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Topical Review

Measurement and treatment of dyspnoea

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Introduction

Dyspnoea is the term generally applied to sensations experienced by individuals complaining of unpleasant or uncomfortable respiratory sensations. In patients with chronic obstructive pulmonary disease (COPD) breathlessness is the most common symptom limiting exercise capacity (EC) and the major reason for referral to respiratory rehabilitation programmes (1–3). A recent official statement of the American Thoracic Society (4) suggests that 'dyspnoea is a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses'.

In the past, dyspnoea has been defined as an uncomfortable sensation of breathing (5), it may include a large class of experiences and feelings such as 'tightness', 'suffocation' and 'heaviness' (6). These different experiences probably arise from different pathophysiological mechanisms. Independent of the underlying mechanisms, dyspnoea is characterized by a sensation of air hunger or increased effort or work of breathing (7,8). 'Breath stops', 'chest tightness' and 'constriction' are often reported in diseases associated with stimulation of irritant receptors in the lungs. Intensity of dyspnoea is influenced by a mismatch between the respiratory motor command from the central nervous system and afferent feedback arising from several receptors in the respiratory system [neuro-ventilatory dissociation (NVD) of the respiratory pump] (9). The concept of NVD implies that in addition to motor output, sensory feedback from peripheral respiratory mechanoreceptors contributes importantly to respiratory sensation (9). In COPD patients during exercise, the relationship between effort (motor output) and the anticipated ventilatory consequence (instantaneous change in tidal volume) is seriously disrupted, i.e. NVD, as a result of weakened or less effective inspiratory muscles due to dynamic hyperinflation. Under these conditions the patient experiences marked inspiratory difficulties. The psychophysical basis of NVD likely resides in the complex central processing of integrated sensory information relative to: (i) the level of central motor command output (10) and (ii) instantaneous feedback from a number of respiratory mechanoreceptors that provide proprioceptive information.

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Measurement

The measurement of dyspnoea is a critical aspect of patient evaluation and management. Both psychophysical methods and clinical scales have been used to assess breathlessness. Psychophysical testing involves the measurement of perception of breathing changes in response to externally added loads (11,12). This approach has lead to greater understanding of respiratory sensations but several factors, including technical aspects and time requirements, limit its application in the routine setting. Because the dyspnoeic patient is frequently unable to perform daily activities of life due to discomfort associated with breathing, the clinical methods used to measure dyspnoea have depended primarily on the magnitude of the exertional task that evokes breathlessness. In 1959 Fletcher and colleagues (13) proposed a five-point rating scale based on the patient's history of dyspnoea. Seven years later, the British Medical Research Council (MRC) proposed a similar four-point scale (14). Patients must indicate the level of activity associated to dyspnoea and then, at following visits, they are monitored to determine if dyspnoea occurs with lower or greater levels of activity. Both of these scales relate primarily to the magnitude of the task inducing dyspnoea, but there is little provision for the associated effort. This consideration is important since the development of dyspnoea during a specific task such as stair climbing may vary with the speed of walking. Another disadvantage of these scales is that functional impairment, an important consequence of dyspnoea is not considered.

There are additional difficulties with a scale based on only few grades. When changes are evaluated to assess an intervention over a short time period, the scale may be too coarse to show distinct alterations. This problem can be circumvented by using the visual analogue scale (VAS) (15), (which consists of a horizontal or vertical measured line which is frequently anchored at each end by the descriptors (no breathlessness and greatest breathlessness) or related

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significant images (16). Alternatively descriptive phrases at various points along the line may indicate severity of dysponea. The patient is instructed to place a mark on the line corresponding to the severity of his/her symptom. Since the line is a measured length (usually 100 mm), the location of the mark provides a quantification of the patients dyspnoea. Although the VAS can provide a dimensional measurement of the severity of dyspnoea, it does not consider the factors contributing to breathlessness. Furthermore there are no apparent criteria or standard principles that would allow the scale to be used consistently by different observers. Serial measurements of dyspnoea using the VAS might be effective for showing changes within a single patient, but not for comparing dyspnoea in different patients nor would be satisfactory for summarising or comparing the conditions of groups of patients.

