

Ventilatory constraints and dyspnea during exercise in chronic obstructive pulmonary disease

Pierantonio Laveneziana, Chris M. Parker, and Denis E. O'Donnell

Abstract: Dyspnea (respiratory difficulty) and activity limitation are the primary symptoms of chronic obstructive pulmonary disease (COPD) and progress relentlessly as the disease advances, contributing to reduced quality of life. In COPD, the mechanisms of dyspnea are multifactorial, but abnormal dynamic ventilatory mechanics are believed to play a central role. In flow-limited patients with COPD, dynamic lung hyperinflation (DH) occurs during exercise and has serious sensory and mechanical consequences. In several studies, indices of DH strongly correlate with ratings of dyspnea intensity during exercise, and strategies that reduce resting hyperinflation (either pharmacological or surgical) consistently result in reduced exertional dyspnea. The mechanisms by which DH gives rise to exertional dyspnea and exercise intolerance are complex, but recent mechanistic studies suggest that DH-induced inspiratory muscle loading, restriction of tidal volume expansion during exercise, and consequent neuromechanical uncoupling of the respiratory system are key components. This review examines the specific derangements of ventilatory mechanics that occur in COPD during exercise and attempts to provide a mechanistic rationale for the attendant respiratory discomfort and activity limitation.

Key words: COPD, exercise, ventilatory mechanics, dyspnea, dynamic hyperinflation.

Résumé : Les principaux symptômes de la maladie pulmonaire obstructive chronique (COPD) sont la dyspnée (trouble de la respiration) et la limitation d'activité; au fur et à mesure que la maladie s'installe, implacable, la qualité de vie se détériore. Dans la COPD, les mécanismes de la dyspnée sont multifactoriels, mais l'anomalie de la mécanique ventilatoire semble jouer un rôle capital. Chez les patients présentant ces troubles de la ventilation, on observe au cours de l'exercice physique une hyperinflation dynamique des poumons (DH) dont les conséquences mécaniques et sensorielles sont graves. D'après certaines études, les indicateurs de DH sont fortement reliés à la sévérité de la dyspnée à l'effort et les stratégies pour diminuer l'hyperinflation au repos (au moyen de médicaments ou d'une intervention chirurgicale) contribuent systématiquement à la réduction de la dyspnée d'effort. Les mécanismes par lesquels la DH aboutit à la dyspnée d'effort et à l'intolérance à l'effort sont complexes, mais de récentes études suggèrent que la charge imposée aux muscles de l'inspiration par la DH, la restriction de l'expansion du volume courant au cours de l'effort et le découplage neuromécanique consécutif en sont les éléments clés. Cet article-synthèse analyse les défaillances spécifiques de la mécanique ventilatoire observées cours de la COPD à l'effort et tente d'expliquer sur le plan de la mécanique les troubles de la respiration et la limitation d'activité.

Mots-clés : COPD, exercice physique, mécanique ventilatoire, dyspnée, hyperinflation dynamique.

[Traduit par la Rédaction]

Introduction

In COPD, exercise limitation is clearly multifactorial and ultimately reflects integrated abnormalities of the respiratory, cardiovascular, neuromuscular, and neurosensory systems in highly variable combinations. Detailed physiological studies during exercise in patients with COPD have

sought to better characterize these abnormalities, and have illustrated that in many individuals (and especially in those with more advanced disease) ventilatory limitation is the most important factor contributing to exercise curtailment (Diaz et al. 2000, 2001; O'Donnell et al. 2001; Puente-Maestu et al. 2005). In patients with severe COPD, ventilatory limitation is often the predominant contributor to exercise intolerance. This implies that at the point when the patient stops exercising as a result of symptom limitation, he or she has achieved or approximated the estimated maximum ventilatory capacity (MVC); at the same time, cardiac and other physiological functions are operating below maximal capacity. An important concept emerging from these studies is that of dynamic hyperinflation, whereby progressive increases in end-expiratory lung volume (EELV) occurs during exercise in patients with expiratory flow limitation

Received 4 October 2006. Accepted 28 February 2007.
Published on the NRC Research Press Web site at apnm.nrc.ca on 15 November 2007.

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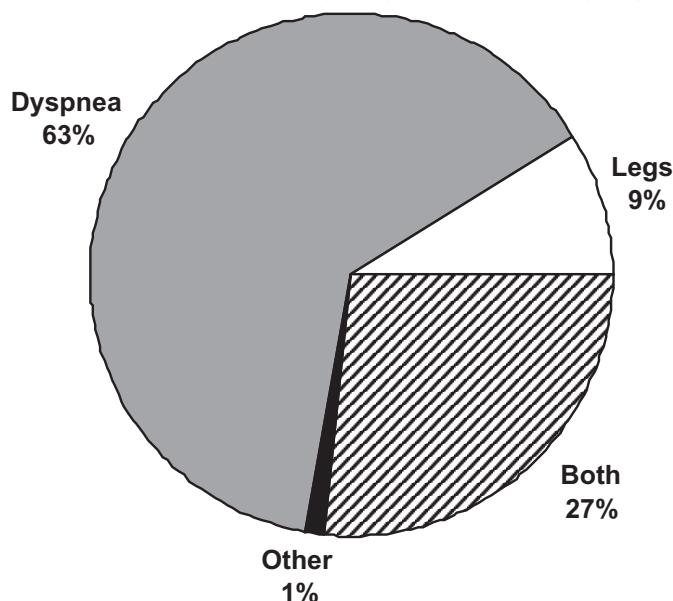
(O'Donnell et al. 1998, 2001; Koulouris et al. 1997). This has dire consequences in terms of pulmonary mechanics and oxygen cost of breathing, and imparts significant disharmony on the coupling of central respiratory drive and the mechanical output of the respiratory system (O'Donnell et al. 1997; O'Donnell and Webb 2003). This review examines these mechanisms in greater detail, and explores the concept that lung hyperinflation provides a mechanistic link between expiratory flow limitation, dyspnea, and exercise intolerance.

Exercise-limiting symptoms in COPD

In patients with COPD, exercise is often limited by intolerable exertional symptoms even before the physiological boundaries dictated by the respiratory and cardiovascular systems are reached (Killian et al. 1992). The importance of increased leg effort as an exercise-limiting symptom in COPD was first highlighted by Killian and colleagues, who measured the intensity of symptoms during incremental exercise in a sample of 97 patients with COPD ($FEV_1 = 46.6\%$ predicted). Using the Borg scale, they found that 43% of the sample rated leg effort higher than dyspnea, 26% rated dyspnea intensity greater than leg effort, and the remainder (31%) noted the intensity of leg effort and dyspnea equally. Among the 31 patients with an average $FEV_1 < 40\%$ predicted, 11 rated intensity of leg effort greater than dyspnea. In that study, patients were not asked which symptom caused them to stop exercise: the intensity of perceived leg "effort" was rated at the peak of exercise but it was not determined if leg "discomfort" was the primary exercise-limiting symptom. It is perhaps not surprising that inactive, deconditioned, elderly patients would experience a sense of heightened leg effort during unaccustomed incremental cycle exercise in the laboratory.

