Mechanisms of activity-related dyspnea in pulmonary diseases

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Abstract
Progressive activity-related dyspnea dominates the clinical presentation of patients afflicted by chronic obstructive and restrictive lung diseases. This symptom invariably leads to activity limitation, global skeletal muscle deconditioning and an impoverished quality of life. The effective management of exertional dyspnea remains an elusive goal but our understanding of the nature and mechanisms of this distressing symptom continues to grow. Refinements in psychophysical measurement of the sensory intensity and quality of dyspnea during laboratory clinical cardiopulmonary exercise testing (CPET) have provided new insights into causation. In this review, we focus on what is known about the physiological mechanisms of dyspnea during physical exertion in patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Although these conditions are pathologically diverse, perceptual and ventilatory responses to exercise are remarkably similar among patients with these two conditions. In both patient groups, dyspnea intensity is increased at any given ventilation compared with age-matched healthy individuals; at the limits of tolerance, most patients predominantly select qualitative descriptors that allude to perceptions of “increased respiratory effort” and “unsatisfied inspiration.” Common abnormal physiological responses to CPET across conditions include: (1) increased central respiratory drive secondary to pulmonary gas exchange and metabolic derangements, (2) abnormal “restrictive” constraints on tidal volume expansion with earlier development of critical mechanical limitation of ventilation and (3) an increasing disparity (as exercise proceeds) between the magnitude of contractile respiratory muscle effort and the thoracic volume displacement achieved. Reductionist experimental approaches that attempt to partition, or isolate, the contribution of central and multiple peripheral sensory afferent systems to activity-induced dyspnea have met with limited success. Integrative approaches which explore the possible neurophysiological mechanisms involved in the two dominant qualitative descriptors of activity-related dyspnea in both diseases may prove to be more fruitful. In this review, we present a hypothetical model for exertional dyspnea that is based on current neurophysiological constructs that have been rigorously developed to explain the origins of perceptions of “effort,” “air hunger” and the accompanying affective “distress” response.

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1. Introduction
Perceived respiratory difficulty or dyspnea is a major symptom of patients with chronic respiratory diseases (Leblanc et al., 1986; Mahler et al., 1995; Hamilton et al., 1996). In many, this symptom progresses relentlessly with time to reach incapacitating levels. Dyspnea leads to activity limitation, and is often associated with major psychological comorbidity, social isolation and poor perceived quality of life. The effective management of dyspnea remains a major challenge for caregivers, and modern treatment strategies that are based on attempts to reverse the underlying chronic condition are only partially successful. Activity-related dyspnea is usually the earliest and most troublesome symptom of patients presenting with chronic pulmonary disorders and is the main focus of this review. Recent studies that have explored the relationship between measured physiological stress during physical exertion (the dyspneogenic stimulus) and the attendant sensory response (intensity and quality of dyspnea) have provided new insights in the nature and mechanisms of perceived respiratory discomfort (Leblanc et al., 1986; Hamilton et al., 1996; O’Donnell et al., 1997b). In this review we will first, enumerate the psychophysical methods that are increasingly employed in the evaluation of dyspnea during cardiopulmonary exercise testing (CPET). Second, we will review the recent studies of the physiological mechanisms of dyspnea during CPET in chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Third, we will compare the perceptual and ventilatory responses to exercise in these conditions so as to identify common mechanisms of dyspnea. Fourth, we will review the...
lessons learned from studies designed to uncover the mechanisms of dyspnea relief following therapeutic interventions. Finally, we will present a hypothetical neurophysiological construct for exertional dyspnea in pulmonary disease.

2. Evaluation of dyspnea during exercise

Classical psychophysical experiments employing external mechanical loading of the respiratory system have taught us that humans can reliably recognize even minor respiratory disruption, quantify sensory intensity and discriminate between different qualitative dimensions of breathing discomfort (Campbell et al., 1961; Bennett et al., 1962; Bakers and Tenney, 1970; Zechman and Davenport, 1978; Killian et al., 1980; Davenport et al., 1981; Zechman et al., 1981; Burdon et al., 1982). Conscious humans can also readily perceive alterations in respiratory sensation during acutely imposed arterial blood gas and acid–base disturbances (Campbell et al., 1969; Banzett et al., 1990; Bloch-Salisbury et al., 1998; Gandevia et al., 1993; Lane and Adams, 1993; Moosavi et al., 2003). Recent studies have confirmed that humans can distinguish between the sensory intensity and affective dimensions of dyspnea (Banzett et al., 2008). We can also conclude from these seminal mechanical and chemical loading experiments that perceived respiratory discomfort, at least under these experimental conditions, is associated with: (1) increased central respiratory neural drive, (2) alteredafferent feedback from respiratory mechanosensors and (3) a dissociation between efferent output and afferent sensory inputs (Campbell et al., 1961, 1969; Bennett et al., 1962; Bakers and Tenney, 1970; Zechman and Davenport, 1978; Killian et al., 1980; Davenport et al., 1981; Zechman et al., 1981; Burdon et al., 1982; Banzett et al., 1990; Gandevia et al., 1993; Lane and Adams, 1993; Bloch-Salisbury et al., 1998; Moosavi et al., 2003).

While these studies have informed us about the possible neurophysiological origins of dyspnea, interpretive limitations are evident. External mechanical and chemical loads imperfectly simulate the intrinsic loading of pulmonary disease. For example, external resistive loading is a poor simulation of the expiratory flow limitation and dynamic lung hyperinflation that characterize obstructive airways diseases (Loughheed et al., 2002). Responses to acute mechano- or chemo-stimulation in the healthy are unlikely to duplicate sensory responses in patients with background intrinsic loading who have developed long-term mechanical and chemical compensatory adaptations.

2.1. Measuring dyspnea intensity during exercise

The study of dyspnea within clinical populations under conditions of measured physiological stress (i.e., exercise) is an attempt to circumvent some of the interpretative difficulties of simulated loading in healthy volunteers. Such studies have been facilitated by the development of reliable instruments to measure dyspnea intensity during exercise. The Borg scale (Borg, 1982), a category scale with ratio properties, has been shown to be reproducible and responsive and ideal for the purpose of dyspnea assessment during CPET (O’Donnell et al., 1998b, in press). The key to successful utilization of the Borg scale is, first, precision concerning the specific respiratory sensation that the participant is being asked to rate (e.g., breathing effort, inspiratory difficulty, air hunger, etc.). Second, the magnitude of respiratory sensation should, a priori, be anchored at both extremes of the scale such that a rating of “10” represents the maximal breathing difficulty that the patient has experienced (or could imagine) and “0” represents no breathing difficulty (Mahler, 2005). Though somewhat less popular, the visual analogue scale is another dyspnea measuring instrument with proven construct validity used during CPET (Wilson and Jones, 1989; Gift, 1989).

