EXPERT REVIEWS

New physiological insights into dyspnea and exercise intolerance in chronic obstructive pulmonary disease patients

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Dyspnea and reduced exercise tolerance are common consequences of chronic obstructive pulmonary disease (COPD) and contribute importantly to poor perceived health status. While the origins of dyspnea and reduced exercise tolerance are complex and multifactorial, there is increasing evidence that lung hyperinflation is an important contributory factor that can be targeted for treatment. In this review, the authors summarize current concepts of the origin and clinical and physiological consequences of both static and dynamic lung hyperinflation in COPD. In particular, they review recent studies that have examined the role of lung hyperinflation in dyspnea causation during exacerbations and physical activity in COPD. Finally, current concepts of the mechanisms of symptom relief and improved exercise tolerance following pharmacological lung volume reduction are reviewed.

Keywords: bronchodilators • chronic obstructive pulmonary disease • dynamic hyperinflation • dyspnea • exacerbations • exercise tolerance • lung volume reduction surgery • respiratory mechanics • spirometry

Definitions

Abnormal increase in lung volumes is present if measurements of functional residual capacity (FRC), residual volume (RV), total lung capacity (TLC) or RV/TLC are above the upper limits of natural variability [1,2]. Traditionally, increase in TLC (preferably measured by body plethysmography), exceeding either the higher limit of normalcy (HLN), or an empiric 120% of predicted is defined as lung overinflation. In chronic obstructive pulmonary disease (COPD), an abnormally increased TLC is due to static factors pertaining to alterations in lung and chest wall compliance, but sometimes it is dynamically determined. Increase in plethysmographic FRC, above either HLN or an empiric 120% of predicted, is also believed to indicate clinically significant lung hyperinflation. An increase in plethysmographic RV, exceeding either HLN or an empiric 120% of predicted, is usually termed pulmonary gas trapping, which is also signified by an increased RV/TLC ratio. Increased gas trapping may result from either static or dynamic factors or both, and consequently, can change with pharmacological treatment. Of note, gas trapping can occur with or without lung hyperinflation and lung overinflation. In practice, values exceeding 120–130% predicted are deemed to be potentially clinically important, but these 'cutoffs' remain arbitrary [3].

The inspiratory capacity (IC) or IC/TLC ratio are also used as indirect measures of lung hyperinflation. For the purpose of this review, dynamic hyperinflation (DH) is defined as a temporary and variable increase in end-expiratory lung volume (EELV; or decrease in IC) relative to the resting baseline value when ventilation (V'_E) is acutely increased. The extent of acute DH is measured by reduction in IC from the resting value [4,5], on the assumption that TLC remains constant [6–8]. The corollary of this is, therefore, that changes in IC accurately reflect changes in EELV during exercise, provided that patients are motivated to make maximal inspiratory efforts during the measurement; they do not suddenly change their breathing pattern in anticipation

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of the measurement; and they do not suffer from clinically significant inspiratory muscle weakness. It should be noted that the IC measurement gives only indirect information about changes in absolute lung volumes but, nevertheless, provides important mechanical information, irrespective of possible minor shifts in absolute TLC that may occur. The IC represents the limits for tidal volume (V_T) expansion in patients with expiratory flow limitation and indicates the proximity of the operating lung volume to TLC and the upper, alinear extreme of the pressure–volume relationship of the respiratory system. When measurements of IC are coupled with those of dynamic inspiratory reserve volume (IRV; i.e., IC–V_T), further valuable information is provided about prevailing mechanical constraints on V'_E. In addition, comparing changes in IC (or IC/TLC) and IRV (or IRV/TLC) within and between patients at a standardized V'_E (iso-V'_E) during exercise gives us important information on the mechanical constraints on V_T expansion that are independent of the level of ventilatory output/demand, therefore reassuring us that any reduction/increase in IC or IRV is not simply the result of higher/lower levels of V'_E.

Natural history of lung hyperinflation in COPD

No longitudinal studies have charted the temporal progression of lung volume changes in large populations of patients with COPD. However, a recent cross-sectional study in 2265 patients found progressive increases in resting gas trapping and lung hyperinflation (measured by RV and FRC) across the continuum of COPD severity (Figure 1) [9]. In fact, gas trapping and lung hyperinflation were shown to occur even in the earliest stages of COPD (i.e., Global Initiative for Obstructive Lung Disease [GOLD] grade I) [9–12] and increased exponentially with severity of airway obstruction (Figure 1) [9,12]. Figure 1 demonstrates that there is considerable heterogeneity in FRC and RV across GOLD grades; but the vast majority of patients have values that are well above the predicted normal values. The magnitude of plethysmographic lung volume components (i.e., expiratory reserve volume [ERV], RV and FRC) in both healthy individuals and in patients with COPD is strongly influenced by body mass: increased BMI is associated with lower static lung volume components, regardless of the severity of airway obstruction [13].

Smaller physiological studies have confirmed extensive small airway dysfunction, increased lung compliance, gas trapping and ventilation–perfusion abnormalities in smokers with minor airway obstruction, by spirometric criteria [9,14–18]. Gas trapping, as assessed by expiratory CT scans, can exist in the absence of emphysema and is believed to indirectly reflect small airway dysfunction in mild COPD [16]. In symptomatic patients with mild COPD, significant dynamic increases in EELV by approximately 0.4 l (or reciprocal decreases in IC) have been measured during incremental cycle exercise suggesting significant small airway dysfunction [10–12]. Similar levels of DH have been reported during exercise in the majority of patients with moderate-to-severe COPD [12]. Here, the negative mechanical consequences are related to the relatively decreased resting IC [12]. In advanced COPD, severe lung hyperinflation (i.e., a reduced IC as percent predicted or an IC/TLC ratio <25–28%) is a risk factor for exacerbation [19,20] and is associated with reduced exercise tolerance [21], poor health status and increased respiratory and all-cause mortality [19,22].

