Exercise Testing in Chronic Respiratory Diseases: Basics and Clinical Implications

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ABSTRACT

Dyspnoea and exercise intolerance are common symptoms experienced by patients with various chronic lung diseases. Cardiopulmonary exercise testing provides a unique opportunity to objectively evaluate the respiratory system’s ability to respond to the metabolic stress of exercise. Although widely underutilized, cardiopulmonary exercise testing can help to unravel the underlying mechanisms of exercise intolerance in a given individual. We propose a simple, ordered approach that measures symptom intensity, metabolic and ventilatory control parameters, and dynamic respiratory mechanics during a standardized incremental test to tolerance.

The aim of this concise review is to examine exercise pathophysiology in chronic obstructive pulmonary disease and interstitial lung disease. We demonstrate striking similarities in the physiological responses to exercise across these pathologically distinct conditions and provide evidence to support common underlying mechanisms of exertional dyspnoea and reduced exercise capacity. Finally, we discuss the clinical implications of these new advances in exercise pathophysiology in the context of targeted therapeutic manipulation. (BRN Rev. 2016;2:274-91)

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INTRODUCTION

Persistent exertional dyspnoea and the associated avoidance of physical activity are frequently the presenting symptoms of patients with chronic respiratory disease and ultimately lead to skeletal muscle deconditioning and perceived poor quality of life. Moreover, dyspnoea, physical inactivity, and reduced peak oxygen consumption (\(\dot{V}_O^2\)) are inextricably linked and have been shown to predict earlier mortality in various pulmonary diseases1-4. Exercise capacity in individuals cannot reliably be predicted by clinical assessment, and resting pulmonary function tests (PFTs) only weakly correlate with peak \(\dot{V}_O^2\)5,6. Only laboratory cardiopulmonary exercise testing (CPET) provides an accurate assessment of the integrated responses of the metabolic, respiratory, cardiovascular, peripheral muscular, and perceptual (neurosensory) systems to graded increases in work rate. Thus, CPET uniquely permits a rigorous evaluation of the interface between the respiratory impairment caused by disease and the resulting exercise intolerance under measured physiological stress.

The proximate limitation of exercise performance in lung disease populations is routinely intolerable dyspnoea and leg discomfort, or their combination, and severe perceived respiratory discomfort usually occurs well before respiratory and cardiovascular physiological limitation7-9. Thus, understanding the underlying mechanisms of limiting exertional symptoms in individual patients is centrally important. The measurement of exertional symptoms using validated scales is an integral component of CPET and is required for comprehensive clinical interpretation10,11.

This review provides an ordered presentation of perceptual and physiological responses to incremental exercise in health and selected disease states: (i) perceptual responses: dyspnoea (Borg) ratings as a function of work rate (and/or minute ventilation, \(V_E\)); (ii) ventilatory control: \(V_E/\text{work rate}, \dot{V}_O/\text{work rate}, \dot{V}_E/\dot{V}CO_2/\text{work rate}\) (where \(\dot{V}CO_2\) represents physiological CO\(_2\) production, primarily from cellular metabolism, but also from production of CO\(_2\) from acid [e.g. lactic acid] after buffering by bicarbonate, HCO\(_3^+\)), \(\text{O}_2\) saturation/work rate, end-tidal CO\(_2\)/work rate, and ventilatory thresholds (e.g. \(\dot{V}CO_2/\dot{V}O_2\) inflection method, a measure of acid-base disturbance); (iii) dynamic respiratory mechanics: change in IC, IRV, VT and breathing frequency, all as a function of increasing work rate (or \(V_E\))6,12-17. Quantitative flow-volume loop analysis and cardio-circulatory responses are not discussed because of space constraints.

