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EXERCISE PRESCRIPTION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation. Apart from the ventilatory limitations, patients with COPD present an impaired exercise capacity that limits their ability to perform the activities of daily living and impacts negatively on their quality of life. Limb muscle dysfunction is a systemic consequence of COPD associated with exercise intolerance, poor quality of life and increased mortality. This COPD-related syndrome is characterized by reduced muscle cross-sectional area, strength and endurance, and is highly prevalent among COPD patients. Thus, pulmonary rehabilitation (PR) is recommended in order to combat the negative consequences of COPD on patients' exercise capacity and quality of life. Exercise training is regarded as the cornerstone of PR and can be implemented at any stage of the disease. To date, the combination of resistance and endurance training (i.e. concurrent training) has demonstrated to be the most beneficial exercise intervention in COPD. Concurrent training provides clinically and statistically significant benefits in exercise tolerance and quality of life to patients with COPD. In addition, there are other potential adjuncts to exercise training and strategies to enhance the implementation of PR programs in COPD patients.
Keywords: resistance training, strength training, endurance training, lung disease, exercise tolerance, quality of life, limb muscle dysfunction, chronic disease

PRESCRIPCIÓN DE EJERCICIO FÍSICO EN PACIENTES CON ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA

RESUMEN

La enfermedad pulmonar obstructiva crónica (EPOC) se caracteriza por la persistencia de síntomas respiratorios y limitación al flujo de aire. Además de las limitaciones ventilatorias, los pacientes con EPOC presentan una reducida capacidad para realizar ejercicio que limita su habilidad para realizar actividades de la vida diaria e impacta negativamente sobre su calidad de vida. La disfunción muscular de las extremidades es un síntoma sistémico consecuencia de la EPOC y está asociada con la intolerancia al ejercicio, la reducción de la calidad de vida y el aumento de la mortalidad. Este síndrome relacionado con la EPOC se caracteriza por la reducción del área de sección transversal del músculo esquelético, la fuerza y la resistencia, y es altamente prevalente entre los pacientes con EPOC. Así, la rehabilitación pulmonar (RP) está recomendada para combatir las consecuencias negativas de la EPOC sobre la capacidad para realizar ejercicio y la calidad de vida de los pacientes. El entrenamiento con ejercicio es considerado una pieza clave de la RP y puede implementarse en cualquier estadio de la enfermedad. Hasta la fecha, la combinación de entrenamiento de resistencia y fuerza (entrenamiento concurrente) ha demostrado ser la intervención con ejercicio más beneficiosa para la EPOC. El entrenamiento concurrente proporciona beneficios clínica y estadísticamente significativos con respecto a la tolerancia al ejercicio y calidad de vida de los pacientes con EPOC. Además, existen otras terapias y estrategias que potencialmente pueden complementar al entrenamiento con ejercicio para la mejora de la implementación de los programas de RP en pacientes con EPOC.
Palabras clave: entrenamiento de fuerza, entrenamiento de resistencia, entrenamiento interválico, tolerancia al ejercicio, calidad de vida, disfunción muscular de las extremidades, enfermedad crónica

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality around the world (Vogelmeier et al., 2017), and affects about 10% of the adult population above 40 years of age (Buist et al., 2007). COPD is defined as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases" (Vogelmeier et al., 2017). This chronic, progressive, and not fully reversible lung disease consists in a mixture of small airways diseases (e.g. obstructive bronchiolitis) and parenchymal destruction (emphysema), with patients showing dyspnea, chronic cough and/or sputum production (Vogelmeier et al., 2017). Exercise capacity is also severely impaired among patients with COPD (Mercken et al., 2005; Rabinovich et al., 2001), limiting their ability to perform the activities of daily living and participate in social life. In addition, patients with COPD may experience exacerbations, which are episodes usually lasting 7-10 days associated with increased airway inflammation, mucus production and marked gas trapping that may require hospitalization, leading to increased dyspnea and functional decline (Maltais et al., 2014; Vogelmeier et al., 2017).

