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Dyspnoea

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Dyspnoea is the major reason for referral for pharmacological treatment and respiratory rehabilitation programmes in patients with chronic obstructive pulmonary disease (COPD). Dyspnoea is a subjective experience of breathing difficulty that consists of qualitatively distinct sensations that vary in intensity. This definition underlines the importance of the different qualities (cluster descriptors) covered by the term dyspnoea, the involvement of integration of multiple sources of neural information about breathing and the physiological consequences. More specifically, it has been postulated that dyspnoea arises when there is a conscious awareness of a mismatch between what the brain expects and what it receives in terms of afferent information from the lungs, airways and receptors in the tendons and muscles of the chest wall (fig. 1 and table 1). The relevance of assessing and documenting dyspnoea stems also from the following observations: 1) up to a quarter of the general population and half of severely ill patients are affected by this symptom; 2) dyspnoea appears to be an important predictor of quality of life, exercise tolerance and mortality in various conditions; in patients with COPD, dyspnoea has been found to be a better predictor of mortality than forced expiratory volume in 1 s (FEV₁); in patients with heart disease referred for clinical exercise testing, it is a better predictor of mortality than angina; 3) dyspnoea is associated with decreased functional status and worse psychological health in older individuals living at home; 4) it is a factor in the low adherence to exercise training programmes in sedentary adults and in patients with COPD; 5) the effective management of exertional dyspnoea 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.

Figure 1. a) Schematic representation of the neurophysiological underpinnings of perceived dyspnoea during exercise in healthy humans. During a voluntary increase in ventilation, the motor cortex increases the outgoing motor signal to the respiratory muscles and conveys a copy (central corollary discharge) through cortical interneurons to the sensory/association cortex, which is informed of the increased motor drive to increase ventilation. Volitional respiratory effort in healthy subjects is harmoniously matched with the appropriate increase in flow or volume displacement *via* concurrent afferent proprioceptive information transmitted *via* vagal, glossopharyngeal, spinal and phrenic nerves. This information is conveyed to the medulla and central cortex, where it is integrated. The result is a harmonious neuromechanical coupling with

avoidance of respiratory discomfort or distress. Reproduced and modified from Scano *et al.* (2010) with permission from the publisher.

Table 1. Putative neurophysiological basis of exertional dyspnoea

Central (corollary discharge)	↑ motor drive (inspiratory effort): cortical
	↑ reflex drive (chemical, neural): medullary
Peripheral (afferent activity)	Airway/lung receptors (pulmonary stretch receptors, C-fibres, J-receptors)
	Ventilatory muscle receptors (muscle spindles, Golgi tendon organs, joint receptors, type III and IV mechano- and metaboreceptors in the diaphragm and chest wall muscles)
	Peripheral chemoreceptors
	Locomotor muscles receptors (type III and IV afferents)

A schematic representation of the most important receptors (afferences) and efferences to respiratory and locomotor muscles involved in the putative pathogenesis of exertional dyspnoea in cardiopulmonary disease. Please see the main text for more details.

Evaluation of dyspnoea during physical tasks

Exertional dyspnoea can be easily defined as ‘the perception of respiratory discomfort that occurs for an activity level that does not normally lead to breathing difficulty’ (Killian *et al.*, 1995). It follows that the intensity of dyspnoea can be determined by assessing the activity level required to produce dyspnoea (*i.e.* dyspnoea at rest is more severe than dyspnoea only when climbing stairs). The Medical Research Council (MRC) dyspnoea scale can be used for this purpose (table 2), as well as other scales such as the Baseline Dyspnoea Index. Dyspnoea can

also be evaluated during a physical task, such as cardiopulmonary exercise testing (CPET). For this purpose, the 10-point Borg scale can be used (table 2). In the Borg scale, the end-points are anchored such that zero represents ‘no breathlessness at all’ and 10 is ‘the most severe breathlessness that one had ever experienced or could imagine experiencing’. Using the Borg scale, subjects rate the magnitude of their perceived breathing discomfort during exercise. Though somewhat less popular, the visual analogue scale (VAS) is another dyspnoea measuring instrument with proven construct validity during cardiopulmonary exercise testing (CPET). Both the VAS and Borg scale have been shown to provide similar scores during CPET, and to be reliable and reproducible over time in healthy subjects, and in patients with asthma and COPD undergoing CPET.