We compare the integrated responses to incremental cycle-exercise testing in patients with obstructive and restrictive lung disorders. This approach exposes similarities and differences in physiological responses to exercise across these diverse diseases, uncovering common mechanisms of dyspnoea and exercise intolerance. Finally, we consider the clinical implications of these physiological derangements in chronic respiratory diseases.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Physiological responses to exercise in mild COPD

Epidemiological studies confirm that activity-related dyspnoea, physical inactivity, poor
quality of life, and increased risk of mortality are present even in symptomatic smokers with only minor spirometric abnormalities. The heterogeneous nature of the physiological impairment in such individuals can be uncovered by tests such as oscillometry and nitrogen washout and by more traditional tests of lung-diffusing capacity and volume measurement. Established abnormalities in mild COPD include: increased alveolar-to-arterial O$_2$ tension gradient (P(A-a)O$_2$) during resting breathing; reduced diffusing capacity for carbon monoxide (D$_L$CO); increased peripheral airways resistance; maldistribution of alveolar ventilation; expiratory flow limitation (EFL) and pulmonary gas trapping (increased RV/TLC); and reduced IC.

During incremental exercise, dominant abnormalities include: (i) increased chemostimulation of bulbopontine respiratory centres secondary to the effects of high physiological dead space, indirectly reflected by higher V$_E$/VCO$_2$ nadir and steeper V$_E$-VCO$_2$ slope and; (ii) increased airways resistance and dynamic lung hyperinflation (DH), an acute, variable increase in end-expiratory lung volume [EELV] above its resting value) due to the combined effects of peripheral airway disease, EFL, and increased ventilatory demand (i.e. increased central inspiratory neural drive). Increased mechanical loading of the muscles and dynamic functional muscle weakness (muscle fibre shortening and increased velocity of shortening) means that efferent cortical motor output to the respiratory muscles must increase to maintain adequate force generation. Combined reductions in IC during exercise (due to increased EELV) and higher inspiratory neural drive (due to pulmonary gas exchange disruption and increased mechanical loading) in COPD force critical mechanical constraints and higher exertional dyspnoea ratings earlier in exercise than in healthy controls (Fig. 1). This is more easily appreciated by examining the behaviour of dynamic IRV than by traditional assessments of breathing reserve (V$_E$ as a fraction of maximal ventilatory capacity, MVC), which can be misleading in mild COPD.

**Physiological responses to exercise with more advanced COPD**

Similar derangements of pulmonary gas exchange, dynamic respiratory mechanics, and muscle function are present in more advanced COPD; however, they are more pronounced at significantly lower V$_E$ and work rate (Fig. 2 and 3).

**Increased inspiratory neural drive**

During exercise, feed-forward efferent activation from respiratory control centres to the respiratory muscles rises in parallel with increased motor command output to the locomotor muscles. In moderate-to-severe COPD (Fig. 2), the progressively increasing intrinsic mechanical loading of the functionally weakened respiratory muscles requires increases in efferent motor drive (from the motor cortex) to achieve a given force generation. Additionally, reflex stimulation of central and peripheral chemoreceptors occurs as a result of: (i) V$_A$/Q abnormalities (decreased ventilatory efficiency, high ventilation-perfusion (V$_A$/Q) lung units, and increased physiological
dead space\textsuperscript{34,29,33}; (ii) critical arterial oxygen (O\textsubscript{2}) desaturation (low $V_A/Q$ lung units and reduced systemic mixed venous O\textsubscript{2} in the blood)\textsuperscript{34,35}; and (iii) increased acid-base disturbances (e.g. early metabolic acidosis) due to deconditioning or impaired cardiac function\textsuperscript{36,37}.

In advanced COPD, alveolar hypoventilation with CO\textsubscript{2} retention can occur, reflecting critical mechanical limitation and respiratory muscle dysfunction, particularly in the setting of high physiological dead space and restricted $V_t$ expansion\textsuperscript{38,39}. Finally, the negative hemodynamic consequences of resting and dynamic hyperinflation may reduce cardiac...
output and $O_2$ delivery to the contracting peripheral muscles, amplifying metabolic acidosis and ventilatory stimulation\textsuperscript{40-43}.

