

# Exercise dyspnea in patients with COPD

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**Abstract:** Dyspnea, a symptom limiting exercise capacity in patients with COPD, is associated with central perception of an overall increase in central respiratory motor output directed preferentially to the rib cage muscles. On the other hand, disparity between respiratory motor output, mechanical and ventilatory response of the system is also thought to play an important role on the increased perception of exercise in these patients. Both inspiratory and expiratory muscles and operational lung volumes are important contributors to exercise dyspnea. However, the potential link between dyspnea, abnormal mechanics of breathing and impaired exercise performance via the circulation rather than a malfunctioning ventilatory pump per se should not be disregarded. Change in arterial blood gas content may affect dyspnea via direct or indirect effects. An increase in carbon dioxide arterial tension seems to be the most important stimulus overriding all other inputs from dyspnea in hypercapnic COPD patients. Hypoxia may act indirectly by increasing ventilation and indirectly independent of changes in ventilation. A greater treatment effect is often achieved after the addition of pulmonary rehabilitation with pharmacological treatment.

**Keywords:** arterial blood gases, bronchodilation, lung volumes, pulmonary rehabilitation, vascular factors

No natural phenomenon can be adequately studied in itself alone, but to be understood must be considered as it stands connected with all nature.

*(Sir Francis Bacon 1561–1626)*

## Preface

Contribution to our understanding of the nature and the mechanisms of dyspnea evolved in the last two centuries. Although the relationship was never formally specified discomfort was assumed to accompany respiratory muscle activity. Hypothesis and theories of dyspnea thus becomes synonymous with the factors controlling the extremes of respiratory muscle activity with expiratory muscle activity and discomfort now being controlled by the same factors. In his introduction to the “Breathlessness symposium” held in Manchester (1995), Julius H Comroe predicted that none of the speakers would deal directly with dyspnea: instead they would present only what they understood—the control of breathing, circumstance in which dyspnea may occur. In the event Comroe was largely right. Few contributors dealt with sensory aspects of the subjects, and what sensory physiology there was naïve (J.B. Howell 1992).

In the quarter of the last century since that symposium, things changed greatly as the contributions to the Moran Campbell Symposium held in Hamilton (1991) testified. Both investigators and clinicians have adopted the attitude of sensory physiology and the methods of psychophysics. Also, the main related topic concerned the respiratory muscles rather than the control of breathing. In both of these changes the influence on Moran Campbell was central.

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## Introduction

Dyspnea is the major reason for referral to pharmacological treatment and respiratory rehabilitation programs in patients with chronic obstructive pulmonary disease (COPD) (ATS 1999; Trooster et al 2005). Dyspnea characterizes a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses (ATS 1999). This definition underlines the importance of the different qualities covered by the term dyspnea, the involvement of integration of multiple source of neural information about breathing, and the physiological consequences.

In the following paragraphs we will try to answer the following questions: (i) Which is the role of the respiratory muscles, operational lung volumes, vascular factors, arterial blood gases in dyspnea? (ii) Does competition between ventilatory and locomotor muscles for the available energy supplies increase with increasing work of breathing and, if any, does this affect dyspnea on exercise in COPD patients? (iii) What is the link between the language of exercise dyspnea and the underlying neurophysiological mechanisms? (iv) On what basis do bronchodilators reduce dyspnea intensity on exercise? and (v) How can rehabilitation program modulate exercise dyspnea?

## Methods

A Medline search of articles published between 1960 and 2006 was undertaken. A large body of scientific information on exercise dyspnea has been published since the last 1960 (Howell and Campbell 1966; Jones and Killian 1992). Starting from those miliar stones on origin and pathophysiology of dyspnea we present the accumulate knowledge with particular emphasis on researches published in the last 16 years. We restricted our presentation to COPD a disease state that compromises the energy supply, increases the work of breathing and decreases the respiratory muscle efficiency and increase dyspnea during exercise.

## Pathophysiology

Given the complexity of disturbances in respiratory mechanics it is difficult to be sure which alterations contribute most strongly to the sensation of dyspnea. This section is an attempt to identify the pathophysiological basis of dyspnea in patients with COPD. We shall consider the contribution of the respiratory muscles, operational lung volumes, vascular factors, and arterial blood gases to dyspnea.