Physiology

The recent American Thoracic Society and European Respiratory Society statements have emphasised the multidimensional nature of dyspnoea in the sensory–perceptual (intensity and quality), affective distress and impact domains. To gain more insight into our understanding of dyspnoea, a case can be made for answering the following questions.

- 1) What is the role of mechanical factors and ventilatory constraints in dyspnoea?
- 2) What are the neurophysiological underpinnings of the most selected cluster descriptors that define the qualitative dimension of dyspnoea in patients?
- 3) Do obstructive and restrictive lung diseases share some common underlying mechanisms?

Dyspnoea is perceived as a sense of effort

During voluntary increase in ventilation, the motor cortex increases the outgoing motor signal to respiratory muscles and conveys a copy (central corollary discharge) through cortical interneurons to the sensory/association cortex, which is informed of the voluntary effort to increase ventilation (V'_E). It is also likely that the sense of the respiratory effort arises from the

simultaneous activation of the sensory cortex and muscle contraction: a variety of muscle receptors provides feedback to the central nervous system about force and tension, and information from these receptors may conceivably underlie the sense of effort. For clinical purposes, the perceived magnitude of respiratory effort is expressed by the ratio of the tidal oesophageal pressure (P_{oes}) to the maximal pressure generation capacity of the respiratory muscles (P_{Imax}). In healthy subjects, volitional respiratory effort is matched by lung/chest wall displacement (*i.e.* change in tidal volume (VT) as percentage of vital capacity (VC)) *via* concurrent afferent proprioceptive information, transmitted *via* vagal, glossopharyngeal, spinal and phrenic nerves, that monitors displacement, and is processed and integrated in the sensory cortex. The result is a harmonious neuromechanical coupling with avoidance of respiratory discomfort or distress (fig. ♠1 and table ♠1).

Dyspnoea is perceived as a sense of air hunger

Under some clinical and experimental circumstances, the relationship between dyspnoea and effort is less apparent. If normal subjects suppress their ventilation to a level below that dictated by chemical drive (carbon dioxide), dyspnoea increases without corresponding increases in indices of respiratory effort. Likewise, in experimental and clinical conditions where peripheral stretch receptors are inhibited, the sensory cortex is not informed of the ventilatory response. In these circumstances, dyspnoea is perceived as a sensation of air hunger, the intensity of which depends on a mismatching between the level of chemically stimulated drive and ongoing inhibition from pulmonary mechanosensors signalling the current level of ventilation. In turn, dyspnoea arises and may qualitatively change when peripheral afferent feedback is altered and inspiratory motor output either increases or stabilises.

Table 2. The MRC dyspnoea scale and the Borg scale

Grade	Description
MRC	
dyspnoea scale	
1	Not troubled by breathlessness except with strenuous exercise
2	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
3	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
4	Stops for breath after walking ~90m or after a few minutes on the level
5	Too breathless to leave the house or breathlessness when dressing or undressing
Borg scale	
0	No breathlessness at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximum)
10	Maximum

Pathophysiology

COPD

Two qualitative descriptor clusters of dyspnoea are commonly selected by patients with COPD during physical activity.

The descriptor cluster that alludes to increased respiratory work/effort ('breathing requires more effort or work') is commonly selected by patients with COPD. Increased sense of work/effort is related to the increased motor drive to the respiratory muscles and increased central neural drive (due to chemostimulation) as a consequence of progressive metabolic and ventilation/perfusion disruptions during exercise. Therefore, increased perceived work/effort during physical activity, in part, reflects the greater ventilatory demand for a given task compared with health. In addition, contractile muscle effort is increased for any given ventilation because of:

- 1) the acutely increased intrinsic mechanical (elastic/threshold) loading; and
- 2) functional respiratory muscle weakness.