To improve the clinical rating of dyspnoea Mahler *et al.* (17) developed two new indexes that include three components: functional impairment, magnitude of effort, and magnitude of task. The Baseline Dyspnoea Index (BDI) was developed to rate the severity of dyspnoea at a single state. An observer scores the patient's severity of breathlessness for each of three components based on responses to various questions as part of clinical history for respiratory diseases. For each dimension the interviewer asks open-ended questions about the patient's experience of breathlessness and simultaneously focuses on specific criteria for evaluating the intensity of difficult breathing. Based on the patient's responses the observer can grade the severity of breathlessness for each of the three dimensions. BDI focal score (range 0–12) is obtained by adding the scores [from 0 (severe) to 4 (not impaired)] for each of the three components. The lower the focal score, the more severe the intensity of dyspnoea. A Transition Dyspnoea Index (TDI) was proposed to evaluate changes from the baseline condition. TDI is an evaluative instrument that measures changes in the three components compared with the baseline state. TDI focal score (range -9–$+9$) represents changes in dyspnoea compared with the baseline condition according to seven possible grades [from -3 (major deterioration) to $+3$ (major improvement) through 0 (no change)] for each component. The interviewer should refer to the grades from the BDI and can remind the individual patient of his/her comments before selecting the component grades for the TDI. Translations of the BDI and TDI are available in German, Italian, Japanese and Spanish (18). The BDI had the highest correlation with the 12-min walking distance (12MWD), while significant but lower correlation existed for lung function (18). More recently, Ferrari *et al.* (19) have shown a good relationship between BDI and indexes of respiratory muscle effort. For TDI there was a significant correlation only with the 12MWD.

Recently, the University of California at San Diego Shortness of Breath Questionnaire (UCSDQ) was developed and validated. It is a 24-item questionnaire measuring dyspnoea during the past week (20), asking patients about the frequency of dyspnoea when performing 21 different activities on a six-point rating scale.

The 0–10 category–ratio scale developed by Borg (21) consists of verbal descriptors adjacent to specific numbers, the spacing of the numbers and corresponding descriptors essentially provide a category scale with ratio properties. A rating about 10 can be used to represent more severe dyspnoea than the individual has ever previously experienced. A number greater than 10 can be selected by the patient if the intensity of dyspnoea exceeds previous experiences. Written instructions are important for the patient to read prior to using the scale. Using a 0–10 category–ratio scale (21), Meja *et al.* observed that patients with symptomatic COPD demonstrated a comparable ability to use dyspnoea ratings and heart rate, as a target to accurately and reliably produce an expected exercise intensity (about 75% of $\dot{V}O_{2max}$) for 10 min of submaximal exertion (22).

With all these approaches validity depends on the accuracy of patient reports. People may over-estimate or under-estimate their capacity to exercise. The established measures correct for some of these limitations but do not deal directly with the suspicion that patients may evaluate their work performance optimistically. To assess symptoms more directly, dyspnoea has been evaluated during performance of supervised tasks.

Dyspnoea ratings during exercise in both healthy individuals and patients with respiratory diseases vary over a wide range (23). Many investigators have focused on ratings of dyspnoea at peak exercise. In practice most patients select submaximal values for the Intensity of dyspnoea at peak exercise performance (23,24), and peak ratings of dyspnoea are similar regardless the type of chronic respiratory disease. Consequently, patients should be asked a Borg score for each level of effort during an incremental test. Borg score should be used to compare severity of dyspnoea at comparable time periods (iso-time) or at similar work intensities (iso-load) efforts. Alternatively, the slope and the intercept of the power–dyspnoea relationship can be calculated to summarize the magnitude of data obtained during a progressive incremental exercise test (25). For most patients with severe COPD dyspnoea is reported to be the major limiting symptom in performing daily activities In contrast, Killian *et al.* (23) have demonstrated that during actual exercise testing patients with mild to moderate COPD frequently report that leg discomfort/effort is more severe than breathlessness.

Guyatt *et al.* (26) described a Chronic Respiratory Questionnaire (CRQ) to assess quality of life (QOL) in patients with chronic lung diseases. The problem of dyspnoea is one of the four components in the CRQ. Each patient is asked to select the five most bothersome activities that elicited breathlessness during the last 2 weeks. The severity of dyspnoea is measured using a 1 (extremely short of breath) to 7 (not at all short of breath) scale. The individual scores are added to obtain an overall CRQ dyspnoea score (range 5–35)

Mahler *et al.* (27) have recently examined the longitudinal changes in dyspnoea, general health and lung function over a 2-year period in a cohort of patients with COPD and no significant co-morbility. Repeated measures analysis showed that there were significant decreases in the

TDI focal scores and physical functioning. Although changes were also noted for FVC and FEV_1, these measures did not increase or decrease consistently over time. The change in dyspnoea were significantly related to changes in lung function. Regression analysis revealed that TDI focal score was a significant predictor for all components of general health status. These authors concluded that dyspnoea, inspiratory muscle force and physical functioning decline in over 2 years in a cohort of patients with symptomatic COPD. Both dyspnoea ratings and lung function (FEV_1) were significant predictors of various components of general health status.