## The respiratory muscles

### Respiratory effort

The intensity of the outgoing central motor command activating the muscular receptors and the copy of the increased motor command to the sensory cortex are consciously appreciated as effort (El-Manshawi et al 1986; Leblanc et al 1988; O'Donnell et al 1997). Emphasis has been put on the importance of the relationships between demands placed on the inspiratory muscles and their capacity to generate pressure in understanding the perception of dyspnea experienced by patients with respiratory disorders (Leblanc et al 1988). The pressure per breath to maximal inspiratory pressure-generating capacity ratio increases during progressive exercise in proportion to the sense of effort in patients with COPD in whom expiratory flow limitation enhances the recruitment of expiratory muscles (Potter et al 1971; Grimby et al 1976; Babcock et al 1995). When expiratory flow is limited, the enforced slowing of expiratory muscle velocity of shortening may increase expiratory pressure which may affect dyspnea (Kaiser et al 1997).

### Respiratory muscle recruitment

Dyspnea may be the signal that rib cage inspiratory muscles are being recruited to assist the diaphragm (Babcock et al 1995). With increased disease severity patients with COPD exhibit a shift in ventilatory muscle recruitment from the diaphragm to the rib cage, and the experienced degree of dyspnea may relate in part to this shift (Ward et al 1988, Martinez et al 1990). During unsupported arm exercise the respiratory muscles of the rib cage actively help maintain the position of the upper torso and extend arms. Hence, by decreasing their participation in respiration (Criner and Celli 1988) contribute to the sensation of dyspnea (Celli et al 1986; Gigliotti et al 2005).

### Respiratory muscle weakness

The intensity of dyspnea is greater in patients with cardio-respiratory disorders and weak respiratory muscles because it takes more effort to drive a weak muscle than it does to drive a strong muscle. During exercise, for a given work load the weaker the inspiratory muscles the greater the dyspnea; a two-fold increase in their power output results in about 30% decrease in dyspnea (Hamilton et al 1995).

### Inspiratory muscle fatigue

Fatigue is defined as a loss of the capability to generate skeletal muscle force and/or velocity which is accompanied by recovery during rest (NHLB 1990). High intensity exercise does

not cause diaphragmatic fatigue (Mador et al 2000) in most patients with COPD of moderate severity. Central inhibitory fatigue of the diaphragm, that is, a low level of activation of the muscle, does not take place in patients while exercising to exhaustion; dynamic hyperinflation during exhaustive exercise reduces diaphragm pressure-generating capacity, while promoting a high level of diaphragm activation (Sinderby et al 2001) contributing to dyspnea (El-Manshawi et al 1986).

### Operational lung volumes

The disparity between respiratory motor output and the mechanical response of the system is thought to play a major role in the increased perception of dyspnea in patients with COPD (O'Donnell and Webb 1993). Decrease in inspiratory capacity, a mirror of increase in dynamic hyperinflation, along with a change in tidal volume and respiratory frequency account for 61% of the variance in rating of breathing difficulty in exercising patients with COPD (O'Donnell and Webb 1993). Even though hyperinflation maximizes tidal expiratory flow rates (Koulouris et al 1997) breathing at high lung volumes has serious mechanical and sensory consequences: (i) tidal volume becomes positioned closer to total lung capacity where there is a significant elastic loading to the inspiratory muscles (O'Donnell and Webb 1993; O'Donnell, Revill et al 2001); (ii) shortening of the operating length of the inspiratory muscles, compromises their ability to generate pressure; (iii) inspiratory muscles are forced to use a large fraction of their maximal force generating capacity during tidal volume (Leblanc et al 1988; O'Donnell and Webb 1993; Gorini et al 1996; O'Donnell, Revill et al 2001); and (iv) effort production without an adequate concurrent volume or flow reflects the neuro-ventilatory dissociation of the respiratory pump (O'Donnell and Webb 1993; O'Donnell, Revill et al 2001).