O'Donnell and colleagues studied the distribution of exercise-limiting symptoms in 105 clinically stable patients ($FEV_1 = 37\%$ predicted) with poor exercise performance (O'Donnell et al. 2001). Severe breathing discomfort was the primary symptom limiting incremental cycle exercise in 61% of this sample; combined dyspnea and leg discomfort limited exercise in 19%; only 18% stopped primarily because of leg discomfort; and 2% stopped for other reasons (general fatigue, discomfort from the bicycle seat, discomfort from noseclips). COPD patients who stopped exercise primarily because of dyspnea had greater ventilatory constraints and poorer exercise performance than the minority who stopped mainly because of leg discomfort. This frequency distribution of exercise-limiting symptoms was very similar to that found in a previous study in 125 patients entering a pulmonary rehabilitation program (O'Donnell and Webb 1995). Recently, combined data from multi-national clinical trials have provided new information on the frequency of exercise-limiting symptoms during constant work-rate exercise in a cohort of 403 patients with moderate-to-severe COPD (FEV_1 43% predicted, FRC 165% predicted, $VO_{2\text{ peak}}$ 61% predicted). In this population, dyspnea was identified as the primary reason for stopping exercise in 63%, whereas leg discomfort alone and in combination with dyspnea accounted for only 9% and 27%, respectively (O'Donnell et al. 2004a; Maltais et al. 2005) (Fig. 1).

Fig. 1. Distribution of reasons for stopping exercise during symptom-limited constant work rate cycle exercise at 75% of maximal work capacity in 403 patients with COPD (mean $FEV_1 = 43\%$ predicted, FRC = 165% predicted, $VO_{2\text{ peak}} = 61\%$ predicted). Data obtained from O'Donnell et al. (2004a) and Maltais et al. (2005).

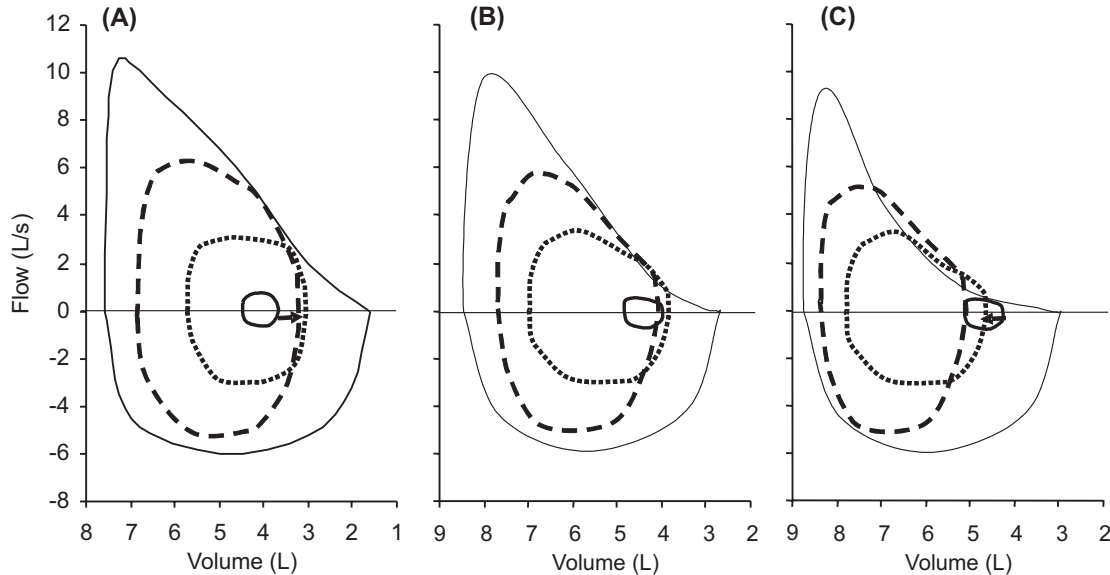


Differences between the results of these studies and those of the original study of Killian likely reflect different methodology in assessing symptom limitation (peak Borg ratings versus direct questioning about limiting symptoms after completion of task), potential qualitative differences in the symptom being evaluated (perceived leg "effort" versus "discomfort"), and differences in disease severity in the study populations. We can conclude, however, that dyspnea appears to be the dominant exercise-limiting symptom in patients with more advanced COPD and that severe leg discomfort is also common during cycle exercise in COPD.

Ventilatory responses to exercise in the elderly

Since COPD is primarily a disease of the elderly, the most appropriate "control group" for the study of cardio-ventilatory responses to exercise is that of age-matched healthy subjects. Cardiovascular factors appear to be the proximate limitation to exercise in fit older individuals, but ventilatory constraints may also be contributing factors. Even in healthy elderly subjects, progressive structural changes in the connective tissue matrix of the lung parenchyma cause loss of the static lung elastic recoil pressures that drive expiratory flow (Anthonisen et al. 1969; Frank et al. 1957; D'Errico et al. 1989; Gibson et al. 1976). Therefore, expiratory flow rates normally decline with age, particularly over the effort-independent portion of the maximal expiratory flow-volume curve, and flow limitation becomes evident (Rizzato and Marazzini 1970) (Fig. 2). Moreover, chest wall compliance is reduced due to decreased intervertebral disc spaces (mild kyphosis) and calcification of the costal cartilage (Rizzato and Marazzini 1970; Knudson et al. 1977). These combined effects alter respiratory system mechanics such that functional residual capacity

Fig. 2. Maximal and tidal flow-volume loops are shown at rest and during incremental cycle exercise in (A) a healthy, 26-year-old male, $\text{VO}_2 \text{ peak} = 47 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $V_E = 92 \text{ L/min}$; (B) a healthy, 66-year-old male, $\text{VO}_2 \text{ peak} = 35 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $V_E = 70 \text{ L/min}$; and (C) a 67-year-old COPD patient, $\text{VO}_2 \text{ peak} = 27 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $V_E = 71 \text{ L/min}$. Tidal flow-volume loops are provided at rest (solid line), at a sub-maximal ventilation of approximately 30 L/min (dotted line), and at peak exercise (dashed line). Note expiratory flow limitation (tidal expiratory flow overlapping the maximal curve) and an increase in dynamic end-expiratory lung volume (EELV) during exercise in the older male and in the patient with mild COPD (left arrow), compared with the healthy younger male (right arrow). See text for definition of abbreviations.



(FRC) and residual volume (RV) are increased with reciprocal decreases of inspiratory capacity (IC) and vital capacity (VC), respectively (Gibson et al. 1976; Knudson et al. 1977). Total lung capacity (TLC), however, is generally preserved in the elderly (Knudson et al. 1977).