Various studies have collectively demonstrated that the VAS as well as two multi-dimensional scales (BDI/TDI and CRQ dyspnoea) are valid, reliable and responsive instruments for measuring breathlessness in chronic respiratory diseases (28). In a study evaluating dyspnoea as a determinant of EC, in patients with chronic airflow obstruction, Foglio *et al.* (29) found that breathlessness measured using VAS and BDI correlated with measures of EC but the proportion of shared variance with exercise loaded to the greatest with breathlessness measured with the BDI. Borg scores for dyspnoea and leg effort, whether at rest or at maximum work rate, did not correlate with any of the measures of EC. In a factor analysis of clinical methods used to evaluate dyspnoea in patients with COPD, Hajiro *et al.* (30) found that the MRC, the BDI, the oxygen–cost diagram, the activity component of the St George's Respiratory Questionnaire (SGRQ) (31) and dyspnoea of the CRQ were grouped into the same factor, and the frequency distribution histograms of these five measurements showed virtually the same distribution. The Borg scale at the end of maximum exercise was found to be a different factor. These measurements demonstrated the same pattern of correlation with physiologic data. In a prospective clinical study in healthy subjects, Grant *et al.* (32) found that subjective scales like VAS, Borg scale or the Likert Scale could reproducibly measure symptoms during steady-state exercise and could detect the effect of drug intervention. The VAS and Borg scales appeared to be the best subjective scales for this purpose.

In conclusion, standard tools to determine the association between levels of activity and dyspnoea are available. In addition, there are tools to relate the severity of symptoms with observed levels of cardiac and pulmonary responses during performance of supervised tasks. Inventories that involve aspects of dyspnoea related to QOL are not yet a routine part of the history and physical examination, but have demonstrated a useful role in the clinic and in pulmonary rehabilitation. Measurement instruments may involve a cost for use, may be self-administered or require an interviewer, and will vary in the time required for completion and scoring.

Pharmacological treatment

Dyspnoea is a complex symptom. Sensation of difficult or laboured breathing that accompanies cardiorespiratory disease may vary in quality and may have different pathophysiological bases. Thus, a better understanding of the underlying mechanisms is necessary for clinicians to improve their ability to treat patients with breathlessness. Many of the therapeutic interventions currently available relieve dyspnoea by addressing different mechanisms. Any intervention that: (i) reduces ventilatory demands, (ii) reduces ventilatory impedance, or (iii) improves inspiratory muscle function, may relieve dyspnoea.

REDUCED VENTILATORY DEMAND

Reducing metabolic load

Reduced ventilatory demand may be obtained by reducing metabolic load. Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance. In the study by Swinburn *et al.* (33) the relationship between minute ventilation ($\dot{V}_E$) and dyspnoea was the same whether patients breathed air or 60% oxygen. The authors concluded that hypoxia had non dyspnogenic effect and that it caused dyspnoea by stimulating $\dot{V}_E$.

According to Stark et al. (34) there are two mechanisms of treatment of dyspnoea. In type I the decrease in dyspnoea is proportional to the decrease in $\dot{V}_E$, while in type II the decrease in dyspnoea is out of proportion to $\dot{V}_E$, i.e. there is less dyspnoea for a given $\dot{V}_E$. Type I is typical of energy conservation techniques. The advantage of type II is that dyspnoea may be relieved without depressing $\dot{V}_E$. Treatments may act by either mechanism or both.

More recent evidence from mildly hypoxaemic COPD patients (35) have shown that the slope of breathlessness and leg effort over time fell significantly during exercise on 60% oxygen compared to room air; exercise time also increased significantly. Furthermore, the slope of lactate over time also fell significantly in hyperoxia. Importantly, Borg score, and $\dot{V}_E$ fell proportionally. The slopes in air and oxygen were superimposed indicating that the decrease in Borg was associated with reduced $\dot{V}_E$ demand. The association with reduced blood lactate levels indicated an improved aerobic metabolism. This study also indicates that oxygen intervention may have non-specific global effects on sense of skeletal muscle contractile effort in general. Regardless of any direct central effect, it is conceivable that improved oxygen delivery to skeletal muscles favourably alters the metabolic milieu within the muscle interstitium, making it more responsive to neural activation (35).