Physiological consequences of resting lung hyperinflation

Lung hyperinflation (static and/or dynamic EELV increase) places the inspiratory muscles, especially the diaphragm, at a significant mechanical disadvantage by shortening its fibers, thereby compromising its force generating capacity [23]. In the presence of static lung hyperinflation, this functional muscle weakness is mitigated,

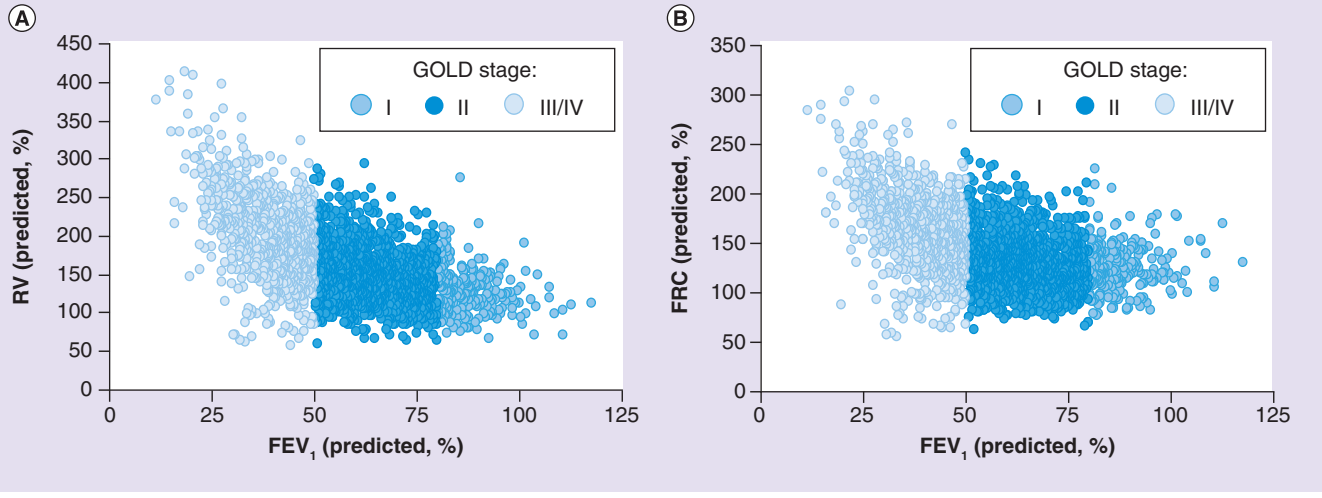

Figure 1. There is an exponential relationship between static lung volumes and disease severity. (A) Residual volume and **(B)** functional residual capacity versus forced expiratory volume in 1 s across GOLD grades (I, II and III/IV). The majority of patients (including many patients with GOLD grade I) were >120% predicted suggesting evidence of static lung hyperinflation.
FEV_1: Forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RV: Residual volume.
(A) Reproduced with permission from [9].

to some extent, by long-term adaptations such as shortening of diaphragmatic sarcomeres [24] and a decrease in sarcomere number [25], which causes a leftward shift of the length–tension relationship, thus improving the ability of the muscles to generate force at higher lung volumes. 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) [26,27] and oxidative capacity (an increase in mitochondrial concentration and efficiency of the electron transport chain) [24] are believed to preserve the functional strength of the overburdened diaphragm [28], making it more resistant to fatigue [24,26,29]. In this regard, Similowski *et al.* demonstrated that the reduction in pressure-generating capacity of the inspiratory muscles of stable COPD patients was related to lung hyperinflation and that diaphragmatic function in such patients was comparable with normal subjects when measurements were compared at the same lung volume [28].

Lung hyperinflation means that tidal breathing must take place near the upper alinear extreme of the respiratory system's sigmoidal static pressure–volume relation where there is increased elastic load. In addition, an inspiratory threshold loading (auto-positive end-expiratory pressure [PEEP] effect) placed on the inspiratory muscles occurs when EELV dynamically increases [30–33]. High lung volumes in COPD serve to attenuate expiratory flow limitation during resting breathing, but this beneficial effect is negated if further acute-on-chronic DH occurs during physical activity [10–12,30,34–36] infective exacerbation [37–39]. In this latter circumstance, acute excessive loading and functional weakness of the inspiratory muscles may be linked to respiratory fatigue or mechanical failure [37].

Acute dynamic hyperinflation during exacerbations

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with severe dyspnea, activity restriction, poor perceived health status, accelerated physiological impairment and increased mortality [19,20,37–41]. These events are associated with worsening expiratory flow reduction, and, in many cases, increased ventilatory requirements [37–39]. These, in combination, give rise to acute DH and dyspnea [37–39]. The impact of AECOPD-associated DH on respiratory physiology depends on the baseline (pre-AECOPD) mechanical status of the patient and the presence of comorbidities such as cardiovascular disease [37,38]. As already mentioned, acute DH will compromise respiratory muscle function by increasing the elastic and threshold loads which, together with functional weakening of the diaphragm, may precipitate hypercapnic respiratory acidosis [37,38].