Although there is much evidence for an increase in end-expiratory-lung-volume (EELV) during exercise in many patients with COPD several more recent studies also indicate that this is not always the case (Calverley 2006): This is in keeping with earlier data suggesting that patients with COPD could also be limited by fatigue of their leg muscles when they exercised rather than simply by ventilatory factors (Hamilton et al 1995). Aliverti et al (2004) by measuring the total chest wall volume non-invasively using opto electronic pletismography have shown that exercise limitation and its attendant dyspnea is not necessarily associated with dynamic pulmonary hyperinflation in COPD. Unlike patients who hyperinflate, a significant number of patients (euvolumics) reduces abdominal volume preventing dynamic hyperinflation. The most likely explanation was a

difference between groups in their resting tidal expiratory flow limitation associated with hyperinflation. Moreover, despite their better flow reserve, euvolumics reduced end-expiratory-thoracic-volume (EETV) largely by reduction in the volume of their abdominal compartment. To do that they developed high intra-abdominal pressure rather than permitting EETV to rise as in the hyperinflators. Subsequent data during endurance exercise (Vogiatzis et al 2005) have shown two significant patterns of change in EETV in patients who hyperinflate during exercise: most patients exhibited a progressive significant increase in EETV (early hyperinflators) while in the remaining patients EETV remained unchanged up to 66% peak of work rate ( $W_{peak}$ ) and increased significantly at  $W_{peak}$  (late hyperinflators). Note that in the two studies (Aliverti et al 2004; Vogiatzis et al 2005) the patterns of response – euvolumics vs hyperinflators, and early vs late hyperinflators – were associated with similar intensity of breathlessness. Prof PT Macklem (2005a) has recently focused on physiological differences between euvolumics and hyperinflators:

“expiratory muscle recruitment, work of breathing, and competition between respiratory and locomotor muscles are all considerably less in hyperinflators than in euvolumics: they have learned to bypass the normal control of the respiratory muscles and hence their expiratory pressure remains low. [...] Without respiratory muscle recruitment dynamic hyperinflation is inevitable if patients are sufficient flow limited”

More recently, O'Donnell et al (2006) have demonstrated that dynamic hyperinflation early in exercise allowed expiratory flow limited patients to increase ventilation while minimizing respiratory discomfort; an advantage negated later – with EELV remaining constant – when tidal volume expanded to reach a critical low respiratory reserve volume of approximately 0.5 L below total lung capacity. After reaching this minimal inspiratory reserve volume dyspnea rose to intolerable level and reflected the disparity between inspiratory effort (near maximal central respiratory drive) and the concurrent fixed tidal volume response. Prof PT Macklem (2005) has recently focused on physiological differences between euvolumics and hyperinflators.

Although “there can be no doubt that dynamic hyperinflation is a common and potent mechanism limiting exercise in COPD, a greater deal of research has show that patients are crippled as a result: recruit your respiratory muscles or not, patients with COPD are damned if they do and damned if they don't” (Macklem 2005a).

## Vascular factors and ventilatory-locomotor muscle competition

Given the complexity of disturbances in respiratory mechanics during exercise, it is difficult to be sure which alterations contribute most strongly to the sensation of dyspnea. Severe respiratory mechanical changes can be responsible for hemodynamic abnormalities and diminished exercise performance in patients with severe COPD. The implication is a potential link between abnormal mechanics of breathing, impaired exercise performance, and dyspnea via the circulation rather than a malfunctioning ventilatory pump per se (Montes de Oca et al 1996). The consequence of the positive pressure swings during strenuous exercise is that mean intra-thoracic pressure during exercise could impede venous return and could impose a limitation to cardiovascular response to exercise in patients, producing a situation similar to a Valsalva maneuver (Aliverti and Macklem 2001; Aliverti, Dellaca, et al 2005).

Locomotor and ventilatory muscles compete for available energy supplies with increase work of breathing in healthy subjects (Harms et al 2000). COPD could deprive the locomotor muscles of considerably more energy than in health because of the high cost of breathing at given level of ventilation (Levison and Charniak 1968; Oelberg et al 1998). This can establish ventilatory-locomotor muscle competition for the available oxygen supply even at low exercise work loads (Aliverti and Macklem 2001; Simon et al 2001; Macklem 2005b). The conclusion is that the major limitation to exercise performance in patients with COPD who exercise beyond lactate threshold is an inadequate oxygen supply. This suggests that the relative ischemia of the respiratory muscles may contribute to the sensation of dyspnea (Aliverti and Macklem 2001).