Oxygen may also modify the strategy of the respiratory muscle recruitment. A small decrease in end-inspiratory oesophageal pressure (Poes: an index of pleural pressure) and a small increase in end-inspiratory gastric pressure (Pga: an index of abdominal pressure) at iso-time with unchanged end inspiratory transdiaphragmatic pressure (Pdi: an index of diaphragmatic activity) was found by Bye *et al.* (36). A study by Criner and Celli (37) dealt indirectly with the effect of oxygen on breathlessness in mildly hypoxic severe COPD. That study showed that 30% oxygen increased EC of diaphragm as shown by a less end-inspiratory Poes and a greater end-inspiratory Pga

after oxygen. This pattern of respiratory muscle recruitment was thought to prevent overloading of other ventilatory muscles (accessory inspiratory and abdominal). In other words, the diaphragm takes over ventilatory task unloading accessory and abdominal muscles; this results in less dyspnoea. These observations are in line with studies showing that breathlessness correlated with the electromyogram (EMG) of sternomastoid but not of the diaphragm (38).

In the study by Ward *et al*. (39) at a given Pdi the sense of effort increased with increasing the Poes contribution to Pdi and a strong correlation with EMG of sternomastoid was found. These studies indicate that a respiratory task performed primarily by the rib cage muscles involves greater neuromotor output than the one performed primarily by the diaphragm.

A recent study by Marin and Celli (40) has shown the role of hypercapnic central drive on perception of breathlessness in exercising COPD patients. Central chemoresponsiveness explained about 28% of the variance in peak breathlessness while no mechanical factor appeared to be involved, as previously reported by Montes de Oca *et al*. (41). Marin and Celli (40) concluded that 'those patients with increased neural drive and dyspnoea response may be candidate for central output modulation independent of the degree of airflow limitation'.

Decreased central drive

Oxygen therapy. Reduced hypoxic drive from chemoreceptors and proportional decrease in $\dot{V}_E$ has been advocated to explain dyspnoea relief during oxygen at rest and during exercise (42). In contrast, Lane *et al*. (43) suggested other factors such as altered perceptual response or non-direct depression of central drive. Afferent information from cutaneous nerve has also been advocated to explain the effect of oxygen on breathlessness in COPD (44). In general, the effect of chronic oxygen therapy on chronic exertional dyspnoea and QOL has not been systematically studied (4).

Pharmacological therapy. Another possibility to reduce ventilatory demand by decreasing the central drive pertains to opiates. Opiates have been shown to decrease $\dot{V}_E$ at rest and during submaximal exercise. They can alter the central processing of neural signals within the central nervous system to reduce sensations associated with breathing (45). Despite safety concerns, these drugs do have place in the management of patients in the terminal phase of their disease (46).

No consistent improvement in dyspnoea over placebo has been shown (34,47–50) with anxiolytics. An initial study (49) showing decrease in breathlessness has not been confirmed in patients (48) and in normal subjects (34). Nonetheless, the ATS statement maintains that 'given the prevalence of severe anxiety in breathless patients with pulmonary disease, it is reasonable to recommend a trial of anxiolytic therapy on an individual basis, particularly in those with morbid anxiety or respiratory panic attacks' (4).

Altering pulmonary afferent information. Decreasing central drive may be obtained by altering pulmonary afferent information. Interventions that alter transmittal of afferent information to central controller potentially reduce dyspnoea. However, there are many concerns about the real usefulness of such interventions in a clinical setting. The following must be considered: (i) aerosolized topical anaesthesia has inconsistent effects on dyspnoea in normals, COPD (34,51) and interstitial lung disease (52); (ii) vagal blockade has highly variable effects on dyspnoea (53) (iii) intact $\dot{V}_E$ response to exercise in post-transplanted vagally-denervated subjects has been reported (54). However, while the vagal block or section differently affected dyspnoea in the studies by Guz (53), vagal section reduced dyspnoea in the study by Bradley *et al*. in patients with emphysema (55). Also, inhaled lidocaine lessens breathlessness associated with bronchoconstriction in asthma (56).

