



Exertional dyspnoea in COPD: the clinical utility of cardiopulmonary exercise testing

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ABSTRACT Activity-related dyspnoea is often the most distressing symptom experienced by patients with chronic obstructive pulmonary disease (COPD) and can persist despite comprehensive medical management. It is now clear that dyspnoea during physical activity occurs across the spectrum of disease severity, even in those with mild airway obstruction. Our understanding of the nature and source of dyspnoea is incomplete, but current aetiological concepts emphasise the importance of increased central neural drive to breathe in the setting of a reduced ability of the respiratory system to appropriately respond. Since dyspnoea is provoked or aggravated by physical activity, its concurrent measurement during standardised laboratory exercise testing is clearly important. Combining measurement of perceptual and physiological responses during exercise can provide valuable insights into symptom severity and its pathophysiological underpinnings. This review summarises the abnormal physiological responses to exercise in COPD, as these form the basis for modern constructs of the neurobiology of exertional dyspnoea. The main objectives are: 1) to examine the role of cardiopulmonary exercise testing (CPET) in uncovering the physiological mechanisms of exertional dyspnoea in patients with mild-to-moderate COPD; 2) to examine the escalating negative sensory consequences of progressive respiratory impairment with disease advancement; and 3) to build a physiological rationale for individualised treatment optimisation based on CPET.



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Introduction

Chronic obstructive pulmonary disease (COPD) is a common and often devastating respiratory illness that afflicts ~10% of individuals over 40 years of age [1, 2]. The most common symptom experienced by patients with COPD is perceived respiratory discomfort (dyspnoea) during physical activity. According to the 2012 American Thoracic Society statement, breathlessness (or dyspnoea) is "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" [3]. Effective management of this troublesome symptom, and the associated poor health status, represents a major

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challenge for caregivers. Chronic breathlessness, reduced exercise capacity and habitual physical inactivity are inexorably linked and are strong predictors of reduced survival in COPD [4–7]. It is no surprise, therefore, that expert guidelines committees uniformly recommend improvement of dyspnoea and exercise tolerance as a major goal of management [8–10].

Dyspnoea assessment is an integral component of the general clinical evaluation of the COPD patient and is usually achieved by careful history. The patient is questioned about the onset, frequency and duration of the symptom (including aggravating and relieving factors, frequency of rescue use of short-acting bronchodilators, *etc.*) and its impact on daily activities. The clinician determines the magnitude of the physical task required to provoke dyspnoea in the individual and is encouraged to record this using a simple questionnaire such as the Medical Research Council (MRC) scale [8, 9]. However, it is generally accepted that such clinical assessments can substantially underestimate the actual degree of activity-related dyspnoea as patients gradually adapt to the presence of unpleasant symptoms by increasingly avoiding activities that provoke them in the first place. Thus, an all too common observation is that many patients with COPD, who claim not to be particularly troubled by activity-related dyspnoea, experience significant respiratory discomfort at low-work intensities during formal cardiopulmonary exercise testing (CPET) compared with healthy age-matched peers [11]. Moreover, traditional resting pulmonary function tests correlate poorly with severity of activity-related dyspnoea [12, 13]. The current review, therefore, examines the clinical rationale for dyspnoea assessment during CPET in the context of our current understanding of the pathophysiology of this symptom in COPD [3, 14–16]. To better understand the mechanisms of dyspnoea, we will first review the abnormal physiological responses to exercise in patients with COPD.

Physiological responses to exercise

Increased efferent respiratory drive

The well-established physiological abnormalities that are amplified during the stress of exercise in patients with moderate COPD, when compared with healthy controls, are highlighted in figure 1 [17]. These include high central inspiratory neural drive from cortical and bulbo-pontine centres in the brain, as indirectly indicated by relatively increased fractional inspiratory neural drive to the diaphragm. Increased efferent