The central neural drive to breathe is generally increased during AECOPD [42] as a result of concomitant ventilation–perfusion inequalities [43]. However, the mechanical/muscular response of the respiratory system is substantially blunted because of the excessive respiratory muscle loading and the volume restricting effect of a sharply reduced IC, reflecting the acute increase in EELV [37–39]. The progressive disparity between increased central neural drive and the abnormal mechanical response (i.e., neuromechanical uncoupling) probably explains, at least in part, the distressing perception of respiratory discomfort that dominates AECOPD [37,38]. Two studies showed that improvement in dyspnea following AECOPD has been linked to the simultaneous progressive improvement in resting IC as dynamic hyperinflation decreases [38,39].

Acute DH may also raise intrathoracic pericardial pressures (equivalent of tamponade), causing mechanical compression of intra-alveolar vessels which, in conjunction with the effects of acute hypoxia, may acutely increase pulmonary arterial resistance and pressure [44]. In addition, the wide intrathoracic pressure swings required to overcome the increased mechanical load, can compromise left ventricular function [44]. It is not surprising that AECOPD is frequently associated with acute cardiac stress, especially in those with preexisting ischemic heart disease [45].

Lung hyperinflation & reduced exercise tolerance

In healthy young individuals, V'_E increases during exercise by a progressive expansion of V_T to approximately 60% of the vital capacity or 75% of TLC [46–49]. At this operating lung volume, the diaphragm muscle fibers are maximally shortened and further increases in V'_E may be achieved solely through increases in breathing frequency. To ensure a progressive and harmonious expansion of V_T, EELV usually decreases leading, therefore, to a concurrent increase in IC during exercise [46–49]. The magnitude of EELV reduction varies with the type and intensity of exercise, with average reductions between 0.3 and 1 l below relaxation volume of the respiratory system [46–49]. The most important advantage of the decrease in EELV (or increase in IC) during exercise is that of allowing V_T to increase by encroaching almost equally on the ERV and IRV, respectively, without end-inspiratory lung volume (EILV = EELV + V_T) encroaching on the stiffer upper portion of the respiratory system's pressure–volume relationship, where there is increased elastic loading [46–49]. Healthy young subjects are able to increase their V_T during exercise by encroaching on the ERV (thus reducing the EELV) because they have sufficient expiratory flow reserve at that lung volume to accommodate their V_T within the ERV available [46–49]. In other words, the flow rates and the volume changes seen during maximal exercise are well within the maximal flow-volume loops obtained at rest, showing no significant expiratory flow limitation (i.e., impingement of tidal flow-volume loops on the maximal flow-volume loop) [46–49].

The situation is different in elderly (but healthy) subjects, in whom progressive structural changes in the connective tissue matrix of the lung parenchyma cause loss of the static lung elastic recoil pressures, which drive expiratory flow [50–53]. The net result of this physiological age-related decline of expiratory flow, particularly over the effort-independent portion of the maximal expiratory flow-volume curve, is the occurrence of expiratory flow limitation. In addition, FRC and RV are usually increased with reciprocal decreases of IC and vital capacity, respectively, while TLC is generally preserved in the elderly [53,54].

In contrast to youth, elderly individuals are less able to reduce EELV (or increase IC) during exercise because of expiratory flow limitation [55–57]. At high levels of V'_E, therefore, reduction in dynamic IC can occur as a result of reduced lung emptying and

gas trapping. This can constrain V_T expansion and increase the elastic work on the inspiratory muscles [55–57].

Although older individuals may demonstrate significant ventilatory constraints during exercise [55–57], it is only in highly fit older individuals with high peak oxygen consumption and V'_E that ventilatory constraints may actually limit exercise performance [55,56].

Exercise limitation is multifactorial in COPD, but respiratory mechanical impairment and the associated dyspnea are major contributors, particularly in advanced disease [35,44,58–61]. The resting IC dictates the limits of V_T expansion during exercise in flow-limited patients with COPD [5,12,34–36,62–65]. Thus, the lower the resting IC because of lung hyperinflation, the lower the peak V_T, and thus V_E, achieved during exercise (Figure 2) [5,12,34–36,62–65]. DH further erodes the already diminished resting IC [5,65]. When V_T reaches approximately 70% of the prevailing IC (or IRV: ~10% of TLC), there is an inflection or plateau in the V_T/V'_E relation (Figure 2) [12,34,36,65]. This critical volume restriction represents a mechanical limit where further sustainable increases in V'_E are impossible [12,34,36,65]. The inability to further expand V_T is associated with tachypnea that has added detrimental effects on inspiratory muscle function including: further elastic loading due to DH, increased velocity of shortening of the inspiratory muscles with associated functional weakness and decreased dynamic lung compliance [30,34]. V_T restriction may also amplify the relative physiological dead space and further compromise the efficiency of CO_2 elimination [66].