These respiratory mechanical/muscular abnormalities are, in part, related to resting and dynamic hyperinflation during exercise, and may lead to either a decrease in $P_{I\max}$ or a further increase in P_{oes} as percentage of $P_{I\max}$. Because of these effects, greater neural drive or electrical activation of the respiratory muscle is required to generate a given force. Furthermore, because of limbic system activation, the corollary discharge may be sensed as abnormal, thus evoking a sensation of distress (fig. ♠1 and table ♠1).

The other descriptor cluster alludes to unsatisfied inspiration. Structural abnormalities (chronic bronchitis and emphysema), *via* their negative physiological consequences, *i.e.* expiratory flow limitation and dynamic hyperinflation (measured during exercise as reduction in Inspiratory Capacity, *i.e.* IC), result in dyspnoea. A patient's physical activity is indeed characterised by a growing mismatch between increase in central neural output to the respiratory muscles and the blunted respiratory mechanical/muscular response (lung/chest wall displacement). This mismatch, which we call neuroventilatory dissociation (NVD), has been proposed to be, at least in part, the neurophysiological basis of the perceived unsatisfied inspiration. In a clinical setting,

the slope that defines NVD (*i.e.* effort *versus* displacement) is steeper and shifted upward compared with healthy subjects. The steeper the slope, the greater the intensity of dyspnoea (fig. 2). In particular, patients experience intolerable dyspnoea during exercise because V_T expansion is constrained from below (by the effects of dynamic lung hyperinflation or the already critically reduced resting inspiratory capacity), as there is no space to breathe. This so-called dyspnoea threshold seems to be at the level at which the inspiratory reserve volume (IRV) critically approaches 0.5-0.4 L. Once this critical IRV is achieved, further expansion in V_T is negated, the effort–volume displacement ratio (P_{oes}/P_{Imax} divided by V_T/VC) increases sharply and dyspnoea intensity rises steeply to intolerable levels. The data support the central importance of mechanical restriction in causing dyspnoea in COPD patients.

Figure 2. NVD. The slope that defines the mismatch between increase in neural output (inspiratory effort, *i.e.* P_{oes}/P_{Imax}) and lung/chest wall displacement (V_T/VC) is steeper and shifted upwards in patients with COPD compared with healthy subjects.

Neuromuscular disorders

Patients with neuromuscular disorder (NMD) exhibit heightened neuromotor output, which is sensed as increased respiratory muscle effort and, as such, is likely to be the principal mechanism of dyspnoea in NMD. Nonetheless, a significant positive relationship between increased dyspnoea per unit increase in ventilation and dynamic elastance affects the coupling between respiratory effort and displacement (fig. 3).

Figure 3. A mismatch between inspiratory effort (swing in oesophageal pressure ($P_{oes,sw}$) as a percentage of oesophageal pressure during a sniff manoeuvre ($P_{oes,sn}$)) and lung/chest wall displacement (V_T as a percentage of the predicted value of the vital capacity (VC_{pv})) in patients with NMD compared with average data from controls. The steeper the slope, the greater the perception of dyspnoea.

Interstitial lung disease

As in COPD, restrictive dynamic respiratory mechanics limits the ability of patients with interstitial lung disease (ILD) to increase ventilation in response to the increased metabolic

demands of physical tasks. One of the characteristic features of ILD is a reduction in lung compliance and lung volumes. This has two major consequences:

- 1) Greater pressure generation is required by the inspiratory muscles for a given V_T
- 2) The resting TLC and IRV are often diminished compared with health

