Is there any treatment other than drugs to alleviate dyspnea in COPD patients?

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Abstract: Patients with chronic obstructive pulmonary disease (COPD) are often limited in their activities by breathlessness. In these patients, exercise training may result in significant improvements in dyspnea, exercise tolerance, and health related quality of life (HRQoL). Further possibilities are to reduce ventilatory demand by decreasing the central respiratory drive or to lessen the perceived breathing effort by increasing respiratory muscle strength through specific respiratory muscle training. Upper limb training may also improve exercise capacity and symptoms in these patients through the modulation of dynamic hyperinflation. Ventilatory assistance during exercise reduces dyspnea and work of breathing and enhances exercise tolerance, although further studies should be required to define their applicability in the routine pulmonary rehabilitation programs. Lung volume resection surgery and lung transplantation in selected patients may control symptoms and improve HRQoL.

Keywords: chronic obstructive pulmonary disease, dyspnea, nonpharmacologic treatment, pulmonary rehabilitation.

Introduction

Dyspnea is the most common symptom of patients suffering from chronic obstructive pulmonary disease (COPD). It progresses with the natural history of disease. Increased breathlessness leads patients with severe COPD to inactivity and related peripheral muscle deconditioning, resulting in a vicious cycle leading to further inactivity, social isolation, fear of dyspnoea, and depression. With increasing severity of disease, drugs may not be enough to alleviate dyspnea. In this review article we summarize the recent literature concerning the nonpharmacological treatment of dyspnea in patients with COPD.

A search of MEDLINE research since 1966 including the terms, "Dyspnea/diet therapy" [MeSH] OR " Dyspnea/rehabilitation" [MeSH] OR " Dyspnea/therapy" [MeSH] NOT " Dyspnea/drug therapy" [MeSH], shows 1157 articles. We focused only on the most significant original papers, reviews, and book chapters (in our view) and related references since 2000.

What does dyspnea mean?

It 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 behavioral responses" (ATS 1999).

Respiratory sensation

Like pain, the subjective perception of dyspnea is an unpleasant physiologic sensation; it is a signal to the conscious brain that there is a somehow disturbed physiologic state. There are many similarities between dyspnea and pain, namely subjective

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characteristics, afferent pathways and cortical areas involved (Mahler 2005). A common neural network underlying the perception of both sensations has been suggested (von Leupoldt and Dahme 2005). Chemo- and airways receptors, lung parenchyma, and respiratory muscle receptors provide sensory feedback via vagal, phrenic, and intercostals nerves to the spinal cord, medulla, and higher centers of the central nervous system (ATS 1999). According to the neuromechanical dissociation theory a patient suffers from dyspnea when there is a disparity between the central reflexic drive to breathe and the appropriate mechanical response of the respiratory system. The qualitative perception of dyspnea is contributed also by the complex central processing of the afferent feedback from peripheral sensory receptors. The inability of COPD patients to expand rib cage appropriately in response to the increased central drive to breathe contributes importantly to the intensity and quality of dyspnea which correlate with the degree of lung hyperinflation. Indeed the descriptors chosen by patients invariably refer to inspiratory difficulty and unsatisfied inspiration (O'Donnell and Webb 1993; O'Donnell et al 1997; Voduc et al 2005). The results of neuroimaging studies have shown that distinct neural networks subserve the respiratory discomfort related to loaded breathing: the first is involved in the concomitant processing of the genesis and perception of respiratory discomfort, the second in the modulation of perceived intensity of the sensation by various factors, including emotional processing (Peiffer et al 2001).

Pathophysiological factors of dyspnea in COPD

Different pathophysiological factors either singly or in combination contribute to exertional dyspnea in COPD patients: increased intrinsic mechanical loading of inspiratory muscles, ie, the intrinsic positive end-expiratory pressure (PEEPi), dynamic airways compression, greater mechanical restriction of the thorax, inspiratory muscle weakness, increased ventilatory demand relative to capacity, gas exchange abnormalities, cardiovascular factors (Scano and Ambrosino 2002). In COPD, the intensity and quality of dyspnea during activity correlate with the magnitude of lung hyperinflation which, in turn, results in severe neuromechanical dissociation (Parker et al 2005).

Psychological aspects

Breathlessness is characterized by measurable intensity and qualitative dimensions, which may vary depending on the individual, the underlying disease, and other circumstances (Scano and Ambrosino 2002). It is strongly related to the Health Related Quality of Life (HRQoL) in COPD patients, and the associated emotional responses contribute greatly to the resulting morbidity (Gonzalez et al 2005). Depressive symptoms are common in elderly patients, especially in those who are most disabled (Yohannes et al 1998). Some data suggest a possible benefit on HRQoL from antidepressant drugs when depressive symptoms are present (Lacasse et al 2004). Episodes of dyspnea are often anticipated by and/or associated with fear and anxiety. This increased physiological arousal can precipitate or exacerbate dyspnea and contribute to overall disability (Singer et al 2001; Dowson et al 2004).