At the limits of exercise tolerance in COPD, central neural drive has increased to near maximal values reflecting a four- to five-fold increase in carbon dioxide production ($V'CO_2$) from resting values as a result of the increased ventilation/perfusion abnormalities and metabolic acidosis due to lactate and strong

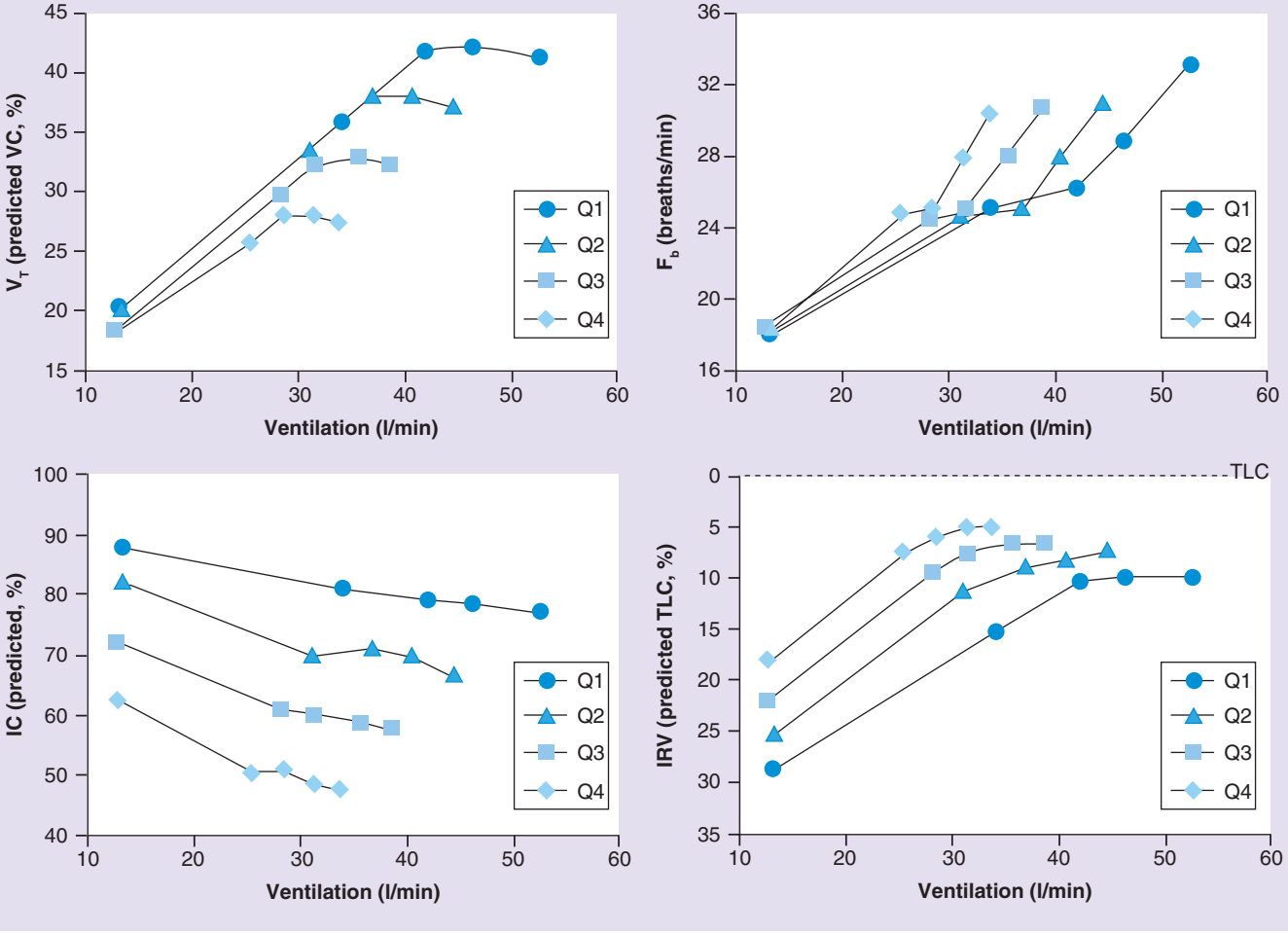

Figure 2. Tidal volume, breathing frequency, dynamic inspiratory capacity and inspiratory reserve volume are shown plotted against minute ventilation (V'_E) during constant work rate exercise for each forced expiratory volume in 1 s (expressed as percent predicted) quartile. The upper through to lower quartiles (Q1–Q4) represent the mildest to most severe groups, respectively. Note the clear inflection (plateau) in the V_T/V_E relationship, which coincides with a simultaneous inflection in the IRV. After this point, further increases in V'_E are accomplished by accelerating F_b. Data plotted are mean values at steady-state rest, isotime (i.e., 2, 4 min), the V_T/V'_E inflection point and peak exercise.
F_b: Breathing frequency; IC: Inspiratory capacity; TLC: Total lung capacity; VC: Vital capacity; V_T: Tidal volume
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ion accumulation [67–70]. In some patients, critical arterial O_2 desaturation during exercise is an additional stimulus to V'_E [71]. Because of the outlined mechanical abnormalities, the ability of the respiratory system to respond to the increased drive is severely limited. Theoretically, these collective physiological derangements of respiratory mechanics can predispose to inspiratory muscle fatigue. However, the evidence that measurable fatigue develops in COPD is inconclusive [72,73], even at the limits of tolerance [29,74]. Acute-on chronic hyperinflation may also have deleterious effects on cardiac performance during exercise [44,75–81], especially in the setting of excessive expiratory muscle activation that limits venous return [82]. The relative importance of such cardiac impairment in contributing to exercise limitation in COPD is uncertain.

Lung hyperinflation, critical volume constraints & dyspnea

Dyspnea is a common symptom in patients with COPD and is often the proximate cause of exercise limitation [5,12,61,65]. The recent American Thoracic Society statement has emphasized the multidimensional nature of the symptom in the sensory-perceptual (intensity and quality), affective distress and impact domains [83]. The dominant qualitative descriptors of dyspnea in COPD patients at end exercise are the following: increased effort ("breathing requires more effort or work") and unsatisfied inspiration ("can't get enough air in") [30,34,36,83,84].

