ERJ Review series: Novelties in rehabilitation of COPD patients

Title: Strategies of muscle training in very severe COPD patients

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Keywords
1. Chronic Obstructive Pulmonary Disease
2. Exercise capacity
3. Dyspnea
4. Peripheral muscle weakness
5. Interval exercise

Word count: 2500
Abstract

There is strong evidence that exercise training, constituting the cornerstone of pulmonary rehabilitation, improves patients’ exercise tolerance, dyspnoea sensations, functional capacity and quality of life in patients with severe COPD. However, intolerable sensations of breathlessness and/or peripheral muscle discomfort may prevent such patients to tolerate high intensity exercise levels for sufficiently long periods of time to obtain true physiological training effects. Accordingly, the major issue that arises is the selection of the appropriate training strategy that is tailored to the cardiovascular, pulmonary and peripheral muscle limitations of the individual patient and is aimed at maximizing the effect of exercise conditioning. Within this context the present review article explores the application of strategies that optimize exercise tolerance by reducing dyspnea sensations, namely non-invasive mechanical ventilation, oxygen and/or heliox supplementation. Administration of heliox or oxygen during exercise also increases peripheral muscle oxygen delivery, thereby delaying the onset of peripheral muscle fatigue. Particular emphasis is also given to interval exercise and resistance muscle training as both modalities allow the application of intense loads on peripheral muscles with tolerable levels of dyspnea sensations. In patients with profound muscle weakness and intense breathlessness upon physical exertion, execution of short bouts of interval or local muscle strength conditioning, along with oxygen breathing, may constitute a feasible and effective approach at the pulmonary rehabilitation setting.
Introduction

Breathlessness and peripheral muscle discomfort are the most common symptoms limiting exercise tolerance in patients with severe COPD. Exercise training constitutes the cornerstone of pulmonary rehabilitation as there is strong evidence that its implementation improves both exercise tolerance and health-related quality of life in these patients [1]. The intensity of exercise is a key variable to allow true physiological training effects and as such it is necessary to be as high as possible in order to optimize the outcome [2]. Nevertheless, in patients with severe COPD intolerable sensations of breathlessness and/or peripheral muscle discomfort may prevent high intensity levels to be tolerated for sufficiently long periods of time to yield true physiological training effects [3]. Along these lines it is important to implement different strategies to optimize exercise tolerance in severe COPD with the objective of enhancing the patient’s ability to tolerate as prolong and intense workloads as possible. These strategies aim at reducing intensity of dyspnea sensations, either by allowing patients to sustain a higher absolute exercise training intensity or prolong the cumulative time a given exercise task can ordinary be sustained. Such strategies refer to the non-invasive mechanical ventilation, to oxygen and/or heliox supplementation and to interval cycling modality. In addition, progressive resistance muscle training will be discussed with the scope of reducing leg muscle discomfort.

Non-invasive mechanical ventilation (NIPV)

Non-invasive positive pressure mechanical ventilation has been shown to reduce the load on the respiratory muscles and the intensity of dyspnea, thereby increasing exercise intensity and endurance capacity [4, 5]. In particular, in patients with severe COPD application of proportional assist ventilation (PAV), has been shown to allow a greater
intensity of exercise to be sustained for longer periods of time than sham exercise, thus potentially yielding significant training physiological effects [6]. PAV is a mode of partial ventilatory assistance endowed with characteristics of proportionality and adaptability to the intensity and timing of spontaneous ventilatory pattern by providing inspiratory flow and pressure in proportion to the patient’s effort [4]. To the extent that intrinsic mechanical loading and functional inspiratory muscle weakness in severe COPD contribute to intense dyspnea sensations, PAV provides a symptomatic benefit by unloading and assisting such overburdened ventilatory muscles, thereby reducing the work of breathing and thus dyspnea sensations [7].

In addition, continuous positive airway pressure (CPAP) has been documented to reduce the inspiratory threshold load on the inspiratory muscles of dynamically hyperinflated COPD patients and also to enhance neuromuscular coupling, thus improving dyspnea sensations and exercise tolerance [8]. The commonly accepted explanation of the effects of CPAP is that it counterbalances intrinsic positive end-expiratory pressure, i.e. the inspiratory threshold load [8]. In two studies conducted by O’Donnell and colleagues [8] in severe patients with COPD, application of CPAP of 4–5 cmH2O during steady-state sub-maximal exercise resulted in a significant increase in exercise endurance time and a highly significant reduction in the sense of breathing effort.

Moreover, pressure support ventilation (PSV) is a pressure-targeted mode in which each breath is patient triggered and supported and can effectively assist ventilation when applied noninvasively to patients with acute and chronic respiratory failure [4]. Application of PSV has shown to yield consistent improvements in endurance capacity as this has been assessed by walking distance [9] and by reductions in the intensity of dyspnea during constant-load cycling [10].
Dolmage and Goldstain [11] investigated which of the two methods, PAV, CPAP or their combination, when applied during constant-load exercise at 60–70% of maximum power was more effective in enabling very severe COPD patients to increase exercise tolerance. Although, exercise tolerance with PAV (7.1 min) or CPAP (8.2 min) alone was not significantly prolonged as compared to sham exercise (6.6 min), their combination significantly increased exercise tolerance (12.9 min). Bianchi et al. [12] investigated the impact of PAV, CPAP or PSV on exercise tolerance and breathlessness in severe stable chronically hypercapnic COPD patients during constant-load cycling at 80% of maximal capacity. In comparison with sham ventilation, PAV, PSV and CPAP were able to increase endurance time (from 7.2 to 12.0, 10.0 and 9.6 min, respectively) and reduce dyspnea sensations. However, the greatest improvement was observed with PAV.

