Lung Hyperinflation in COPD: Mechanisms, Clinical Implications and Treatment

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Summary

Lung hyperinflation is highly prevalent in patients with chronic obstructive pulmonary disease (COPD) and occurs across the continuum of the disease. A growing body of evidence suggests that lung hyperinflation contributes to dyspnea and activity limitation in COPD and is an important independent risk factor for mortality. In this review, we will summarize the recent literature on pathogenesis and clinical implications of lung hyperinflation. We will outline the contribution of lung hyperinflation to exercise limitation and discuss its impact on symptoms and physical activity. Finally, we will examine the physiological rationale and efficacy of selected pharmacological and non-pharmacological 'lung deflating' interventions aimed at improving symptoms and physical functioning.

Keywords: COPD; lung hyperinflation; respiratory mechanics; respiratory muscles; dyspnea.

Introduction

COPD is a common respiratory condition that is characterized by inflammation of the large and small peripheral airways, the alveoli and adjacent capillary networks.[1,2] Expiratory flow limitation (EFL) is the pathophysiological hallmark of the disease and spirometric assessment of EFL at rest is used to establish a clinical diagnosis.[3] Lung hyperinflation is another important and related physiological manifestation of COPD that has major clinical consequences. Resting lung hyperinflation may be due to increased lung compliance (i.e., reduced lung elastance), the effects of EFL, or a combination of both. Lung hyperinflation can be acutely amplified above resting values when the respiratory system is stressed during a sudden worsening of symptoms or during physical activities. Indices of lung hyperinflation in patients with COPD have been shown to be predictive of respiratory and all-cause mortality,[4] and disease exacerbations.[5] Both resting and dynamic lung hyperinflation are more closely associated with symptoms and exercise performance than spirometric assessments of reduced maximal expiratory flow rates.[6] The progressive increase in resting hyperinflation as the disease advances, has major implications for dyspnea and exercise limitation in COPD.[7] During exercise, hyperinflation may cause functional respiratory muscle weakness, increased work of breathing, and impaired cardio-circulatory function, which collectively impair performance.[8-10] The negative consequences of dynamic hyperinflation may also be a factor in reduced participation in daily physical activity,[11] which is an important component of quality of life in COPD.[12] For these reasons, there is increasing interest in therapeutic manipulation of lung hyperinflation to improve clinical outcomes in this population.

The aim of this review was to concisely summarize the recent literature on pathogenesis and clinical implications of lung hyperinflation. We attempted to clarify definitions of lung hyperinflation (resting versus dynamic), review causative mechanisms, and describe the consequences of hyperinflation across the disease continuum. We outlined the contribution of lung hyperinflation to

exercise limitation and discussed its impact on symptoms of dyspnea and physical inactivity. Finally, we examined the physiological rationale and effectiveness of selected pharmacological and non-pharmacological 'lung deflating' interventions aimed at improving symptoms and physical functioning.

Resting and dynamic lung hyperinflation: definitions and determinants

For the purpose of this review, we define 'resting' lung hyperinflation as an increase in plethysmographically-determined end-expiratory lung volume (EELV) beyond the upper limits of the predicted normal range. Resting EELV and functional residual capacity (FRC) are used interchangeably in this review. Resting hyperinflation has static and dynamic determinants. Static components of lung hyperinflation in patients with emphysema can be attributed to an increase in the static relaxation volume of the respiratory system due to loss of lung elastic recoil.[13] Thus, reduced lung elastance combined with the natural outward elastic recoil of the chest wall resets the lung-chest wall balance to a higher EELV than the predicted normal. In this setting, alveolar pressure at end-expiration remains atmospheric and, depending on the severity of EELV increase and chest wall compliance, total lung capacity (TLC) may increase above the predicted value.[13]

Additionally, in patients in whom EFL is present during resting breathing, EELV is dynamically determined to a variable extent. In such patients, the mechanical time constant (i.e., the product of compliance and resistance) for lung emptying is prolonged but the time available for expiration during the breathing cycle may not be sufficient to allow EELV to decline to the predicted EELV of the relaxed respiratory system – lung hyperinflation is the result. In this circumstance, the alveolar pressure at end-expiration becomes higher than the atmospheric pressure and is termed: intrinsic positive end-expiratory pressure (PEEPi). In the presence of PEEPi, the inspiratory muscles must offset an inspiratory threshold load to initiate inspiratory flow with each breath.[14] The dynamic factors controlling EELV in COPD become even more important when the respiratory system is abruptly stressed by increased

ventilatory demands (e.g., physical activity, voluntary hyperventilation, during anxiety/panic attacks, transient hypoxemia) or when EFL is suddenly worsened (e.g., during exacerbation or increased bronchospasm). The resultant variable and temporary increase of EELV above resting levels is usually referred to as 'dynamic hyperinflation' (DH).

The value of measuring inspiratory capacity (IC) to estimate lung hyperinflation

Recently, the value of measuring IC when evaluating lung hyperinflation in patients with COPD at rest and during exercise has become increasingly popular.[7,15,16] Measurement of resting IC provides important information about the position of tidal volume (V_T) relative to TLC and the upper less compliant reaches of the respiratory system's pressure-volume (PV) relation.[16] It should be acknowledged, however, that measurement of plethysmographic lung volume components is required to determine if the cause of reduced IC is restrictive (pulmonary fibrosis, chest wall restriction or inspiratory muscle weakness) or obstructive (lung hyperinflation).