**Abnormal dynamic respiratory mechanics**

Increased respiratory motor drive and respiratory muscle effort occur due to increased elastic loading (including increased inspiratory threshold loading due to the effect of intrinsic positive end-expiratory pressure), decreased dynamic lung compliance and increased resistive loading of the respiratory muscles\textsuperscript{13,44}. Inspiratory capacity is a useful noninvasive marker of dynamic respiratory mechanics in pulmonary diseases as it indicates how close the patient is breathing to TLC. In COPD, critical dynamic mechanical constraints are indicated by DH and by premature encroachment of end-inspiratory lung volume (EILV)
on TLC, i.e. the attainment of a critically reduced IRV (Fig. 3)\(^5\)\(^-\)\(^45\). Thus, \(V_T\) becomes positioned close to TLC and the upper reaches of the S-shaped pressure-volume relation 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 of COPD. Increased breathing frequency and velocity of shortening of inspiratory muscles causes further functional weakness of the inspiratory muscles\(^46\). Expiratory muscle activity is relatively increased in COPD, but fails to prevent DH\(^17\)\(^,\)\(^48\). However, excessive expiratory muscle recruitment may have deleterious cardiac effects, which further compromise exercise performance\(^49\)\(^,\)\(^50\). Evidence that respiratory muscle fatigue is present at the limits of tolerance in advanced COPD is inconclusive, but some degree of dynamic functional weakness of the overloaded inspiratory muscles is measurable in
such patients\textsuperscript{51}. Overt “static” (resting) inspiratory muscle weakness is reported in a subset of patients and is multifactorial\textsuperscript{52,53}. While not further discussed in the present work, inspiratory muscle adaptations to chronic hyperinflation (including, but not limited to, alterations in the relative amounts of type I versus II fibres, diaphragm shortening, and improved endurance characteristics) can help prevent, and sometimes overcome, static inspiratory muscle weakness\textsuperscript{54}. For a detailed discussion of the impact of COPD on peripheral muscle function, please see a recent review by Maltais et al.\textsuperscript{55}.

**Worsening ventilatory efficiency with advancing COPD**

The ventilatory response to exercise is coupled to metabolic demand, $\dot{V}_{\text{CO}_2}$, throughout incremental exercise: $\dot{V}_E/\dot{V}_{\text{CO}_2} = 1/[\text{PaCO}_2 \times (1-V_D/V_T)]$, where $V_D$ is the volume of dead space. In other words, $\dot{V}_E/\dot{V}_{\text{CO}_2}$ is higher (i.e. ventilation is less “efficient”) the lower the level at which arterial partial pressure of CO\textsubscript{2} (PaCO\textsubscript{2}) is regulated (i.e. CO\textsubscript{2} set-point) and the greater the fraction of the breath is wasted in $V_D$. Poor ventilatory efficiency is a key physiological abnormality in symptomatic patients with largely preserved FEV\textsubscript{1}\textsuperscript{12,14-17,29,56}. The physiological basis for this seems to stem from an enlarged $V_D$ *per se*, rather than a small $V_T$ or a low PaCO\textsubscript{2}\textsuperscript{14}. In fact, added external $V_D$ predictably increases $\dot{V}_E/\dot{V}_{\text{CO}_2}$ in these patients\textsuperscript{12}. Regardless of the mechanism(s), the excessive ventilatory response erodes the mechanical reserves, thereby contributing to exertional dyspnoea and exercise intolerance\textsuperscript{12,14-17,56}. Similar to heart failure\textsuperscript{57}, $V_D/V_T$ worsens in tandem with COPD severity\textsuperscript{39}. Interestingly, while the most commonly used parameter of ventilatory efficiency ($\dot{V}_E-\dot{V}_{\text{CO}_2}$ slope) increases from mild to severe heart failure\textsuperscript{58}, it decreases in severe to very severe versus milder COPD\textsuperscript{29}. This seemingly paradoxical finding is explained by worsening mechanical constraints to $\dot{V}_E$ increase\textsuperscript{39} and, in end-stage disease, to hypercapnia\textsuperscript{38,59}. Thus, $\dot{V}_E-\dot{V}_{\text{CO}_2}$ analysis cannot be used as a surrogate for measurement of physiological dead space in patients with limiting mechanical constraints.