## Effects of interaction between ventilatory and circulatory mechanics on dyspnea during exercise

The mechanisms that couple ventilation to cardiac output during exercise are not well understood. Increased right ventricular after-load led Morrison et al (1987) to speculate that exercise limitation in COPD occurs as a result of the dynamic interaction between disordered right heart function and ventilation. High expiratory pleural pressure in COPD were reported indeed by Potter et al (1971), confirmed by Dodd et al (1984), Montes de Oca et al (1996) and more recently by Aliverti et al (2004). The high expiratory pleural pressure interferes with venous return to right heart; and a high alveolar pressure increases pulmonary vascular resistance and decreases both left heart filling and cardiac output

(Aliverti and Macklem 2001). In presence of tidal expiratory flow the expiratory muscles might develop excessive pressure in the vain attempt to increase flow; above the anaerobic threshold the perfusion of locomotor and respiratory muscles provides insufficient oxygen to meet the demands (Aliverti and Macklem 2001). It seems that combination of high ventilatory demands and limitation of cardiac output (Aliverti, Dellaca et al 2005) – both caused by excessive expiratory pressure – can be potent factor limiting exercise performance in COPD.

## Arterial blood gases

Hypercapnia and hypoxia drive breathing and, therefore, must influence the perception of the motor events. Recent evidence indicates that hypercapnia makes an independent contribution to dyspnea. Banzett et al (1989) showed the effect of increasing hypercapnia in mechanically ventilated quadriplegics in whom air hunger, as the dyspnea descriptor, increased when end-tidal  $\text{CO}_2$  fraction ( $\text{PetCO}_2$ ) was surreptitiously raised by 7–11 mmHg. Similar results were obtained in ventilated healthy subjects (Banzett et al 1990). These studies contrast sharply with previous studies of Campbell et al (1967, 1969). They showed in two conscious volunteer physicians paralyzed with curare that the distressing sensation normally associated with breath holding was completely absent when ventilation was suspended for over 4 min and  $\text{PaCO}_2$  was allowed to rise. The observation that the less you breathe at given  $\text{PCO}_2$  the more breathless you fill argues against the Campbell's criticism about a subject reporting the extreme air hunger at  $\text{PaCO}_2$  of (only) 45 mmHg (Campbell 1992). Indeed, if arterial  $\text{PCO}_2$  is increased and breathing is not allowed to increase the subject experiences air hunger; likewise if  $\text{PCO}_2$  is held constant and tidal volume is decreased the subject experiences air hunger (Banzett 2006).

Marin et al (1999) found that central chemoresponsiveness can explain a part of the variance in peak dyspnea in exercising COPD. As reported later by the same group central chemoresponsiveness explained about 28% of the variance in peak dyspnea, whereas no mechanical factors appeared to be involved (Montes de Oca et al 1998). Cloosterman et al (1998) found in patients with a wide range of obstructive pulmonary disease performing an incremental cycle ergometer test that ventilatory muscle could be one of the important factors that correlated with the sensation of dyspnea in the group without  $\text{CO}_2$  retention; in contrast in the group with  $\text{CO}_2$  retention an increase in  $\text{PaCO}_2$  appeared to be the most important stimulus overriding all other inputs for dyspnea.

Dyspnea may be generated by hypoxia but it is a much weaker stimulus of dyspnea. Nonetheless, more effort is required to generate any given muscle power as arterial oxygen content declines (eg, altitude or anemia). Change in oxygen content may affect dyspnea directly or indirectly. Hypoxia may act indirectly by increasing ventilation, and directly independent of change in ventilation in patients with COPD (Lane et al 1987). Swimburn et al (1984) showed similar relationship of ventilation with dyspnea whether COPD patients breathed air or 60% oxygen. The data suggested to the authors that hypoxia had no dyspnoegenic effect, and that it caused dyspnea by stimulating ventilation.

## How can we measure exercise dyspnea?

### Quantitative assessment

Multidimensional instruments such as baseline dyspnea index (BDI) and transitional dyspnea index (TDI) and dyspnea components of chronic respiratory questionnaires provide comprehensive measurement of dyspnea as related to activities of daily living (Ambrosino and Scano 2004).