Development of hyperinflation from mild to advanced COPD

The natural history of the development of lung hyperinflation in COPD patients is unknown but it is probably a process that occurs over decades with a time course of change in the various volume compartments that is highly variable among patients. Genetic susceptibility, burden of tobacco smoke, and the frequency and severity of disease exacerbations may all be important determinants. It is noteworthy that increases in body mass index have been shown to be consistently associated with lower static lung volume components (expiratory reserve volume [ERV], and EELV) and increased IC, regardless of the severity of airway obstruction; therefore, this needs to be considered when evaluating hyperinflation.[17] Until recently, no large longitudinal studies had tracked the temporal progression of physiological abnormalities in COPD beyond a decline in the forced expiratory volume in one second

(FEV_1).[18] The recently completed UPLIFT trial documented a mean rate of decline in pre-bronchodilator IC of 34 to 50 mL/year in 3569 patients with moderate to very severe COPD that were followed-up in 490 investigational centers in 37 countries during a 4 year period.[19] Patients with the lowest baseline IC were those with highest exacerbation rates and mortality.[19] A recent cross-sectional study in 2265 patients with COPD found progressive increases in pulmonary gas trapping (increased residual volume [RV]) and resting lung hyperinflation (increased EELV), and a corresponding decrease in IC with increasing severity of airway obstruction (**Figure 1**).[20] Despite considerable variability in EELV and RV across severity grades, these lung volume changes have been shown to occur even in some patients with milder airway obstruction and to increase exponentially as the severity of airway obstruction increases (**Figure 1**).[7,20]

Hyperinflation in patients with milder airway obstruction

It is well established that the widespread inflammatory damage to the peripheral airways (< 2 mm diameter), lung parenchyma and pulmonary vasculature can be present with only minor airflow obstruction.[21] It is postulated that loss of peripheral airways precedes the onset of centrilobular emphysematous destruction.[21] Alveolar inflammation with destruction of alveolar walls and attachments to airways is thought to form the basis for the pathogenesis of lung hyperinflation.[22] Previous studies in mild COPD have reported increased static lung compliance,[23] and quantitative computed tomography (CT) scans show emphysema and gas trapping.[24-26] 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.[1] Corbin and coworkers, in a 4-year longitudinal study of smokers with chronic bronchitis, reported a progressive increase in lung compliance leading to gas trapping manifested by an increase in RV without significant changes in FEV_1.[23] Concomitant increases in TLC in this study population served to preserve forced vital capacity (FVC) and IC in the setting of

increased RV and FRC, respectively.[23] This suggests that the classic view of the natural history of COPD as a progressive decline in FEV_1 [18] may be over-simplistic as it may underestimate the extent of injury to the small airways and consequent pulmonary gas trapping.[27] The pathogenic mechanisms of progressive lung hyperinflation in advancing COPD have not been studied longitudinally but are thought to reflect the dual effects of progressive changes in the elastic properties of the lung and worsening EFL.

Pathophysiological implications of resting lung hyperinflation

Impact on respiratory muscle function

The impact of resting lung hyperinflation on respiratory mechanics and respiratory muscle function is variable in patients with COPD and can range from minor diaphragmatic dysfunction to severe hypercapnic respiratory failure. Resting lung hyperinflation can significantly diminish ventilatory reserve which can become further critically reduced during exacerbations,[28,29] or the stress of exercise (see below). Resting lung hyperinflation in moderate to severe COPD places the inspiratory muscles on an inefficient part of their length-tension relationships, thereby compromising their force generating capacity.[30-34] The mechanical advantage of the external intercostals and the accessory muscles is possibly less affected than that of the diaphragm but this has not been studied in much detail.[30,32] When EELV becomes positioned above ~55% of vital capacity (VC), the inspiratory muscles have to work, not only against the elastic recoil of the lungs, but also against the inward elastic recoil of the thoracic cage (**Figure 2**).[35] The net effect is that resting lung hyperinflation contributes to an increased elastic load (aggravated by PEEPi in more severe patients with EFL at rest) on the inspiratory muscles while simultaneously impairing their force generating capacity.[10]

Physiological adaptations of the diaphragm to resting lung hyperinflation

In the presence of chronic lung hyperinflation, functional muscle weakness (outlined above) is partly compensated by diaphragm shortening due in part to sarcomere loss, as well as to shortening of

diaphragmatic sarcomeres.[36] This results in a leftward shift of the length-tension relationship of the diaphragm and improves the ability to generate force at higher lung volumes. Force generating capacity at most overlapping absolute lung volumes (corresponding to FRC in severely hyperinflated patients) have been shown to be higher in patients than in healthy subjects.[34,37] These volumes, however, correspond to volumes at which the diaphragm is maximally shortened in healthy subjects (close to TLC). When comparing both groups at muscle lengths that are used during spontaneous breathing at rest (i.e., at FRC), force generating capacity is much higher in normal subjects than in patients with COPD.[36-38] Nevertheless, the diaphragm undergoes remarkable adaptations to chronic hyperinflation and functions better than expected under these circumstances.[36,38] One common feature in COPD is a shift towards improved endurance characteristics and increased oxidative capacity.[36] Alterations in muscle fiber composition (an increase in the relative proportion of slow-twitch, fatigue resistant, type I fibres),[39] and an increase in mitochondrial concentration and the efficiency of the electron transport chain,[40,41] are believed to contribute to the relatively well preserved force generating capacity and higher fatigue resistance of the overburdened diaphragm.[34] Despite these impressive adaptations, the presence of severe resting lung hyperinflation means that ventilatory reserve in COPD is diminished and the ability to increase ventilation (V'_E) when the demand suddenly arises is greatly limited.[7] Even though the described adaptations serve to optimize force-generating and endurance capacity, and are partially successful during resting breathing, the abruptly increased ventilatory needs during physical activities with accompanying dynamic hyperinflation and breathing pattern adaptations pose ‘acute-on-chronic’ challenges to the respiratory muscles that are discussed in more detail below.[36]