Increased sense of effort in COPD is related to an increased central neural drive (chemo-stimulation) to the respiratory muscles as a result of progressive disruption of normal ventilation/perfusion relations and acid–base disturbance during exercise [30,34,36,83,84]. Thus, increased perceived effort in COPD patients during activity partly reflects the higher ventilatory requirements, for a given power output, compared with healthy individuals [30,34,36,83,84]. In addition, contractile muscle effort is increased for any given V'_E in COPD because of the increased intrinsic mechanical (elastic/threshold) loading and functional muscle weakness, in part, due to DH at rest and during exercise [30,34,36,83,84]. Because of these effects, greater neural drive or electrical activation of the muscle is required to generate a given force [30,34,36,83,84]. There is evidence from animal studies that the amplitude of central motor command output (originated from motor cortical and medullary centers in the brain) to the respiratory muscles is sensed via neural interconnections (i.e., central corollary discharge) between cortical motor and medullary centers in the brain and the somato-sensory cortex [30,34,36,83,84].

The other dominant respiratory sensation in COPD, unsatisfied inspiration, may have different neurophysiological underpinnings [30,34,36,83,84]. The V_T/V'_E inflection during exercise marks the point where dyspnea intensity sharply increases towards the end of exercise and the dominant descriptor selected by patients changes from increased effort to unsatisfied inspiration (Figure 3) [36]. The V_T inflection represents the onset of a widening disparity between increasing central neural drive and the mechanical/muscular response of the respiratory system [34,36]. In advanced COPD, the ratio of respired effort (and presumably central neural drive) to V_T increases steeply from rest to peak exercise reflecting progressive neuromechanical uncoupling of the respiratory system (Figure 4) [34,36]. This is in contrast to healthy people, in whom this ratio is largely preserved throughout exercise: V_T expands normally within the linear compliant portion of the respiratory system's pressure–volume relation [30]. Thus, in healthy individuals, unsatisfied inspiration is rarely selected as a representative descriptor even at the limits of tolerance [30]. It is postulated that both increased central corollary discharge (reflecting increased activation of motor and medullary respiratory centers) and altered afferent sensory information (from an abundance of mechanoreceptors throughout the impaired respiratory system) are centrally processed, integrated and conveyed to consciousness where the determination is made that breathing is threatened: vigorous inspiratory efforts become unrewarded [30,34,36,83,84]. This threat response evokes affective distress (anxiety, fear and panic) that is characterized, in brain imaging studies in simulated dyspnea in healthy people, by sudden activation of the limbic and para-limbic system [85].

Dyspnea intensity appears to be more closely correlated with the change in IRV during exercise than the change in EELV (i.e., DH) *per se* [12,34,36,65]. However, in patients with a low resting IC, further acute decreases in IC (increases in EELV) can force earlier mechanical limitation and onset of intolerable dyspnea [12,34,36,65]. Many previous studies have shown that sense of air hunger or unsatisfied inspiration is provoked in healthy individuals under any circumstance where normal spontaneous V_T expansion is constrained (either volitionally or extrinsically) in the face of normal or increasing central neural drive [30,34,36,83,84]. For example, the addition of a chest wall strap to constrain V_T together with added dead space to stimulate V'_E evokes sensations of unsatisfied inspiration during exercise in healthy subjects [86].

Effects of interventions on lung hyperinflation & dyspnea

The contention that static and dynamic lung hyperinflation contribute substantially to exercise curtailment in COPD is bolstered by several studies that have demonstrated that pharmacological lung volume reduction is associated with significant improvements in exertional dyspnea and exercise endurance. Other interventions that have been shown to decrease resting lung hyperinflation or the rate of DH during exercise in COPD include: oxygen, heliox, exercise training, biofeedback techniques, lung volume reduction surgery and related endoscopic techniques and various combinations of these. These therapies either improve airway conductance and lung emptying (bronchodilators, heliox and lung volume reduction surgery) or reduce the rate of DH by decreasing V'_E (oxygen and exercise training) or decreasing the respiratory rate by increasing expiratory time (biofeedback techniques) or both. Besides those strategies directed at reducing EELV and/or the rate of DH, reducing respiratory muscle effort via noninvasive ventilation might also have beneficial sensory consequences in COPD. This review includes consideration of only pharmacological lung volume reduction.