In accordance with the principals of psychophysical measurement, comparisons of dyspnea intensity within and between patients should be undertaken at a standardized power output, oxygen uptake (VO2) or ventilation (V̇E) during exercise. Stimulus–response relations can be analysed as slopes of dyspnea intensity (Borg) over work rate or VO2 (each expressed as %predicted) and compared in clinical populations and in age-matched healthy controls.

CPET allows systematic analysis of the physiological source(s) of exertional dyspnea in the individual patient (O’Donnell et al., 2007). For example, CPET will help identify abnormal ventilatory responses (slopes of V̇E over carbon dioxide output (VCO2) are invariably increased in pulmonary disease) and the underlying cause of increased ventilatory drive (i.e., metabolic or pulmonary gas exchange abnormalities). The nature and degree of the mechanical abnormality can be assessed by measurement of dynamic operating lung volumes, while cardiovascular impairment can be recognized by indirect measurements (e.g., heart rate, oxygen pulse, anaerobic threshold, etc.) (Yan et al., 1997; O’Donnell et al., 1998b, in press).

2.1.1. Correlative analysis

Leblanc et al. (1986) were among the first to employ correlational analysis to identify potential contributory factors to dyspnea intensity in health and disease. Regression analysis is undertaken with dyspnea as the dependent variable versus a number of relevant independent physiological variables. Using stepwise multiple regression analysis, putative contributory variables can be identified and weighted while controlling for confounders such as age, sex, body mass index and the existence of comorbidities. The strength and validity of the association is subsequently tested by specific manipulations of the contributory variable(s). For example, if reduced inspiratory capacity (IC) at a standardized power output during exercise emerged as the variable that explained most of the variance in dyspnea intensity ratings in COPD then the validity and strength of this association can be tested by specific therapeutic manipulation of the IC (O’Donnell et al., 1997b, 1999, 2001b). Thus, increase in IC following bronchodilatation correlated well with reduction in activity-related dyspnea (O’Donnell et al., 1999, 2004a,b; Marin et al., 2001).

2.1.2. Analysis of mechanisms of dyspnea improvement

The study of the mechanisms of dyspnea relief in chronically dyspneic patients can provide valuable insights into causation. Placebo-controlled studies using a number of therapeutic interventions (e.g., hyperoxia, heliox, exercise training, bronchodilators, opiates, lung volume reduction techniques, mechanical ventilation, inhaled furosemide) have been undertaken (Bradley et al., 1978, 1980; Woodcock et al., 1981; Stein et al., 1982; Swinburn et al., 1984; Bye et al., 1985; O’Donnell et al., 1995, 1997a, 1998, 1998c, 1999, 2001a, 2004a,b; Light et al., 1989; Young et al., 1989; Petrof et al., 1990; Dean et al., 1992; Maltais et al., 1995; Martinez et al., 1997; Oelberg et al., 1998; Somfay et al., 2001; Johnson et al., 2002; Appleton et al., 2003; Celli et al., 2003; Gigliotti et al., 2003; Foral et al., 2004; Laghi et al., 2004; Ong et al., 2004; Palange et al., 2004; Eves et al., 2006; Peters et al., 2006; Jensen et al., 2008a). It is generally possible through analysis of CPET responses to discern whether the mechanism of dyspnea relief is: (1) reduced central ventilatory drive, (2) improved dynamic ventilatory mechanics or respiratory muscle function or (3) a combination of both. Specific manipulations to reduce central respiratory drive (e.g., hyperoxia) will, when compared to placebo, reduce dyspnea/work rate slopes but have no effect on dyspnea/V̇E slopes (Peters et al., 2006) (Fig. 1a). Thus, dyspnea relief following interventions that alter chemoreceptor input is linked to the decreased V̇E. By contrast, interventions that improve respiratory mechanics (e.g., bronchodilators, surgical
lung volume reduction in COPD) are associated with reduction in both dyspnea/VO₂ and dyspnea/V₆ slopes (Fig. 1b). In this circumstance, dyspnea intensity ratings fall at a given V₆ during exercise reflecting the effects of inspiratory muscle unloading (Peters et al., 2006).

2.1.3. Qualitative dimensions of dyspnea

Simon et al. (1990) developed a series of 19 qualitative descriptors of dyspnea that highlight its multidimensional nature. It is reasonable to postulate that different qualitative descriptors have different neurophysiological underpinnings. There is evidence that descriptor choices can vary among patients with different cardiopulmonary diseases, although accurate diagnostic discrimination is not possible (Elliott et al., 1991; Mahler et al., 1996). This qualitative dyspnea questionnaire has been used at the end of exercise when dyspnea intensity is severe. Descriptor clusters that allude to increased effort/work of breathing (e.g., “my breathing requires more work or effort”) are pervasive across health and disease (O’Donnell and Webb, 1993; Chau et al., 1996; O’Donnell et al., 1997b, 2000). Descriptor choices that refer to inspiratory difficulty (e.g., “unsatisfied inspiration”) are selected across the spectrum of pulmonary conditions but are rarely selected in health even at the peak of exhaustive exercise.