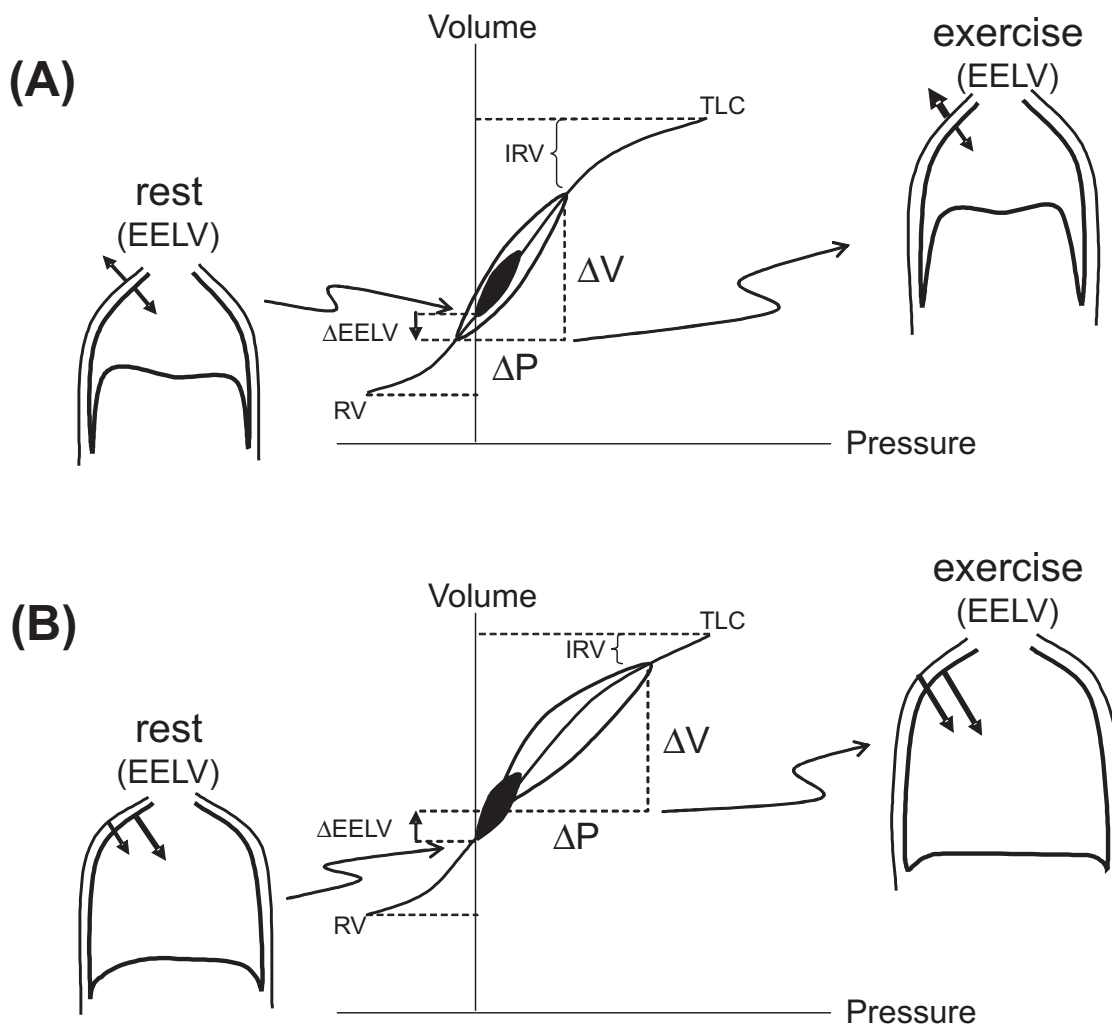
In contrast to youth, older individuals may demonstrate significant ventilatory constraints, particularly under conditions of high ventilatory demand (Johnson et al. 1994; Johnson and Dempsey 1991; Johnson et al. 1991a, 1991b). In youth, ventilation (V_E) increases during exercise by a progressive expansion of tidal volume (V_T) to approximately 60% of the VC. Thereafter, further increases in V_E are achieved primarily by increasing breathing frequency. V_T expansion occurs by almost equal expansion into the expiratory (by expiratory muscle recruitment) and inspiratory reserve volume (IRV). During strenuous exercise in the elderly, the ability to reduce EELV below the resting relaxation volume of the respiratory system is diminished because of expiratory flow limitation (Fig. 2). In fact, at high levels of ventilation, increases in dynamic EELV may occur as a result of reduced lung emptying and air trapping (Johnson and Dempsey 1991; Johnson et al. 1991a, 1991b). Although DH optimizes expiratory flow rates by avoiding expiratory flow limitation at volumes near RV, it can constrain V_T expansion and increases the elastic work on the inspiratory muscles (Johnson and Dempsey 1991). As a result, the pressures generated by the inspiratory muscles during tidal breathing in the elderly represent a higher fraction of the maximal possible dynamic inspiratory force-generating capacity than in youth for a given V_E and oxygen consumption (VO_2) (Johnson and Dempsey 1991; Leblanc et al. 1988). Consequently, the oxygen cost of breathing at maximal exercise represents approximately 13% of the total

body VO_2 or almost 40% greater than in an untrained youth at a similar V_E (Johnson et al. 1994; Johnson and Dempsey 1991). Therefore, in many respects, the ventilatory response to exercise in the elderly is similar to that of mild COPD (see below). However, in the elderly, metabolic demands and ventilatory capacity appears to fall in parallel with the passage of time, and it is only in highly fit individuals with high $\text{VO}_2 \text{ peak}$ and V_E that ventilatory constraints may actually curtail exercise performance (Johnson et al. 1994).

Ventilatory responses to exercise in COPD

Expiratory flow limitation that is only partially reversible with bronchodilation is the pathophysiological hallmark of COPD. Expiratory flow limitation occurs when the flows generated during spontaneous tidal expiration represent the maximal possible flows that can be generated at that operating lung volume (Hyatt 1983). While in health the EELV during relaxed resting breathing corresponds with the actual static equilibrium position of the respiratory system, this is often not the case in COPD (Pride and Macklem 1986). Several factors, including both an increase in lung compliance (due to emphysematous parenchymal destruction with subsequent loss of elastic recoil pressure that normally drives air out of the lungs) and an increase in airway resistance (due to remodeling of the airways and the presence of excessive mucus in the setting of chronic inflammation) compromise lung emptying during expiration. In advanced COPD, expiratory flow may be significantly limited at rest, and lung emptying is incomplete. In this way, EELV in COPD is often increased relative to health (Fig. 3). This situation is further aggravated during times of increased ventilatory demand, such as exercise, where an increase in respiratory rate

Fig. 3. Pressure–volume (P – V) relationships of the total respiratory system in health and in COPD. Tidal pressure–volume curves during rest (filled area) and exercise (open area) are shown. In COPD, because of resting and dynamic hyperinflation (a further increased EELV), exercise tidal volume (V_T) encroaches on the upper, alinear extreme of the respiratory system's P – V curve where there is increased elastic loading. In COPD, the ability to further expand V_T is reduced, i.e., inspiratory reserve volume (IRV) is diminished. In contrast to health, the combined recoil pressure of the lungs and chest wall in hyperinflated patients with COPD is inwardly directed during both rest and exercise; this results in an inspiratory threshold load on the inspiratory muscles. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; RV, residual volume; TLC, total lung capacity. Reproduced with permission from D.E. O'Donnell and P. Laveneziana. 2006. *J. Chronic Obstruct. Pulm. Dis.* 3: 219–232.



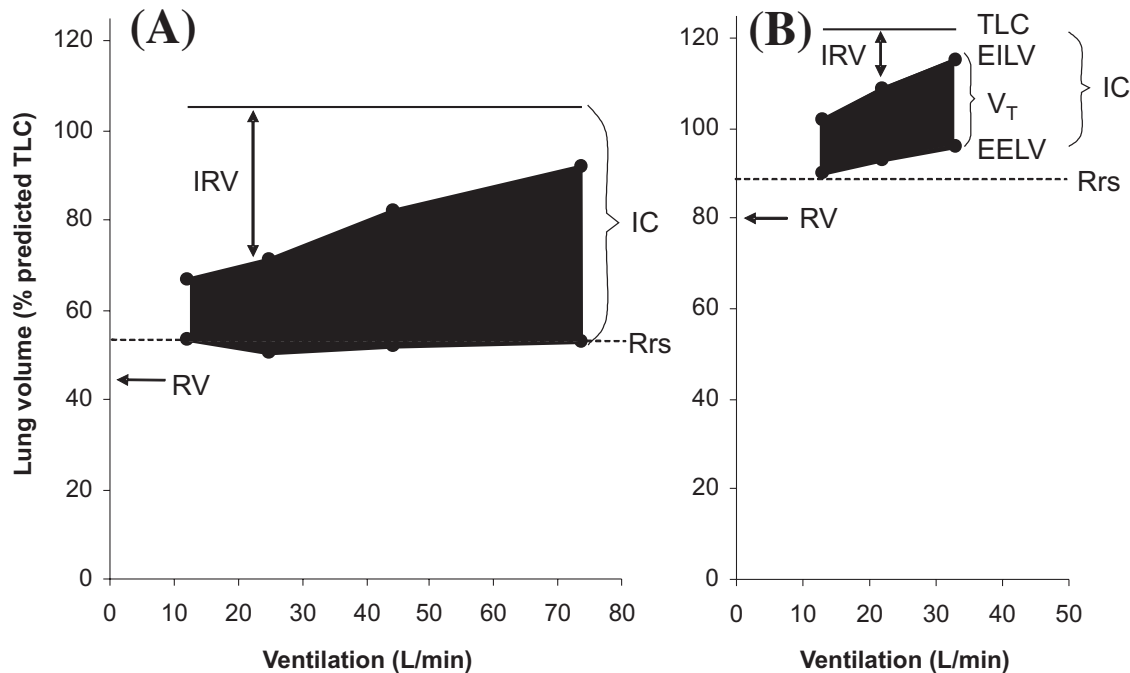
results in a further decrease in the amount of time available for expiration. Importantly, even in patients with less severe disease who may not have evidence of hyperinflation at rest, increases in V_E during exercise can lead to dynamic increases in EELV above the baseline resting value. In this way, EELV becomes a dynamic variable that fluctuates widely between rest and activity, dependent on such factors as the degree of flow limitation and breathing pattern, the extent of dynamic airway compression during expiration and the pattern of recruitment of ventilatory muscles.