Impact on cardiac function

The complex cardiocirculatory consequences of dynamic lung hyperinflation will be discussed in detail when we consider the additional challenges brought about by physical exercise. Recent cross-sectional

and observational data suggest a negative relationship between lung hyperinflation and cardiac function. In a large population-based sample made up of both smokers and non-smokers, a greater extent of emphysema on CT scanning correlated inversely with reductions in left ventricular (LV) diastolic volume, stroke volume and cardiac output, as estimated by magnetic resonance imaging (MRI).[42] In a subgroup of this study population, pulmonary vein dimensions have recently been shown to be reduced in patients with emphysema, suggesting a pulmonary mechanism of under filling of the LV.[43] Severe hyperinflation, defined as an IC/TLC ratio <25%, has been shown to be associated with increased all-cause (including cardiovascular) mortality,[4] and impaired LV filling determined by echocardiography.[9] Severe lung hyperinflation has been linked to reduced intra-thoracic blood volume and reduced LV end-diastolic volume as assessed by MRI.[44]

Pathophysiological implications of dynamic lung hyperinflation during exercise

Measuring DH during exercise

DH can be defined as the temporary and variable increase of EELV above the resting value.[45] Changes in EELV during exercise can be reliably estimated from repeated IC measurements,[46,47] assuming that TLC remains constant.[48,49] The methodology to perform these measurements has recently been reviewed by Guenette et al.[16] Even though the IC measurement gives only indirect information about changes in absolute lung volumes, it nevertheless provides important mechanical information, irrespective of possible minor shifts in absolute TLC that may occur.[46,47] Valuable information about the mechanical limits on ventilation during exercise can be derived from combining serial IC measurements with those of dynamic inspiratory reserve volume (IRV, calculated as IC - V_T) and breathing pattern.[7,50-52] Comparing changes in IC and IRV at standardized levels of V'_E (iso-V'_E) during exercise reveals important information concerning the mechanical limits on V_T expansion, independent of the ventilatory demand.

The reproducibility and responsiveness of serial IC measurements in moderate to severe COPD has been demonstrated in small, single-center studies involving detailed physiological measurements, as well as in large, multicenter clinical trials.[46,47] Increases in EELV in the range of 0.3-0.5 L (corresponding to decreases in IC) have typically been reported during exercise in the majority of patients with moderate to severe COPD.[7,46,47,50,51,53] Similar average increases in EELV have been measured in symptomatic patients with mild COPD during incremental cycle exercise.[7,54,55]

The IC represents the operating limits for V_T expansion and influences breathing pattern and peak ventilatory capacity during exercise. In this context, it should be appreciated that the static PV relationship of the relaxed respiratory system is sigmoid-shaped (**Figure 2**). In health, V_T is normally positioned on the linear mid-section of the PV relation where the muscles of breathing function optimally and there is harmonious neuromechanical coupling of the respiratory system. In other words, lung-chest wall displacement is optimized for a given respiratory neural drive (and transpulmonary pressure gradient). This has important implications for minimizing the work of breathing and the respiratory sensations associated with increasing ventilation. During exercise in healthy subjects, V_T expands mainly within the linear part of the PV relation, thus avoiding the upper less compliant part of the S-bend closer to TLC where elastic loading of the inspiratory muscles is increased. In obstructive lung disease, the IC is limited from below as a result of lung hyperinflation. The reduced IC means that V_T operates closer to TLC where the respiratory muscles are disadvantaged, particularly in situations where ventilatory requirements suddenly increase (e.g., during exercise) and V_T must expand.

Potential benefits of dynamic lung hyperinflation during exercise

DH can be seen as both an essential component of adaptation to EFL and an impediment to normal inspiratory muscle function.[10] Increases in EELV at low exercise intensities help attenuate EFL and possibly improve ventilation-perfusion relationships and pulmonary gas exchange by reducing airway

resistance and improving ventilation distribution.[51,52] DH during early stages of exercise, by reducing airway resistance, should help to preserve the balance between central neural drive and the mechanical/muscular response of the respiratory system (i.e., neuromechanical coupling) and thus attenuate the rise in dyspnea.[51,52] However, this benefit is quickly neutralized when end-inspiratory lung volume (EILV) approaches its maximum value (>90% TLC) with corresponding increases in elastic and threshold loading on the inspiratory muscles.[10,56]

Negative effects of dynamic lung hyperinflation during exercise

Important negative consequences of DH include: 1) limits on V_T expansion resulting in early ventilatory mechanical limitation;[7,50-53] 2) increased elastic and threshold loading on the inspiratory muscles resulting in an increased work and oxygen (O_2) cost of breathing (reduced efficiency);[10,13,52,56-58] 3) increased functional inspiratory muscle weakness due to mechanical disadvantage and increased velocity of shortening of the muscles;[52,56,59-61] 4) negative impact of increased inspiratory muscle work on leg blood flow and muscle fatigue;[62-65] 5) carbon dioxide (CO_2) retention;[66] and 6) adverse effects on cardiac function and central hemodynamics.[9,67-69]

Dynamic lung hyperinflation and V_T constraints

As airway obstruction increases in severity, the progressive decline in resting IC causes the respiratory system to reach its physiological limits at a progressively lower peak V'_E during exercise.[7] This is related to the fact that the resting IC limits the possibility for V_T expansion during exercise in patients with EFL (**Figure 3**).[7,47,50-53] The lower the resting IC, because of resting lung hyperinflation, the lower the peak V_T and peak V'_E that can be achieved during exercise **(Figure 4)**.[7,47,50-53] When V_T during exercise reaches approximately 75% of the prevailing IC (or IRV reaches 5-10% of the TLC), there is an inflection or plateau in the V_T/V'_E relation **(Figure 4)**.[7,50-52] The V'_E during exercise at which the