Drugs affecting-prostanoids. Indometacine inhibits 4-cyclooxygenase. In normals it seems to act by a type II mechanism but in patients it does not change the $\dot{V}_E$ to dyspnoea relationship (57). Prostaglandin E seems to change the $\dot{V}_E$ to dyspnoea relationship in normals (58) but no data are available in patients.

REDUCED VENTILATORY IMPEDANCE

Reducing dynamic lung hyperinflation and resistive load

O'Donnel *et al*. (59,60) have shown that the end-expiratory lung volume (EELV) increases during exercise in controls and COPD. Due to the increase in EELV, tidal volume (V_T) oscillates on the nonlinear portion of the pressure/volume characteristics of the respiratory system. Thus respiratory muscles must generate a greater effort to expand V_T. The increased mechanical load results in a greater inspiratory effort for a given flow or V_T, which is the basis of NVD of the ventilatory pump. Also, the inspiratory threshold load overburdens the inspiratory muscles. The increase in breathlessness is associated with these phenomena. Comparing patients with CAO and controls during exercise it is evident in the former a steeper regression line of the relationship between $\dot{V}O_2$ and both NVD and inspiratory difficulty, with NVD being the strongest correlated to Borg (59,60). Furthermore, as exercise progresses, V_T progressively encroaches upon the inspiratory reserve volume (IRV). It stems that IRV is an important covariate of breathlessness. Nonetheless, one has also to consider that not always mechanical variables are associated with dyspnoea in patients. For instances, respiratory effort dyspoea in controls, but it does not in very severe COPD patients (41).

β_2-agonists. As compared to placebo, albuterol resulted in a relatively lower increase in both EELV and, even if to a less extent, end-inspiratory lung volume (EILV); besides, the drug decreased the inspiratory muscle effort (61). This study also shows the interrelationships between operational lung volumes and breathlessness.

Anti-cholinergics. In stable COPD 200 mcg oxitropium bromide was found to reduce breathlessness and to improve the 6MWD; both were unrelated to changes in FEV_1 but were supposed to stem from decrease in hyperinflation (62). The underlying mechanism has been clarified more recently by O'Donnel *et al*. (63), showing the superior effect of 500 mcg nebulised ipratropium bromide (IB) versus placebo on exercise time to dyspnoea relationship. The study has also shown the effect of IB on operational lung volumes before and during exercise at any given exercise time. EELV was lower and IRV was greater with IB. Also, change in exercise endurance time and Borg correlated with resting inspiratory capacity (IC) but much better with concurrent exercise measurements.

Theophylline. With oral theophylline, Crystyn *et al*. (64) have shown a dose-dependent improvement in exercise tolerance, reduced thoracic gas volume and modest but significant decrease in dyspnoea on a VAS scale. Murciano *et al*. (65) reported that 2-month oral theophylline increased the maximal Poes ($Poes_{max}$), and decreased the inspiratory effort as assessed by the Poes swings ($Poes_{sw}$) to $Poes_{max}$ ratio, decreased VAS score without changes in functional residual capacity and the EMG activity of the diaphragm (66). These data suggest that amelioration of dyspnoea results from better respiratory muscle performance. Actually we can consider the relieve of dyspnoea as the consequence of a decreased respiratory muscle effort. Evidence indicates that theophylline ameliorates the sensation of dyspnoea. The mechanism by which theophylline relieves dyspnoea is probably related to mechanism other than bronchodilation alone (67).

Supplemental oxygen. In patients with airflow limitation, dynamic hyperinflation increases with exercise as a function of $\dot{V}_E$ increase in V_T and/or in respiratory frequency (Rf)]: increase in EILV with no change in expiratory time and increase in Rf with less time available to expire a given V_T. In as much as V_T increases exercise-induced dynamic hyperinflation, supplemental oxygen, by reducing $\dot{V}_E$ at given work load, reduces the concomitant level of dynamic hyperinflation (35).

IMPROVED INSPIRATORY MUSCLE FUNCTION

Alterations in respiratory muscle function are currently being detected in patients with COPD due to alteration in respiratory muscle energy balance (reduction in energy supply/increase in energy demand ratio) (4,68–74).

Nutritional repletion

Nutritional repletion may improve respiratory muscle function (75–77) but uncertainty remains as whether nutritional repletion may relieve dyspnoea. Goldstein *et al*. (78) found that a 4-month nutrition supplementation program did not result in any improvement in dyspnoea as assessed by VAS.