2.1.4. Evaluation of the role of mechanical factors in exertional dyspnea

Measurement of dynamic operating lung volumes (by serial IC measurements) and the ratio of contractile respiratory muscle effort to volume displacement [tidal esophageal pressure (Pes) relative to maximum inspiratory pressure: tidal volume (V₆) expressed as %predicted vital capacity] throughout exercise allow an exploration of the contribution of mechanical factors to dyspnea causation (O’Donnell et al., 2000, 2006a). In young healthy individuals, several mechanical adaptations ensure that the expanding V₆ during exercise is accommodated within the most compliant, linear portion of the respiratory system’s pressure–volume (P–V) relation (refer to Jensen et al., this issue for review). The operating position of V₆ on this sigmoidal P–V curve dictates the relationship between central respiratory neural drive and the dynamic mechanical/muscular response of the respiratory system during exercise (Younes, 1991). In health, the effort–displacement ratio is maintained relatively constant during exercise (O’Donnell et al., 2000, 2006a; Jensen et al., 2008b). This indicates optimal positioning of V₆ on the P–V curve where harmonious neuromechanical coupling is preserved and perceived respiratory difficulty is avoided (or attenuated) even at high ventilations. In respiratory diseases, the respiratory system’s P–V curve is contracted along its volume axis but retains its sigmoidal shape. Therefore, the operating V₆ becomes positioned closer to total lung capacity (TLC) on the upper, non-compliant portion of the P–V curve where effort–displacement ratios are increased compared with health. It follows that during exercise in disease there is a progressively increasing disparity between contractile respiratory muscle effort (and central neural drive) and simultaneous volume displacement starting at relatively low ventilations (O’Donnell and Webb, 1993; O’Donnell et al., 1998a). The increased effort–displacement ratio is a crude index of...
Fig. 2. Perceptual and ventilatory responses to cycle exercise are shown in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and in age-matched healthy controls. In patients with COPD compared with health: dyspnea intensity measured by the Borg scale was greater for a given oxygen consumption (VO$_2$) and ventilation; ventilation was greater; breathing pattern was more rapid and shallow; tidal respiratory effort was greater and; the effort–displacement ratio was greater. $F$, breathing frequency; $V_T$, tidal volume; VC, vital capacity; Pes$/P_{\text{Imax}}$, tidal esophageal pressure swings relative to maximum inspiratory pressure. Adapted and modified with permission from O'Donnell et al. (1997a,b)(permission pending).

neuromechanical uncoupling (or dissociation) and may be relevant to the origins of dyspnea in pulmonary disease states.

3. Perceptual and ventilatory responses to CPET

3.1. Chronic obstructive pulmonary disease

Intolerable dyspnea is a major exercise-limiting symptom in patients with COPD. Dyspnea intensity is increased at any given exercise VO$_2$, work rate or $V_T$ compared with age-matched healthy controls (Fig. 2). Qualitative descriptor choices by patients at the peak of exercise predominantly allude to perceptions of increased “work/effort” [i.e., “my breathing needs more effort (work)”] and “unsatisfied inspiration” (i.e., “I cannot get enough air in,” “I have difficulty breathing in,” “I cannot take a big breath in,” “my breath does not go in all the way”) (O'Donnell et al., 1997b, 1998a) (Fig. 3).

3.1.1. Increased central respiratory drive

Neural drive to the diaphragm is elevated at rest and increases progressively during exercise in patients with COPD to near maximal levels at peak VO$_2$ (DeTroyer et al., 1993; Sinderby et al., 2001). Ventilatory demand is increased during exercise reflecting a high fixed physiological dead space secondary to increased ventilation–perfusion (V/Q) abnormalities (Wagner et al., 1977; Wagner, 1985). Early metabolic acidosis (secondary to skeletal muscle deconditioning), increased peripheral muscle metabo- and mechanoreceptor activation (Haouzi et al., 2004; Haouzi, 2006) and in some cases critical arterial hypoxia may also stimulate $V_T$.
...continuous breath sounds at both lung bases are present. The net effect of these metabolic and dynamic respiratory muscle abnormalities is to increase ventilatory demand to a level that reaches or exceeds maximal ventilatory capacity (MVC) in patients with more severe COPD (O’Donnell, 2002) (Fig. 2). In some patients, mechanical constraints on V̇̇̇̇ reveal the possibility of flow limitation due to dynamic pulmonary hyperinflation (DH) in the setting of severe pulmonary V̇̇̇̇Q̇̇̇̇ abnormalities (i.e., high fixed physiological dead space) leads to CO2 retention and arterial oxygen desaturation during exercise (O’Donnell et al., 2002).

3.1.2. Mechanical factors

It is clear that extensive small airways disease and V̇̇̇̇Q̇̇̇̇ disruption may be present even in smokers with early COPD (Buist and Ross, 1973; Barbera et al., 1991). In symptomatic mild COPD, the resulting combination of abnormal static and dynamic respiratory mechanics (i.e., DH) and increased ventilatory demand is associated with increased dyspnea intensity at a given VO2 and V̇̇̇̇E during exercise compared with age-matched healthy controls (Babb et al., 1991; Ofir et al., 2008). DH is likely to arise in flow-limited patients under conditions of abruptly increased neural drive and ventilatory demand (Grimby et al., 1968; Olafsson and Hyatt, 1969; Potter et al., 1971; Stubbing et al., 1980; Dodd et al., 1984; O’Donnell et al., 2001b; O’Donnell and Laveneziana, 2006c). In moderate-to-severe COPD, static and dynamic pulmonary hyperinflation as a consequence of expiratory flow limitation, result in reduction of the resting IC and inspiratory reserve volume (IRV) such that as V̇̇̇̇E increases during exercise, and a critically minimal IRV (at ~0.5 L below TLC) is reached at a relatively low V̇̇̇̇E compared with healthy (O’Donnell and Webb, 1993; O’Donnell et al., 1997b, 2006a) (Fig. 4). Attainment of this minimal IRV early in exercise is an important mechanical event and likely has important sensory consequences. At this point, there is a plateau in the V̇̇̇̇E response despite continued progressive increases in contractile respiratory muscle effort. Thus, at the V̇̇̇̇E plateau, effort–displacement ratios abruptly increase and dyspnea intensity quickly escalates to intolerable levels in COPD at relatively low work rates and ventilation (O’Donnell and Webb, 1993; O’Donnell et al., 1997b, 2006a).