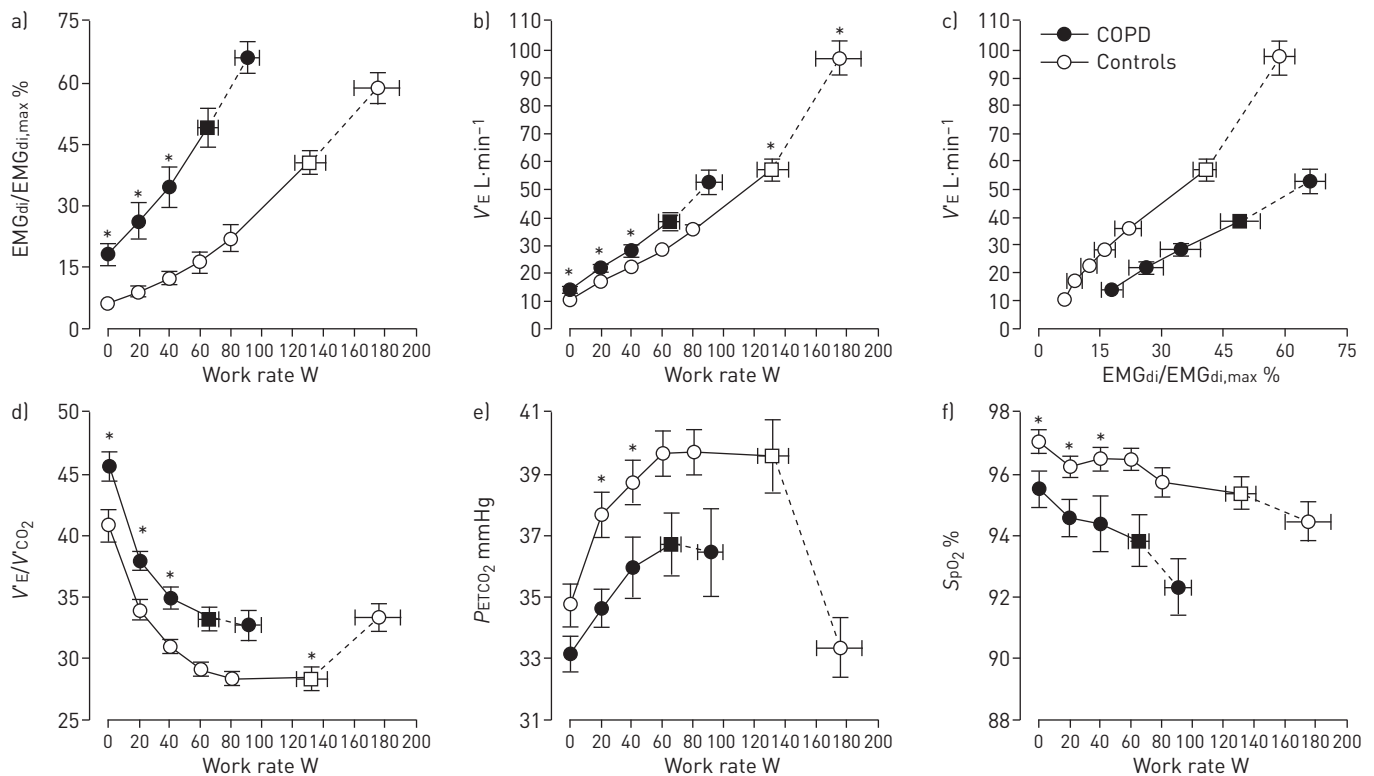


FIGURE 1 a–f) Diaphragm electromyography (EMG_{di}) and selected ventilatory and indirect gas exchange responses to incremental cycle exercise test in patients with moderate chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean ± SEM. Square symbols represent tidal volume-ventilation inflection points. EMG_{di}/EMG_{di,max}: an index of inspiratory neural drive to the crural diaphragm; V_E: minute ventilation; V_E/V_{CO₂}: ventilatory equivalent for carbon dioxide; P_{ETCO₂}: partial pressure of end-tidal carbon dioxide; SpO₂: arterial oxygen saturation measured by pulse oximetry. *: p < 0.05 for COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Reproduced and modified from [17] with permission.

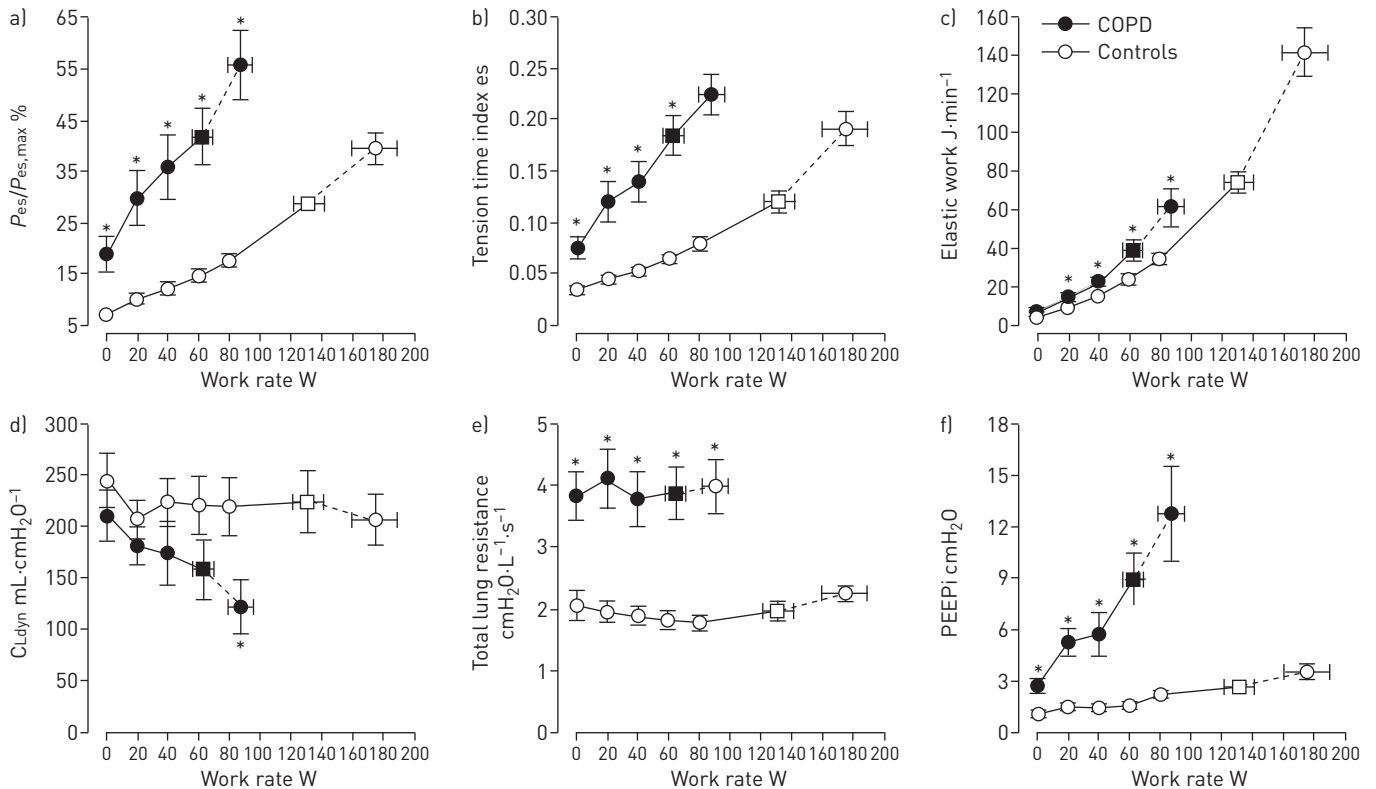


FIGURE 2 a–f) Respiratory mechanical measurements during incremental cycle exercise in patients with moderate chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean \pm SEM. Square symbols represent tidal volume-ventilation inflection points. P_{es} : oesophageal pressure; $P_{es,max}$: maximal P_{es} ; CL_{dyn} : dynamic lung compliance; PEEPi: intrinsic positive end-expiratory pressure. *: $p < 0.05$ COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Reproduced and modified from [17] with permission.

drive in COPD is ultimately the consequence of increased chemostimulation and excessive mechanical loading, as well as functional weakness of the muscles of breathing, in highly variable combinations.

Increased reflex chemostimulation

Increased stimulation of central and peripheral chemoreceptors in COPD occurs as a result of: 1) alveolar ventilation/perfusion ($V'A/Q'$) abnormalities (decreased ventilatory efficiency, high $V'A/Q'$ lung units and increased physiological dead space) [18–20]; 2) critical arterial oxygen (O_2) desaturation (low $V'A/Q'$ lung units and reduced systemic mixed venous O_2 in the blood) [21, 22]; and 3) increased acid–base disturbances (e.g. early metabolic acidosis) due to deconditioning [23, 24]. The negative haemodynamic consequences of hyperinflation may increase pulmonary vascular resistance and decrease left ventricular filling pressures [25]. The consequent impairment in cardiac output may reduce O_2 delivery to the contracting peripheral muscles contributing to further increase afferent ventilatory stimuli (acidosis and ergo-receptor stimulation) [26–29].

Thus, increased reflex ventilatory stimulation may also arise from increased activation of ergo- and metabo-receptors in the active peripheral muscles [30], where the metabolic milieu is often acidic. Finally, increased intrinsic mechanical loading of the functionally weakened respiratory muscles also means that increased efferent motor drive is required to achieve a given force generation by these muscles [31, 32].