Many of the currently available therapeutic interventions relieve dyspnea by addressing a combination of different mechanisms, namely: 1. reduction of ventilatory demand, 2. reduction of ventilatory impedance, 3. improvement in ventilatory muscle function (Ambrosino and Scano 2001, 2004).

Exercise training

Reducing the metabolic load may result in reduced ventilatory demand and therefore in dyspnea. Mild to severe COPD patients of any age may obtain improvement in dyspnea, exercise tolerance, and HRQoL as a result of exercise training programs (Casaburi et al 1991; Baltzan et al 2004; Nici et al 2006). The symptom improvement is multifactorial and not fully understood. Exercise training results in enhanced oxidative capacity and higher capillary density in the trained muscles (Casaburi et al 1997; Maltais et al 1997). A slower deeper breathing pattern develops by lowering respiratory rate and increasing tidal volume (Casaburi 1995). These changes may result in a reduction of the end-expiratory lung volume, an improvement in dead space to tidal volume ratio, a lower ventilatory requirement for exercise, and a reduction in dynamic hyperinflation (Casaburi et al 1991; Gigliotti et al 2003).

The greater physiological training response and exercise tolerance can be achieved with high intensity training programmes (above 80% of maximal work rate), rather than with low intensity ones (below 50% of maximal work rate), but no further gains in HRQoL are associated with these additional physiological results (Puente-Maestu et al 2000). An "intermittent" training modality may be better tolerated and allows greater amount of work performed in COPD subjects with more limited lung function (Sabapathy et al 2004).

Strength training promotes muscle growth and strength, and may induce less dyspnea than aerobic exercise in COPD patients. The combination of strength and aerobic training seems to be a more physiologically complete approach (Saey and Maltais 2005) although additional improvement in exercise capacity and HRQoL are not clearly proven when strength training is added to an aerobic training program.

Exercise training or at least stimulation to active life should be offered to all symptomatic COPD patients (Nici et al 2006).

Electrical stimulation

Neuromuscular electrical low-voltage stimulation (NMES) has been shown to induce an increase in the muscular oxidative capacities. Small controlled studies of this technique in severe COPD patients have been reported (Neder et al 2002; Bourjeily-Habr et al 2002; Zanotti et al 2003; Ambrosino and Strambi 2004; Vivodzev et al 2006).

Not enough studies have been performed in order to include NMES among the routine nonpharmacological treatment of COPD patients.

Upper limb training

COPD patients often complain dyspnea for daily activities requiring arm exercise, mostly related to the dynamic hyperinflation. There is a relationship between upper limb muscle strength and dyspnea (Dourado et al 2006). Some data suggest an adjunctive effect of arm training in improving exercise capacity and symptoms in stable COPD patients and in patients recently weaned from mechanical ventilation (Holland et al 2004; Gigliotti et al 2005; Porta et al 2005).

This is a promising tool especially in most severely disabled patients.

Respiratory muscle training

Most COPD patients have inspiratory and expiratory muscle weakness. The improvement in inspiratory muscle performance obtained by specific controlled training is associated with an improvement in the sensation of dyspnea, exercise tolerance, and HRQoL. When the expiratory muscles are specifically trained, a significant increase in exercise performance has also been shown, but it does not appear to be supplementary to the effect of inspiratory muscle training. Although its clinical long-term effectiveness in COPD patients must be confirmed, evidence is growing that specific inspiratory muscle training is an important addition to pulmonary rehabilitation programs whereas the role of expiratory muscle training remains still unclear (Gosselink 2005; Weiner and McConnell 2005; Hill et al 2006; Nici et al 2006).

This is still a controversial topic. Further studies are needed.

Breathing maneuvers

Different techniques are included under this term such as pursed-lips breathing and diaphragmatic breathing.

Pursed-lips breathing

Pursed-lips breathing (PLB) is a technique attempting to prolong active expiration through constricted lips. This maneuver is routinely taught as a breathing retraining exercise as it is often spontaneously adopted by COPD patients to alleviate dyspnea. Compared with spontaneous breathing, PLB reduces respiratory rate, dyspnea and arterial carbon dioxide tension, and improves tidal volume and arterial oxygenation at rest (Bianchi et al 2004). Not all patients obtain dyspnea relief by PLB when performed volitionally during exercise (Gosselink 2005; Spahija et al 2005). When PLB is done by patients who do not naturally adopt this technique, a reduction in exercise respiratory rate and recovery time is observed, and better results are found in patients with higher resting breathlessness (Garrod et al 2005).