Indices of dynamic hyperinflation during exercise

It has been established for some time that DH occurs in flow-limited patients under conditions of increased ventilatory demand during exercise (Grimby et al. 1968; Potter et

al. 1971; Stubbing et al. 1980; Dodd et al. 1984) (Fig. 4). However, the measurement of EELV during exercise is cumbersome, so other surrogate measurements are often used. The rate and magnitude of DH during exercise is generally measured in the laboratory setting by serial IC measurements (Maltais et al. 2005; O'Donnell et al. 1998, 2001, 2004a, 2004c). Since TLC does not change during activity (Stubbing et al. 1980; Vogiatzis et al. 2005), the change (decrease) in IC reflects the change (increase) in dynamic EELV, or the extent of DH. This simple method has been shown to be reliable and recent multi-centre clinical trials have confirmed its reproducibility and responsiveness (O'Donnell et al. 2004b). The use of change in IC to track DH is further validated by studies that have used esophageal manometry to demonstrate that even severely dyspneic patients are capable of generating maximal inspiratory pressures at the end of exhaustive exercise (O'Donnell et al.

Fig. 4. Changes in operating lung volumes are shown as ventilation increases with exercise in COPD ($n = 105$) and in age-matched normal subjects ($n = 25$). Restrictive constraints on tidal volume (V_T , solid area) expansion during exercise are significantly greater in the COPD group from both below (reduced inspiratory capacity (IC)) and above (minimal inspiratory reserve volume (IRV), open area). EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; RV, residual volume; TLC, total lung capacity; VC, vital capacity. Reproduced with permission from D.E. O'Donnell and P. Laveneziana. 2006. *J. Chronic Obstruct. Pulm. Dis.* 3: 219–232.



1997; Yan et al. 1997). This implies that the reductions in IC seen during exercise in COPD are not due to submaximal efforts, and indeed reflect changes in underlying EELV.

A number of small physiological studies have shown that the extent of DH in patients with moderate to severe COPD is in the range of 0.3–0.6 L above resting values (O'Donnell et al. 1997, 1998, 2001). In combined studies conducted in over 500 patients with moderate-to-severe COPD, the change in EELV during cycle ergometry averaged 0.4 L, representing a reduction in IC by ~20% of the resting value, but with wide variation in the range (Maltais et al. 2005; O'Donnell et al. 2001, 2004b) (Fig. 5). Eighty-five percent of this population sample showed increases in EELV from rest to peak exercise, confirming the presence of significant DH (Maltais et al. 2005; O'Donnell et al. 2001, 2004b). The minority of patients who showed little reduction in IC with exercise demonstrated the most severe resting lung hyperinflation (O'Donnell et al. 2001). The rate of rise of DH was steeper in patients with the most severe expiratory flow limitation (as estimated by the FEV_1 -FVC ratio), the lowest diffusing capacity for carbon monoxide, and the highest ventilatory demand (reflecting greater ventilation-perfusion abnormalities), and generally reached a maximal value early during exercise (O'Donnell et al. 2001).

Recent studies employing optoelectronic plethysmography to evaluate the dynamic change in chest wall volume during exercise have determined that some patients with COPD do not show significant DH during exercise. Aliverti et al. (2004) reported that among 20 patients with COPD (mean $FEV_1 = 44\%$ predicted), 40% did not show DH and were labelled "euvolumics". These patients had significantly higher FEV_1 (50% predicted) than those who in-

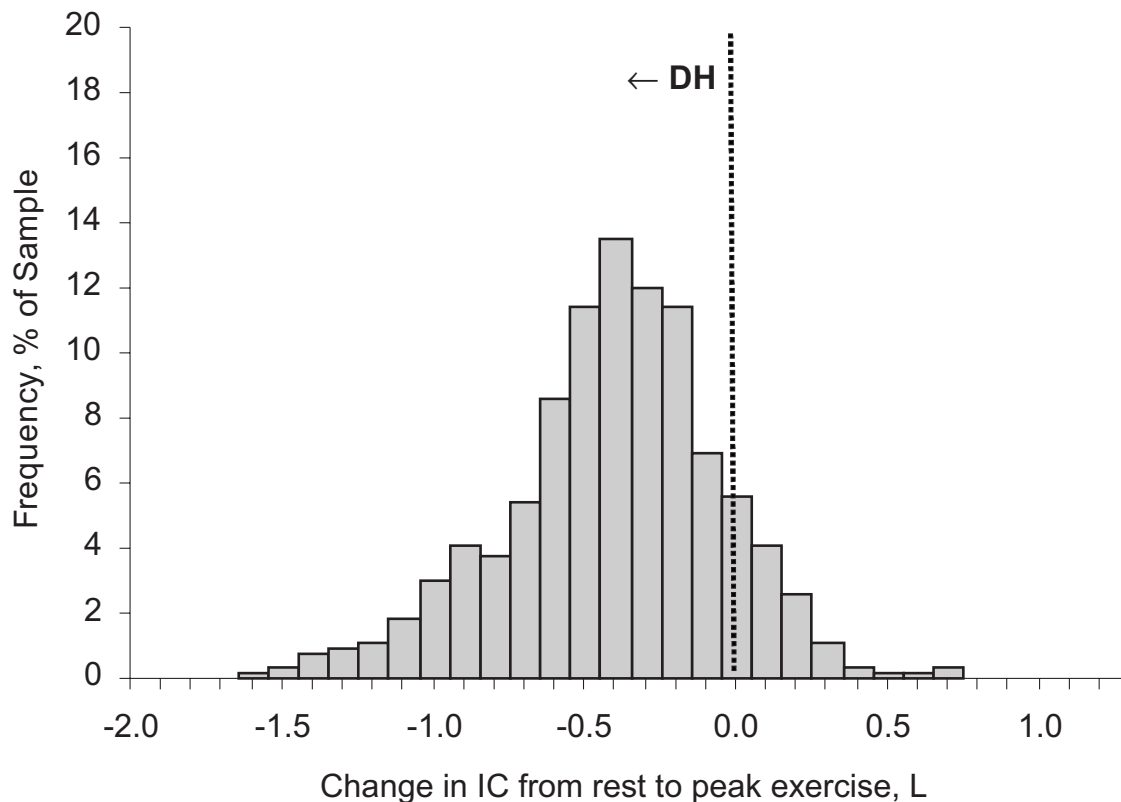
creased EELV ($FEV_1 = 39\%$ predicted), but surprisingly, had poorer exercise performance. Vogiatzis et al. (2005), using identical methodology in 20 patients with COPD (mean $FEV_1 = 35\%$ predicted) showed that all patients exhibited DH, but some did so later in exercise. The larger proportion of "euvolumics" found in the Italian studies compared with larger population studies employing spirometric IC measurements point to differences in methodology (chest wall motion detectors versus integrated airflow measurement), different exercise protocols (incremental versus constant work-rate exercise), and differences in patient posture during exercise (seated upright with arms held at mid-sternum level versus arms relaxed with hands resting on handle bars).