BDI and TDI questionnaires and chronic respiratory questionnaire (CRDQ) are valid, reliable and responsive instruments (Mahler et al 1991). The BDI exhibits consistently high correlations with Medical Research Council (MRC) questionnaire, 6 min walking distance test (6 mWD), and quality of well being score (Mahler and Harver 1992). BDI and TDI adequately reflects the beneficial effects of pulmonary rehabilitation programs (Mahler et al 1995).

Category ratio scale (CR-10) developed by Borg (1982) and visual analogue scale (VAS) could reproducibly measure symptoms during incremental and steady state exercise, and could detect the effect of drug intervention. During cycle ergometry, power production or work performed are used as a stimulus (independent variable) for examining the dyspnea response (dependent variable) (Mahler et al 1991) assessed as Borg score. Continuous rating of dyspnea on response to a stimulus (ie,  $B_2$  agonist, work rate) during both incremental and constant work exercise offers some advantages to discrete rating of the symptom (Mahler et al 2005).

### Qualitative assessment

In general the language of dyspnea complements physiological measurements, both being essential to a comprehensive understanding of exercise tolerance and dyspnea. When requested to qualitatively assess their dyspnea on the base of the language of dyspnea (Simon et al 1990; Mahler et al 1996; Scano et al 2005) COPD patients describe the

symptom as an increased respiratory work/effort at rest and unrewarded inspiration and/or inspiratory difficulty during exercise (O'Donnell et al 1997). The following, however, requires consideration: (1) cultural, socio-economic, linguistic and educational backgrounds may influence the use of the language of dyspnea; and (2) whether improvement of the physiological derangements modifies the language of dyspnea has yet to be defined.

## Clinics

### Physical examination

A male with a long history of heavy cigarette smoking, long been complaining of dyspnea during walking on the level. Patient sits forward while bracing their hands or elbows against a table or their knees. He manifests excessive inward motion of intercostal spaces during inspiration (Hoover sign) (Hoover 1920) and adopts a pursed lip breathing pattern (Casciari et al 1981; Breslin 1992; Bianchi et al 2004). During daily activity requiring the use of arms such as combing, dressing, washing, brushing and so on, he feels arm fatigue and greater dyspnea (Celli et al 1986; Criner and Celli 1988; Gigliotti et al 2005). Speaking, limited to a few words, increases dyspnea. On the other hand when requested to qualitatively assess their dyspnea on the basis of its language he describes increases of respiratory effort at rest, and denies chest tightness (Mahler et al 1996). If one acknowledges that asthma and COPD involve different pathophysiological derangements, one can also conceivably accept the possibility of different descriptors for the two conditions. Preliminary evidence has been provided that chest tightness characterizes asthma more than COPD. The reported sensitivity of chest tightness was 0.86 for asthma and 0.07 for COPD: the specificity was 0.69 and 0.64, respectively. The data indicate that over 86% of the patients who report chest tightness have asthma not COPD, and about 69% of patients who do not report chest tightness do not have asthma. Another descriptor, I feel I cannot get a deep breath has high specificity for COPD and fairly less for asthma and low sensitivity for both (Harver et al 2000).

### Lung function test

The scenario is one of a typical fixed obstructive pattern with severe decrease in  $FEV_1$  with hyperinflation (increased functional residual capacity). Flow limitation is evident on the flow volume curve. Muscle weakness is coupled with an increased requirement of inspiratory pressure generation. Diffusion lung properties are remarkably reduced. Mild hypoxia and mild carbon dioxide retention are also found.

Measurement of dyspnea complements the clinical evaluation of patients in who administration of standard dose of  $B_2$  short acting agonist does not result in any significant change in baseline pulmonary function despite less dyspnea.

### Submaximal and maximal exertional testing

Patients walk a less than predicted timed distance and during incremental cycling exercise are less than predicted peak work rate, ventilation, and oxygen uptake; they also exhibit a decreased inspiratory capacity (ie, dynamically hyperinflated), stop cardiopulmonary exercise test complaining either dyspnea or leg effort, or both (Hamilton et al 1995, 1996). The presence of high heart rate reserve and the absence of ventilatory reserve support the conclusion that they have ventilatory limitation. The clinical findings, abnormal baseline normal function, and chest Xr pattern clearly differentiate these patients from subjects who complain of difficult breathing with activities, but actually report higher rating for leg effort than dyspnea at submaximal and maximal exercise intensity (Mahler and Harver 1998). These findings combined with a reduced peak oxygen uptake, and a normal breathing reserve (>30%) strongly single out individuals actually limited by deconditioning or musculoskeletal factors, rather than respiratory disease (Mahler and Horowitz 1994).