Abnormal dynamic mechanics

Increased respiratory motor drive and contractile respiratory muscle effort occur as a result of increased elastic loading (including increased inspiratory threshold loading due to the effect of intrinsic positive end-expiratory pressure (PEEP)), decreased dynamic lung compliance and increased resistive loading of the respiratory muscles (figure 2) [17, 33–36]. Critical dynamic mechanical constraints are indicated by dynamic lung hyperinflation during exercise (i.e. the transient increase of end-expiratory lung volume (EELV) above the resting value) and by premature encroachment of end-inspiratory lung volume (EILV) on total lung capacity (TLC) (i.e. the attainment of a critically reduced inspiratory reserve volume (IRV)) [37, 38]. Thus, tidal volume (V_T) becomes positioned close to TLC and the upper reaches of the S-shaped pressure–volume relationship of the relaxed respiratory system, where compliance is decreased and the inspiratory muscles are functionally weakened. This explains the blunted V_T response and relative tachypnoea in COPD compared

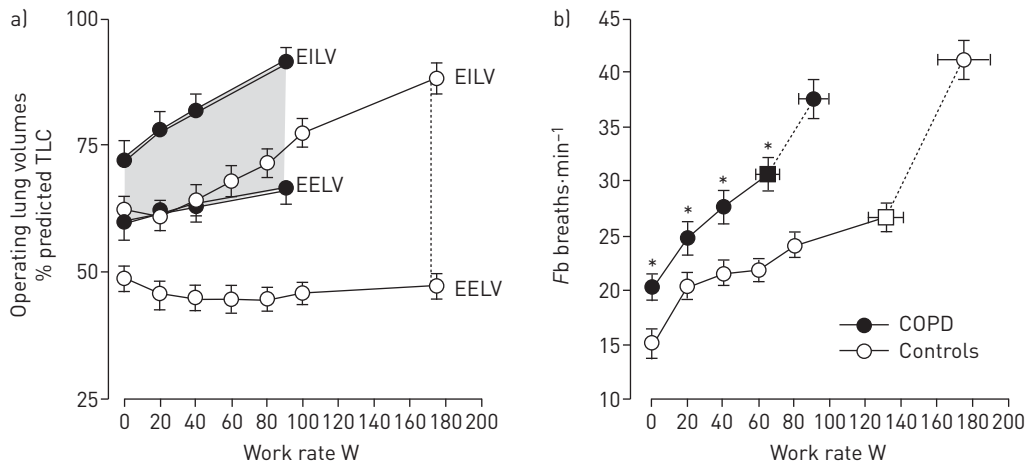


FIGURE 3 a) Operating lung volumes and b) breathing frequency (F_b) during incremental cycle exercise in patients with moderate chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean \pm SEM. Square symbols represent tidal volume-ventilation inflection points. TLC: total lung capacity; EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume. *: $p < 0.05$ COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Reproduced and modified from [17] with permission.

with healthy controls. Increased breathing frequency and the attendant increased velocity of shortening of inspiratory muscles causes further functional weakness of the inspiratory muscles [39].

A simple noninvasive assessment of dynamic respiratory mechanics can be made by plotting operating lung volumes, derived from serial inspiratory capacity (IC) manoeuvres throughout exercise, and concomitant breathing pattern (figure 3) [17, 37, 38]. EELV can be calculated by subtracting IC from the pre-determined TLC; thus, change in IC reflects change in EELV on the assumption that TLC remains stable during rest and exercise [38]. The dynamic IRV is calculated as IC minus V_T and plotted at standardised work rates during the exercise test. The V_T plateau generally occurs when the V_T/IC ratio is ~ 0.7 (or when IRV is 0.5–1.0 L) regardless of disease severity [37].

Tidal flow-volume loop analysis with reference to the maximal flow-volume “capacity” envelope also provides important information about the mechanical reserves of the respiratory system [40, 41]. Flow-volume loop analysis provides a crude qualitative assessment of expiratory flow limitation, but nevertheless clearly exposes the prevailing dynamic mechanical constraints on volume expansion during progressive exercise (outlined earlier in this review) [40, 41].

Although exercise limitation is undoubtedly multifactorial, multiple studies uniformly highlight that ventilatory factors are often the proximate limitation to exercise performance across the continuum of COPD [20, 33, 37, 42–45]. Furthermore, it is reasonable to surmise that attendant perceived respiratory discomfort is integral to the concept of ventilatory limitation in COPD [17, 45]. Moreover, it has now become clear that reliance on traditional estimates of breathing reserve (estimated maximal ventilatory capacity (MVC) minus peak minute ventilation (V_E)) can underestimate true ventilatory limitation indicated by premature attainment of critical respiratory mechanical constraints and accompanying intolerable dyspnoea at relatively low work rates [45, 46].

Mechanisms of dyspnoea

Sensory intensity of dyspnoea

Broadly speaking, dyspnoea during exercise reflects an imbalance between the increased demand to breathe and the ability to meet that demand [47]. Thus, the intensity of dyspnoea during exercise in COPD correlates closely with the following physiological ratios: ventilation as a fraction of MVC (V_E/MVC); respiratory effort relative to maximal effort as measured by oesophageal pressures ($P_{es}/P_{es,max}$); V_T/IC or EILV/TLC; and inspiratory neural drive to the diaphragm relative to the maximum as measured by electromyography (EMG_{di}/EMG_{di,max}) (figure 4) [17, 33, 48–51]. Taken together, these studies suggest that the onset of perceived intensity of respiratory discomfort corresponds with a point during exercise where there is critical encroachment on reserves of ventilatory output, muscle force generation, V_T expansion and inspiratory neural drive to the diaphragm [17, 33, 48–51]. Although expiratory muscles are usually recruited during exercise in most patients with COPD, they do not mitigate the rise in EELV, the relatively early respiratory mechanical constraints or the attendant perceived inspiratory difficulty [52].

