot{V}E$: Minute ventilation; V_r: Relaxation volume; VT: Tidal volume.

Competing interests

The authors declare that they have no competing interest.

Authors' contributions

All authors played a role in the content and writing of the manuscript. All authors read and approved the final manuscript.

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