Therefore, it is recommended for patients diagnosed with COPD to be immediately treated for their symptoms in order to prevent or slow down the progression of the disease. The exertional dyspnea is usually multifactorial in origin, partly reflecting limb muscle dysfunction, the consequences of dynamic hyperinflation, increased respiratory load, or defective gas exchange (Debigare & Maltais, 2008). Thus, due to the complexity of COPD, its treatment must not be limited to the ventilatory limitations (i.e. chronic and progressive dyspnea) (Vogelmeier et al., 2017). There are other systemic consequences of COPD and associated comorbidities that have been reported to produce a further worsening in health-related quality of life (HRQoL) and increased mortality risk, which also need to be treated (Barnes & Celli, 2009; Sin, Anthonisen, Soriano, & Agusti, 2006). In this sense, exercise training has been demonstrated to be effective in the treatment of several of the most common comorbidities prevalent in patients with COPD (such as coronary heart disease, metabolic syndrome, osteoporosis or depression) (Pedersen & Saltin, 2015). In addition, exercise training is so far the most effective treatment for limb muscle dysfunction, a major systemic consequence of COPD (Maltais et al., 2014). Thus, our main goal was to provide the reader with the main evidence regarding the effects of exercise training on limb muscle dysfunction, exercise tolerance and HRQoL in patients with COPD, including the exercise parameters that should be prescribed in COPD patients in order to maximize the benefits derived from exercise training.

LIMB MUSCLE DYSFUNCTION IN COPD

Limb muscle dysfunction is a systemic consequence of COPD characterized by the presence of a decreased proportion of type I muscle fibers (Gosker, Zeegers, Wouters, & Schols, 2007) and oxidative capacity (Green et al., 2008), and reduced muscle cross-sectional area, strength and endurance (Couillard, Koechlin, Cristol, Varray, & Prefaut, 2002; Couillard et al., 2003). From the sixth decade of life, the annual decline in quadriceps strength increases in patients with COPD compared with the values usually observed in healthy older individuals (~ 4 vs 1.5%, respectively) (Hopkinson et al., 2007). On the contrary, the strength of the upper extremities seems to be better preserved than that of the lower extremities (Bernard et al., 1998).

Importantly, limb muscle dysfunction has been found to be strongly associated with poor HRQoL, greater use of health care resources, and increased mortality in COPD (Decramer, Gosselink, Troosters, Verschueren, & Evers, 1997; Maltais et al., 2014; Marquis et al., 2002; Swallow et al., 2007). Therefore, the understanding of the main causes leading to limb muscle dysfunction in COPD and the potential therapies for its treatment is currently an important research focus. A particular characteristic of limb muscle dysfunction in COPD is that, in contrast with normal aging, there is a shift in fiber type distribution from type I fibers to type II fibers (Gosker et al., 2007). Much debate exists around the question whether limb muscle dysfunction is the result of years of physical inactivity or whether factors related to COPD might be involved. In other words, the question is whether limb muscle dysfunction in COPD is due to disuse or disease. It is well-known that physical inactivity (and immobilization) produce muscle weakness and atrophy, and lead to a reduced number of type I fibers, impaired oxidative enzyme capacity and decreased capillary-to-fiber ratio (Booth & Gollnick, 1983; Larsson & Ansved, 1985). However, there is evidence supporting the notion that differences in muscle function and structure between patients with COPD and healthy counterparts remain even when they present similar levels of physical activity (Couillard & Prefaut, 2005; Gifford et al., 2018). Thus, although physical inactivity and aging are important contributors to limb muscle dysfunction in COPD, it is likely that this situation may be aggravated by a myopathy associated with COPD. In this line, oxidative stress has been reported to be a major contributor to this myopathy in COPD (Couillard & Prefaut, 2005). Oxidative damage is the result of the imbalance between the production of reactive oxygen and nitrogen species and the tissue antioxidant capacity. This process can alter the structure and function of membrane lipids, proteins and DNA, eventually leading to cell injury and death (Wedzicha & Seemungal, 2007). Patients with COPD show increased levels of oxidative stress under resting and exercising conditions (Couillard et al., 2002; Couillard et al., 2003; Puig-Vilanova et al., 2015), which are negatively associated with muscle mass, strength and exercise tolerance (Barreiro et al., 2009; Barreiro et al., 2008; Puig-Vilanova et al., 2015; van Helvoort et al., 2007; van Helvoort et al., 2006). In addition, other important contributors to limb muscle dysfunction are nutritional imbalance and the use of systemic corticosteroids (Maltais et al., 2014).