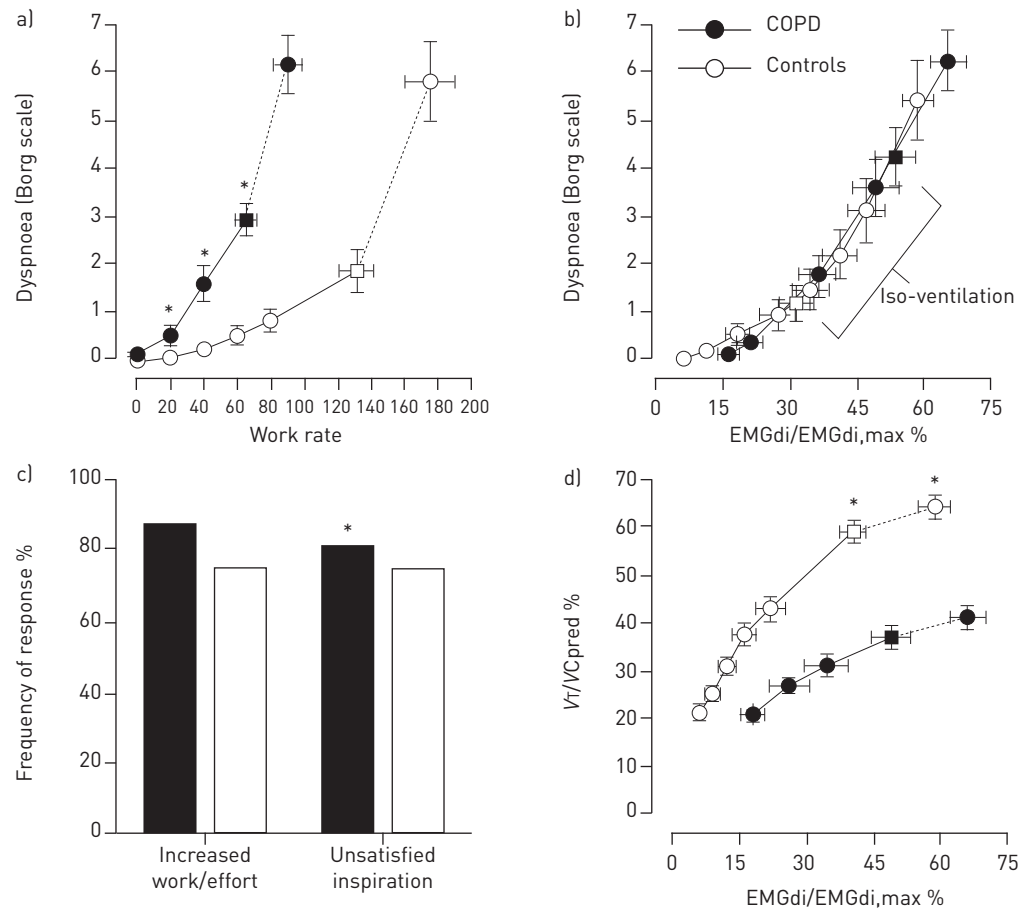


FIGURE 4 Exertional dyspnoea intensity is shown relative to a) work rate and b) diaphragm electromyography relative to maximum (EMGdi/EMGdi,max) during incremental cycle exercise in patients with moderate chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. c) Selected qualitative dyspnoea descriptors at the end of incremental cycle exercise in patients with moderate COPD and age-matched healthy controls. d) The relationship between tidal volume (V_T) as a function of predicted vital capacity (VC_{pred}) and EMGdi/EMGdi,max. Square symbols represent the tidal volume-ventilation inflection points in panels a) and d) and the point at the highest equivalent ventilation ($50 \text{ L}\cdot\text{min}^{-1}$) in panel b). Data are presented as mean \pm SEM. *: $p < 0.05$ COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Reproduced and modified from [17] with permission.

There is corroborative evidence that intensity of breathlessness rises with increasing tidal inspiratory efferent neural activity from bulbo-pontine and cortical motor centres in the brain relative to the maximum possible neural activation (indirectly represented by physiological ratios outlined above) [17, 33, 48]. It is further postulated that attendant increased central corollary discharge to the somato-sensory cortex, where unpleasant respiratory sensations are consciously perceived, is a final common sensory pathway [53, 54].

Quality of dyspnoea

It is postulated that the main qualitative dimension of breathlessness in COPD (*i.e.* “unsatisfied inspiration”) has its neurophysiological basis in the widening dissociation between increasing efferent central neural drive and the blunted respiratory muscular/mechanical response of the compromised respiratory system (*i.e.* neuromechanical dissociation), due partly to the combined effects of resting and dynamic lung hyperinflation (figure 4) [17, 55–57]. We have demonstrated that the descriptor “unsatisfied inspiration” becomes more frequently selected than the descriptor of increased “work/effort” after the V_T plateau [17, 57], where neuromechanical dissociation increases more abruptly. In line with this theory, it has been repeatedly shown that external imposition of mechanical loads to impede respiration in healthy volunteers in the face of constant or increasing chemostimulation reliably provokes respiratory sensations such as “air hunger” akin to “unsatisfied inspiration” [58–61]. Although definitive experimental verification is lacking, it is also entirely plausible that afferent inputs from the lungs to the somato-sensory cortex (*via* the vagus nerve) or from a multitude of mechanoreceptors in the respiratory muscle and chest wall (*via* spinal pathways) can directly induce unpleasant respiratory sensations that shape the clinical

expression of dyspnoea [62]. There is new information that endogenous opiate production can further modulate multidimensional dyspnoea in patients with COPD [63].

The affective dimension

Respiratory discomfort beyond a certain threshold evokes an emotive or affective response such as anxiety, fear, panic or distress. The threshold for affective distress probably varies between individuals and is ultimately thought to be linked to increased activation of limbic and paralimbic “flight or fight” centres in the brain and associated over-activation of the sympathetic nervous system [64–70].

Measuring dyspnoea during CPET

Prior to CPET, and in addition to a careful history (as outlined earlier in this review), it is important to ascertain the impact of dyspnoea on the patient's daily living using simple magnitude of task (*e.g.* MRC dyspnoea scale) or multidimensional questionnaire (Baseline Dyspnoea Index) [71]. An assessment of the patient's habitual physical activity level is helpful to ascertain if skeletal muscle deconditioning is potentially contributing to low cardio-respiratory fitness and associated higher ventilatory demand [72]. Full pulmonary function tests (spirometry, lung volume components including IC, diffusing capacity of the lung and resting arterial O₂ saturation) are also a prerequisite. Documentation of comorbidities potentially associated with exertional dyspnoea (obesity [73–76], cardio-circulatory disorders [77–79], anaemia, *etc.*) is also essential for proper CPET interpretation.

Intensity of dyspnoea during exercise can be measured using one of two validated scales: the modified 10-point Borg scale [80] or a visual analogue scale [81]. In practice, the 10-point Borg scale, a category scale with ratio properties, is more commonly used and easy to administer in clinical and research settings. It has been shown to be reliable, being both reproducible and responsive in COPD populations [82]. Care must be taken to precisely clarify the respiratory sensation that the patient is being asked to quantify (*e.g.* breathing discomfort, breathing effort or unpleasantness of breathing). The sensation in question should be anchored to the numeric extremes of the scale: 0=no breathing discomfort and 10=the strongest intensity of breathing discomfort that the patient has experienced or can imagine [80]. Before CPET, the patient should be thoroughly familiarised with the range of numerals and the associated word descriptors. The patient is then asked to rate the strength of intensity of breathing discomfort every 2 min throughout exercise by pointing to the appropriate numeral. Borg dyspnoea ratings are then plotted as a function of increasing oxygen uptake ($\dot{V}O_2$), work rate or $\dot{V}E$ and compared with reference values from a healthy age- and sex-matched population, preferably developed in the same exercise laboratory [83].

Measuring the affective component of dyspnoea during CPET remains challenging and there is currently no consensus as to the best approach. Preliminary studies have measured dyspnoea-related anxiety using the 10-point Borg scale during CPET and show that this is responsive to interventions such as pulmonary rehabilitation [84, 85]. In these studies patients with COPD could differentiate (and separately rank) sensory intensity and affective domains of dyspnoea.