Dynamic hyperinflation and exercise intolerance in COPD

Dynamic hyperinflation has emerged as a central concept in explaining the ventilatory limitations experienced by COPD patients during exercise, whereas other spirometric correlates of airflow obstruction, such as FEV_1 , are relatively poor predictors of exercise tolerance (Gilbert et al. 1964; Jones et al. 1971; Carlson et al. 1991).

The presence of expiratory flow limitation appears to be an important predictor of exercise tolerance in patients with COPD. A number of recent studies have ascertained that (i) reduced IC is a good and validated marker of flow limitation and the propensity to develop worsening DH during exercise (Koulouris et al. 1997; O'Donnell et al. 1997; Yan et al. 1997), (ii) resting IC represents the operating limits for V_T expansion during the increased ventilation of exercise (Diaz et al. 2000; O'Donnell et al. 2001), and (iii) resting

Fig. 5. The distribution of the extent of change in inspiratory capacity (IC) during exercise is shown in moderate-to-severe COPD ($n = 534$). A reduction (negative change) in IC reflects dynamic hyperinflation (DH) during exercise. Each bar width corresponds to a change in IC range of 0.10 L. The majority of patients with COPD experienced significant DH during exercise. Graphs represent cumulative data from O'Donnell et al. (2001), Maltais et al. (2005), and O'Donnell et al. (2004a). Reproduced with permission from D.E. O'Donnell and P. Laveneziana. 2006. *J. Chronic Obstruct. Pulm. Dis.* 3: 219–232.



IC can predict symptom-limited $\dot{V}O_{2\text{ peak}}$ in patients with expiratory flow limitation at rest (Diaz et al. 2000; O'Donnell et al. 2001; Puente-Maestu et al. 2005).

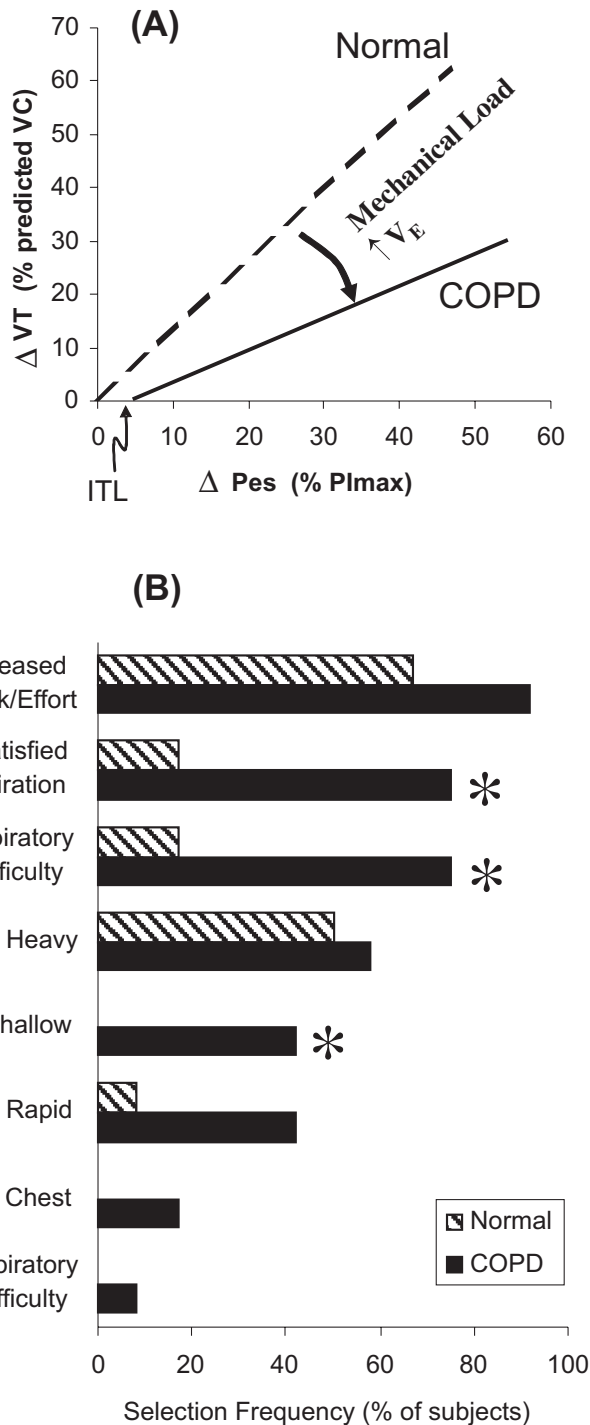
Indices of lung hyperinflation have repeatedly emerged as predictors of exercise intolerance in patients with COPD. For example, using symptom-limited $\dot{V}O_{2\text{ peak}}$ as the dependent variable, O'Donnell et al. (2001) found that peak V_T (standardized as percent predicted VC) emerged as the strongest predictor of exercise tolerance in patients with COPD ($r = 0.68$, $p < 0.0005$). In turn, peak V_T was most strongly predicted by the peak IC during exercise ($r = 0.791$, $p < 0.0005$) and by the resting IC ($r = 0.75$, $p < 0.0005$), expressed as percent predicted. Furthermore, the relationship between peak V_T during exercise and peak IC was particularly strong in the patients who showed an IC $< 70\%$ predicted (and presumably, therefore, significant expiratory flow limitation; $r = 0.87$, $p < 0.0005$), but was not significant in the patients who had preserved IC ($r = 0.27$, $p = 0.244$). In addition, the ratio of V_T to IC (taken as an index of the mechanical constraint on V_T expansion) was the best correlate of the level of ventilatory limitation (i.e., peak \dot{V}_E as a fraction of MVC) during exercise (O'Donnell et al. 2001). Similarly, Diaz and colleagues found that IC was a significant spirometric correlate of both peak workload ($r = 0.48$) and $\dot{V}O_{2\text{ peak}}$ ($r = 0.63$) in 52 patients with COPD (Diaz et al. 2000). Recently, Puente-Maestu and colleagues (2005) showed a good correlation between the resting IC (expressed as % predicted) and the $\dot{V}O_{2\text{ peak}}$ in 27

patients with severe COPD during constant work-rate exercise at different intensities (i.e., 65%, 75%, 85%, and 95% of the peak incremental work rate; $r = 0.64$ to 0.69).