**Exertional dyspnoea in COPD**

Exercise performance in COPD is primarily limited by ventilatory factors and accompanying intolerable respiratory discomfort. Progressive reduction of resting IC (as resting lung hyperinflation increases) with disease progression helps explain the diminishing operating limits for $V_T$ expansion and progressively earlier attainment of a minimal IRV during exercise (Fig. 4)\textsuperscript{6}. The point at which $V_T$ reaches a critical minimal IRV is important during exercise. This is where the disparity between increasing inspiratory neural drive and the muscular response of the respiratory system abruptly widens, i.e. where neuromechanical dissociation (NMD) begins, and marks the threshold beyond which dyspnoea intensity rises sharply to intolerable levels\textsuperscript{6,60,61}. The fact that increased inspiratory neural drive and NMD contribute to activity related dyspnoea and exercise intolerance in COPD is supported by studies showing that bronchodilator therapy, which improves dynamic mechanics (increases resting IC), delays mechanical limitation and partially restores neuromechanical coupling, thereby delaying the dyspnoea
threshold and prolonging exercise endurance time\textsuperscript{60,61}. Additionally, interventions that directly or indirectly reduce inspiratory neural drive and breathing frequency (e.g. supplemental oxygen, opiates, exercise training) can further improve dyspnoea and exercise tolerance\textsuperscript{5,62,63}.

### RESTRICTIVE LUNG DISEASES

Restrictive lung disorders (e.g. lung parenchymal diseases, neuromuscular disorders, chest wall restriction, and pulmonary resection) are characterized by an inability to expand $V_T$ appropriately during the increased
metabolic demand of exercise. Here, we focus solely on the interstitial lung diseases (ILD). Exercise intolerance is multifactorial in ILD, but intolerable exertional symptoms and increased central inspiratory neural drive relative to maximum and abnormal cardiac function, in varying combinations, are important contributors.

The pathophysiological hallmark of ILD is reduced static lung compliance (i.e. increased elastic lung recoil), which simultaneously restricts lung volume expansion and increases the driving pressure for expiratory airflow; thus, TLC, vital capacity (VC), and IC are reduced while the ratio of FEV\textsubscript{1}/FVC is usually increased. Disruption of the pulmonary microvasculature and the alveolar-capillary interface in ILD causes impaired gas exchange (i.e. decreased arterial oxygen saturation (\textit{SaO}\textsubscript{2}) and widened \textit{P}(A-a)O\textsubscript{2}), and a decreased diffusing capacity for carbon monoxide (\textit{D}_{L}\text{CO})\textsuperscript{64,66-68}. At rest, arterial blood gases may appear normal or reveal mild hypoxemia and a compensated respiratory alkalosis\textsuperscript{69}. The increased ventilatory demand secondary to increased \textit{VA}/Q abnormalities and coupled with increased elastic loading of the inspiratory muscles results in increased work and oxygen cost of breathing at rest in ILD\textsuperscript{13,69}.

**Physiological responses to exercise in interstitial lung disease**

**Increased respiratory neural drive**

Similar to COPD, the central drive to breathe is increased when metabolic and ventilatory demands acutely increase during exercise in patients with ILD versus healthy individuals\textsuperscript{13} (Fig. 3). This reflects (in highly variable combinations) the increased chemostimulation of central respiratory control centres and increased efferent motor output as a result of increased elastic loading of the respiratory muscles\textsuperscript{70}.

**Increased reflex chemostimulation**

As for COPD, increased chemostimulation in ILD is similarly the result of the effects of wasted ventilation (high \textit{V}_{E}/\textit{VCO}_{2} (Fig. 2); reduced efficiency of \textit{CO}_{2} elimination and/or relative alveolar hyperventilation due to changes in the \textit{CO}_{2} set-point\textsuperscript{71}. Critical arterial hypoxemia with widened \textit{P}(A-a)O\textsubscript{2} is common during exercise in more severe disease\textsuperscript{72-75} and can occur in early ILD, even before resting PFTs show overt impairment in \textit{D}_{L}\text{CO} and lung mechanics\textsuperscript{76-78}.

The mechanisms of arterial oxygen desaturation include: inter- and intra-regional \textit{VA}/Q inequalities in the lungs, low mixed venous oxygen concentration in the setting of low \textit{VA}/Q, diffusion disequilibrium with decreased pulmonary capillary transit time and, in some individuals, increased intra-cardiac and intra-pulmonary right-to-left shunting\textsuperscript{72-75}. Alveolar hypoventilation is not commonly reported during exercise, even in advanced ILD, but severe \textit{VT} restriction in the setting of a fixed high \textit{V}_{D} can potentially cause \textit{CO}_{2} retention. Correlations have been found between the low resting \textit{D}_{L}\text{CO} and arterial hypoxemia during exercise\textsuperscript{72}, but there is considerable overlap in this relationship, particularly in patients with mild-to-moderate disease.
Additional sources of ventilatory stimulation in ILD may include: altered reflex afferent activation of vagal receptors in the lung parenchyma and airways; early metabolic acidosis due to deconditioning, and increased peripheral muscle ergo-receptor activation. As in COPD, additional ventilatory stimulation may arise in some individuals due to comorbidities or complications such as obesity (i.e. increased metabolic loading), pulmonary arterial hypertension, emphysema, and cardio-circulatory disease.