There is debate about the best exercise modality (treadmill or cycle exercise) for the purpose of clinical assessment of exertional dyspnoea [86–89]. Within individuals with COPD, dyspnoea/work rate plots and dyspnoea/ $\dot{V}E$ are similar during treadmill and cycle exercise when the increase in incremental work rate is matched [73, 90]. Moreover, the relative increase in perceived leg effort ratings at higher exercise intensities during cycle exercise, compared with treadmill walking, does not influence Borg/ $\dot{V}E$ or Borg/work rate slopes of dyspnoea intensity [73, 90]. Interestingly, the earlier metabolic acidosis and corresponding rise in $\dot{V}E$ during cycle exercise is associated with an earlier rise in dyspnoea than during treadmill walking, when work rate increases are matched across modalities [73, 86, 88]. When abnormalities of pulmonary gas exchange are suspected as a source of increased ventilatory stimulation and exertional dyspnoea, treadmill testing is likely to be more sensitive than cycling since arterial blood gas perturbations are exaggerated for a given $\dot{V}O_2$ with weight-bearing walking compared with cycling [73, 86, 88].

CPET interpretation: panel displays

Since evaluation of exertional dyspnoea is the focus of the current review, we propose an ordered presentation of perceptual and physiological responses as presented, in part, in figure 5 [45]. 1) perceptual responses: dyspnoea (Borg) ratings as a function of work rate (and/or $\dot{V}E$); 2) ventilatory control: $\dot{V}E$ /work rate, $\dot{V}O_2$ /work rate, ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$)/work rate, O₂ saturation/work rate, end-tidal CO₂/work rate and ventilatory thresholds (*e.g.* carbon dioxide output ($\dot{V}CO_2$)/ $\dot{V}O_2$ inflection method, a measure of acid–base disturbance); 3) dynamic respiratory mechanics: change in IC, IRV, VT and breathing frequency, all as a function of increasing work rate (or $\dot{V}E$); and 4) cardio-circulatory responses: heart rate relative to predicted peak heart rate and O₂ pulse [17, 20, 33, 37, 44, 45].

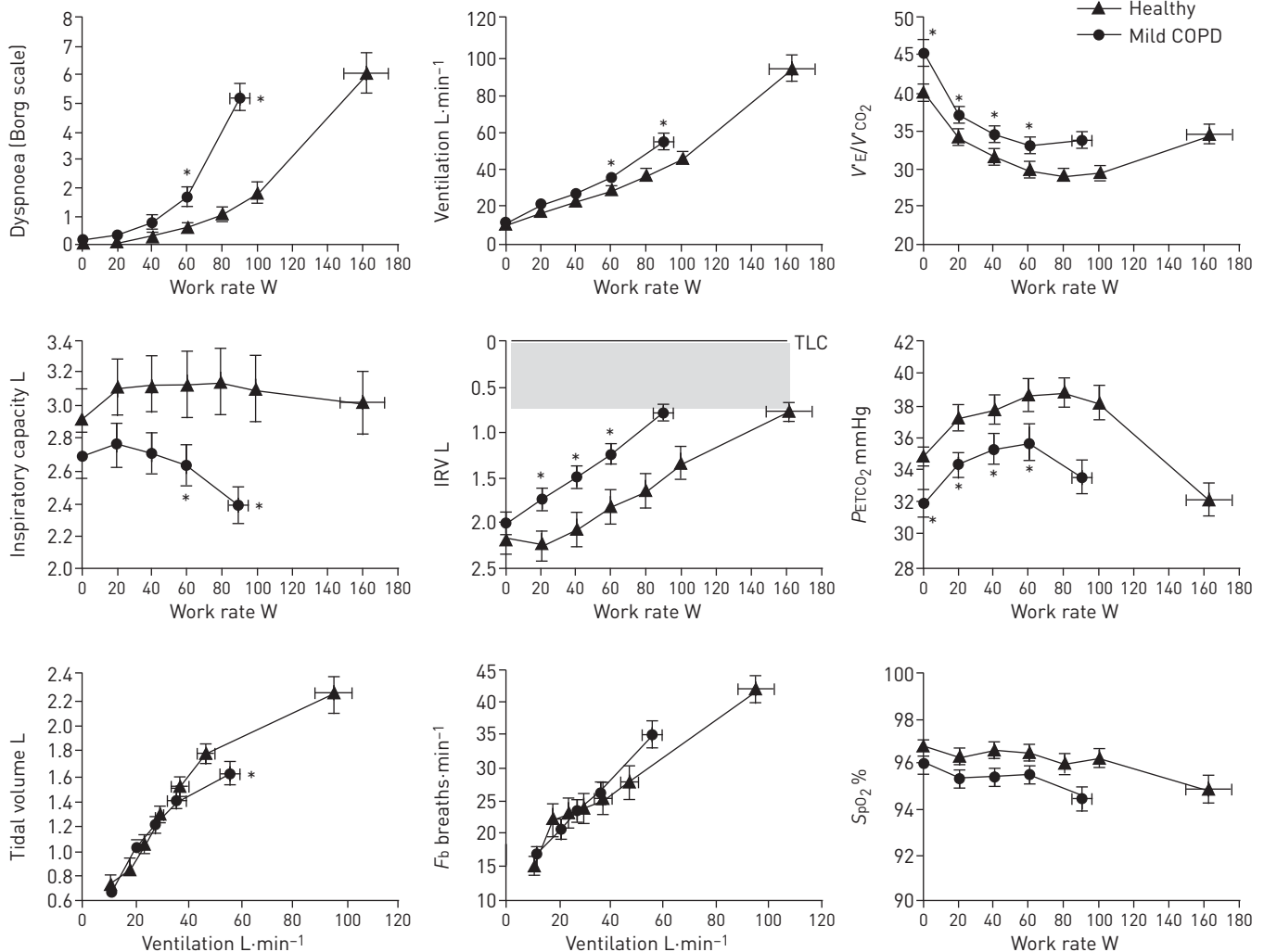


FIGURE 5 Proposed panel displays during interpretation of an incremental exercise test. Data showing selected perceptual, ventilatory control and dynamic respiratory mechanics to incremental cycle exercise in patients with mild chronic obstructive pulmonary disease (COPD) and age-matched healthy controls. Data are presented as mean \pm SEM. V^E/V^{CO_2} : ventilatory equivalent for carbon dioxide; IRV: inspiratory reserve volume; F_b : breathing frequency; P_{ETCO_2} : partial pressure of end-tidal carbon dioxide; S_{pO_2} : arterial oxygen saturation measured by pulse oximetry; TLC: total lung capacity. *: $p < 0.05$ mild COPD versus healthy controls at rest, at standardised work rates or at peak exercise. Reproduced from [45] with permission.