Negative physiological effects of dynamic hyperinflation

Mechanically, the resting IC and, in particular, the dynamic IC during exercise represent the true operating limits for V_T expansion. Therefore, when V_T approximates the peak dynamic IC during exercise, or the dynamic end-inspiratory lung volume (EILV) approaches the TLC envelope, further volume expansion is impossible, even in the setting of increasing central drive and inspiratory muscle activation (Figs. 4 and 6). The consequence of this saturation of V_T is that further increases in \dot{V}_E beyond this point (where IRV has declined to a critically low value of approximately 0.5 L below TLC) must rely on increases in breathing frequency. However, in these already flow-limited patients, increases in breathing frequency may further aggravate DH in a vicious cycle. The more severe the COPD, the lower the \dot{V}_E during exercise at which the V_T (and IRV) shows plateau responses. These discernible plateaus on the \dot{V}_E/V_T Hey plots coincide with the acceleration of both breathing frequency and breathing difficulty during incremental cycle exercise (see below). Although DH serves to optimize expiratory flow rates by avoiding expiratory flow limitation at lower lung volumes, it has the deleterious effect of forcing V_T to

Fig. 6. The relationship between tidal swings of respiratory effort ($P_{es}/P_{I_{max}}$) and tidal volume (V_T expressed as a percentage of predicted vital capacity (VC)) at the end of a symptom-limited peak exercise test in health and in COPD (left). Note the inspiratory threshold load (ITL) and the disparity between effort and V_T . Descriptors of dyspnea at the end of exercise are also shown in COPD compared with age-matched healthy subjects (right panel). Data from O'Donnell et al. (1997). Reproduced with permission from D.E. O'Donnell and K.A. Webb. 2005. *Dyspnea: mechanisms, measurement, and management*. 2nd ed. Taylor & Francis Group, New York, N.Y. pp. 29–58.



operate on the upper, flatter part of the respiratory system's compliance curve where increases in pressure no longer generate significant incremental volume change (Fig. 3), and, in essence, imposes "restrictive" mechanics on the respiratory system. In some patients, the mechanical constraint on V_T expansion, in the setting of severe ventilation-perfusion abnormalities (i.e., high fixed physiological dead space), leads to CO_2 retention and arterial O_2 desaturation during exercise (O'Donnell et al. 2002; Dempsey 2002).

Dynamic hyperinflation results in sudden increases in the elastic and threshold loads on the inspiratory muscles, thus increasing the work and oxygen cost of breathing. In fact, in patients with very poor exercise tolerance (i.e., $VO_{2\ peak} < 1$ L/min), the respiratory muscles may consume upwards of 1/3 of total body VO_2 , as compared with 5%–7% in health (Evison and Cherniack 1968). In fact, it has recently been postulated that competition between the over-worked ventilatory muscles with the active peripheral muscles for a reduced cardiac output (see below) may compromise blood flow and oxygen delivery to the peripheral muscles, with negative consequences for exercise performance (Simon et al. 2001; Harms et al. 1997; Richardson et al. 1999). The inspiratory threshold load (ITL) reflects the force that the inspiratory muscles must generate to counterbalance the inward (expiratory) recoil of the lung and chest wall at end-expiration and can be substantial in COPD (O'Donnell et al. 1997). Dynamic hyperinflation results in functional inspiratory muscle weakness by maximally shortening the muscle fibers in the diaphragm (Sinderby et al. 2001). The combination of excessive mechanical loading and increased velocity of shortening of the inspiratory muscles can also predispose them to fatigue (Bye et al. 1985; Sinderby et al. 2001). However, there is little evidence that inspiratory muscle fatigue actually occurs during incremental cycle exercise even in patients with severe COPD. In fact, there is increasing evidence to the contrary and a suggestion that structural adaptations in the inspiratory muscles, particularly in the diaphragm, render them resistant to fatigue (Levine et al. 1997; Mador et al. 2000; Orozco-Levi et al. 1999).

The adverse effects of DH on cardiac performance during exercise are complex and not completely understood and are beyond the scope of this review. There is evidence that DH can be associated with increased right ventricular preload and afterload, together with left ventricular dysfunction (Pepe and Marini 1982; Magee et al. 1988; Agusti et al. 1990; Light et al. 1984; Mahler et al. 1984; Oswald-Mammosser et al. 1991; Matthay et al. 1980; Scharf et al. 2002; Vizza et al. 1998).

Dynamic hyperinflation and exertional dyspnea

Dyspnea, or the perception of respiratory discomfort, is a complex, multifaceted, and highly personalized sensory experience, the source and mechanisms of which are incompletely understood. Several studies, however, have demonstrated an association between dyspnea intensity during exercise and indices of lung hyperinflation (Marin et al. 2001; O'Donnell et al. 1997, 1998, 2001; Puente-Maestu et al. 2005). For example, using multiple regression analysis,

subjective Borg ratings of dyspnea intensity were found to be most strongly correlated with changes in EILV (expressed as %TLC; $r = 0.63$, $p = 0.001$) during cycle exercise in 23 patients with advanced COPD (average $FEV_1 = 36\%$ predicted). Furthermore, the measured change in EELV and the subsequent constraint of V_T expansion also emerged as independent significant contributors to exertional breathlessness in these patients (O'Donnell and Webb 1993). In another study by O'Donnell et al. (1997), exertional Borg dyspnea ratings measured at a standardized submaximal work rate correlated well with the concurrent ratio of EELV to TLC ($r = 0.69$, $p < 0.001$) (Fig. 7). Similarly, Puente-Maestu et al. (2005) found that dyspnea at the end of constant work rate cycle exercise correlated significantly with EELV as a percentage of TLC ($p < 0.001$). In a larger study of 105 patients with moderate-to-severe COPD (O'Donnell et al. 2001), the V_T -IC ratio, as an index of V_T constraint, emerged as the strongest predictor of exertional dyspnea ($r = 0.32$, $p < 0.0005$). Dyspnea intensity has also been shown to correlate significantly with the extent of DH (decrease in IC) during the 6 min walk test (Marin et al. 2001).

Neuromechanical dissociation and unsatisfied inspiration

In health, during resting spontaneous breathing and during exercise, the mechanical output of the respiratory system, measured as V_E , changes in accordance with the level of central neural drive. Complex proprioceptive information (obtained from muscle spindles, Golgi tendon organs, and joint receptors), as well as sensory information pertaining to respired flows and volume displacement (from mechanosensors in the lung parenchyma and airways) provide simultaneous feedback that ventilatory output is appropriate for the prevailing drive (Gandevia and Macefield 1989; Homma et al. 1988; Banzett et al. 1989; Altose et al. 1989; Matthews 1982; Roland and Ladegaard-Pederson 1977; Noble et al. 1970). In many respects, the sensory experience in COPD differs fundamentally from that of age-matched healthy individuals at $VO_{2\text{ peak}}$ (O'Donnell et al. 1997) (Fig. 6). Although the sense of increased effort, work, or heaviness of breathing is common to both groups, only COPD patients consistently select descriptors that allude to unsatisfied inspiration (i.e., "I can't get enough air in"), and it is reasonable to assume that these different qualitative dimensions of exertional dyspnea in COPD reflect different underlying mechanisms (O'Donnell et al. 1997) (Fig. 6).

Our understanding of the physiological events that occur at the end of exercise, when dyspnea becomes intolerable, continues to increase. The neural drive to breathe reaches near maximal values, driven by the elevated carbon dioxide production (VCO_2) that accompanies exercise and the early metabolic acidosis that may occur in many deconditioned COPD patients (Sinderby et al. 2001). In some patients, critical arterial oxygen desaturation, sympathetic nervous system over-activation, and altered feedback from peripheral muscle metaboreceptors may additionally stimulate ventilation. As already outlined, however, the ventilatory response to the increased drive is often markedly diminished because of derangements of ventilatory mechanics and subsequent constraint of V_T response (Figs. 4 and 8). It is noteworthy

that in contrast to health, the effort-displacement ratio (the ratio of inspired effort (tidal esophageal pressure relative to maximum inspiratory pressure, i.e., P_{es}/PI_{max}) to volume displacement (V_T expressed as a percentage of predicted VC)) continues to rise in COPD as exercise proceeds (Fig. 8). This increased ratio, which crudely reflects the position of the operating V_T on the compliance curve of the respiratory system (and thus the degree of neuromechanical dissociation), correlates well with perceived intensity of inspiratory difficulty and unsatisfied inspiration (Fig. 6). For example, in 12 patients with severe COPD ($FEV_1 = 37\%$ predicted), the effort-displacement ratio was the strongest correlate of dyspnea intensity during exercise ($r = 0.86$, $p < 0.001$), and also correlated strongly with dynamic hyperinflation (EELV/TLC; $r = 0.78$, $p < 0.001$) (Fig. 7) (O'Donnell et al. 1997).