“failure to generate the required or expected force on first testing”, can be impacted by changes in static or dynamic length or velocity elements, and occurs independently of muscular fatigue, which is defined as a reversible “loss in capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load and which is reversed by rest”. Consequently, in most instances, exercise intolerance in ILD is explained by true ventilatory limitation and associated severe dyspnoea.

In ILD, the pressure-volume relationship of the entire respiratory system is contracted along its volume axis, but retains its S-shape. As illustrated in figure 5, the resting IC and IRV are usually diminished. With exercise, EILV encroaches further on the upper alignment extreme of the pressure-volume relationship “beyond the S-bend” where there is significant elastic loading. Tidal volume reaches a plateau at 50-60% of the reduced VC (or ~ 70% of IC) early in exercise: minimal dynamic IRV and the VT plateau are reached together with a step increase in breathing frequency.

A few studies report that IC remains largely unaltered throughout exercise, reflecting a diminished expiratory reserve volume (ERV) and a reduced ability to decrease EELV. However, EFL has been described in some patients with ILD and may reflect co-existent airway obstruction as a result of smoking or actual airway involvement as part of the interstitial disease process (e.g. hypersensitivity pneumonitis). Interestingly, the presence of EFL in ILD was associated with worsening dyspnoea compared with those with ILD with normal airway function.
Inspiratory muscle function is often relatively preserved in patients with ILD, reflecting the training effects of intrinsic mechanical loading and the mechanical advantage of the inspiratory muscles at the lower than normal operating lung volumes\textsuperscript{90,92}. However, in some individuals, involvement of these muscles in the underlying systemic inflammatory disease process, the effects of cachexia, high-dose oral steroids, malnutrition, electrolytic disturbances, and global skeletal muscle deconditioning may have a deleterious impact on function\textsuperscript{93}.

**Exertional dyspnoea in interstitial lung disease**

The increase in intensity of dyspnoea during CPET correlates well with the increasing amplitude of the neural inspiratory drive to the diaphragm, the increasing oesophageal pressure relative to maximum, and the increasing V\textsubscript{T}/IC ratio – a measure of prevailing mechanical constraints\textsuperscript{13,90}. Thus, as in COPD, dyspnoea rises as a function of the increasing neural drive to the inspiratory muscles.
muscles, increased contractile respiratory muscle effort, and intrinsic restriction of appropriate $V_T$ expansion. Similarly, interventions that attenuate chemostimulation, delay the rise in metabolic $\dot{V}CO_2$ (e.g., exercise training), or reduce efferent output from respiratory centres (e.g., oxygen supplementation, opiates) alleviate exertional dyspnoea in patients with ILD$^{67,94,95}$.

**COMPARISON OF EXERCISE RESPONSES IN COPD AND INTERSTITIAL LUNG DISEASE**

At first glance, COPD and ILD are remarkably different in underlying pathology, static respiratory mechanics (i.e., absolute lung volumes), nature and extent of the mechanical loads, and respiratory muscle characteristics and recruitment patterns. The major differences in mechanical loading and activation patterns of the respiratory muscles have recently been highlighted$^{13}$. Patients with ILD often have better preservation of inspiratory muscle force-generating capacity, reflecting the mechanical advantage of lower operating lung volumes. Furthermore, such patients, unlike those with COPD, do not usually have to contend with inspiratory threshold and resistive loading, and expiratory muscle activity is generally lower. However, clinically stable ILD patients generally have earlier onset of more severe gas exchange abnormalities during exercise than patients with COPD (Fig. 2). In COPD, $V_T$ is restricted from below by the effects of resting and dynamic lung hyperinflation, whereas in ILD, the restriction is from above, reflecting the reduced TLC and IRV. Remarkably, ventilation, breathing pattern, and the behaviour of dynamic IRV during conventional CPET are similar in obstructive and restrictive diseases (Fig. 3).