This simple format allows the clinician to evaluate the magnitude of perceived intensity of dyspnoea and exercise intolerance (peak work rate or V^{O_2} achieved) in the individual and then to identify potential contributory factors. These include: increased ventilatory demand or drive and its underlying cause(s) (increased ventilatory inefficiency, critical hypoxaemia or early ventilatory threshold), or reduced mechanical/metabolic efficiency, as occurs in obesity (parallel upward shift of V^{O_2} /work rate relationship); and severe mechanical constraints (increase in EELV, rapid reduction of IRV to its minimal value, early V_T plateau/ventilation and corresponding onset of tachypnoea) [17, 20, 33, 37, 44, 45]. Cardio-circulatory responses are often nonspecific, but may demonstrate relative tachycardia, reduced O_2 pulse, reduced V^{O_2} /work rate relationship and early ventilatory threshold that suggest the presence of either skeletal muscle deconditioning or reduced cardiac output [91, 92]. 12-lead electrocardiography, normally incorporated into CPET, can uncover hitherto undiagnosed ischaemic heart disease.

The $V^E-V^{CO_2}$ relationship is invariably helpful for the clinical interpretation of CPET in patients with COPD. This relationship has been analysed either in the ventilatory equivalent for CO_2 (V^E/V^{CO_2} ratio) versus work rate plot (figure 5) or in the V^E versus V^{CO_2} plot. During mild-to-moderate exercise, V^E/V^{CO_2} decreases in tandem with the physiological dead space/ V_T ratio [93]. The lowest (nadir) V^E/V^{CO_2} is reached just before V^E starts to compensate for lactic acidosis thereby providing an indicator of the "wasted" ventilation (ventilatory inefficiency) [94]. It should be noted, however, that the V^E/V^{CO_2} response contour depends on how V^E changes in relation to V^{CO_2} taking into consideration its starting point. The former is reflected by the slope of the V^E versus V^{CO_2} regression line and the latter by its intercept, *i.e.* V^E when

$V'_{CO_2}=0$. In other words, the V'_E/V'_{CO_2} nadir equals the slope plus intercept [95]. As discussed in the following section of this review, COPD severity strongly influences the different metrics of ventilatory inefficiency (nadir, slope and intercept) [19, 96, 97].

This approach not only allows an objective assessment of severity of activity-related dyspnoea in the patient but will also often reveal abnormal physiological responses, which cannot easily be predicted from a thorough history and/or the results of resting pulmonary function tests [12]. These include: the presence of critical dynamic mechanical constraints of the respiratory system, high ventilatory demand at low exercise intensities indicating a preponderance of lung units with high V'_A/Q' ratios or alveolar hyperventilation, significant arterial O_2 desaturation, or a pattern of responses that suggest decreased cardio-respiratory fitness [17, 20, 33, 37, 44, 45]. All of these factors, singly or in combination, can help explain the underlying dyspnoea and their discovery during CPET helps facilitate a more personalised management strategy for the patient with COPD.

Increasing exertional dyspnoea with disease progression

CPET in mild COPD

CPET is particularly useful for evaluation of mechanisms of exertional dyspnoea in individuals in whom this symptom seems disproportionate to the degree of respiratory impairment as assessed by simple pulmonary function tests (figure 5) [45]. In this context, recent epidemiological studies have confirmed that activity-related dyspnoea and activity restriction are present in many smokers with normal spirometry [98–100]. A series of studies have recently exposed heterogeneous dynamic physiological abnormalities during exercise in such symptomatic smokers without spirometrically defined COPD [48, 98]. The dominant abnormalities in patients with spirometrically determined mild COPD include: 1) increased inspiratory neural drive to breathe, secondary to measured high physiological dead space as indirectly assessed by V'_E/V'_{CO_2} (nadir and slope); and 2) increased pulmonary gas trapping due to the combined effects of peripheral airway disease (expiratory flow limitation) and increased ventilatory demand, which together force earlier critical mechanical constraints and higher exertional dyspnoea ratings than in healthy controls [20, 33, 44, 45, 101]. Thus, relatively preserved mechanical reserves during the early phases of exercise allows increased physiological dead space to be readily translated into a higher $V'_E-V'_{CO_2}$ relationship in patients with mild COPD, *i.e.* higher V'_E/V'_{CO_2} nadir and steeper $V'_E-V'_{CO_2}$ slope compared with healthy controls (figure 6) [19].

CPET in moderate-to-severe COPD

In more advanced COPD, the same physiological derangements apply as in mild COPD but occur at significantly lower V'_E and work rate. Inspiratory neural drive is substantially greater at lower exercise intensities than in patients with milder COPD reflecting worsening pulmonary gas exchange and mechanical constraints, in various combinations (figure 1) [17, 19, 37]. Increased drive in more advanced COPD is compounded in many patients by negative effects of low ventilatory thresholds (and metabolic acidosis) secondary to deconditioning and, in some cases, critical arterial O_2 desaturation (arterial O_2 tension <60 mmHg or <8 kPa). It is noteworthy that, in contrast to mild COPD, V'_E/V'_{CO_2} (nadir and slope) is a less reliable reflection of V'_A/Q' abnormalities in advanced COPD where mechanical constraints blunt the V'_E response and underestimate the magnitude of the prevailing inspiratory neural drive [19]. Progressive reduction of resting IC (as resting lung hyperinflation increases) with disease progression helps explain the ever-diminishing operating limits for V_T expansion and progressively earlier attainment of a minimal IRV during exercise (figure 7) [37]. The point at which V_T expands to reach a critical minimal IRV, the point where neuromechanical dissociation begins, is an important mechanical event during exercise and marks the threshold beyond which dyspnoea intensity rises sharply to reach intolerable levels (figure 8) [37, 55]. The lower the resting IC, the earlier in exercise this threshold is reached. Similarly, the progressively higher dyspnoea/ V'_E slopes as the disease advances are in large part explained by the worsening dynamic respiratory mechanics and muscle function described above.

It is noteworthy that, in contrast to mild COPD, mechanical constraints blunt the dynamic changes in V'_E increases in more advanced COPD. Thus, despite the progression of “wasted” ventilation, the slope decreases as the disease evolves [19, 96, 97]. Concomitant increases in intercept, however, frequently uncover the presence of ventilatory abnormalities leading to a high nadir (slope+intercept) in most moderate-to-severe COPD patients (figure 6) [19]. Some patients with end-stage, very severe COPD in whom the nadir is pronouncedly reduced and the CO_2 set-point increased may present with normal-to-low nadirs [102]. As a corollary, V'_E/V'_{CO_2} (nadir and slope) is a less reliable reflection of V'_A/Q' abnormalities in advanced COPD where it underestimates the prevailing inspiratory neural drive [19].