There is strong evidence that either dyspnea or leg effort, or both limit exercise performance (O'Donnell and Webb 1993; Hamilton et al 1996; O'Donnell et al 1997; Gigliotti, Coli et al 2003; Stendardi et al 2005). Leg fatigue appears to be more important in those with less COPD (Hamilton et al 1995). This is consistent with the belief that perception of effort to drive both respiratory and peripheral muscles plays an important role in limiting muscular performance (Hamilton et al 1996; Jones and Killian 2000; Scano et al 2006). In this connection it has been postulated that in conditions of moderate intensity of submaximal exercise when cardiac output is abnormally low and ventilatory work is high the effect of respiratory muscle load on maximal exercise performance might be due to the associated reduction in leg blood flow which increases both leg effort and intensity with which leg effort and dyspnea are perceived (Harms et al 2000). During prolonged submaximal exercise with a constant load both the perceived effort of breathing and the perceived effort of exercising the skeletal muscles gradually increase with time, eventually reaching the subject's tolerable limit (Kearon et al 1991). During progressively increasing exercise both the perceived effort of exercising and the perceived effort to breathing begin to increase at threshold of about 25% of maximal capacity and most subjects stop when

they reach 4–7 on the Borg scale (Killian et al 1992). Patients' data showing that after exercise rehabilitation programs a similar decrease in exertional dyspnea as in leg effort is associated with unchanged inspiratory effort and maximal oxygen pulse (ie, the ratio of oxygen consumption to maximal heart rate) indicate other reasons for decreased perception being in play. On the other hand, the sedentary lifestyle of the patients with COPD contributes to peripheral muscle deconditioning, and there is evidence that peripheral muscle function is impaired in moderately severe COPD (Bernard et al 1998). Specific muscle weakness has been attributed to a possible COPD peripheral myopathy (Palange and Wagner 1999). This has been proposed on the basis of biochemical and histological changes in the quadriceps muscle of the patients. However, there is debate about the adequacy of oxygen delivery during exercise in these circumstance and whether this rather than any intrinsic abnormality explains the poor performance (Cuillard et al 1999; Richardson et al 1999). In this connection, strong evidence has been provided that exercise performance is limited by inadequate energy supply in COPD (Richardson et al 1999). These data suggested to the authors that reduced whole body exercise capacity in patients is the result of central restraints rather than peripheral skeletal muscle dysfunction and that the respiratory system is not the sole constraint to oxygen consumption.

It follows that treatment of airflow resistance alone may not improve the exercise capacity of patients whose muscles are weak or produce excess lactate, unless muscle strength and aerobic capacity are concurrent improved (Maltais et al 1996).

## Treating exercising dyspnea

### Pharmacological treatment

Optimal bronchodilatation can be seen as a first step in improving exercise endurance and exertional dyspnea intensity in patients with COPD (Belman et al 1996; O'Donnell et al 1999; Mahler et al 2002; O'Donnell, Fluge et al 2004; O'Donnell Voduc 2004). Despite apparent non reversibility in spirometric parameter, long term administration of once-daily inhaled anticholinergic demonstrates sustained improvement in inspiratory capacity, reduction in thoracic gas volume, and health outcomes (Celli et al 2003; O'Donnell, Fluge et al 2004; Maltais et al 2005). Although the precise neurophysiopathological mechanisms of dyspnea relief remains speculative the ability of bronchodilators to increase tidal volume represents the basis for reducing dyspnea intensity, or for alteration of its quality (O'Donnell, Voduc et al 2004). A number of bronchodilator studies have

shown that the reduced dyspnea score on exercise at isotime correlates well with reduced operational lung volumes (ie, reduced end expiratory lung volume and increased inspiratory reserve volume) and improved breathing pattern (Celli et al 2003; O'Donnell et al 2000). The evidence supports the idea that the beneficial effect of bronchodilators on respiratory sensation of COPD patients potentially relates to increase in neuromechanical coupling of the ventilatory pump as a result of improved dynamic ventilatory mechanics (Belman et al 1996; O'Donnell et al 1999).