It is clear that regardless of the precise mechanism of restriction, the inability to expand $V_T$ in response to the increasing inspiratory drive or effort during exercise contributes to low peak ventilatory capacity in both COPD and ILD.

**Common mechanisms of dyspnoea**

Dyspnoea during exercise in COPD and ILD fundamentally reflects an imbalance between the increased demand to breathe and the ability to meet that demand, and its intensity correlates closely with the following physiological ratios: $V_E/MVC$; oesophageal pressure ($Pes/Pes_{max}$), $V_T/IC$ or EILV/TLC, and inspiratory neural drive to the diaphragm relative to maximum diaphragmatic electromyography ($EMGdi/EMGdi_{max}$) (Fig. 6)$^{13,16,21,46,96}$. This indicates that respiratory discomfort is provoked when there is critical encroachment on reserves of ventilatory output, muscle force generation, $V_T$ expansion, and inspiratory neural drive to the diaphragm$^{13,16,21,46,96}$.

Current neurophysiological constructs propose that the intensity of dyspnoea rises with increasing tidal inspiratory efferent neural activity relative to the maximum possible neural activation (from bulbopontine and cortical motor centres in the brain) as indirectly represented by the above physiological ratios$^{13,16,21}$. It is further postulated that concomitant increased central corollary discharge from control centres to the somatosensory cortex, where unpleasant respiratory sensations are consciously perceived, is a final common pathway$^{97,98}$ (Fig. 7).
Exertional dyspnoea at the limits of tolerance is qualitatively similar in COPD and ILD\textsuperscript{13,90,99} (Fig. 6). We postulate that the dominant qualitative respiratory sensations that allude to “unsatisfied inspiration” (“can’t get enough air in”) ultimately have their neurophysiological basis in the conscious awareness of a disparity between the increased drive to breathe and the restricted mechanical response of the respiratory system. At exercise termination in both COPD and ILD, central respiratory efferent drive reaches almost maximal values, but the respiratory muscle pump, which is overloaded and functionally weakened, responds inadequately to the increased electrical activation\textsuperscript{13} (Fig. 6). Thus, despite near-maximal drive and effort, very little air enters the lungs with each breath\textsuperscript{13,60,99,100}. This disparity is perceived as unpleasant and is the result of integration of efferent central outputs and multiple afferent peripheral inputs from the respiratory muscles chest wall and lungs (Fig. 7). 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 increasing chemostimulation reliably provokes respiratory sensations akin to “unsatisfied inspiration”\textsuperscript{81,101,102}.

Although definitive experimental verification is lacking, it is believed that vagal afferent input from the lungs directly to the somatosensory cortex, or spinal input from mechanoreceptors in the respiratory muscle and chest wall, can directly induce unpleasant respiratory sensations that shape the clinical

**Figure 6.** Inter-relationships are shown between exertional dyspnoea intensity, ventilation and the tidal volume/inspiratory capacity ratio in four disease severity quartiles based on forced expiratory volume in 1 second percentage predicted during constant work rate exercise in chronic obstructive pulmonary disease (COPD). After the tidal volume/inspiratory capacity ratio plateaus (i.e., the tidal volume inflection point), dyspnoea rises steeply to intolerable levels. There is a progressive separation of dyspnoea/minute ventilation plots with worsening quartile. Data plotted are mean values at steady-state rest, isotime (i.e. 2 min, 4 min), the tidal volume/minute ventilation inflection point and peak exercise (reproduced with permission from O’Donnell et al\textsuperscript{2}).

IC: inspiratory capacity; \(V_T\): tidal volume.
Figure 7. Exertional dyspnoea intensity is shown relative to ventilation (a) and diaphragm electromyography relative to maximum (b) during incremental cycle exercise in patients with moderate chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and age-matched healthy controls. Panel (c) shows selected qualitative dyspnoea descriptors at the end of incremental cycle exercise in patients with moderate COPD, interstitial lung disease, and age-matched healthy controls. Panel (d) shows the relation between tidal volume as a fraction of predicted vital capacity and diaphragm electromyography relative to maximum. Square symbols represent the tidal volume-ventilation inflection points in panels (a, c) and the point at the highest equivalent ventilation (50 l/min) in panel (b). Values are mean ± standard error of mean. *p < 0.05 COPD versus interstitial lung disease versus healthy controls at rest, at standardized work rates or at peak exercise (reproduced with permission from Faisal et al.13).