Minimising the use of steroids

Until more consistent findings are available on the effect of systemic steroids on respiratory muscles, their use for the purpose of reducing dyspnoea must still be balanced against the deleterious effects on muscle wasting and weakness (4). On the other hand, no studies have assessed whether oral or inhaled steroids may affect the perception of breathlessness in COPD. This possibility has already been reported in patients with chronic asthma (79,80).

Non pharmacological intervention

Marked functional limitation often occurs in patients with respiratory disease (81). Dyspnoea, responsible for a vicious cycle of negative feedback, is the main deconditioning stimulus. Progressive decrease of physical activity is in fact the patient's natural response to such an unpleasant symptom. Less exertion leads to reduced muscle mass, which in turn results in more dyspnoea at increasingly lower levels of exertion. Thus, a main goal of exercise training is to break this debilitating pattern. Improvements in exercise tolerance may be achieved through both physiological and psychological interventions (1). Although exercise training programmes by cycling and/or treadmill walking, stair climbing etc, have been widely used in different respiratory diseases, in the COPD patient they should not be considered until optimal medical control of the disease has been achieved. It is safe to state that *any patient capable of undergoing training* will benefit from a programme that includes leg exercise (2). However the optimal exercise intensity, modality, need for supervision, duration and maintenance programme remain to be determined (3).

Exercise training is based on general principles of exercise physiology: intensity, specificity and reversibility. The level of intensity is of key importance (3,82,83). This may be relevant also in the light that the recent development of new therapeutical approaches like lung transplantation and lung volume reduction surgery make also most severe COPD patients (e.g. those with chronic respiratory failure) candidates to rehabilitation programmes (84). Indeed, until recently there was the common idea that patients with advanced lung disease have a ventilatory limitation to exercise which precludes the aerobic training levels necessary for beneficial physiological adaptations. However, recent studies have demonstrated that anaerobic metabolism and early onset of lactic acidosis are observed during exercise training of COPD patients (3). Greater improvements in maximal and submaximal exercise responses can be obtained after exercise at high (e.g. 60% of maximal work rate, i.e. above the anaerobic threshold) exercise levels (3). Training respiratory patients at 60–75% of maximal work rate results in substantial increases in maximal exercise capacity, with reduction in ventilation and lactate levels at a given work rate. Most rehabilitation programmes include endurance training with periods of sustained exercise for about 20–30 min two–five times a

week. In patients who cannot tolerate high-intensity exercise, interval training consisting of 2–3 min of high-intensity training alternating with equal periods of rest, is considered an alternative.

Because of the association between respiratory muscle dysfunction and dyspnoea, inspiratory muscle training (IMT) has been proposed as a tool to reduce the symptom. A meta-analysis (85) found inconsistent results in COPD patients and further studies are needed to state the real effectiveness of this technique, especially in COPD patients (2,4).

Although in COPD patients with long-term hypoxaemia peripheral muscle function has been shown to deteriorate, the effects of supplemental oxygen during rehabilitation are still debated. In a controlled study, pulmonary rehabilitation improved exercise performance and QOL in COPD patients with hypoxaemia at peak exercise, irrespective of whether breathed air or supplemental oxygen during the training (86).

Although the exact underlying physiopathological mechanism is still unclear, there is laboratory evidence that continuous positive airway pressure (CPAP) and different modalities of mechanical ventilation may reduce breathlessness and increase exercise tolerance in these patients, allowing them to reach a higher exercise intensity. Respiratory muscle unloading and reduction in intrinsic Positive end-expiratory pressure (PEEP) have been considered among mechanisms underlying these effects in COPD patients. Nevertheless the role of mechanical ventilation during rehabilitation (if any) is still to be defined (87). Recently, Garrod *et al.* (88) randomized severe COPD patients to receive non-invasive ventilation plus exercise training or exercise training alone and found that a significant greater improvement in exercise tolerance and health-related quality of life in the non-invasive ventilation group compared with those undergoing training alone. They concluded that domiciliary ventilatory support can be used successfully to augment the benefits of rehabilitation in severe COPD.

Dyspnoea is relieved after lung volume reduction surgery (84,89), probably as a consequence of the reduction in the operational lung volumes and related better efficiency of respiratory muscles. Nevertheless this concept has been recently questioned (90), therefore further studies are needed in this field.

In conclusion, dyspnoea should be related to pathophysiology rather than specific disease (4). Cumulative benefit of interventions targeting pathophysiologic mechanism of dyspnoea must be searched to treat patients with shortness of breath.

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