This is a very simple and useful maneuver spontaneously adopted by patients and probably needs no instruction.

Diaphragmatic breathing

Diaphragmatic breathing is an old technique aimed to learn to move the abdominal wall predominantly during inspiration and to reduce upper rib cage motion. On an "experience basis" this technique has for a long time been suggested to be effective in reducing dyspnea in COPD patients although no controlled randomized trials have confirmed this. Furthermore, this modality has been recently found to be accompanied by increased asynchronous and paradoxical breathing movements, increased work of breathing with related worsening in dyspnea (Vitacca et al 1998).

We would not teach such controversial maneuvers to COPD patients.

Oxygen supplementation

A way to reduce metabolic load is oxygen supplementation. Arterial hypoxia has a complex effect in resting and exercise dyspnea. Critical hypoxia (<60mm Hg) (Voduc et al 2005) can stimulate peripheral chemoreceptors whose afferent

activity may reach consciousness. The hypoxemic ventilatory stimulation however may contribute to breathing discomfort by increasing the central motor output and the respiratory muscle activation (Palange et al 2005). Peripheral muscle hypoxia may alter sensory afferent activity during exercise and respiratory muscle fatigue may induce an increase in the motor activation.

Supplemental oxygen during exercise reduces exertional breathlessness and improves exercise tolerance of the hypoxemic COPD patient by different mechanisms: reduction of hypoxic stimulation of the carotid bodies, pulmonary vasodilation, and increase in arterial oxygen. The latter two mechanisms may potentially reduce carotid body stimulation at heavy levels of exercise by increasing oxygen delivery to the exercising muscles and reducing carotid body stimulation by lactic acidemia (Somfay et al 2002). Recent studies indicate that oxygen administration during maximal exercise can reduce the degree of dynamic hyperinflation, and lower the degree of post-exertional dyspnea (O'Donnell et al 2001; Stevenson and Calverley 2004). Supplemental oxygen generally increases exercise tolerance in patients with only mild to moderate hypoxemia (Fujimoto et al 2002).

Early studies (McDonald et al 1995; Rooyackers et al 1997; Fichter et al 1999; Garrod, Paul, et al 2000; Wadell et al 2001) failed to demonstrate benefits of supplemental oxygen during rehabilitation. Mild hypoxemia accelerates peripheral muscle adaptation (Terrados et al 1990) so that the use of supplemental oxygen during training of mildly hypoxemic patients may not be advantageous. At difference with those studies a recent double blind study (Emtner et al 2003) of nonhypoxemic patients with severe COPD showed that patients trained with oxygen supplementation increased training intensity and endurance more rapidly than patients trained without. More recently it has been shown that by combining the benefits of bronchodilators (reduced hyperinflation) and O_2 (reduced ventilatory drive), there are additive effects on exercise endurance in patients with normoxic COPD (Peters et al 2006).

Oxygen supplementation is a clear example of difference between physiological concepts and practical application. Further clinical, ranzomized, controlled studies are needed.

Air-Heliox mixtures

Heliox breathing can improve high-intensity exercise endurance capacity in moderate-severe COPD by reducing airflow limitation, dynamic hyperinflation, and dyspnea sensation (Palange et al 2004, 2005; Laude et al 2006).

Assisted ventilation

Several studies have examined the acute effects of different modalities of ventilatory assistance during exercise on dyspnea and exercise tolerance in advanced COPD (Ambrosino and Strambi 2004). Assisted ventilation, either delivered through nasal or facial mask during exercise, reduces dyspnea and work of breathing and enhance exercise tolerance in COPD patients (van't Hul et al 2002). The commonly accepted explanation of these effects is that continuous positive airway pressure counterbalances the PEEPi and the related inspiratory threshold load; whereas inspiratory pressure support (IPS) provides symptomatic benefit by unloading and assisting the overburdened ventilatory muscles, reducing fatigue and allowing greater training workload (Petrof et al 1990; Hawkins et al 2002). Two similar studies of well structured programs of exercise training with proportional assist ventilation have given conflicting results (Bianchi et al 2002; Hawkins et al 2002). Nevertheless, the role of assisted ventilation in pulmonary rehabilitation is still controversial. The additional benefit of assisted ventilation on exercise tolerance, dyspnoea, and health status was not clearly demonstrated when compared with training alone. More recently, a randomized controlled study evaluated the effects of training with IPS ventilation comparing two levels of IPS: 10cmH_2O and 5cmH_2O; no information about the use of an external positive end-expiratory pressure (PEEP) was provided. Significantly larger improvements in exercise performance resulted with the higher level of IPS, whereas no differences on health status were observed (van't Hul et al 2006).