V_T plateau occurs is closely related to the magnitude of the resting IC. In patients with a smaller IC, the V_T plateau occurs earlier in exercise at a relatively lower V'_E.[7,50-52] Associated tachypnea causes further functional weakening of the inspiratory muscles by forcing them to increase their velocity of contraction, and also contributes to reduction in dynamic lung compliance.[51,52,56,60,61,70] The resulting rapid, shallow breathing pattern combined with high physiological dead space can further compromise the efficiency of CO_2 elimination.[66] The point at which further V_T expansion is mechanically constrained marks the onset of a rising disparity between increasing central neural drive and the mechanical/muscular response of the respiratory system.[51,52] As disease progresses, this plateauing of V_T (with resulting neuromechanical dissociation) occurs at progressively lower work rates and V'_E.[7,11,47,50-53,55,71]

Mechanical consequences of dynamic lung hyperinflation on respiratory muscle function

The previously mentioned effects of resting lung hyperinflation on respiratory mechanics and muscle function are further aggravated by dynamic increases in EELV during exercise in patients with moderate to severe COPD. Acute-on-chronic (i.e. resting plus dynamic) lung hyperinflation increases elastic mechanical loading while simultaneously forcing inspiratory muscles to work at shortened lengths and perform contractions at higher velocities.[10,13,52,56-61] Thus, there is both an increase in demand and a further reduction in the capacity to meet the demand during exercise and this is imposed on top of the functional disturbances that are already present at rest.[60,61,72] Adaptations to chronic mechanical loading at rest can therefore become quickly overwhelmed during exercise.[59,60,73,74] The net effect of this increased load/capacity ratio is that further increases in V'_E can no longer be sustained. In particular, the increased O_2 cost of breathing and reductions in efficiency in the setting of reduced O_2 delivery might predispose the inspiratory muscles to fatigue during exercise in severe COPD.[10,13,57,58] However, there is no definitive evidence that diaphragm fatigue systematically

occurs in these patients.[75,76] Nevertheless, due to the high O_2 requirements of breathing at peak exercise a competition between limb and respiratory muscles for the available O_2 might contribute to the exercise limitation in these patients (see below).[10,13,58]

Dynamic hyperinflation and limb muscle function

Limb muscle weakness is present in many patients with COPD and the sensation of increased 'leg effort' has been shown to contribute to exercise limitation.[77-80] Circumstantial evidence has accumulated in recent years linking DH to impairments in peripheral O_2 delivery and muscle function during exercise.[64,65,81,82] Data from healthy young athletes suggest that high levels of respiratory muscle work during prolonged high-intensity endurance exercise reflexively induces sympathetically mediated vasoconstrictor activity, thereby compromising blood flow and O_2 delivery to the active limb muscles.[83] A reduction in locomotor muscle blood flow and O_2 delivery is hypothesized to result in an accelerated rate of development of limb muscle fatigue during exercise. The increase in work and O_2 cost of breathing associated with DH should theoretically aggravate these mechanisms.[84] Studies that have unloaded the respiratory muscles of hyperinflated patients with COPD during constant work rate exercise (i.e., same peripheral O_2 demand) have resulted in lower limb muscle fractional O_2 extraction in the absence of significant changes in arterial oxygenation. According to the Fick principle (O_2 extraction= O_2 uptake / blood flow), the most likely explanation for these results would be a higher muscle blood flow.[64,65,81] Louvaris and colleagues recently demonstrated that reducing operating lung volumes in hyperinflated COPD patients with heliox enhanced quadriceps muscle O_2 delivery during exercise.[82] Since cardiac output was similar between exercise conditions (heliox versus room air), the increases in muscle blood flow could have been caused by blood flow redistribution from the respiratory muscles.[82] Chiappa et al. found that increased muscle O_2 delivery during constant work rate exercise with heliox supplementation was associated with lower intensity of 'leg effort' at isotime and

electromyographic evidence of diminished recruitment of easily-fatiguing type II fibres.[64] In line with these data, mechanical unloading of the inspiratory muscles reduced post-exercise limb muscle fatigue in patients with COPD.[62]

Dynamic lung hyperinflation and cardiac function during exercise

The effect of acute-on-chronic lung hyperinflation and PEEPi on dynamic cardiac function during exercise remains largely speculative as much of the knowledge on the topic stems from intensive care studies. It should be noted that lung hyperinflation per se (i.e., independent of PEEPi) may have deleterious effects on the cardiopulmonary interactions in patients with COPD. For instance, lung hyperinflation increases pulmonary vascular resistance and, due to downward diaphragmatic displacement, intra-abdominal pressure.[85] Moreover, the hyperinflated lungs exert a direct compressive effect on the heart chambers and ventricular interdependence increases secondary to the lung 'stiffening' effect of hyperinflation.[86] **Figure 5** brings a schematic and simplified view of the potential negative effects of increased operating lung volumes and PEEPi upon patients' hemodynamics during exercise.[9,44,85-88] Despite these potential abnormalities, seminal studies reported that while stroke volume is generally smaller and heart rate correspondingly higher, cardiac output increased normally as a function of oxygen consumption ($V'O_2$) during submaximal exercise in COPD patients without cardiac morbidity.[87,89] Peak cardiac output typically reaches a lower maximal value during exercise, which may not necessarily indicate cardiac abnormalities as early ventilatory limitation might preclude greater cardiovascular stresses in more advanced COPD.[87,89,90] In contrast, recent studies reported a more consistent relationship between exercise-induced dynamic hyperinflation in combination with cardiac dysfunction and impaired central hemodynamics with reduced daily physical activity.[4,15,69,91,92] Patients with severe resting lung hyperinflation (IC/TLC ratio <25%), for instance, have been shown to have a decreased peak exercise O_2 pulse (a crude estimate of stroke volume),[69]

and reduced exercise tolerance.[4,15,69] Interventions that reduce resting hyperinflation, such as lung volume reduction surgery, have shown improvements in cardiac function such as increased left ventricular dimensions and filling,[44] and improved end-expiratory pulmonary artery wedge pressure.