3.1.3. Respiratory muscle dysfunction

It is important to note that intolerable respiratory discomfort is generally the proximate source of exercise limitation even before physiological maxima are attained, at least in severe COPD. Our observation has been that for most patients with moderate-to-severe COPD, true mechanical limitation is discernible at the limits of tolerance, i.e., at a point where there is apparent reserve for further inspiratory and expiratory muscle force generation. This position is bolstered by carefully conducted studies that have shown lack of overt diaphragmatic fatigue even at peak VO2 in patients with advanced COPD (Polkey et al., 1997; Mador et al., 2000). The increased elastic and inspiratory threshold loads (secondary to DH), as well as the increased resistive loading of the respiratory muscles means that the effort required to support a given ventilation, together with the work and oxygen cost of breathing is increased compared with healthy (Everson and Cherniack, 1968; O’Donnell and Webb, 1993; O’Donnell et al., 1997b). The tachypneic response to exercise that is characteristic of COPD (Fig. 2) is associated with reduced dynamic lung compliance. Moreover, the concomitant increased velocity of shortening leads to functional weakness of the inspiratory muscles (Leblanc et al., 1988). There is evidence that respiratory muscles in COPD admirably adapt to altered geometric configurations of the thorax as well as to long-term intrinsic mechanical loading (Cassart et al., 1997; Macklem et al., 1997). Thus, force-generating capacity of the diaphragm is preserved, or increased, when corrected for the increased lung volume at which it is measured (Similowski et al., 1991). However, clinically significant inspiratory muscle weakness is present in some patients (Harver et al., 1989). Contributory factors include: electrolytic and acid–base disturbance, systemic steroid use, malnutrition and muscle wasting.

3.1.4. Expiratory muscle activation in COPD

Vigorous expiratory muscle recruitment has been documented during exercise in several studies in patients with moderate-to-severe COPD (Grimby et al., 1968; Potter et al., 1971; Aliverti et al., 2004). In flow-limited patients, expiratory muscle activation...
(beyond the critical airway closing pressure) may be counterproductive as it does not increase expiratory flow rates but results in widespread dynamic airway compression. Excessive expiratory muscle activation can also have negative cardiovascular effects during exercise (Potter et al., 1971; Aliverti et al., 2004).

3.2. Interstitial lung diseases

The ILD represent a broad, heterogeneous group of lung parenchymal disorders (ATS/ERS, 2002). Dyspnea intensity ratings are increased in patients with ILD at any given exercise VO\textsubscript{2} work rate or V\textsubscript{T} compared with healthy controls (Marciniuk et al., 1994; O’Donnell et al., 1998a; O’Donnell and Fitzpatrick, 2003) (Fig. 5). Severe dyspnea is often the dominant exercise-limiting symptom. Increased “effort/work” of breathing and “unsatisfied inspiration” are the most common qualitative descriptors at peak VO\textsubscript{2} during incremental CPET (O’Donnell et al., 1998a) (Fig. 3).

3.2.1. Increased central respiratory drive

Typical ventilatory response patterns in ILD include: low peak V\textsubscript{E}, high peak V\textsubscript{E}/MVC ratio, high submaximal V\textsubscript{E} (increased slopes of the V\textsubscript{E}–VO\textsubscript{2} and V\textsubscript{E}–VCO\textsubscript{2} relationships), with a high breathing frequency and low V\textsubscript{T} at any given ventilation (Jones and Rebuff, 1979; Spiro et al., 1981) (Fig. 5). Increases in submaximal V\textsubscript{T} in ILD reflect ventilatory inefficiency due to high physiological dead space, critical arterial hypoxemia, and early metabolic acidosis (Austrian et al., 1951; Georges et al., 1975; Wagner et al., 1976; Hansen and Wasserman, 1996; Lamberto et al., 2004). Other possible but less well studied contributors include increased sympathetic nervous system activation, increased altered vagal afferent activity, increased pulmonary vascular receptor stimulation and increased peripheral muscle mechanoreceptor/metaboreceptor activation (Turino et al., 1963; Lourenco et al., 1965; Painth, 1973; Widdicombe, 1981; Haouzi et al., 2004; Bell, 2006; Haouzi, 2006). Significant widening of the alveolar-to-arterial O\textsubscript{2} gradient can occur during exercise in early ILD and relative alveolar hyperventilation is not uncommon (Johnson et al., 1960; Keogh et al., 1984; Risk et al., 1984). In more severe disease, profound arterial oxygen desaturation at rest and during exercise is the rule (Hamper, 1964; Weitzenblum et al., 1983; Agusti et al., 1991; Hughes et al., 1991). Alveolar hypoventilation is not commonly reported during exercise, even in advanced ILD.

3.2.2. Abnormal dynamic ventilatory mechanics

The static P–V curve of the lung is shifted downward and rightward, indicating an increased static recoil pressure of the lung at any given lung volume (Yernault et al., 1975; Gibson and Pride, 1977). In ILD, the P–V relationship of the entire respiratory system is contracted along its volume axis. The resting IC and IRV are usually diminished in ILD, and with exercise the end-inspiratory lung volume encroaches further on the upper, alinear extreme of the P–V relationship where there is significant elastic loading (Fig. 4). Effort–displacement ratios are elevated compared with normal at any given exercise VO\textsubscript{2} or V\textsubscript{T} (O’Donnell et al., 1998a) (Fig. 5). The work and oxygen cost of the muscles of breathing are also consistently elevated in ILD compared with health. A few small studies have indicated that IC throughout exercise remains largely unaltered (Marciniuk et al., 1994; O’Donnell et al., 1998a). Expiratory flow limitation has been described in some patients with ILD during exercise, and in one study its presence was associated with greater perceived dyspnea intensity (Marciniuk et al., 1994).
3.2.3. Respiratory muscle dysfunction

Inspiratory muscle function is often relatively preserved in patients with ILD reflecting the mechanical advantage of the inspiratory muscles at the lower operating lung volumes (DeTroyer and Yernault, 1980; O’Donnell et al., 1998a). However, in some individuals, involvement of the ventilatory muscles in the underlying systemic inflammatory disease process, the effects of high dose oral steroids, malnutrition, and electrolytic disturbances may have a deleterious impact on muscle function (Baydur et al., 2001).

3.2.4. Cardiovascular responses

The characteristic cardiac abnormality in ILD is increased pulmonary vascular resistance (PVR) with consequent right ventricular hypertrophy that ultimately leads to the development of cor pulmonale during the terminal phase of the illness (Weitzenblum et al., 1983; Sturani et al., 1986). Left ventricular ejection fraction is usually preserved, as are pulmonary artery occlusion pressures (Lupi-Herrera et al., 1985; Bush and Busst, 1988). Cardiac output is usually normal at rest and during low levels of exercise in ILD, but its rate of rise is diminished at higher work rates due, in part, to increased PVR (Hawrylkiewicz et al., 1982; Weitzenblum et al., 1983; Jezek et al., 1985; Sturani et al., 1986). Obliteration of the vascular bed by progressive parenchymal fibrosis and alveolar hypoxia are the main explanations for the reduced vascular bed and the increased PVR in ILD (Enson et al., 1975; McLees et al., 1977).