Evaluation of therapeutic interventions using CPET

Based on our current understanding of the pathogenesis of activity-related dyspnoea, we can attempt to strategically intervene to treat this distressing symptom on an individual patient basis. The main goals are to: 1) improve respiratory mechanics and muscle function; 2) reduce the increased central neural drive;

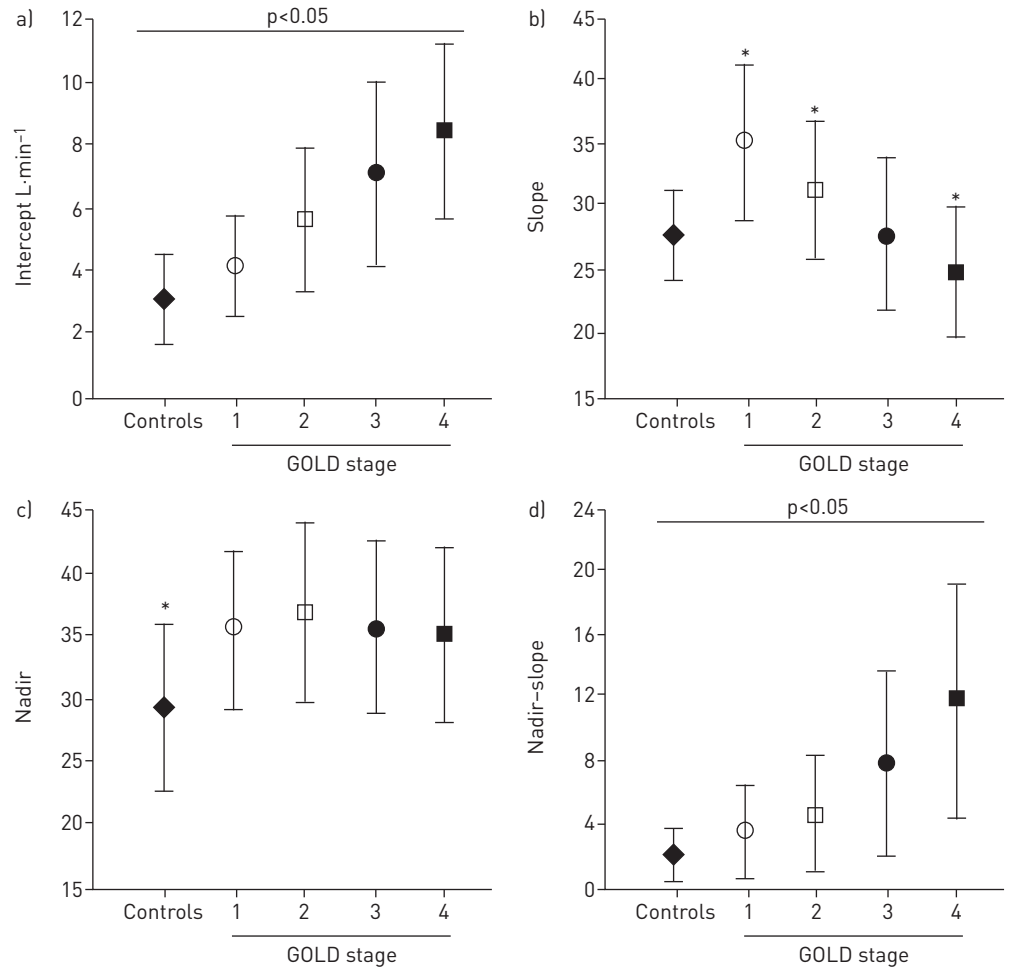


FIGURE 6 Effects of chronic obstructive pulmonary disease [COPD] severity on different parameters of ventilatory inefficiency during incremental cardiopulmonary exercise testing [CPET]. a) Minute ventilation (V_E)-carbon dioxide output ($V\dot{V}CO_2$) intercept increased and b) $V_E-V\dot{V}CO_2$ slope diminished as the disease progressed from Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages 1-4. c) As the $V_E/V\dot{V}CO_2$ nadir depends on both slope and intercept, it remained elevated (compared with controls) across disease stages. d) Increasing nadir-slope differences from GOLD stages 1-4 reflects the impact of a progressively higher intercept. *: $p < 0.05$ COPD versus controls (panel b) or controls versus all COPD groups (panel c). Reproduced from [19] with permission.

and 3) address the affective component of dyspnoea. Combined interventions which impact all three of these goals are likely to have the greatest effect on dyspnoea alleviation during exercise [103]. For the purpose of evaluating the efficacy of various interventions in relieving activity-related dyspnoea in clinical or research settings, a constant work rate exercise protocol set at a fixed fraction of a pre-established peak work rate (e.g. 60-80%) is preferable [104]. This is justified on the grounds that any beneficial changes in lung mechanics and dyspnoea are more readily translated into increases in time to exercise intolerance (endurance) than changes in maximal exercise capacity [105]. Moreover, the ability to complete a given task is arguably more relevant to daily life than reaching greater levels of exertion, *i.e.* the constant work rate holds greater external validity compared with incremental CPET [104].

Improving mechanics

Bronchodilators of all classes and duration of action have consistently been shown to decrease lung hyperinflation, with reciprocal increases in resting IC in patients with COPD [103, 106-120]. By increasing resting IC, bronchodilators also increase the available IRV and thereby delay the onset of critical respiratory-mechanical constraints on V_T expansion during exercise [55, 103, 106, 120]. Thus, throughout exercise, less central neural drive and respiratory muscle effort is required to achieve greater V_T expansion: neuromechanical dissociation is partially reversed, onset of intolerable dyspnoea is delayed and exercise tolerance is improved [55, 120]. Both classes of inhaled bronchodilators (β_2 -agonists and muscarinic antagonists) have been shown to increase the resting IC in patients with COPD by ~0.2-0.4 L or ~10-15% [103, 106, 112-114, 116]. Increases in cycle exercise endurance time in response to bronchodilator therapy