Similarly, lung deflation following bronchodilation or heliox was associated with modest but consistent improvements in cardiac output and $V'O_2$ kinetics during the transition from rest to exercise.[64,93] Moreover, continuous and interval exercise training significantly improved systolic function of both right and left ventricle function in patients with moderate to severe COPD.[94] The implications of these improvements for exercise performance and daily physical activity remain unknown.[92]

Dynamic hyperinflation and dyspnea

Physiological correlates of dyspnea intensity in COPD

It is a long held belief that imbalances in the ratio of demand to capacity relate to the intensity and quality of dyspnea in COPD.[95]. It has been shown that dyspnea intensity ratings correlate well with a number of physiological ratios such as: 1) the ratio of V'_E to maximum ventilatory capacity (V'_E/MVC);[96] 2) the ratio of tidal esophageal pressure to maximum pressure (Pes/PImax) as an indicator of relative respiratory muscular effort;[61] 3) the ratio of Pes/PImax to the V_T response (V_T/IC or V_T/VC) relating the relative respiratory muscular effort to volume displacement;[51,52,56] and 4) the ratio of electrical activation of the diaphragm during tidal breathing relative to maximal activation (e.g., during a sniff maneuver), a measure of respiratory neural drive.[97,98] Dyspnea intensity ratings during exercise usually correlate well with indices of DH or its restrictive mechanical effects on V_T expansion (**Figure 6**).[7,51,52,56] The proximity of V_T to TLC and the upper portion of the respiratory system's PV relation during exercise, as reflected by changes in EILV or IRV, seem to correlate more strongly with dyspnea intensity ratings than changes in EELV or IC.[7,50-52] The extent to which DH will contribute to

dyspnea intensity seems to depend primarily on the resting IC, reflecting the extent of mechanical constraints on V_T expansion.[50,99]

Unsatisfied inspiration and lung hyperinflation

Unsatisfied inspiration ('can't get enough air in') is a qualitative descriptor of dyspnea during exercise that, in contrast to the situation in healthy subjects, is frequently reported by patients with COPD.[56] This sensation is perceived as unpleasant, in some cases is perceived as life-threatening and evokes powerful emotive responses (fear, anxiety, panic, frustration). During physical activity it alerts the patient that ventilation cannot be sustained and triggers abrupt behavioural modification (i.e., stopping the task, seeking emergency help). It has been speculated that the sensation of unsatisfied inspiration has its neurophysiological origins in the so called 'neuromechanical dissociation' of the respiratory system.[51,52,56] When V_T expansion becomes mechanically limited, dyspnea intensity rises sharply to intolerable levels and the dominant qualitative descriptor changes from increased work/effort to unsatisfied inspiration.[51,52]

The neurobiology of unsatisfied inspiration remains understudied. Many studies in healthy subjects have shown that artificially imposed mechanical constraints on the V_T response during chemostimulation of the respiratory centers result in sensations that mimic unsatisfied inspiration.[100-104] Perceived unpleasantness associated with the act of breathing is thought to involve cortico-limbic affective processing,[105] but has so far mainly been studied in healthy subjects,[106-108] and in asthmatics.[109,110] At the point during exercise when unpleasantness associated with the sensation of unsatisfied inspiration arises, central neural drive (and central corollary discharge) approximate maximum values while the mechanical and muscular response of the respiratory system becomes critically limited.[32]

Pharmacological and non-pharmacological treatment of hyperinflation

Pharmacological interventions

Bronchodilator/lung deflation therapy

Inhaled bronchodilators of all classes and duration of action favorably alter the dynamically-determined component of resting lung hyperinflation by reducing airway resistance, thus improving the mechanical time constants for lung emptying. Recruitment of resting IC and IRV in this manner results in delayed onset of mechanical limitation and corresponding intolerable dyspnea and exercise limitation (**Figure 7**).[52,111,112] DH is often not directly modified after administration of bronchodilators. Rather, pharmacotherapy delays the moment at which V_T expansion becomes mechanically limited during exercise by reducing EELV and increasing IRV at rest. The resulting increase in resting IC causes a parallel downward shift in operating lung volumes during exercise in comparison with exercise performed without bronchodilation **(Figure 8)**.[16,113] Thus, for any given exercise intensity or ventilation, patients breathe on the more linear portion of the respiratory system PV curve, which delays the onset of neuromechanical dissociation and the attendant dyspnea. The absolute magnitude of increase in EELV (and reduction in IC) during exercise in comparison with rest (i.e., DH) may even increase at peak exercise, reflecting the higher levels of ventilation that can be achieved following release of V_T restriction with pharmacological bronchodilation.[6,114,115]

Non-pharmacological interventions

Ventilatory support

The use of non-invasive ventilatory support consistently increases endurance time and reduces dyspnea perception during constant load cycling tasks in selected patients with COPD.[116,117] Assisting ventilation by either continuous positive airway pressure (CPAP) or pressure support is less likely to affect hyperinflation at rest or the increase in EELV during exercise.[118] Improvements in dyspnea

during exercise in response to these interventions are probably mostly related to adjustments in the demand/capacity imbalance, which are achieved by unloading the inspiratory muscles during exercise.[117,119-122] Optimal CPAP counterbalances the PEEPi thereby minimizing the threshold load on the inspiratory muscles while pressure support provides variable resistive and elastic unloading of ventilatory muscles during exercise.[118,123] Unloading of the respiratory muscles by proportional assisted ventilation (PAV) improved leg blood flow and exercise performance during sustained high intensity exercise in healthy trained cyclists.[124,125] In patients with COPD, Borghi-Silva and colleagues found positive effects of respiratory muscle unloading by PAV during a relatively short constant load cycling task on endurance time, leg muscle oxygenation, and dyspnea and leg fatigue symptoms.[81] Amann and colleagues found reductions in leg muscle fatigue after exercise in response to unloading the inspiratory muscles by combining PAV with heliox.[62] These data support the hypothesis of a competition between limb and respiratory muscles for the available O_2 delivery during exercise (see below).