A recent mechanistic study in our laboratory has attempted to reconcile the beneficial effects of DH in early exercise with its deleterious sensory effects that ultimately contribute to exercise limitation. Thus, DH early in exercise allowed flow-limited patients to increase V_E while minimizing respiratory discomfort (O'Donnell et al. 2006a). As a result of this early DH, the airways are maximally stretched at the higher lung volumes (close to TLC) and expiratory flow limitation is attenuated, thereby allowing patients to maximize expiratory flow rates. Thus, patients with severe COPD could abruptly increase V_E commensurate with increased metabolic demand, i.e., to approximately 40 L/min, and generate tidal inspiratory pressures exceeding 40% of the maximal possible pressure generation while experiencing minimal increases in dyspnea (modified Borg dyspnea ratings 1–2). Effort-displacement ratios are therefore well maintained early in exercise even in advanced COPD. However, this advantage of DH was quickly negated when V_T expanded to reach a critically low IRV of approximately 0.5 L (or 10% predicted TLC) below TLC (Fig. 8). At this "threshold", V_T becomes fixed on the upper, less-compliant, extreme of the respiratory system's sigmoid-shaped pressure-volume relation, where there is increased elastic loading of the inspiratory muscles. At this operating volume, the diaphragm muscle fibers are maximally shortened and the increased breathing frequency leads to increased velocity of shortening and significant reductions in dynamic lung compliance. After reaching this minimal IRV, dyspnea (described as unsatisfied inspiration) soon rose to intolerable levels and reflected the widening disparity between inspiratory effort (reaching near-maximal central neural drive) and the simultaneous V_T response, which becomes essentially fixed, i.e., increased effort-displacement ratio (O'Donnell et al. 2006a) (Fig. 8). As in other studies, dyspnea intensity correlated well with the increase in this effort-displacement ratio during exercise in COPD (O'Donnell et al. 1997, 2001, 2006a).

Several previous studies in resting healthy humans have shown that when chemical drive is increased in the face of voluntary suppression or imposed restriction of the spontaneous breathing response (i.e., V_T expansion), dyspnea quickly escalates to intolerable levels (Chonan et al. 1987; Fowler 1954; Harty et al. 1999; O'Donnell et al. 2000; Schwartzstein et al. 1989; Xu et al. 1993). Moreover, resumption of spontaneous breathing was associated with im-

Fig. 7. Significant intercorrelations between indices of dyspnea, neuromechanical dissociation, and hyperinflation at a standardized time during exercise. Dyspnea intensity assessed by the Borg scale correlated significantly with the effort–displacement ratio (i.e., the ratio of $P_{es}/P_{I_{max}}$ to V_T/VC , where P_{es} is esophageal pressure, $P_{I_{max}}$ is the maximal inspiratory pressure, V_T is tidal volume, and VC is vital capacity) as an index of neuromechanical coupling. Dyspnea intensity is also significantly predicted by hyperinflation, as assessed by the end-expiratory lung volume (EELV) as a proportion of total lung capacity (TLC). The effort–displacement ratio and hyperinflation are also strongly correlated. Reproduced with permission from D.E. O’Donnell and K.A. Webb. 2005. *Dyspnea: mechanisms, measurement, and management*. 2nd ed. Taylor & Francis Group, New York, N.Y. pp. 29–58.

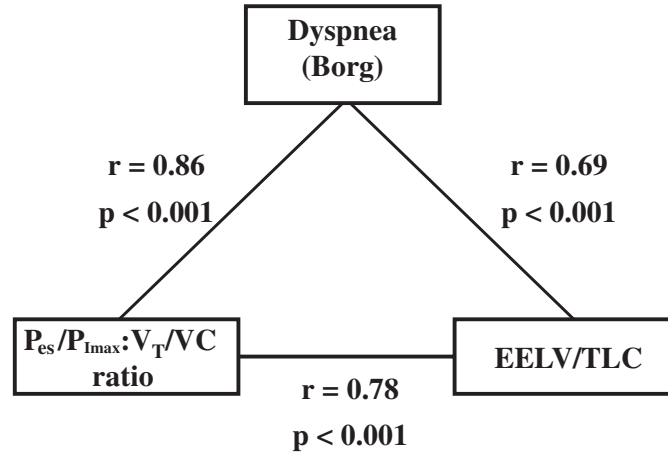
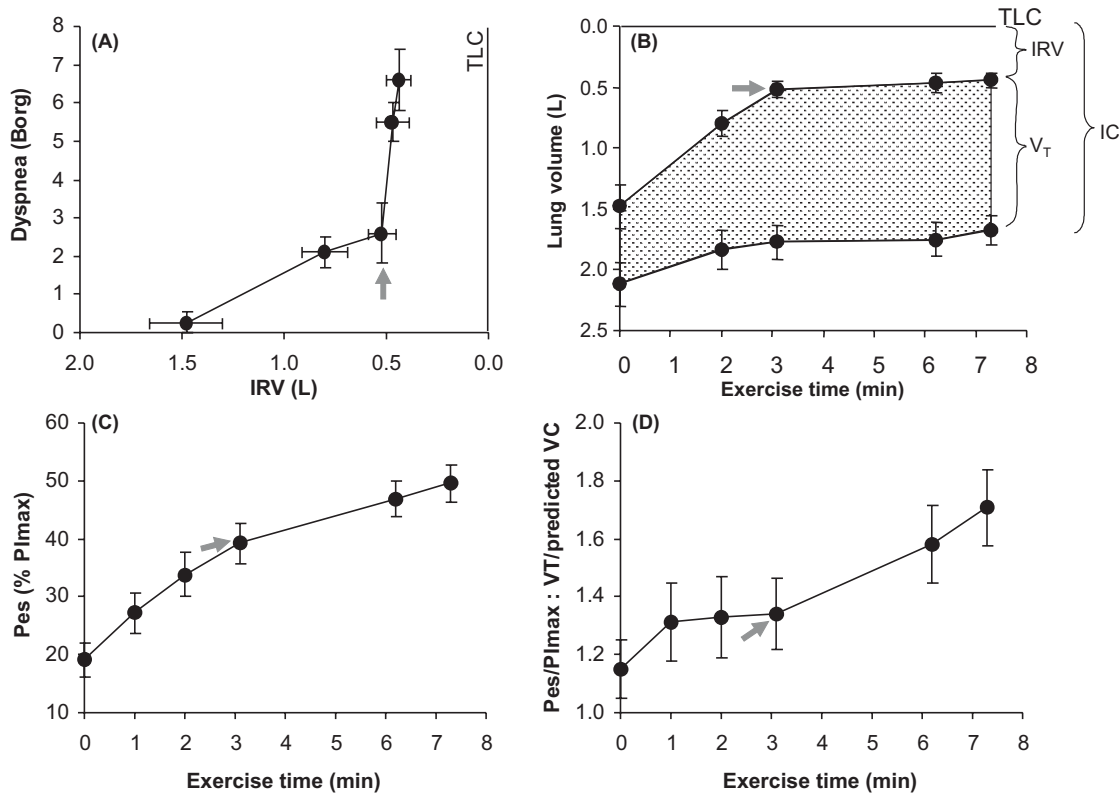