Intending to give more insight into the pathophysiological mechanisms of improvement in exercise tolerance by using non-invasive mechanical ventilation in COPD, a more recent study [13] implemented respiratory muscle unloading via PAV during high-intensity exercise (70-80% peak) and demonstrated improved peripheral muscle oxygenation assessed by near-infrared spectroscopy despite unaltered systemic oxygen delivery in patients with advanced COPD. These findings are indicative that a fraction of the available cardiac output might be redirected from ventilatory to locomotor muscles due to respiratory muscle unloading, thereby enhancing peripheral muscle oxygen delivery and thus exercise tolerance.

**Oxygen/heliox supplementation**

Supplemental oxygen has the potential to increase exercise tolerance of the hypoxemic COPD patients by means of increase in arterial oxygen content and vasodilation of the pulmonary circulation [14]. These two mechanisms increase oxygen delivery to the exercising muscles and may potentially reduce carotid body stimulation at heavy levels of exercise with
or without lactic acidosis [15]. Ambulatory oxygen therapy has widely been shown to increase exercise performance and to relieve exercise breathlessness in severe COPD patient [16, 17]. Studies indicate that reduction in the rate of exercise-induced dynamic hyperinflation plays an important role in the oxygen-related relief of dyspnea [16, 17]. In addition, improvement in exercise performance via oxygen supplementation was primarily related to the reduced ventilatory demand, which, in turn, led to improved operational lung volumes and delayed attainment of limiting ventilatory constraints on exercise and the onset of intolerable dyspnea. Interestingly, supplemental oxygen generally increases exercise tolerance not only in hypoxemic but also in non-hypoxemic patients [16]. In fact, modest changes in sub-maximal ventilation and dynamic ventilatory mechanics have been documented to result in relatively large improvements in symptom intensity and exercise capacity [16]. Besides improvements in respiratory function, oxygen supplementation has been documented to increase leg muscle oxygen delivery and oxygen uptake, thereby justifying the ability of the peripheral muscle to perform more work [18].

In patients with severe COPD supplementation of normoxic heliox decreases turbulence within medium to large airways, increases expiratory flow rate, reduces the work of breathing, as well as the degree of exercise-induced dynamic hyperinflation and the intensity of dyspnea, thereby enhancing exercise tolerance. However, there is emerging evidence [19] indicating that enhanced exercise tolerance by heliox is also due to an increase in locomotor muscle oxygen delivery during constant-work rate sub-maximal exercise. Enhanced oxygen delivery to peripheral muscles following administration of heliox during exercise in severe COPD may occur via a number of mechanisms, namely: 1) improved cardiac output secondary to reduced intra-thoracic pressures and/or pleural pressure swings; 2) improved arterial oxygen content; and 3) blood flow redistribution from respiratory to peripheral muscles secondary to reduction in the mechanical load of the respiratory muscles
A recent study in patients with severe COPD confirmed that heliox administration during constant-load exercise (at 75% of peak capacity) reduces total respiratory muscle power by unloading both inspiratory and expiratory muscles as well as it improves central hemodynamic responses (increase in stroke volume) and arterial oxygen content. These findings confirmed those of a previous study showing faster cardio-dynamic responses following heliox administration but disputed suggestions that the increase in locomotor muscle oxygen delivery as inferred by deoxy-hemoglobin kinetics determined by near-infrared spectroscopy (an index of tissue oxygen extraction) was indicative of blood flow redistribution from the respiratory to locomotor muscles as heliox administration during exercise improved blood flow and oxygen delivery to both respiratory and locomotor muscles. In addition, reductions in the degree of exercise-induced dynamic hyperinflation with heliox administration have been shown to be associated with improvements in several indices of cardio-circulatory function.

*Interval exercise*

Intensity and duration of exercise are important determinants of the physiologic adaptations that occur in response to training. In patients with COPD there are indications that greater physiological benefits can be obtained through high-intensity compared to moderate intensity exercise training. However, high-intensity exercise training may not be applicable to those COPD patients who are unable to sustain such intensities for long periods of time due to symptom limitation. In fact, patients with severe COPD are so limited by dyspnea and/or locomotor muscle weakness that their ability to exercise is restricted to very low intensity levels.