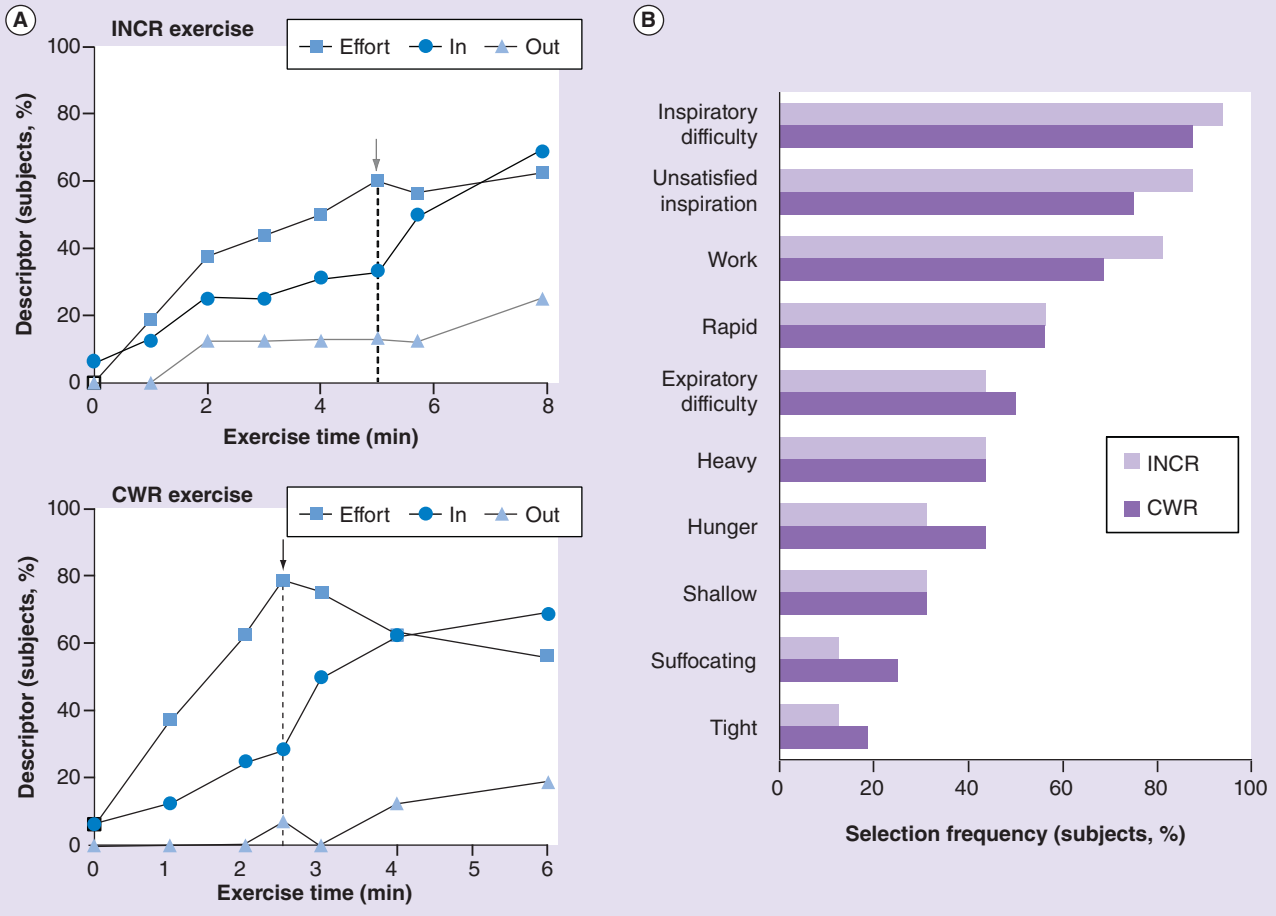

Figure 3. Qualitative descriptors of exertional dyspnea in chronic obstructive pulmonary disease. (A) Selection frequency of the three descriptor phrases evaluated during incremental and constant work rate exercise: increased work/effort (effort), unsatisfied inspiration (in) and unsatisfied expiration (out). Arrows indicate the point corresponding to the inflection point of the tidal volume-ventilation (V_T/V'_E) relation during exercise. **(B)** Selection frequency of the dyspnea descriptors collected by questionnaire at the end of exercise. Descriptor choices were similar in both tests with dyspnea described predominantly as a sense of 'inspiratory difficulty', 'unsatisfied inspiration' and increased 'work' of breathing.
CWR: Constant work rate; INCR: Incremental work rate.
Reproduced with permission from [36].

Bronchodilator therapy

Bronchodilator responsiveness has traditionally been assessed by the forced expiratory volume in 1 s (FEV_1) [1]. However, changes in FEV_1 do not reliably predict symptom responses, and some patients with COPD can achieve significant symptom benefit with little or no change in FEV_1 [4,87–94]. In COPD patients, assessment of lung volume responses to bronchodilators probably has more clinical relevance in light of the associations that have been shown between measurements of lung hyperinflation, exertional dyspnea and exercise performance [4,34,63,87–94]. All classes of short- and long-acting bronchodilators have been shown to consistently reduce dynamic lung hyperinflation and gas trapping (FRC and RV), with reciprocal increases in IC and vital capacity [4,34,63,87–94]. Combinations of different classes of bronchodilators have shown additive effects [95,96], the addition of an anti-inflammatory to a LABA bronchodilator has also been shown to amplify the effects [97–99], and triple therapy may result in even further improvements [100,101]. Although the effects of sustained bronchodilation on lung deflation have yet to be determined, there is potential for even more long-term benefit.

There now exists a sound physiological rationale for improvement in dyspnea and exercise tolerance in response to pharmacological lung volume reduction in patients with COPD. By improving airway conductance and the mechanical time constants for lung emptying, bronchodilator therapy results in lung deflation [34]. By reducing lung hyperinflation at rest and throughout exercise, several of its negative mechanical consequences are improved: V_T during exercise is permitted to increase more appropriately in the face of the increased respiratory effort (or drive) [34] and elastic loading of the inspiratory muscles is reduced which results in a decreased work and

oxygen cost of breathing, with the net effect being a decrease in the effort–displacement ratio (Figure 4) reflective of enhanced neuromechanical coupling [34]. These changes have beneficial clinical consequences that include increased exercise endurance, decreased exertional dyspnea intensity and a decreased perception of 'unsatisfied inspiration' [34,102].