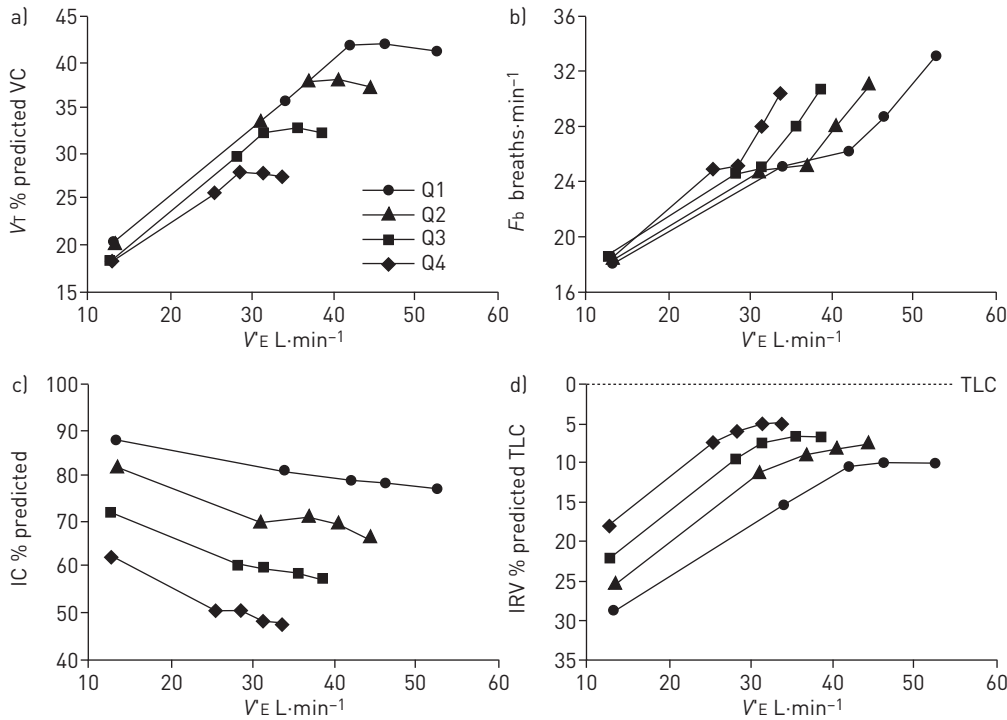


FIGURE 7 a) Tidal volume (V_t) (presented as % predicted of vital capacity (VC)), b) breathing frequency (F_b), c) dynamic inspiratory capacity (IC) and d) inspiratory reserve volume (IRV) (presented as % predicted of total lung capacity (TLC)) are shown plotted against minute ventilation ($V'E$) in four disease severity quartiles based on forced expiratory volume in 1 s % predicted during constant work rate exercise. Note the clear inflection (plateau) in the $V_t/V'E$ relationship which coincides with a simultaneous inflection in the IRV. After this point, further increases in $V'E$ are accomplished by accelerating F_b . Data are presented as mean values at steady-state rest, isotime (i.e. 2 min, 4 min), the $V_t/V'E$ inflection point and peak exercise. Reproduced from [37] with permission.

are of the order of 20%, on average [103, 106, 114, 115, 121]. Such increases in cycling endurance time are typically within the range that is thought to be clinically important, i.e. about 100 s.

Reducing central respiratory drive

Our ability to reduce the increased central neural drive during exercise is limited since the proximate source is often increased chemostimulation as a result of $V'A/Q'$ abnormalities (compromised CO₂ elimination), which are often irreversible. In some individuals with more moderate COPD who are sufficiently motivated, multi-modality exercise training can result in a delay in the rise of metabolic CO₂ output (by improving aerobic capacity) and consequently, a delay in the rise of central neural drive, the rate of dynamic hyperinflation and the onset of intolerable dyspnoea [85, 122–125]. In selected individuals, supplemental O₂ [103, 126–129] or opioid

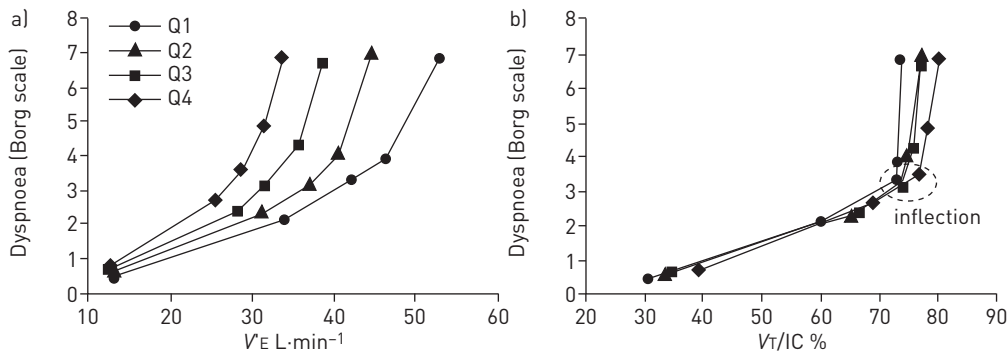


FIGURE 8 Interrelationships are shown between exertional dyspnoea intensity and a) minute ventilation ($V'E$) and b) the tidal volume (V_t)/inspiratory capacity (IC) ratio in four disease severity quartiles based on forced expiratory volume in 1 s % predicted during constant work rate exercise. After the V_t/IC ratio plateaus (i.e. the V_t inflection point) dyspnoea rises steeply to intolerable levels. There is a progressive separation of dyspnoea/ $V'E$ plots with worsening quartile. Data are presented as mean values at steady-state rest, isotime (i.e. 2 min, 4 min), the $V_t/V'E$ inflection point and peak exercise. Reproduced from [37] with permission.

medication [63, 130–135], which directly or indirectly reduces central respiratory drive, can ameliorate dyspnoea during physical activity and improve exercise endurance. Reduced neural drive following these interventions usually manifests as reduced breathing frequency (and increased expiratory time) often with an attendant decrease in the rate of dynamic hyperinflation [108, 113, 126, 128, 131]. Supplemental O₂ can also improve O₂ delivery and utilisation at the peripheral muscle level thereby delaying onset of metabolic acidosis and the attendant rise in ventilatory stimulation [126, 136–140]. The most recent meta-analysis on the efficacy of low-dose opiates found that dyspnoea was reduced (eight studies with 118 participants): standardised mean difference in favour of intervention of -0.34 (95% CI -0.58 – -0.10) [132]. However, it failed to demonstrate a significant effect on exercise capacity (standardised mean difference of 0.06 (95% CI -0.15 – 0.28)) [132].

In patients in whom anxiety is a major feature, a trial of anxiolytic medication and psychological counselling, usually within the framework of pulmonary rehabilitation [84, 85], can help address this important affective aspect of exertional dyspnoea [141, 142].

Conclusion

Activity-related dyspnoea affects a great many patients with COPD worldwide. Our understanding of the underlying mechanisms continues to grow and a central factor in causation seems to be increased efferent neural drive to the inspiratory muscles, originating in bulbo-pontine and cortical motor centres of the brain. Inspiratory drive is amplified in patients with COPD, compared with healthy individuals, because of relatively increased chemostimulation and abnormal dynamic respiratory mechanics and muscle function that collectively reflect the pathophysiology of the underlying disease. Progressive worsening of activity-related dyspnoea and exercise tolerance as COPD severity increases is fundamentally explained by progressively increasing central respiratory drive and neuromechanical dissociation of the respiratory system. CPET offers the clinician a unique opportunity to evaluate the severity of dyspnoea and its underlying mechanisms on an individual patient basis, and is particularly useful when symptom intensity seems disproportionate to the results of resting pulmonary function tests. In fact, recent studies provide compelling evidence that persistent respiratory symptoms and exercise intolerance are poorly correlated with spirometry and underline the importance of additional clinical evaluation of respiratory impairment. In this context, CPET can provide a comprehensive physiological assessment of the dyspnoeic COPD patient and is likely to have expanded clinical utility in the future. A simple ordered approach which examines symptom intensity, “noninvasive” ventilatory control parameters and dynamic respiratory mechanics during a standardised incremental exercise test to tolerance can identify mechanisms underlying perceived respiratory discomfort that are amenable to targeted treatment.

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