Therefore, V_T expansion is constrained from above early in exercise (reflecting the reduced TLC and IRV), which results in greater reliance on increasing breathing frequency to increase ventilation. Differences in dynamic ventilatory mechanics, including possible expiratory flow limitation in some patients, account for distinct qualitative perception in ILD patients, namely inspiratory difficulty/unsatisfied inspiration and rapid shallow breathing. Because of increases in both dynamic elastance and efferent respiratory drive, inspiratory difficulty/unsatisfied inspiration may have its neurophysiological basis in the conscious awareness of a dissociation between the increased drive to breathe (and concurrent increased respiratory effort, *i.e.* P_{oes}/P_{Imax}) and the restricted mechanical response of the respiratory system (*i.e.* V_T/VC), *i.e.*, the inability to expand V_T appropriately in the face of an increased drive to breathe. In turn, the possibility has also been put forward that intensity of exertional dyspnoea in ILD is more closely linked to mechanical constraints on volume expansion than to indexes of inspiratory effort *per se*.

Chronic heart failure

The key message that has emerged from therapeutic intervention studies in patients with CHF is that exertional dyspnoea alleviation is consistently associated with reduced excessive ventilatory demand (secondary to reduced central neural drive), improved respiratory mechanics and muscle function and, consequently, enhanced neuromechanical coupling of the respiratory system during exercise. Pressure support is reported to reduce the tidal inspiratory pleural pressure–time slope without affecting submaximal dyspnoea ratings but allows patients to exercise for additional time without experiencing any significant rise in dyspnoea. The available data suggest that increased ventilatory demand, abnormal dynamic ventilatory mechanics and respiratory muscle dysfunction are instrumental in causing exertional dyspnoea in patients with severe cardiac impairment.

Obesity

An increase in respiratory neural drive is deemed to be the reason for the similar increase in dyspnoea in obese and lean subjects. However, different underlying mechanisms may affect dyspnoea in obese subjects. Exercise performance is impaired compared with healthy, normal-weight subjects when corrected for the increased lean body mass, but normal when expressed as a percentage of predicted for ideal body weight in subjects who hyperinflate their lungs to the same extent as those obese subjects who deflate their lungs, with both volume subgroups reaching similar dyspnoea scores. In ‘hyperinflators’, dynamic hyperinflation, along with a decrease in IRV, increases respiratory muscle loading, respiratory drive and perception of respiratory discomfort. In contrast, ‘deflators’ exhibit a negative relationship between resting end-expiratory lung volume (EELV) and perceptual respiratory response during exercise: the lower the EELV, the greater the Borg score. A low EELV has three important consequences linked together during exercise:

- 1) Decrease in expiratory reserve volume
- 2) Dynamic airway compression
- 3) Changes in transmural airway pressure resulting in airway dynamic compression

Thus, an alteration in the central drive to the respiratory muscles in response to afferent activity from upper airway mechanoreceptors may also contribute to the unpleasant respiratory sensation in obese subjects.

Asthma

Three dominant qualitative descriptors of exertional dyspnoea emerge in patients with asthma: 1) chest tightness, 2) increased work/effort (“breathing requires more work or effort”), and 3) unsatisfied/unrewarded inspiration (“can’t get enough air in”). It has been pointed out that regardless of the global score of intensity of dyspnoea, different descriptors may be selected by asthmatic patients during short cycle exercise sessions and methacholine challenge test. Airway obstruction and dynamic lung hyperinflation, as measured by the decrease in IC, correlates best with dyspnoea during methacholine challenge test. Chest tightness is the highest reported