3.3. Summary

In both COPD and ILD, dyspnea intensity is increased and reaches intolerable levels at relatively low power outputs and ventila-
tions (Figs. 2 and 5). Qualitative descriptors of dyspnea at the peak of symptom-limited cycle exercise are remarkably similar (Fig. 3). Abnormal physiological responses to exercise are also broadly similar and include: (1) increased central neural respiratory drive (secondary to pulmonary gas exchange and metabolic derangements), (2) restrictive dynamic ventilatory mechanics with increased effort–displacement ratios (Figs. 2, 4 and 5), (3) impaired respiratory muscle function due to excessive intrinsic loading and variable functional weakness and (4) variable cardiovascular abnormalities, including pulmonary arterial hypertension. All of these factors are relevant to the origins of exertional dyspnea across these conditions.

4. Putative mechanisms of exertional dyspnea in pulmonary diseases

Reductionist experimental approaches which are designed to identify specific sources of exertional dyspnea located in specialized central and peripheral sensory systems are fraught with difficulty when applied to CPET. A major limitation is our inability to precisely quantify central respiratory neural drive or afferent sensory inputs from peripheral afferents in the lung, airways, respiratory muscles and chemoreceptors. This, coupled with the remarkable redundancy inherent in sensory systems, has hampered our ability to make progress in elucidating the precise neurophysiological substrate of dyspnea in the clinical domain. However, we concur with the generally held belief that afferent inputs from any one of an abundance of respiratory sensors can, under certain circumstances, directly modulate (or dominate) the intensity and quality of activity-related dyspnea in patients with lung diseases.

4.1. Increased central respiratory neural drive

In all cardiopulmonary disorders, dyspnea intensity rises during exercise as $E$ increases as a fraction of MVC. In fact, the $V_E/MVC$ ratio is the original dyspnea “index” (Gandevia and Hugh-Jones, 1957). It is reasonable to suggest that dyspnea intensity rises as a function of the amplitude of central motor command output that originates in the brainstem (automatic) and/or in cortical (voluntary) motor areas in the brain (Gandevia, 1982; Killian et al., 1984; Banzett et al., 1990; Chen et al., 1992; Gandevia et al., 1993; Jensen et al., this issue). Voluntary increases in isocapnic $V_E$ in healthy volunteers to mimic the hyperpnea of exercise are associated with substantially less perceived respiratory discomfort than during actual exercise, suggesting that efferent output from the brainstem is crucially important in inducing dyspnea (Lane et al., 1987; Chonan et al., 1990).

It is reasonable to assume that in patients with pulmonary disease, in whom metabolic derangements drive the increase in ventilation, the brainstem is an important locus of unpleasant respiratory sensation. It is postulated that central corollary discharge, which provides efferent copy of information from the brainstem respiratory centers to the somatosensory cortex, may be instrumental in dyspnea perception, but this lacks definitive experimental verification in humans (Chen et al., 1991, 1992; Chen and Eldridge, 1997). The question arises whether excessive chemoreceptor stimulation during exercise in disease directly influences the intensity and quality of dyspnea at any given ventilation, i.e., independent of the attendant increased activity of the respiratory muscle pump. Studies in healthy volunteers have shown that increased chemoreceptor stimulation (by added hypercapnia or hypoxia) at a given $V_E$ during exercise can, under these conditions, directly influence exertional dyspnea perception. However, the magnitude and direction of this effect appears to be inconsistent across studies (Ward and Whipp, 1989; Lane et al., 1990). The question of the role of direct chemoreceptor inputs in the genesis of perceived respiratory sensations during exercise becomes even more complex in chronic lung diseases where long-term acid–base compensation is variably present.

4.2. Vagal influences on respiratory sensation

There is evidence that inputs from pulmonary vagal afferents (i.e., rapidly and slowly adapting receptors) can convey unpleasant respiratory sensation in conscious humans under experimental conditions where inputs from other sensory systems (e.g., the chest wall and its musculature) are abolished or diminished (Banzett et al., 1987; Flume et al., 1996; Lougheed et al., 2002). However, given the methodological limitations previously alluded to, the relative importance of direct nociceptive-like influences on exertional dyspnea via abnormally activated pulmonary vagal receptors in disease states is unknown. Nevertheless, abnormal afferent inputs from pulmonary vagal receptors have long been considered as possible direct sources of unpleasant respiratory sensation in patients with pulmonary diseases (Guz et al., 1970; Paintal, 1995; Binks et al., 2002). However, vagal blockade or surgical resection had inconsistent effects on dyspnea in humans at rest and during exercise (Harty et al., 1996; Butler et al., 2001; Zhoa et al., 2002a,b, 2003). Recently, inhaled furosemide has been shown to increase breath-holding time in healthy volunteers and to improve dyspnea intensity ratings in patients with COPD during exercise, presumably through its direct action on airway and lung vagal receptors (Ong et al., 2004; Moosavi et al., 2007). However, sensory responses to inhaled furosemide are variable among exercising patients with COPD and appear to be linked, at least in part, to a coconmitant bronchodilator action (i.e., improved ventilatory mechanics) (Jensen et al., 2008a).

Dynamic airway compression in flow-limited patients with COPD at rest induced by applied negative pressure at the mouth causes abrupt increases in unpleasant respiratory sensation, presumably via activation of mechanoreceptors in the larger airways due to mechanical distortion (O’Donnell et al., 1987). However, although widespread dynamic airway compression during expiration is common in patients with COPD during exercise its role in exertional dyspnea causation is unknown.