In addition, consequently to reduced peripheral muscle oxygen delivery and muscle fibre dysfunction, premature occurrence of lactic acidosis puts particular stress on the
ventilatory system in COPD. Hence, the small increase in arterial lactate concentration observed during interval exercise as compared to continuous exercise [22-24] appears to be beneficial to COPD patients by reducing some of the acid stimulus to breathe [2], thereby allowing ventilation and dyspnea sensations to be tolerated for a prolonged period of time. Vogiatzis and co-workers [23] have shown that patients with severe COPD can almost triple the total exercise duration with significantly lower and more stable metabolic and ventilatory responses compared to continuous exercise. Although patients exercised for longer time (~30 min) at a higher intensity (100 % of peak exercise capacity) with the interval mode, they had lower metabolic demands and less ventilatory restrictions at the end of symptom-limited exercise [23] (Figure 1).

Conversely, exercising continuously without any rest periods, severe COPD patients can tolerate high work rates (50-80% of their maximum exercise capacity) for only 5 to 12 minutes, at the end of which they are completely exhausted [24]. At intensities of 65% to 85% of peak exercise capacity, COPD patients can sustain only 4 to 5 minutes of exercise [24] and only up to 13 minutes for lower intensities (50-60% of peak exercise capacity) [24]. As such, implementing continuous exercise training for patients with severe COPD will be ineffective as they will have to interrupt exercise in order to rest for several minutes before they start exercising again. In contrast, interval training can enable patients to complete short periods of high-intensity exercise that would not be possible with a continuous exercise mode. When patients exercise for short periods (eg, 30 seconds), alternated with short rest intervals lasting for 30 seconds, they complete the total work with moderate exertion and relatively stable metabolic and ventilatory response [22, 23] (Figure 1). Indeed, patients with severe COPD can endure high-intensity interval training in a rehabilitation setting for long periods of time with lower symptoms of dyspnea and leg discomfort compared to the conventionally implemented continuous training [25-27]. A recent study [28] showed that interval exercise
training allows severe COPD patients (GOLD stage IV) to exercise at a sufficiently high intensity to obtain true physiological training effects manifested by improvements in muscle fiber size, typology and capillarization.

**Progressive resistance muscle training**

Patients with severe COPD are often exposed to risk of profound peripheral muscle de-conditioning as a result of disease severity and progression. Intense leg discomfort sensations often deter COPD patients from participating on daily activities that require body mobility and strength. Since skeletal muscle weakness has a negative impact on exercise tolerance in the majority of patients with severe COPD, an intervention of resistance exercise during pulmonary rehabilitation is deemed essential [1]. Accordingly, rehabilitation experts often prescribe resistance muscle training programs as clinical outcomes are definitely promising for the severe COPD patient [29].

In a recent systematic review of eighteen controlled trials, including mainly patients with severe COPD, significant effects for increases in muscle strength after short-term progressive resistance exercise were demonstrated [30]. The key features of progressive resistance exercise protocols used in these trials included an average of 12 weeks of training with training session taking place two to three times per week. A median of five resistance exercises for the muscles of the arm, leg and trunk were performed during each exercise session. The majority of training sessions comprised two to four sets of 8 to 12 repetitions for each exercising muscle group, at intensities progressing from ~30% to ~90% of 1 repetition maximum.

Evaluating the effectiveness of progressive resistance exercise in nine trials [30], the adaptations after concluding the training program were important for increasing arm and leg muscle strength in severe COPD patients. More specifically, a meta-analysis was conducted
and showed an increase in maximum knee extensor muscle strength of 25% after progressive exercise training compared to no intervention or aerobic training that presented an increase of only 10% in the knee extensor muscle strength. However, progressive resistance exercise did not show significant improvements in maximal exercise capacity or respiratory function [30]. Body composition was examined in two trials and showed an increase in total lean mass and a reduction in total fat percentage after 12 weeks of progressive resistance exercise [31, 32].

Accordingly, short-term progressive resistance muscle training can be beneficial for severe COPD patients in terms of enhancing muscle strength and increase the performance of some daily activities. Progressive resistance exercise can develop arm and leg muscle strength and increase performance of tasks such as stair climbing and rising from sitting [30]. However, the effects of progressive resistance exercise on measures of body composition, psychological function, and societal participation still remain inconclusive.

**Conclusion**

Exercise training should be tailored to address the individual patient’s limiting factors (central cardiorespiratory and/or peripheral muscle) to exercise. In patients with intense dyspnea symptoms, interval exercise is more appropriate than continuous exercise. Resistance exercise should be complementary to interval exercise so as to improve the strength of both the upper and the lower body muscles. In patients with profound muscle weakness interval and resistance exercise should constitute a training priority. Future research is required and it should scrutiny the longer term outcomes and optimal methods for maintaining the rehabilitative-induced physiological adaptations in patients with severe COPD.
REFERENCES


Figure 1: Metabolic and respiratory responses during interval versus continuous exercise in COPD

Oxygen uptake (\(\dot{V}O_2\)) and minute ventilation (\(V_E\)) in a patient with severe COPD (\(FEV_1\): 0.85 L) during interval (○ open circles) and constant-load (● closed circles) exercise protocols. Interval exercise was sustained for 30 sec at 100% of peak baseline capacity alternated by 30 sec rest, whereas continuous exercise was sustained at 75% of peak baseline capacity. With permission from Kortianou et al 2010 (24).