descriptor (68%) during methacholine inhalation. During short cycle exercise V'E is the best predictor of dyspnoea, and work/effort is the highest reported descriptor (72%). IC may decrease in a subgroup of asthmatic patients during exercise. Of interest, this subgroup of patients shows a similar degree of hyperinflation during methacholine challenge test but their description of dyspnoea is different between the two tests: during methacholine challenge test, 60% of the responses are chest tightness, 10% inspiratory effort and 30% are expiratory effort; during exercise, 90% are inspiratory effort and 10% chest tightness. More recently, it has been argued that the presence of expiratory flow limitation at rest and during exercise may explained the significant decrease in IC (i.e., dynamic lung hyperinflation) observed in a subgroup of patients with stable mild asthma undergoing high-intensity constant work-rate cycle exercise. A strong correlation is found between the extent of expiratory flow limitation and the reduction in IC (expressed as % of predicted TLC) during exercise ($r=-0.82$, $p=0.04$). The quantitative and qualitative aspects of dyspnoea in patients with asthma may also be evaluated. In this regard, it has been showed that even mild stable asthmatics are able to perceive critical mechanical constraints on VT expansion during exercise. It has been demonstrated that VT expansion becomes constrained due to dynamic lung hyperinflation at a critically reduced inspiratory reserve volume (IRV) only in 37.5% of subjects and it marks the point where dyspnoea intensity rises abruptly and there is a transition in the dominant qualitative descriptor choice from work/effort to difficult/unsatisfied inspiration. In contrast, VT expansion flattens at a preserved IRV in 62.5% of subjects and it does not mark a mechanical event with important sensory consequences. The corollary of this is that therapeutic interventions that effectively delay the appearance of the VT constraints at a critically reduced IRV should theoretically reduce the attendant dyspnoea during physical activity even in patients with mild stable asthma. The clinical relevance of these findings is that, pending confirmation in larger samples, by asking the quality of dyspnoea at the end of an exercise bout, one can ascertain whether a critical IRV (difficult/unsatisfied inspiration) or not (work/effort) has been reached, i.e., the likelihood of developing exercise-related critical volume constraints in asthmatics.

Pulmonary Arterial Hypertension

Exertional dyspnoea is by far the dominant symptom in patients with Pulmonary Arterial Hypertension (PAH). Recent advances in PAH have clearly demonstrated that some PAH

patients (up to 60%) may exhibit reduced expiratory flows in tidal operating range, which could promote exercise-induced dynamic lung hyperinflation. Few studies examined the impact of potential dynamic lung hyperinflation-induced critical mechanical constraints on the intensity of dyspnoea in young non-smoking patients with idiopathic and heritable PAH undergoing symptom-limited incremental CPET. These studies showed that reduced expiratory flows at low lung volumes at spirometry exist in a large proportion of idiopathic and heritable PAH patients (60%) despite a preserved FEV₁/VC ratio. When increased ventilation/perfusion mismatching is superimposed on pre-existing abnormal airway function, greater troublesome exertional symptoms ensue. Although dyspnoea in these patients is likely multifactorial, these results clearly indicate that increased ventilatory demand and abnormal dynamic ventilatory mechanics should be considered in PAH patients, in the absence of respiratory muscle dysfunction or TLC changes.

Asymptomatic subjects with airway obstruction

In at-risk subjects who complain of symptoms, early detection of COPD has been proven to be effective and is now recommended. Nevertheless, this strategy is unable to detect COPD in subjects who do not report any symptom. COPD screening programmes in asymptomatic at-risk individuals have, therefore, been evaluated. Identifying airway obstruction, as defined by an FEV₁/FVC ratio below the fixed cut-off of 0.70 in asymptomatic subjects, does not appear to be beneficial because they do not have an accelerated decline in FEV₁ and are not at higher risk of premature death. In contrast, even in the absence of COPD-related symptoms, subjects with persistent airway obstruction defined by a postbronchodilator FEV₁/FVC ratio below the statistically based, age-specific lower limit of normal (LLN) are at risk of premature death and/or of development of respiratory symptoms, suggesting that their identification is pertinent. It has recently been demonstrated that subjects with mild airway obstruction, defined as post-bronchodilator FEV₁/FVC < LLN together with normal FEV₁, who do not complain of any COPD symptom had, however, greater dyspnoea intensity during incremental exercise and poorer peak exercise capacity than matched healthy subjects with normal spirometry; these asymptomatic subjects with airway obstruction had a greater reduction in IC than healthy controls during exercise, and half of them had significant dynamic lung hyperinflation on exertion.