Small increases in resting IC, in the order of approximately 0.3 l or 10–15% predicted, appear to be clinically relevant and have been shown to correlate well with improvements in exercise endurance and exertional dyspnea intensity in patients with COPD [4,34,63,90,92,102,103]. Improvements in such resting measurements of lung hyperinflation are carried through into exercise so that dynamic measurements of lung hyperinflation are also improved [4,34,63,90,92,102,103]. There is typically a parallel shift downwards in plots of operating lung volumes during exercise after a bronchodilator (compared with placebo). Recent mechanistic studies have shown that increases in the dynamic IC correlate with increases in V_T and with decreases in the effort–displacement ratio which, in turn, correlate with decreases in dyspnea intensity and increases in exercise endurance [34]. The contention that the perception of 'unsatisfied inspiration' is a sensory consequence of the mechanical constraints on V_T expansion during exercise in COPD is supported by the finding of a decreased selection frequency of descriptors alluding to this sensation after a bronchodilator [34,102].

To date, the majority of studies that have evaluated therapeutic efficacy in COPD have been performed in patients with advanced COPD. Although bronchodilator-induced improvements in static lung hyperinflation are greatest in those with the most severe disease [9], salutary effects are also seen in patients with milder disease [9,104]. A recent mechanistic study in symptomatic patients with GOLD grade I COPD showed that a short-acting anticholinergic resulted in modest improvements in airway function at rest and during exercise, as well as small reductions in exertional dyspnea intensity measured at higher levels of V'_E [104]. Although these improvements did not translate into a mean increase in exercise endurance, it is noteworthy that patients with greater baseline levels of lung hyperinflation derived greater symptom benefit [104], thus warranting a trial of bronchodilators in this subgroup of patients.

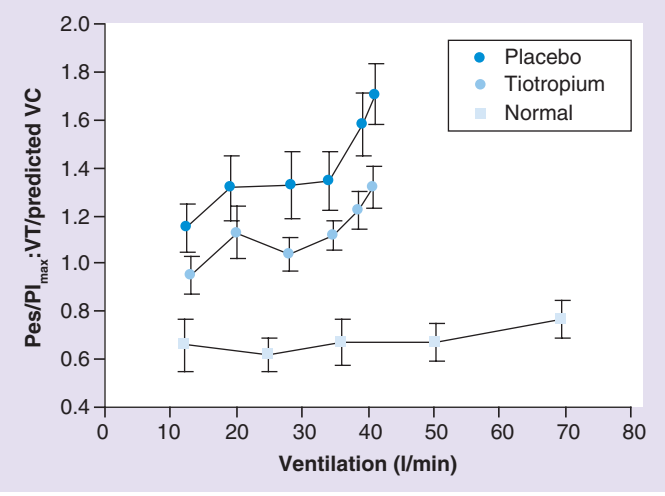

Figure 4. The relationship between respiratory effort (tidal esophageal pressure relative to maximum inspiratory pressure, i.e., Pes/PI_{max}) and V_T displacement (V_T standardized as a fraction of predicted VC, i.e., V_T/predicted VC), an index of neuromechanical coupling, is shown during constant work rate exercise after tiotropium and placebo in patients with moderate-to-severe chronic obstructive pulmonary disease. Compared with placebo, tiotropium enhanced neuromechanical coupling throughout exercise in chronic obstructive pulmonary disease. Values are means ± standard error of the mean. Data from a group of age-matched healthy subjects during exercise is also shown.
VC: Vital capacity; V_T: Tidal volume.
Data for chronic obstructive pulmonary disease patients taken from [34] and for healthy normal individuals taken from [30].

Conclusion

Progressive expiratory flow reduction in COPD is associated with the development of increasing lung hyperinflation and decline in the resting IC. A number of physiological adaptations partially preserve diaphragmatic function in the face of chronic hyperinflation; but the restrictive mechanical effects of a low IC limits the ability to increase V'_E during activity. The situation is further compounded by the deleterious effects of acute-on-chronic DH. This occurs when expiratory flow reduction is abruptly amplified during AECOPD or when ventilatory requirements suddenly increase during exercise in flow-limited patients. During exercise, further reduction of the already diminished IC due to DH critically restricts V_T expansion, mechanically loads and weakens the inspiratory muscles and forces early respiratory mechanical limitation. In addition, the growing disparity between increased central neural drive and the blunted respiratory muscular/mechanical response (neuromechanical uncoupling) after the V_T inflection probably contributes to perceptions of respiratory discomfort across its intensity, quality and affective distress domains. The corollary is that pharmacological lung volume reduction partially releases V_T restriction, unloads the inspiratory muscles and improves neuromechanical coupling, dyspnea and exercise tolerance in COPD. Sustained lung deflation with modern pharmacotherapy has the potential to delay progressive mechanical deterioration with time, decrease activity restriction and improve survival in this population. However, this has yet to be determined.

Expert commentary

COPD is characterized by inflammation of the airways, lung parenchyma and its vasculature [14–17]. There is evidence that peripheral airways (<2 mm) are initially affected by the inflammatory process [15,16], and recent studies have suggested that narrowing and obliteration of these airways may precede the development of centrilobular emphysema [15,16,105–107]. The ultimate consequence of extensive small airway inflammation is expiratory flow limitation: the expiratory flows generated during spontaneous tidal breathing represent the maximal possible flow rates than can be generated at that lung volume [108]. Tidal expiratory flow reserve is critically reduced in COPD because of the reduced driving pressure (reduced static lung recoil) due to destructive emphysema and the increased airways resistance due to airway narrowing [108,109].