Unmyelinated pulmonary and bronchial C-fibers (Paintal, 1973; Colledge and Colledge, 1977) have been shown to be activated by mechanical distortion (alveolar fluid accumulation) and various chemicals (e.g., capsaicin, phenyl diguanide, lobeline) and can directly lead to unpleasant respiratory sensation (Butler et al., 2001; Ho et al., 2001). The role of these afferent inputs in exertional dyspnea causation in COPD and ILD remains conjectural at present (Paintal, 1973; Wead et al., 1987). COPD and ILD, in their more advanced stages, are associated with the development of secondary pulmonary arterial hypertension, which is further amplified during exercise (Behr and Ryu, 2008; Naeije, 2005; Barberà et al., 2003; Wead et al., 1987). Activated mechanosensors in the right ventricle and pulmonary vasculature and central veins have consistent effects on breathing pattern, at least in animal models (Harrison et al., 1932a,b; Haouzi, this issue), but their role in dyspnea causation in clinical populations is unknown.

4.3. Afferent inputs from respiratory muscles

The primary and secondary muscles of respiration are richly innervated by mechanosensors that project to the somatosensory cortex and convey precise proprioceptive and kinesthetic information about their dynamic performance status (Gandevia and Macefield, 1989; Supinski et al., 1992; Davenport et al., 1993). The muscle spindles are ideally suited to sense changes in muscle length
and tension in response to central motor command during exercise. Campbell and Howell (1963) proposed that “length-tension inappropriateness” sensed at the level of muscle spindles in the rib cage may form the basis for the conscious detection of externally applied mechanical loads in humans and by extension, play a pivotal role in dyspnea causation in disease (Campbell et al., 1961).

Remmers demonstrated that stimulation of muscle spindles and Golgi tendon organs (by external chest compression, intercostal muscle stretch or rib vibration) inhibited phrenic nerve discharge in anaesthetized and vagotomized cats and dogs (Remmers et al., 1968; Remmers, 1970). In these studies, hypercapnia increased the amount of inspiratory muscle mechanoreceptor activity required to inhibit phrenic nerve discharge. It is conceivable that these normal inhibitory inputs from the chest wall and its musculature are disrupted in disease states with important sensory consequences. Chest wall vibration in-phase with inspiration in patients with COPD has been shown to ameliorate dyspnea intensity in some studies but not in others (Sibuya et al., 1994; Fujie et al., 2002; Bloch-Salisbury et al., 2003).

It is now known that respiratory muscle activity is not obligatory for the perception of “air hunger” during experimental hypercapnia in humans (Banzett et al., 1990; Gandevia et al., 1993). However, this does not preclude a contributory role of muscle afferents in exertional dyspnea in patients with respiratory impairment. As we have seen the respiratory muscles are invariably stressed in COPD and ILD as a result of increased intrinsic mechanical loading (elastic, resistive or both) which increases abruptly during the high V\textsubscript{E} of exercise. Geometrical changes in thoracic configuration alter the operating muscle fiber length and further compromise inspiratory muscle function, particularly in COPD (Pride and Macklem, 1986). Moreover, the contractile and metabolic functions of these muscles are variously impaired in all chronic respiratory conditions. The existence of respiratory muscle weakness in COPD and in ILD means that greater electrical activation (and associated sense of effort) is required for a given force generation by the muscle (Jones et al., 1985).

The postulated role of respiratory muscle mechanosensors in the genesis of exertional dyspnea in pulmonary diseases can be summarized as follows: (1) altered afferent proprioceptive feedback from muscle sensors that can signal that the ventilatory response (and respiratory muscle pump activity) is inappropriate for the prevailing motor command output; (2) increased central motor command output (and perceived increased contractile muscle effort), is required to sustain a given ventilation in the face of overloaded and weakened (or fatigued) respiratory muscles; (3) lack of the normal inhibitory influences on central neural drive because of disrupted feedback from chest wall intercostal mechanosensors imposed by disease; (4) direct noxious-like afferent inputs from these stressed respiratory muscles; or (5) any combination of the above.

5. Lessons learned from dyspnea-relieving treatments

Most of the studies that have examined potential mechanisms of dyspnea alleviation following the administration of different treatments were undertaken in COPD. Randomized placebo-controlled, crossover CPEF studies of therapeutic interventions have been undertaken in an attempt to uncover physiological mechanisms of dyspnea causation and amelioration. Therapeutic interventions that reduce central neural drive during exercise (e.g., supplemental oxygen, opiates, reduced or delayed metabolic acidosis after exercise training) consistently reduce V\textsubscript{E} relative to maximal capacity (Bradley et al., 1978; Santiago et al., 1979; Woodcock et al., 1981; Stein et al., 1982; Swinburn et al., 1984; Bye et al., 1985; Light et al., 1989; Young et al., 1989; Dean et al., 1992; O'Donnell et al., 1995, 1997a, 1998c, 2001a; Martinez et al., 1997; Somfay et al., 2001; Johnson et al., 2002; Appleton et al., 2003; Gigliotti et al., 2003; Foral et al., 2004; Peters et al., 2006) (Fig. 1a). Thus, reduced dyspnea ratings generally correlate with reduced V\textsubscript{E} or V\textsubscript{E}/MVC. Similarly, interventions that improve ventilatory mechanics or strengthen the respiratory muscles (i.e., bronchodilators, lung volume reduction procedures, inspiratory muscle training, mechanical ventilation) are often associated with reduced dyspnea ratings at a given ventilation during exercise (O'Donnell et al., 1988, 1996, 1999, 2004a,b; Harver et al., 1989; Petrof et al., 1990; Maltais et al., 1995; Polkey et al., 1996; Martinez et al., 1997; Appleton et al., 2003; Maltais et al., 2005; Peters et al., 2006) (Fig. 1b). Combined therapies in COPD (bronchodilators/hyperoxia or bronchodilators/exercise training or helium/hyperoxia) that both reduce central drive and improve respiratory mechanics have additive beneficial effects on dyspnea intensity and exercise endurance (Palange et al., 2004; Porszasz et al., 2005; Eves et al., 2006; Laude et al., 2006; Peters et al., 2006).