Mild COPD

Symptomatic smokers with only modest physiological abnormalities at rest might present with activity-related dyspnoea leading to chronic inactivity restriction, reduced health-related quality of life and poorer prognosis. A number of physiological anomalies at rest have the potential to impact on exercise responses in patients with mild COPD: increased peripheral airways resistance; heterogeneous distribution of alveolar ventilation; expiratory flow-limitation (EFL), pulmonary gas trapping and reduced IC; increased alveolar-arterial O₂ tension difference; and low lung transfer factor for carbon monoxide and transfer coefficient. During exercise, a decreased ventilatory efficiency (increased $\dot{V}'E/\dot{V}'CO_2$ nadir and a steeper $\dot{V}'E/\dot{V}'CO_2$ slope) compared with healthy controls, reflecting heightened chemo-stimulation due to high physiological dead space, and dynamic lung hyperinflation secondary to EFL and high ventilatory demand can be found. The combination of reduced IC and high inspiratory neural drive may result in early attainment of critical mechanical constraints and higher exertional dyspnoea ratings compared with age-matched healthy controls.

Effects of interventions on dyspnoea

Effective improvement in exertional dyspnoea represents one of the most challenging targets of management in patients with cardiopulmonary disease. Traditionally, the approach to improving exertional dyspnoea in all of the major cardiopulmonary diseases involves interventions that:

- 1) reduce ventilatory demand (by reducing the drive to breathe);
- 2) improve ventilatory capacity;
- 3) improve respiratory mechanics (by reducing the mechanical load);
- 4) increase the functional strength of weakened ventilatory muscles;
- 5) address the affective dimension of dyspnoea; and
- 6) any combination of the above.

It is of note that interventions should be selected based on the underlying pathophysiological background of the specific disease under examination and may differ from one disease to another. However, multiple interventions are generally required and appear to have additive or synergistic effects.

Some of these interventions include the following:

- Bronchodilators
- Oxygen
- Heliox
- Exercise training
- Biventricular pacing (specific for CHF patients)
- Biofeedback techniques
- NIV
- Lung volume reduction surgery and related endoscopic techniques
- Various combinations of these

All of the above strategies have proven to provide beneficial sensory consequences in a variety of patients with cardiopulmonary diseases.

In selected patients, interventions such as opiates (oral and inhaled) reduce respiratory drive and alter affective components of dyspnoea. Recently, it has been shown that inhaled furosemide may modulate respiratory sensation by altering afferent inputs from vagal receptors within the lungs. Psychological counselling, cognitive/behavioural modification and anxiolytics can have favourable influences on the affective dimension of chronic dyspnoea.

Conclusions

We are still a long way from understanding the symptom of dyspnoea. Although mechanical factors are important contributors to dyspnoea, the precise mechanisms of dyspnoea remain obscure. One approach to the study of this symptom is to identify the major qualitative dimensions of the symptom in an attempt to uncover different underlying neurophysiological mechanisms. The remarkable similarity in choices of qualitative descriptors (work/effort, inspiratory difficulty/unsatisfied inspiration, air hunger and rapid breathing) for exertional dyspnoea in patients with restrictive and obstructive syndromes raises the intriguing possibility that they share some common underlying mechanisms.

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Key points

- Dyspnoea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.
- The mechanisms of dyspnoea are complex and multifactorial: there is no unique central or peripheral source of this symptom.
- The sense of heightened inspiratory effort is an integral component of exertional dyspnoea and is pervasive across health and disease.
- The NVD theory of dyspnoea states that the symptom arises when there is a disparity between the central reflex drive (efferent discharge) and the simultaneous afferent feedback from a multitude of peripheral sensory receptors throughout the respiratory system. The feedback system provides information about the extent and appropriateness of the mechanical response to central drive.
- Despite the diversity of causes, the similarity of described experiences of dyspnoea suggests common underlying mechanisms.