Increase in lung volumes in COPD has static and dynamic components. A change in the elastic properties of the lungs due to emphysema (i.e., increased lung compliance) resets the relaxation volume of the static respiratory system to a higher level than in age-matched healthy individuals [110]. This has been termed static lung hyperinflation. Of note, 'static' does not mean 'at rest'. Thus, FRC or the lung volume at the end of resting expiration (i.e., EELV; both terms are used interchangeably in this review) is increased in COPD patients compared with healthy individuals. Thus, an abnormally increased FRC signifies an abnormal relaxation volume but mouth pressure at end expiration remains atmospheric. Static lung hyperinflation cannot be modified by pharmacotherapy, unless such medications can alter the elastic properties of lung parenchyma.

A major consequence of the increased compliance and resistance of heterogeneously distributed alveolar units is ineffective gas emptying on expiration: the mechanical time constant (i.e., the product of compliance and resistance [τ]) for lung emptying is therefore prolonged [110]. The net result is that inspiration begins before the respiratory system has returned to its relaxation volume and, consequently, the inspiratory muscles have to offset a threshold load termed auto or intrinsic PEEP before inspiratory flow can begin. Lung hyperinflation is therefore defined as 'dynamic' (either in the presence or in the absence of static hyperinflation) when FRC is abnormally increased (above the relaxation volume of the respiratory system in the presence of intrinsic PEEP). The extent of dynamic hyperinflation is influenced by the prevailing breathing pattern, the presence of expiratory flow limitation and the time-constant abnormalities [111]. Unlike static hyperinflation, dynamic hyperinflation can be influenced by pharmacological treatment. In more severe COPD, these factors can induce dynamic hyperinflation even at rest (earlier in the supine position), but more frequently it occurs during exercise or exacerbations of COPD (AECOPD). Of note, 'dynamic' does not mean 'during exercise'.

Five-year view

The natural history of lung hyperinflation in COPD has not been studied and we have yet to understand the factors that influence the time course of change of the various lung volume components. Mild COPD remains an understudied population. We are only beginning to understand the mechanisms of dyspnea and activity restriction in this population. We need to determine if earlier introduction of inhaled pharmacotherapy has long-term impact on dyspnea, exercise endurance and measures of respiratory mechanics in symptomatic patients with mild COPD. The impact of the various clinical COPD phenotypes (predominant emphysema vs small airway bronchiolitis, localized vs heterogeneous emphysema and others) on dynamic ventilatory mechanics, dyspnea, activity limitation and the response to pharmacotherapy has not been adequately studied. We know little about the effects of acute regional lung hyperinflation on lung and chest wall mechanics, ventilatory muscle recruitment patterns, cardiovascular function, cardiopulmonary interactions and pulmonary neurosensory reflexes. Lung hyperinflation probably influences the interaction between cardiac, ventilatory and locomotor muscles during exercise, but the precise nature of this physiological interaction remains contentious.

Acute lung hyperinflation becomes particularly problematic during exacerbations of COPD. The question arises whether acute regional alveolar overdistention modulates the inflammatory response, which could, along with the obvious mechanical stresses, lead to permanent destructive changes within the lung parenchyma and irreversible step increases in resting hyperinflation. The question arises, therefore, whether more aggressive therapeutic lung deflation during exacerbations (beyond maximal bronchodilator treatment), using interventions such as heliox in conjunction with specific noninvasive ventilation strategies, results in better short- and long-term clinical outcomes. There is intense interest in newer noninvasive, endoscopic, volume reduction procedures (one way valves, fenestrations and others) designed to improve regional

Key issues

- Dyspnea is the major reason for referral for pharmacological treatment and respiratory rehabilitation programs in patients with chronic obstructive pulmonary disease (COPD).
- Dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.
- In COPD, the mechanisms of dyspnea are multifactorial but the combination of increased central neural drive and abnormal dynamic ventilatory mechanics is believed to play a central role.
- A growing body of evidence suggests that lung hyperinflation contributes importantly to dyspnea and activity limitation in COPD and, moreover, is an important independent risk factor for mortality in this population.
- The mechanisms by which lung hyperinflation gives rise to exertional dyspnea and reduced exercise tolerance are complex, but recent mechanistic studies suggest that lung hyperinflation-induced inspiratory muscle loading, restriction of tidal volume expansion during exercise and consequent neuromechanical uncoupling of the respiratory system are key components.
- In addition, it has recently been shown that dyspnea intensity rises linearly in the early phase of exercise to reach moderate intensity at the tidal volume (V_T)/minute ventilation (V'_E) inflection, a point corresponding to a critically reduced dynamic inspiratory reserve volume.
- The V_T/V'_E inflection represents an important mechanical event, after which dyspnea intensity rises more quickly to intolerable levels and the dominant qualitative descriptor choice changes from increased work/effort to unsatisfied inspiration.
- The resting inspiratory capacity determines the V'_E at which the V_T inflection occurs: the smaller the inspiratory capacity, the lower the V'_E during exercise at which the V_T inflection occurs and the earlier the onset of severe dyspnea and unsatisfied inspiration.
- The corollary is that pharmacological and nonpharmacological lung volume reduction partially releases V_T restriction, unloads the inspiratory muscles and improves neuromechanical coupling, dyspnea and exercise tolerance in COPD.

deflation in emphysematous lungs. Clinical trials currently underway will determine their eventual clinical utility. With modern pharmacotherapy, now we have the ability to achieve sustained pharmacological volume reduction but know little of the long-term consequences with respect to impact on respiratory muscle function, ventilatory mechanics and cardiovascular function across the continuum of COPD. The as yet unanswered question of greatest interest to the clinician is: what is the impact of comprehensive management (including maximal bronchodilator and lung deflation, exercise training and collaborative self-management) on disease progression, quality of life and survival?

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