The most effective interventions (hyperoxia and exercise training) impact multiple sensory systems making it difficult to evaluate the relative importance of each. The dominant mechanism that underlies dyspnea alleviation during a particular treatment may vary from patient to patient. Possible contributory factors to dyspnea relief following hyperoxia or exercise training can be summarized as follows: (1) reduced central respiratory drive (as a result of altered chemoreceptor activation and improved metabolic function of the peripheral muscles); (2) improved respiratory muscle function and mechanics (i.e., reduced respiratory muscle activity, increased strength and endurance of these muscles, delayed fatigue and reduced DH as a result of reduced breathing frequency); (3) improved cardiopulmonary interactions (i.e., reduced pulmonary arterial pressures as with hyperoxia, and reduced DH); (4) altered central processing of dyspneogenic signals (hyperoxia) or altered affective response to dyspnea (exercise training); and (5) any combination of the above (Casaburi et al., 1991; Maltais et al., 1996; O'Donnell et al., 1998c; Porszasz et al., 2005; Travers et al., 2007; Laveneziana et al., 2008).

5.1. Interventions that improve respiratory mechanics

More specific treatment interventions, such as bronchodilators in COPD, permit a clearer delineation of possible underlying mechanisms. Thus, inhaled bronchodilator treatment (compared with placebo) is associated with improved lung emptying and deflation during rest and exercise, greater V\textsubscript{E} recruitment, decreased effort–displacement ratios and improved respiratory muscle function, dyspnea intensity and exercise endurance (Figs. 1b and 6). The improvements in dyspnea occur despite increased submaximal and peak ventilation (O'Donnell and Webb, 1993; Belman et al., 1996; Tantucci et al., 1998; O'Donnell et al., 1999, 2006a,b; Celli et al., 2003; Maltais et al., 2005). Unloading of the ventilatory muscles by mechanical ventilation (e.g., pressure support, continuous positive airway pressure or proportional assist ventilation) during exercise in COPD is associated with reduced dyspnea intensity ratings or greater tolerance of dyspnea over a longer duration of exercise. Reduced contractile respiratory muscle effort is thought to be one important dyspnea relieving mechanisms in this setting (O'Donnell et al., 1988; Petrof et al., 1990; Maltais et al., 1995; Polkey et al., 1996).

6. The neurophysiology of exertional dyspnea: a synthesis

It is clear that the neurological mechanisms of activity-induced dyspnea are highly complex and multifactorial. To the extent that different qualitative aspects of dyspnea reflect different neurophysiological underpinnings, further scrutiny of the two dominant
The distressing sensation of "unsatisfied inspiration" seems to be characteristic of respiratory diseases and is rarely reported in health, even at the symptom-limited peak of exercise (O'Donnell and Webb, 1993; Chau et al., 1996; O'Donnell et al., 2000). There appears to be considerable semantic overlap in the terms "air hunger" (the uncomfortable urge to breathe) described in the original hypercapnic experiments (Hill and Flack, 1908) and the qualitative descriptor cluster "unsatisfied inspiration" selected by patients with pulmonary disease at end-exercise. It is reasonable to speculate that the neurophysiological constructs that have evolved to explain the origins of "air hunger" also apply to "unsatisfied inspiration." The results of classical physiological experiments on the origins of "air hunger" can be summarized as follows: (1) increasing hypercapnia during voluntary breathing-holding or rebreathing is associated with the perception of correspondingly increasing intensity of "air hunger" but not increased respiratory effort; (2) the brain continuously monitors afferent inputs generated by the motor act of breathing—imposed disruptions in lung volume displacement, or in the tension or force development of the respiratory muscles are readily sensed and scaled via multiple mechanosensors in the lung and chest wall which project directly to the somatosensory cortex; (3) lack of breathing movements or any restriction in the act of breathing (either voluntarily or by external imposition) during fixed or increasing chemostimulation causes respiratory distress often termed "air hunger"—accordingly, increased thoracic motion (increased tidal breathing frequency), either voluntarily or by mechanical ventilation, increases tolerance to hypercapnia; (4) "air hunger" arises in conscious humans when the mechanical/muscular response of the respiratory system falls short of that which is expected for the prevailing level of central respiratory motor output command (Hill and Flack, 1908; Fowler, 1954; Remmers et al., 1968; Chonan et al., 1987; Schwartzstein et al., 1989; Demediuk et al., 1992; Manning et al., 1992; Flume et al., 1994; Oku et al., 1996; Harty et al., 1999; Evans et al., 2002; O’Connor et al., 2000).

Can these fundamental constructs be applied to the exercise setting? In young healthy males, increased chemostimulation (by dead space loading) during exercise which increased \( V_t \) by \( \sim 10 \text{L/min} \) was well tolerated with no increase in dyspnea intensity as effort–displacement ratios remained unaltered (O'Donnell et al., 2000). Thus, in health the spontaneous ventilatory response (increased \( V_t \)) to increasing chemostimulation was unhindered and increased respiratory discomfort was therefore avoided.
However, moderate mechanical restriction of the normal V\textsubscript{T} expansion during exercise (by chest strapping) in the setting of the added chemical loading induced severe dyspnea (described predominantly as “unsatisfied inspiration”) and reduced exercise tolerance (O’Donnell et al., 2000) (Fig. 7a and b). Chest strapping resulted in a blunted V\textsubscript{T} response to exercise (compared with unloaded control) and caused a large increase in the effort–displacement ratio which correlated well with the increased dyspnea ratings (Fig. 7a).