Manipulations of inspired gas delivery

Supplemental O_2 during exercise consistently improved endurance and maximal exercise capacity and reduces ventilation and breathlessness at isotime during endurance exercise testing in COPD patients with and without resting hypoxemia.[126] O_2 supplementation during exercise delays ventilatory limitation and accompanying dyspnea mainly by reducing ventilatory demand.[115,127-130] O_2 supplementation has variable effects on DH and reduced DH is not a prerequisite for dyspnea relief (**Figure 8**).[115,118,127-130] Both improved oxygen delivery to the peripheral muscles (resulting in less reliance on anaerobic metabolism) with altered afferent inputs from leg muscle mechanoreceptors,[131] and attenuated peripheral chemoreceptor stimulation are possible explanations for the reduction in ventilatory demand for a given level of exertion.[129,130]

Heliox is a low density gas mixture (79% helium, 21% oxygen) that has been used in patients with COPD to reduce airflow resistance during the increasing ventilatory needs of exercise.[132] Heliox supplementation has been shown to improve exercise performance in patients with COPD in comparison with room air breathing.[133] Effects on dyspnea are likely but less clearly documented in the current literature.[133] Studies evaluating shortness of breath at isotime during an endurance cycling task, however, consistently showed significant reductions in dyspnea perception.[64,128,132,134] Heliox breathing increases the size of the maximal resting flow-volume envelope and seems to actually slow down the increase in EELV during exercise by decreasing airflow resistance, thereby directly altering DH.[127,132] Improvements in exercise capacity were correlated with the magnitude of changes in EELV during exercise.[132] In three studies, the response to hyperoxic helium (60-70% helium, 30-40% oxygen) and oxygen supplementation alone was compared during a constant load cycling task in patients with moderate (non-hypoxemic),[128] severe,[135] and very severe (patients on long term O_2 therapy) symptoms.[134] These studies all found significant differences in endurance time in favor of the hyperoxic helium group. [128,134,135] They further demonstrated reductions in the resistive work of breathing,[128] and reductions in exercise induced DH,[134,135] in comparison with hyperoxia alone.

Lung volume reduction surgery (LVRS)

In selected patients, LVRS has been shown to improve operating lung volumes, effort/displacement ratios, respiratory muscle function, exertional dyspnea, and exercise performance.[136-139] LVRS has been shown to increase maximal ventilatory capacity, as evidenced by increases in both maximal voluntary ventilation and maximal minute ventilation at peak exercise after surgery.[136,138-142] The positive effects of the intervention have been mainly ascribed to increases in lung elastic recoil (and driving pressure for expiratory flow) and a reduction in lung hyperinflation to have a positive impact on

inspiratory muscle function. The exact mechanisms of improved elastic recoil, however, remain incompletely understood.[143] Besides the effects on resting hyperinflation, the intervention may also exert a direct effect on DH during exercise.[136,138,139] While V'_E has been reported to be stable at comparable workrates after LVRS, decreases in EELV and increases in V_T have been observed with reductions in breathing frequency. LVRS thus improves airway conductance and lung emptying both at rest and during exercise.[143]

Exercise training

Rehabilitative exercise training improves exercise capacity and reduces symptoms of dyspnea in patients with COPD.[144] The improvements observed in constant load cycling tasks after properly conducted exercise training programs are larger than those observed with any of the previously described interventions.[145] Several physiological and psychological factors have been proposed to explain these improvements.[146-148] Reduction in DH has been put forward as one of them.[149-151] A recent study provides evidence that improvements in the affective aspect of dyspnea after exercise training can also occur without changes in dynamic respiratory mechanics.[152]

It is generally accepted that exercise training, unlike bronchodilators, does not have an impact on resting pulmonary mechanics.[149] Similar to the acute effects of O_2 supplementation, exercise training seems to reduce ventilatory needs for a given level of exertion.[127,149-151] This is probably mainly related to improvements in peripheral muscle function after training, with accompanying reduced reliance on anaerobic metabolism during exercise.[146,148] Less ventilation will allow patients to reduce their breathing frequency, increase V_T and reduce EELV for a given workload, and thereby result in reduced symptoms of dyspnea and improved exercise endurance.[146,148] Higher V_T decreases the dead space/V_T ratio, thus further reducing the ventilatory requirments during exercise. For a given level of ventilation, EELV does not seem to be altered after exercise training.[127,146-148]

Breathing exercises

Pursed lip breathing (PLB) is used spontaneously by patients with severe dyspnea, airflow obstruction, and lung hyperinflation.[153] Therapeutically, it is aimed at reducing breathing frequency and increasing V_T during exercise. On the basis of physiological models, this should be more efficient than the typically adopted rapid, shallow breathing pattern in these patients and should theoretically result in improvement of DH, reductions in the work of breathing and increased exercise capacity.[27] PLB has only been applied in very few small studies, with mixed results in terms of dyspnea reduction and improvements in exercise capacity.[153-156] Spahija et al. observed that during constant work bicycle exercise, a reduction in dyspnea sensation during application of PLB was related to observed changes in EELV and pressure generation of the inspiratory muscles.[153] Another small study applying breathing retraining based on yoga breathing also showed that patients were able to adopt a slower, deeper pattern of breathing.[157] Finally, a study by Collins and colleagues used a computerized ventilation feedback intervention aimed at slowing respiratory rate, in combination with an exercise training program, showed surprising reductions in respiratory rate, ventilation and DH at isotime during a constant load cycling task.[158] Feasibility and persistence of the these positive effects in the absence of the feedback still need to be determined in order to make this approach applicable for clinical practice.

