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.

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.
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 \((\text{FEV}_1 = 46.6\% \text{ predicted})\). 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 \(\text{FEV}_1 < 40\% \text{ predicted}\), 11 rated 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 \((\text{FEV}_1 = 37\% \text{ predicted})\) 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 \((\text{FEV}_1 = 43\% \text{ predicted}, \text{FRC} = 165\% \text{ predicted}, \text{VO}_2\text{peak} = 61\% \text{ predicted})\). 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 \(\text{FEV}_1 = 43\% \text{ predicted}, \text{FRC} = 165\% \text{ predicted}, \text{VO}_2\text{peak} = 61\% \text{ predicted})\). Data obtained from O’Donnell et al. (2004a) and Maltais et al. (2005).

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 cardiovascular 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, VO$_2$ peak = 47 mL·kg$^{-1}$·min$^{-1}$, $V_T$ = 92 L/min; (B) a healthy, 66-year-old male, VO$_2$ peak = 35 mL·kg$^{-1}$·min$^{-1}$, $V_T$ = 70 L/min; and (C) a 67-year-old COPD patient, VO$_2$ peak = 27 mL·kg$^{-1}$·min$^{-1}$, $V_T$ = 71 L/min. Tidal flow-volume loops are provided at rest (solid line), at a submaximal 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.

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
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. 2004b).
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 FEV1–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).

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 FEV1, 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 VT expansion during the increased ventilation of exercise (Diaz et al. 2000; O’Donnell et al. 2001), and (iii) resting increased EELV (FEV1 = 39% predicted), but surprisingly, had poorer exercise performance. Vogiatzis et al.(2005), using identical methodology in 20 patients with COPD (mean FEV1 = 35% predicted) showed that all patients exhibited DH, but some did so later in exercise. The larger proportion of “euvolumes” 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).
IC can predict symptom-limited VO\textsubscript{2} 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 VO\textsubscript{2} peak as the dependent variable, O’Donnell et al. (2001) found that peak VT (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 VT 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 VT 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 VT to IC (taken as an index of the mechanical constraint on VT expansion) was the best correlate of the level of ventilatory limitation (i.e., peak VE 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 VO\textsubscript{2} 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 VO\textsubscript{2} 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 VT expansion. Therefore, when VT 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 VT is that further increases in VE 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 VE during exercise at which the VT (and IRV) shows plateau responses. These discernible plateaus on the VE/VT 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 VT to
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., $V_O2$ peak < 1 L/min), the respiratory muscles may consume upwards of 1/3 of total body $V_O2$, as compared with 5%–7% in health (Evison and Cherniack 1968). In fact, it has recently been postulated that competition between the overworked 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 \( V_{O_2} \text{ peak} \) (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., \( P_e/\text{P}_{\text{Imax}} \)) 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; \( r = 0.78, p < 0.001 \)) (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 \( V_T \) 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-
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-

**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 mechano-receptors 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 hypcapnia (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 between 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 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 mechanisms, 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.

References


Anthonisen, N.R., Danson, J., Robertson, P.C., and Ross, W.R. 1986. The response to the increased neural drive of exercise. Recent strains the ability to expand tidal volume appropriately in pulmonary reserves of patients with COPD and greatly constricted the ability to expand tidal volume appropriately in response to the increased neural drive of exercise. Dynamic hyperinflation, which ultimately triggers intolerable respiratory distress. Dynamic hyperinflation, therefore, represents an important therapeutic target in COPD.