Fig. 8. The mechanical threshold of dyspnea is indicated by the abrupt rise in dyspnea after a critical “minimal” inspiratory reserve volume (IRV) is reached, which prevents further expansion of tidal volume (V_T) during exercise. Beyond this dyspnea–IRV inflection point during exercise, dyspnea intensity, respiratory effort ($P_{es}/P_{I_{max}}$), and the ratio of $P_{es}/P_{I_{max}}$ to tidal volume displacement (V_T standardized as a percentage of predicted vital capacity (VC)) all continued to rise. Arrows indicate the dyspnea–IRV inflection point. Values are expressed as means \pm SEM. IC, inspiratory capacity. Modified from O’Donnell et al. (2006a).



mediate improvement in respiratory discomfort, despite persistent (or even increased) chemical loading. During exercise in health, mechanical restriction of V_T (by chest strapping) induced severe dyspnea (described as unsatisfied inspiration) in the setting of added chemical loading (O’Donnell et

al. 2000). We postulate that in COPD a similar mismatch between central drive and a restricted mechanical response (as a result of DH) is fundamental to the origin of dyspnea. This hypothesis is supported by a number of controlled therapeutic studies that have shown a correlation between re-

duced dyspnea intensity ratings and the extent of release of V_T restriction following pharmacological lung volume reduction (Belman et al. 1996; O'Donnell et al. 1998, 1999, 2004a, 2004c, 2006a, 2006b; Peters et al. 2006).

Perception of inspiratory muscle effort

Recent theories on the mechanisms of dyspnea have emphasized the central importance of the perception of increased contractile inspiratory muscle effort (Campbell et al. 1980; Chen et al. 1991, 1992; Davenport et al. 1986; el-Manshawi et al. 1986; Gandevia 1982; Killian et al. 1984; Supinski et al. 1987). When skeletal muscles are mechanically loaded, weakened, or fatigued, increased electrical activation of the muscle is required to generate a given force, and motor output to these muscles is amplified. It is hypothesized that increased motor output is accompanied by increased corollary discharge to the sensory cortex, where it is directly perceived as a heightened sense of effort (Chen et al. 1991, 1992; Davenport et al. 1986; Gandevia and Macefield 1989; Homma et al. 1988). In COPD, inspired effort and central motor command output are increased compared with health, reflecting the relatively higher V_E , increased loading, and functional weakness of the inspiratory muscles. In the presence of DH, altered afferent information from activated mechanoreceptors in the overworked and shortened inspiratory muscles may contribute to an increased sense of work or effort, but this remains conjectural (Homma et al. 1988). Beyond a certain threshold, increased effort may be consciously registered as respiratory discomfort (Campbell et al. 1980; Chen et al. 1991; el-Manshawi et al. 1986; Gandevia 1982; Killian et al. 1984; Supinski et al. 1987). Qualitative descriptors at end-exercise that allude to increased effort or work of breathing are pervasive across health and disease and increased corollary discharge remains a plausible mechanistic explanation for this (O'Donnell et al. 1997).

However, it must be remembered that increased sense of effort is only one component of this multidimensional symptom, and it is acknowledged that dyspnea can rise to severe levels even in the absence of increases in contractile muscle effort (Chonan et al. 1987; Harty et al. 1999; Manning et al. 1995; O'Donnell et al. 2000; Schwartzstein et al. 1989, 1990; Sibuya et al. 1994). Mechanical ventilation, which successfully unloads the ventilatory muscles (thereby reducing effort), may not fully alleviate dyspnea (Wijkstra 2003; Kyroussis et al. 2000). Chemoreceptor stimulation (by adding CO_2) can induce breathing discomfort, described as air hunger, even in the absence of increased ventilation as evidenced in patients with spinal cord injury who are maintained on fixed ventilation by a mechanical ventilator (Banzett et al. 1989) and in normal subjects in whom muscular paralysis is induced under condition of hypercapnia (Banzett et al. 1990). Finally, increasing breathing effort to a high fraction of the maximal possible effort is not necessarily perceived as discomfort in all circumstances.

The affective dimension

It is reasonable to assume that when perceived respiratory discomfort exceeds a certain threshold (which varies be-

tween individuals), it will elicit behavioural or affective responses. This affective dimension, which in many instances involves feelings of fear that can quickly escalate to panic and helplessness, are key components of perceived respiratory distress. Sudden fear or overt panic will elicit neurohumoral responses (via pathways in the amygdala, adrenals, and sympathetic nervous system), which will trigger patterned ventilatory and circulatory responses that can further amplify respiratory discomfort.

Recently, the use of functional imaging techniques such as positron-emission tomography (PET) scanning and functional magnetic resonance imaging (fMRI) have been used to investigate the mechanisms underlying the central processing and perception of dyspnea (Banzett et al. 2000a, 2000b; Evans et al. 2002; Kukorelli et al. 1969; Liotti et al. 2001; Peiffer et al. 2001). These studies have shown activation of central limbic structures including the anterior insula, pars opercularis, anterior cingulate gyrus, amygdala, putamen, and caudate. These phylogenetically ancient areas of the central nervous system have an integral role in the perception and genesis of primal emotions, and it has been suggested that air hunger and dyspnea evoke programmed neurohumoral and behavioural responses similar to those that occur in response to pain (Casey 1999; Coghill et al. 1999; Hsieh et al. 1996), extreme hunger (Tataranni et al. 1999), or thirst (Denton et al. 1999). Other data suggest that the anterior insula is also activated in the setting of panic attacks (Javanmard et al. 1999), which may provide a common pathway for the disabling sensations of panic, anxiety, and fear that often accompany severe dyspnea (Banzett et al. 1996).

Therapies to reduce dynamic hyperinflation

The contention that DH contributes importantly to exercise limitation in COPD is supported by numerous studies that have shown that pharmacological and surgical lung volume reduction are associated with consistent improvements in dyspnea and exercise endurance. Interventions that have been shown to decrease resting lung hyperinflation or the rate of DH during exercise in COPD include bronchodilators, oxygen, heliox, oxygen-bronchodilator combination, exercise training, and lung volume reduction surgery (LVRS) and related endoscopic techniques. These therapies either improve airway conductance and lung emptying (bronchodilators, heliox, LVRS), reduce the rate of DH by suppressing ventilation (oxygen, exercise training) or both (Belman et al. 1996; Laghi et al. 1998; Laude et al. 2006; Martinez et al. 1997; O'Donnell et al. 1996, 1998, 1999, 2004a, 2004c, 2006a, 2006b; Palange et al. 2004; Peters et al. 2006).

Summary

Severe dyspnea is a major exercise-limiting symptom in moderate-to-severe COPD and every effort should be made to alleviate it. Although exercise limitation is multifactorial, there is considerable evidence that deranged ventilatory mechanics, specifically dynamic lung hyperinflation, may represent the most important mechanical limit to exercise performance in patients with advanced disease. Dynamic hyperinflation occurs during activity in the vast majority of flow-limited patients with COPD and has been shown re-

peatedly to correlate with dyspnea intensity ratings. Dynamic hyperinflation stresses the already limited cardio-pulmonary reserves of patients with COPD and greatly constrains the ability to expand tidal volume appropriately in response to the increased neural drive of exercise. Recent studies have proposed that this acute neuromechanical dissociation of the respiratory system may form the basis for the perception of respiratory discomfort, which ultimately triggers intolerable respiratory distress. Dynamic hyperinflation, therefore, represents an important therapeutic target in COPD.

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