Inspiratory muscle training (IMT)

Strengthening inspiratory muscles by specific training programs has been applied frequently in patients with COPD to alleviate dyspnea symptoms and improve exercise capacity.[159,160] The rationale for IMT is to compensate for the functional weakening that DH and the accompanying rapid, shallow breathing pattern impose on the inspiratory muscles.[61,72,159,160] Similar to assisting ventilation by CPAP or PAV, IMT is not likely to directly affect hyperinflation at rest or the increase in EELV during

exercise. Improvements in dyspnea during exercise in response to these interventions are probably mostly related to adjustments in the demand/capacity imbalance in the setting of high inspiratory muscle work induced by DH.[122,159-161] This is aimed to be achieved by either unloading (CPAP, PAV), or strengthening the inspiratory muscles (IMT). The direct effects of IMT on operating lung volumes during exercise have so far only been investigated in a single study.[162] Petrovic and colleagues showed that IMT could reduce the rate of DH but, unfortunately, did not provide data on inspiratory muscle work and neuromechanical dissociation during exercise.[162]

IMT has been shown to improve inspiratory muscle function (strength and endurance) and to reduce dyspnea and improve exercise capacity when applied as a stand-alone intervention with controlled training loads.[159] The intervention seems to be most effective in patients with compromised inspiratory muscle function.[159] Significant enhancement in the velocity of inspiratory muscle shortening during resistive breathing tasks, and increases in the size of type II muscle fibres following IMT have been previously observed in patients with COPD.[163,164] These improvements might be of clinical relevance to patients with respiratory muscle weakness secondary, in part, to lung hyperinflation since improved muscle performance characteristics may improve dynamic function during exercise. Detailed measurements of inspiratory muscle function during exercise in response to inspiratory muscle training have however not been performed so far.

Expert commentary

Over the past decade, lung hyperinflation has emerged as an important physiological marker that is linked to clinical outcomes in COPD and that can be partially reversed. Measures of lung hyperinflation are increasingly used in clinical trials designed to evaluate efficacy of bronchodilator therapy in improving dyspnea and exercise tolerance in COPD. Our understanding of the mechanisms by which resting and dynamic hyperinflation compromise respiratory muscle and cardio-circulatory function

during physical activity (and the attendent negative sensory consequences) has substantially increased. We now know that variability in dyspnea and exercise capacity among patients with COPD with similar FEV_1 can be explained, at least in part, by the concomitant magnitude of lung hyperinflation and reduction in inspiratory capacity.

Five-year view

Lung hyperinflation remains an active and fruitful area of translational research in COPD. Studies are currently in progress to chart the natural history of lung hyperinflation and its biological, physiological and sensory underpinnings. Currently, there is great interest in identifying clinical phenotypes in COPD that will ultimately permit a more personalized approach to management. In this context, ongoing studies will help determine if the patient with dominant lung hyperinflation will qualify as a distinct phenotype, amenable to specific therapeutic approaches. Physiological studies will continue to address the challenge of managing acute severe hyperinflation during exacerbation, which in many instances can be life threatening. Thus, future refinements of lung deflation strategies during both invasive and non-invasive mechanical ventilation for patients with actual or impending respiratory failure will potentially improve outcomes in acute care settings. Given the clear links between chronic lung hyperinflation and exercise intolerance, researchers will continue to optimize pharmacological and non-pharmacological interventions (e.g., endoscopic lung deflation techniques) for lung deflation. Optimization of respiratory mechanics in this manner should improve the success of exercise training protocols which is often elusive in chronically dyspneic patients with advanced COPD.

Key issues

- Lung hyperinflation is closely associated with expiratory flow limitation and has major clinical consequences for breathlessness and exercise intolerance.

- Measurements of IC provide a clinically useful strategy to quantify resting hyperinflation and track dynamic hyperinflation during exercise.
- Acute-on-chronic hyperinflation (e.g. exercise, exacerbations) negatively impacts the demand/capacity imbalance of the already compromised respiratory muscles and influences clinical outcomes.
- A growing disparity between increased central neural drive and the reduced respiratory muscular/mechanical response due to hyperinflation contributes importantly to the perception of respiratory discomfort during exertion.
- Dynamic hyperinflation-related increases in PEEPi may have important negative hemodynamic effects.
- Decreases in resting lung hyperinflation with bronchodilators result in a downward shift in operating lung volumes and a delay in the attainment of critical volume constraints during exercise.
- In addition to variable effects on resting lung hyperinflation, heliox, lung volume reduction surgery and slow and deep breathing can decrease the rate of dynamic hyperinflation for a given level of ventilation in selected patients.
- Pressure-generating capacity of the overburdened inspiratory muscles can be passively (assisted ventilation) or actively (inspiratory muscle training) improved with beneficial effects on dyspnea.
- Decreases in the ventilatory demands with exercise training and oxygen supplementation in some patients result in less dynamic hyperinflation for a given work rate and better tolerance to physical exertion.

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Reference annotations

7. **O'Donnell DE, Guenette JA, Maltais F, Webb KA. Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise. Chest 2012;141:753-762.****
Results of this study illustrate how the progressive increase in resting hyperinflation as the disease advances has major implications for dyspnea and exercise limitation in COPD.