EMGdi: diaphragmatic electromyography; EMGdi_max: diaphragmatic electromyography maximum; ILD: interstitial lung disease; VC: vital capacity; VT: tidal volume.
expression of dyspnoea\textsuperscript{99}. This notwithstanding, a recent study provides strong evidence that the relationship between increased dyspnoea intensity and increased inspiratory neural drive to the diaphragm during exercise is not affected by major disease-specific differences in afferent inputs from the airways, lung parenchyma, chest wall, and respiratory muscles.

Respiratory discomfort beyond a certain threshold evokes emotive responses, such as anxiety, fear, panic, or distress (Fig. 7). The threshold for affective distress likely varies between individuals and is thought to be linked to increased activation of limbic and paralimbic centres in the brain and associated over activation of sympathetic nervous system\textsuperscript{103-109}.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

Traditional CPET focuses on measuring peak \( \dot{V}O_2 \) and incorporates a quantitative assessment of cardiac and ventilatory reserves as well as aerobic capacity\textsuperscript{110}. The simple format proposed here extends this approach to include evaluation of perceived intensity of exertional dyspnoea and its origins. This assessment of ventilatory constraints based on breathing pattern and operating lung volumes is arguably more sensitive than crude assessments on breathing reserve (\( \dot{V}_E / \text{MVC} \)), at least in patients with milder COPD and ILD.

Cardiopulmonary exercise testing allows for a more comprehensive physiological characterization of pathophysiology in symptomatic patients in the early phases of COPD and ILD, whose pulmonary function tests are close to the normal range and whose dyspnoea seems disproportionate to resting PFT abnormalities. Using the approach outlined above, it is possible to uncover unanticipated abnormalities in \( \dot{V}_E / \dot{V}CO_2 \), breathing pattern, and operating lung volumes, helping to explain the origin of dyspnoea in the individual. CPET can also expose hitherto unknown physiological abnormalities such as arterial oxygen desaturation, DH and impairment of cardio-circulatory function, which require further diagnostic evaluation and targeted treatment. For example, the finding of DH in a symptomatic patient with ILD might lead to a therapeutic trial of a bronchodilator. Other clinical scenarios in which CPET might influence disease management include: (i) demonstration of mechanical-ventilatory and/or gas exchange abnormalities limiting exercise tolerance in patients in whom deconditioning is a major confounder; (ii) pre-enrolment assessment in patients referred for exercise training in order to exclude cardiovascular/ischaemic abnormalities and guide the initial target training intensity; and (iii) risk prediction using submaximal, effort-independent measurements such as \( \dot{V}_E / \dot{V}CO_2 \) nadir in patients with COPD\textsuperscript{29}.

The finding that intolerable dyspnoea in COPD and ILD can be mostly explained by near-maximal inspiratory neural drive in the setting of a blunted respiratory system response underlines the formidable challenge faced by caregivers trying to alleviate their patients’ dyspnoea and activity restriction. In both conditions \( V_A / Q \) abnormalities, which largely underpin the increased inspiratory neural drive, are often irreversible. It follows that in some COPD patients, bronchodilators, which improve mechanics but have little or
no effect on the increased $\dot{V}_E/\dot{V}CO_2$ may have only limited effects on dyspnoea alleviation.

Knowledge of the common mechanisms of exertional dyspnoea in both COPD and ILD allows us to develop a cogent physiological rationale for personalized management, preferably in the context of pulmonary rehabilitation. Thus, interventions that reduce the heightened inspiratory neural drive (exercise training, supplemental $O_2$ or opioid medication) can successfully ameliorate dyspnoea during physical activity in selected patients. Similarly, interventions that improve respiratory mechanics and dynamic respiratory muscle function (e.g. bronchodilators in COPD) can partially diminish NMD of the respiratory system and improve exercise intolerance.

REFERENCES