On the other hand, Aliverti, Rodger et al (2005) have recently shown that patients who increased their end expiratory abdominal compartmental volume during exercise after treatment with short acting  $B_2$  agonist were able to exercise for longer. In contrast, less hyperinflated patients after the active drug reduced the abdominal compartmental volume in a fashion analogous to the euvolumic patients with COPD studied during incremental exercise (Aliverti et al 2004), and this paradoxically reduced their exercise capacity with higher isotime levels of dyspnea. The kinematic difference between improvers and worseners was the degree of expiratory muscle recruitment. The worseners were using the abdomen to pump the lung much more than the improvers. This requires coordinated activity of the abdominal muscles and the diaphragm. As stated above excessive expiratory pleural pressure during flow-limited exercise acts as a Valsalva maneuver decreasing cardiac output and producing the blood shift from trunk to extremities (Aliverti et al 2002, 2005; Iandelli et al 2002). It seems that a combination of high ventilatory demands and limitation of cardiac output (Levison and Cherniack 1968) both caused by excessive expiratory pressures can be a potent factor limiting exercise performance in COPD (Macklem 2005b).

There is no consensus regarding which exercise test to use to evaluate the functional impact of exercise dyspnea in patients with COPD (Palange et al 2000; Mann et al 2003). In particular, recent data indicate that endurance shuttle walking is a sensitive test to detect changes in exercise tolerance following bronchodilation. Difference in the occurrence of quadriceps muscle fatigue may explain in part the different responsiveness to change between cycling and walking (Pepin et al 2005). Nonetheless, greater treatment effects (eg, improvement in exercise performance, symptoms, health-related quality of life) are often achieved only after the addition of pulmonary rehabilitation (Troosters et al 2005).

### Pulmonary rehabilitation program

A six week outpatient pulmonary rehabilitation program includes education, breathing retraining and limb exercise

training. Let first consider how quantitatively and qualitatively does a patient modulate dyspnea at baseline by breathing retraining (Gigliotti, Romagnoli et al 2003). He/she spontaneously adopts a pursed lip breathing pattern (PLB). Despite improvement in gas exchange and efficient ventilation, the efficacy of PLB in relieving dyspnea varies greatly among patients (Troosters et al 2005) and is still a matter of debate (Spahija et al 2005). It has been recently shown that whatever the level of baseline hyperinflation the effect of PLB on dyspnea relies upon its deflationary effect on the chest wall abdominal compartment by an increased expiratory time (Bianchi et al 2004). Leaning forward (LF) attenuated patient's dyspnea sensation. While standing position increases activation of the diaphragm and its force production, LF decreases both (Sharp et al 1980). The reason for the association of LF with less dyspnea lies in the common belief that dyspnea is linked to increased central motor command to the respiratory muscles (El-Manshawi et al 1986; Leblanc et al 1988; O'Donnell et al 1997); hence, a decreased respiratory muscle activation lowers dyspnea in this patient with partial restoration. During daily activities requiring the use of the arms patient exhibits increased sensations of arm effort and dyspnea. Bracing their arms partially restores the increased sensation of arm effort and dyspnea, whereas arm training program increases arm endurance at 7% maximal work rate, modulates dynamic hyperinflation and lowers the Borg score of arm effort and dyspnea (Gigliotti et al 2005).

Let now consider how does exercise training modulate exercise dyspnea in patients with COPD. Although the physiologic mechanisms involved in the reduction of dyspnea after training are likely to be complex the following seems to play a major role: (i) cardiovascular factors, (ii) decreased ventilatory demand, (iii) decreased impedance to ventilatory muscle action, and (iv) non physiologic factors.

### Cardiovascular factors

Ventricular dysfunction in addition to respiratory impairment may limit exercise performance in some patients with COPD (Mahler et al 1984). Inadequate  $O_2$  delivery is important in the impairment of exercise performance (Montes de Oca et al 1996). Should these factors play a role in increasing exercise performance with exercise training we would observe an increased ratio of oxygen consumption to maximal heart rate ( $V_{O2}/HR$ ), a non invasive estimate of stroke volume.