As we have already seen, critical V\textsubscript{T} restriction in the face of progressively increasing central reflexic drive is evident across pulmonary diseases during CPET. In COPD, V\textsubscript{T} is truncated from below by the effects of DH, whereas in ILD, the restriction is from above reflecting the reduced TLC and IRV (Fig. 4). Dyspnea intensity ratings during exercise correlated well with indices of mechanical restriction (reduced V\textsubscript{T} increased V\textsubscript{T}/IC ratio) in COPD and ILD (O’Donnell and Webb, 1993; O’Donnell et al., 1998a). In COPD, partial release of V\textsubscript{T} restriction as a result of bronchodilator-induced lung volume deflation correlated well with reduced dyspnea intensity ratings (O’Donnell et al., 2004b). Furthermore, descriptors of “unsatisfied inspiration” were selected less frequently following bronchodilator in COPD patients compared with placebo (O’Donnell et al., 2004b). In both conditions, effort–displacement ratios were elevated compared with normal and correlated with dyspnea intensity. In COPD, bronchodilator treatment and volume reduction surgery were both associated with reduced effort–displacement ratios and corresponding dyspnea relief (O’Donnell et al., 1996, 2006a; Laghi et al., 2004). Collectively, these results suggest that in COPD and ILD, a mismatch between central neural drive and the respiratory mechanical/muscular response (neuromechanical dissociation) of the respiratory system, as crudely reflected by the
Fig. 8. Proposed neurophysiological model of perceived respiratory discomfort (dyspnea) during exercise. Refer to text for details. Briefly, the somatosensory cortex calibrates and interprets the appropriateness of the mechanical/muscular response of the respiratory system to the prevailing level of central respiratory motor drive. When the mechanical/muscular response of the respiratory system is constrained, by disease, below the level dictated or pre-programmed by central respiratory motor drive then the intensity of "unsatisfied inspiration" increases in direct proportion to the widening disparity between drive and mechanics (i.e., neuromechanical uncoupling). Increased activation of central limbic structures as a result of neuromechanical uncoupling are also likely components of "respiratory distress." \(\dot{V}O_2\) and \(\dot{V}CO_2\), metabolic rate of oxygen consumption and carbon dioxide production; Type III and IV mechano- and metabosensitive afferents in the peripheral locomotor (and respiratory) muscles and their vasculature; PSRs, pulmonary stretch receptors; C-fibers, bronchopulmonary C-fibers; J-receptors, juxtapulmonary capillary receptors; GTOs, Golgi tendon organs; \(P_{CO_2}\), partial pressure of carbon dioxide; \([H^+]\), hydrogen ion concentration; \([La^-]\), lactate ion concentration; \(PaO_2\), arterial partial pressure of oxygen; \(SaO_2\), arterial blood oxygen saturation.

increased effort–displacement ratio, is fundamental to the origin of perceptions of unrewarded inspiratory effort (Fig. 8).

As illustrated in Fig. 8, components of the neuromatrix of perceived "unsatisfied inspiration" may include neural inputs that reach the sensory/association cortex from: (1) increased central corollary discharge from brainstem and cortical (motor) centers; (2) altered afferent inputs from respiratory mechanosensors in the muscles, lung, airways and chest wall; (3) reduced inhibitory inputs to central neural respiratory drive from vagal and intercostal afferents as a result of restricted thoracic volume displacement imposed by disease; and (4) increased limbic/paralimbic system activation underscores the affective (fear) component of "unsatisfied inspiration" which is precipitated by a perceived imminent threat to survival (Remmers et al., 1968; Remmers, 1970; Chen et al., 1991, 1992; Eldridge and Chen, 1992; Banzett et al., 2000; Evans et al., 2002).

6.3. Dyspnea: the emotional dimension

We have seen that at peak \(\dot{V}O_2\) in patients with both COPD and ILD, the drive to breathe is greatly increased, yet very little air enters the lungs with each breath despite mustering vigorous
inspiratory efforts. It is reasonable to assume that when perceived respiratory difficulty during physical exertion exceeds a certain threshold (which likely varies between individuals), it will be perceived as a threat and elicit an affective response which in turn will precipitate an abrupt behavioral reaction (e.g., exercise termination). This affective dimension, in many instances encompasses feelings of fear that can quickly escalate to panic. Studies have shown that perceptions of dyspnea intensity are distinguishable from perceptions of anxiety and fear during CPET in patients with COPD (Carrieri-Kohnlin, 2005). Sudden fear will provoke neurohumoral responses (via pathways in the amygdala, adrenal glands and sympathetic nervous system), which will trigger patterned ventilatory and cardio-circulatory responses that can further amplify respiratory discomfort.

Unfortunately, this affective aspect of exertional dyspnea has received little attention. Recently, studies using brain imaging techniques such as positron emission tomography scanning and functional magnetic resonance imaging have shown that reduction of V̇̇ below the spontaneous level dictated by chemical drive (end-tidal P⁰₂, 40–45 mmHg) evoked moderate to severe “air hunger.” This was associated with activation of central limbic structures including the anterior insula, pars opercularis, anterior cingulate gyrus, and amygdala (Banzett et al., 2000; Evans et al., 2002). These results support the notion that the sensory intensity and affective dimensions of perceived “air hunger” and, by extension, intolerable “unsatisfied inspiration” may be linked to the uncoupling of the normally harmonious relationship between central brainstem neural drive and the simultaneous thoracic volume displacement (Fig. 8).

7. Summary

Activity-related dyspnea is a dominant symptom of patients with chronic lung conditions and contributes to significant long-term morbidity. Application of established psychophysical methods to the setting of clinical laboratory exercise testing has increased our understanding of the mechanisms of exertional dyspnea in these patients. We have seen that, although the pathological abnormalities in obstructive and restrictive lung diseases are distinctly different, perceptual and ventilatory responses to the stress of exercise are broadly similar. Both are characterized by an augmented ventilatory response compared with health as a result of variable pulmonary gas exchange and metabolic abnormalities. Breathing pattern is more shallow and rapid in both diseases than in health, and reflects the dynamic mechanical constraints on tidal volume expansion imposed by disease. Although the nature of the intrinsic mechanical loads differs across these conditions, the net effect is dynamic functional respiratory muscle weakness which occurs to a variable degree. Clearly, dyspnea occurs during physical exertion under conditions of increased central respiratory neural drive and an abnormal dynamic mechanical/muscular response of the respiratory system. Mechanical studies have confirmed that the magnitude of respiratory effort required to support a given ventilation, together with the respiratory effort to tidal volume displacement ratio are elevated throughout exercise compared with health. Exertional dyspnea causation in chronic lung diseases is undoubtedly multifactorial. Attempts to identify specific peripheral afferent sources of dyspnea during exercise and to partition the contributions of central and peripheral sensory systems have met with limited success to date. The existence of two dominant qualitative dimensions of exertional dyspnea in both conditions, “increased respiratory effort” and “unsatisfied inspiration,” suggest shared neurophysiological mechanisms. The perception of increased respiratory effort for a given power output during exercise reflects the increased ventilatory demand and excessive mechanical loading of the respiratory muscles in pulmonary diseases. The perception of “unsatisfied inspiration,” which may evoke a powerful affective (fear) response, likely has its basis in the growing disparity between increasing central neural drive and the constrained thoracic volume displacement as exercise progresses. Therapeutic interventions that reduce contractile respiratory muscle effort and enhance neuromechanical coupling of the respiratory system consistently improve exertional dyspnea in patients with respiratory disease.

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