10. **Loring SH, Garcia-Jacques M, Malhotra A. Pulmonary characteristics in COPD and mechanisms of increased work of breathing. J Appl Physiol 2009;107:309-314.***
This paper summarizes the mechanisms of increased work of breathing in COPD, as caused by increases in resistive and elastic loading, using pressure-volume plots popularized by E.J.M. Campbell.

50. **Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur Respir J 2012;40:322-329.****
This paper illustrates how the proximity of V_T to TLC and the upper portion of the respiratory system's pressure-volume relation during exercise, as reflected by changes in EILV or IRV, correlate more strongly with dyspnea intensity ratings than changes in EELV or IC.

51. **Laveneziana P, Webb KA, Ora J, Wadell K, O'Donnell DE. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. Am J Respir Crit Care Med 2011;184:1367-1373.****
This study illustrates how the intensity and quality of exertional dyspnea evolve separately and are strongly influenced by mechanical constraints on Vt expansion during exercise in COPD due to hyperinflation.

95. **Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435-452.****
This statement provides an update on the mechanisms, assessment, and management of dyspnea and illustrates how imbalances in demand-to-capacity ratios caused by hyperinflation relate to the intensity and quality of dyspnea in COPD.

134. **Queiroga F, Jr., Nunes M, Meda E, et al. Exercise tolerance with helium-hyperoxia versus hyperoxia in hypoxaemic patients with COPD. Eur Respir J 2013;42:362-370.****
This paper illustrates the effects of heliox breathing on dynamic hyperinflation during exercise in patients with severe COPD on long term oxygen therapy.

160. **Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013;188:e13-e64.***
This statement summarizes the rehabilitative treatment options available for improving dynamic hyperinflation, dyspnea, exercise capacity, and quality of life in patients with COPD.

Figure legends

Figure 1. Relationships between total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC) and inspiratory capacity (IC) are shown against FEV_1 in COPD (all measurements shown are post-bronchodilator and are expressed as % of predicted normal values). As FEV_1 decreased, TLC, RV and FRC increased exponentially and IC decreased linearly. These relationships were not affected by gender. Constructed with data from reference [**20**].

Figure 2. Static lung volumes and adjacent pressure-volume (PV) plots are shown for a typical COPD patient and a healthy normal individual. Tidal (filled area) and exercise (open area) PV curves are shown on the total respiratory system PV curve. In COPD, an increased resting EELV is further increased (IC decreases) during exercise so that tidal volume encroaches on the upper, alinear extreme of the respiratory system's PV curve where there is increased elastic loading. In health, EELV decreases (IC increases) during exercise and tidal volume remains primarily within the linear portion of the respiratory system's PV curve. Abbreviations: EELV, end-expiratory lung volume; ERV, expiratory reserve volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; RV, residual volume; TLC, total lung capacity; ΔIC, change in IC from rest to exercise; ΔP, change in pleural pressure during a tidal breath during exercise; ΔV, change in volume during a tidal breath during exercise.

Figure 3. Changes in lung volumes at rest and during exercise are shown in healthy normal individuals and in patients with COPD. TLC, total lung capacity; VC, vital capacity; RV, residual volume; EELV, end-expiratory lung volume; IC, inspiratory capacity. From reference [**165**].

Figure 4. Inspiratory capacity (IC), inspiratory reserve volume (IRV), tidal volume (V_T), and breathing frequency (F_b) are shown relative to minute ventilation during constant work rate symptom-limited cycle exercise across the continuum of health and COPD severity. The IC at rest and throughout exercise progressively decreases with advancing disease. Note the clear inflection (plateau) in the V_T-ventilation relationship, which coincides with a simultaneous inflection in the IRV-ventilation relationship. After this point, further increases in ventilation are accomplished by accelerating F_b. Data from age-matched healthy normal subjects and GOLD stage I (i.e., mild COPD) are from Ofir et al. [**55**]. 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) from O'Donnell et al. [**7**]. Abbreviations: VC, vital capacity; TLC, total lung capacity; GOLD, Global Initiative for Obstructive Lung Disease. Reproduced from reference [**16**].

Figure 5. Schematic representation of the potential deleterious effects of lung hyperinflation and PEEPi on cardiopulmonary interactions during dynamic exercise 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 and comorbidities (e.g., pulmonary hypertension and chronic heart failure) 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.

Figure 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 separation of dyspnea/ventilation plots 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) from O'Donnell et al. [**7**].

Figure 7. Improvements in cycle exercise endurance time and dynamic IC measured at isotime during exercise are shown in response to treatment with long-acting bronchodilators versus placebo. White bars = long-acting $beta_2$-agonists (LABA); gray bars = long-acting muscarinic antagonists (LAMA); black bar = LABA/LAMA combination; peak = peak exercise instead of isotime during exercise. Treatment effects (Δ) were statistically significant ($p<0.05$) unless marked NS (not significantly different from placebo). Constructed with data from references [**52,112-114,166-175**].

Figure 8. Operating lung volumes are shown during constant work rate cycle exercise in COPD patients following acute high-dose anticholinergic therapy versus placebo (*left*) and during hyperoxia versus room air breathing (*right*). End-expiratory (EELV) and end-inspiratory lung volumes (EILV) were reduced at rest (0 min) and throughout exercise following anticholinergic therapy; the parallel shift downwards meant that the magnitude of dynamic hyperinflation (DH) at peak exercise (i.e., the difference in EELV from resting values) did not change following bronchodilation. The magnitude of dynamic hyperinflation was also similar at peak exercise during hyperoxia compared with room air in hypoxemic patient with COPD. Abbreviations: IRV, inspiratory reserve volume; TLC, total lung capacity; V_T, tidal volume. Reproduced from reference [**16**].