### Decreased ventilatory demand

The decrease in both ventilation and carbon dioxide production at standardized work rate indicates a decreased ventilatory demand. An increased aerobic capacity with exercise

training is in line with a decrease in lactate production reported in older severely obstructed patients (Mahler and Horowitz 1994).

### Decreasing impedance

Despite an unaltered ventilatory equivalent for carbon dioxide there is less Borg per unit change in ventilation after training. This would suggest an improved mechanical efficiency which is usually accomplished by a decrease in dynamic elastance in association with decrease in dynamic hyperinflation. Change in inspiratory capacity is a mirror of changes in dynamic end-expiratory-lung-volume. The role of dynamic hyperinflation on dyspnea and that of increased respiratory muscle effort on the perception of inspiratory effort have been elucidated in the section of Pathophysiology. According to this scenario, exercise training reduced dyspnea by reducing the inspiratory effort, end-expiratory-lung-volume and respiratory rate. In turn it reduces the neuromuscular decoupling (ie, the ratio of respiratory effort to concurrent volume, or flow).

### Non-physiologic factors

An increased tolerance to dyspnea may play an important role in the referred reduction of dyspnea at equivalent ventilation. Moreover, breathing retraining may actually improve the breathing pattern slowing respiratory rate, and indirectly contributing to modifying dyspnea (Hamilton et al 1996).

During leg exercise patients may also be given supplemental oxygen to improve exercise tolerance (Scano et al 1982) and reduce exertional dyspnea (O'Donnell, D'Arsigny et al 2001). Most importantly, Borg score and ventilation fall proportionally; the slope in air and oxygen are superimposed indicating that the decrease in Borg is associated with reduced ventilatory demand. As a consequence of the improved aerobic metabolism, dyspnea decreases at iso-work load. Oxygen can also modify the strategy of respiratory muscle recruitment in these patients by increasing exercise performance of the diaphragm and unloading the accessory and abdominal muscles, with dyspnea being less (Criner and Celli 1987). This pattern was thought to prevent overloading of other respiratory muscles (accessory inspiratory and abdominal muscles), with this resulting in less dyspnea. The results of a recent study in non hypoxemic COPD patients have shown that supplemental oxygen given during high-intensity endurance training adds to the benefit of training: endurance capacity, and dyspnea improves significantly (Emtner et al 2003).

Finally, based on the findings that unloading the respiratory muscles by pressure support produces a substantial reduction in inspiratory effort and dyspnea (Maltais et al 1995; Dolmage et al 1997; Polkey et al 2000), and that a more pronounced improvement is obtained in patients with respiratory muscle weakness the possibility has been considered for the application of inspiratory support to enhance training intensity. Further studies, however, are needed to evaluate the effects of long term non invasive ventilation on change in daily dyspnea in these patients (Rossi and Hill 2000).

### Lung volume reduction surgery (LVRS)

Surgical intervention for patients with severe bullous emphysema who remain incapacitated by dyspnea despite optimal pharmacological therapy and pulmonary rehabilitation has emerged as a useful therapeutic option. LVRS has shown to improve pulmonary function and elastic recoil (Sciurba et al 1996), neuromechanical coupling of the diaphragm (Laghi et al 1998), exercise tolerance and quality of life, with reduction in the degree of airflow obstruction and dynamic hyperinflation (Martinez et al 1997). Much of the success of LVRS depends on patients selection criteria. Preoperative screening assessment and pulmonary rehabilitation should be used to select those patients most likely to benefit from surgery.

## In summary

The mechanisms contributing to dyspnea must be approached in an integrative manner. Respiratory muscle function and its relationship to metabolic and cardio-pulmonary variables during exercise identify some of the factors that limit exercise performance in patients with COPD. The identification of other factors that contribute to variability in dyspnea during exercise could result in improvement in patient's exercise capacity. Regardless of the relationships between respiratory and cardiovascular factors, a consistent amount of the variability of dyspnea remains unexplained. This is probably due to the fact that dyspnea is a subjective sensation which is dependent on the stimulus involved, the central processing, integration of many sensory inputs, the situational context in which it occurs, behavioral influences, and patient's ability to describe sensations.

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