Larger prospective controlled studies should be required to determine if assisted ventilation may eventually have a routine applicability, and in which subgroups of patients (Ambrosino 2006).

An improvement in dyspnea and HRQoL was shown as result of domiciliary noninvasive positive pressure ventilation added to long term oxygen (Clini et al 2002). Home nocturnal noninvasive ventilation added to daytime exercise training has been found to significantly increase exercise capacity and quality of life compared with exercise training alone (Garrod, Mikelsons, et al 2000).

Psychological support

The encouraging psychological effect of controlled exercise training can also contribute to increase exercise tolerance at higher levels of breathing discomfort and overcome the patient's fear of dyspnea (Voduc et al 2005).

Developing an adequate support system is a most important component of pulmonary rehabilitation (Guell et al 2006). Patients with chronic respiratory disease will benefit from supportive counseling to address their concerns, either individually or in a group format (Nici et al 2006). Treating depression may make a significant difference in the patient's quality of life. However, while moderate levels of anxiety or depression may be addressed in the pulmonary rehabilitation program, patients identified as having significant psychosocial disturbances should be referred to an appropriate mental health practitioner prior to the start of the program (Emery 1993; Kim et al 2000; Nici et al 2006).

Surgical treatment

Lung volume reduction surgery (LVRS) has become more widely accepted in selected patients with severe symptomatic emphysema. Bilateral LVRS procedures appear to result in greater short-term improvement than unilateral LVRS, whereas physiological benefits appear similar with video-assisted thoracoscopy or median sternotomy techniques (Make 2005).

Several studies comparing the effects of pulmonary rehabilitation with those of LVRS found a greater improvement in physiological parameters, exercise, and HRQoL in patients receiving LVRS compared with patients who continued pulmonary rehabilitation; the effects were showed stable for 6 months to 1 year.

The underlying lung disease, co-morbidities, and associated physiological abnormalities often impact the outcome of LVRS. Many of these factors may be modified by standard medical care and by comprehensive pulmonary rehabilitation programs. Patients with upper-lobe predominant emphysema and a low post-rehabilitation exercise tolerance exhibited a decreased risk of mortality after LVRS.

Patients with upper lobe predominant emphysema and a high post-rehabilitation exercise capacity or patients with nonupper lobe predominant emphysema and a low post-rehabilitation exercise capacity do not have a survival advantage or disadvantage, whereas those with upper lobe predominant emphysema treated surgically are more likely to improve their exercise capacity after surgery.

Higher mortality with LVRS than with medical management was found: 1. in patients with severely impaired lung function (post-bronchodilator forced expiratory volume in 1 second [FEV_1] ≤20% predicted and diffusing capacity for carbon monoxide (DLCO) ≤20% predicted) or homogeneous emphysema; 2. in patients with nonupper lobe predominant emphysema and a high post-rehabilitation exercise capacity. In severe emphysema, LVRS improved health status in survivors but was associated with higher mortality risk (Martinez and Chang 2005).

Lung transplantation is an option for a more limited number of patients. A COPD patient can be considered an appropriate candidate for transplantation when the FEV_1 is below 25% predicted and/or the pressure of carbon dioxide ($PaCO_2$) is ≥ 55mm Hg.

Pulmonary function generally improves after lung transplantation, but exercise capacity remains below predicted values, primarily due to a peripheral muscle myopathy. Pulmonary rehabilitation programs can improve the exercise tolerance and HRQoL, in both short and long term after lung transplantation (Gay and Martinez 2005).

Long-term results of lung transplantation are limited by significant complications that impair survival; an approximately 80% 1-year, 50% 5-year, and 35% 10-year survival has been reported. Bronchiolitis obliterans is the most important long-term complication of lung transplantation resulting in decreased pulmonary function (Hillerdal et al 2005; Martinez and Chang 2005; Miller et al 2005).

Conclusion

Although drug therapy remains the main corner of comprehensive treatment of dyspnoea in COPD patients, there are also several nonpharmacological approaches. Exercise training programs represent the best cost-effective modalities to add to pharmacological treatment of COPD. Other interventions like education, nutrition, psychological counseling should be used as adjuncts to well-designed comprehensive respiratory rehabilitation programs and tailored to the specific patient (Nici et al 2006). Surgical option should be confined to most disabled and/or end-stage patients.

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