Apart from smoking cessation, pharmacological therapy (overall bronchodilators, oral steroids, phosphodiesterase-4 inhibitors, theophylline and antibiotics) is on the front line for the prevention and treatment of COPD. However, no existing medication has proved to reduce the long-term decline in lung function and exercise capacity, while they do present several side-effects, such as increase in cardiovascular events (Anthonisen, Connett, Enright, & Manfreda, 2002; Michele, Pinheiro, & Iyasu, 2010), diabetes (Suissa, Kezouh, & Ernst, 2010), osteoporosis (Loke, Cavallazzi, & Singh, 2011; Pauwels et al., 1999), nausea and weight loss (Chong, Leung, & Poole, 2017). Thus, COPD management requires additional evidence-based strategies able to counteract the negative consequences of this chronic and progressive disease.

PULMONARY REHABILITATION AND EXERCISE TRAINING IN COPD

Pulmonary rehabilitation (PR) is defined as “a comprehensive intervention based on a through patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors” (Spruit et al., 2013). PR can be implemented at any stage of the disease by an interdisciplinary team, including physicians and other health-related professionals (e.g. nurses, exercise physiologists, physiotherapists and nutritionists), with the main goals of minimizing symptom burden, improving exercise capacity and autonomy, increasing participation in everyday activities, and ultimately improving HRQoL (Spruit et al., 2013). Importantly, PR has demonstrated to improve HRQoL and exercise capacity in COPD patients (McCarthy et al., 2015; Puhan, Gimeno-Santos, Cates, & Troosters, 2016), even in those with mild COPD severity (Rugbjerg, Iepsen, Jorgensen, & Lange, 2015). Furthermore, the pooled results obtained from ten randomized controlled trials showed a significant reduction in hospital admissions derived from PR participation (Moore et al., 2016), which also occurred in those COPD patients who had recently suffered an exacerbation (Puhan et al., 2016). Preliminary meta-analytical evidence showed a positive effect of PR on mortality in patients with COPD (Puhan et al., 2011). However, in a recent update of the evidence, the effect of PR on mortality did not reach statistical significance, which the authors attributed to the great heterogeneity observed across studies in the parameters prescribed in PR programs (Puhan et al., 2016).

In this context, exercise training is regarded as the cornerstone of PR, and programs focusing mainly on exercise training have been found to achieve greater improvements in exercise capacity and HRQoL than those that do not integrate exercise training as a component (Kruis et al., 2014). The benefits and positive adaptations achieved by exercise training in COPD patients have been previously reviewed in the literature (De Brandt et al., 2016; De Brandt et al., 2018). The evidence on the benefits of PR in COPD is such that the Cochrane Airways editorial board made the unusual decision of closing the review on this topic (Lacasse, Cates, McCarthy, & Welsh, 2015; McCarthy et al., 2015). Instead, it has been stated that future research should focus on further factors that remain uncertain, such as to find the optimal exercise parameters to maximize the benefits of PR in COPD (McCarthy et al., 2015).

Exercise training programs encountered in the literature are usually based on guidelines from international organizations such as the American College of Sports Medicine (Ferguson, 2014), the American Thoracic Society/European Respiratory Society (Spruit et al., 2013), and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) (AACVPR, 2011). All these organizations coincide in establishing endurance and resistance training as the core components of exercise prescription in COPD (Garvey et al., 2016), with some variations regarding exercise type, volume, intensity, frequency and/or progression. The main particularity of exercise training in COPD is the necessity of monitoring peripheral capillary oxygen saturation (SpO2) during exercise, which should be > 88%; and in case of SpO2 being ≤ 88% while breathing room air, supplemental oxygen should be used to maintain SpO2 at > 88% (AACVPR, 2011; Ferguson, 2014). Apart from the latter, it has been stated that no differences exist in terms of training principles between patients with COPD and healthy individuals, meaning that "total training load must reflect the individual's specific requirements, it must exceed loads encountered during daily life to improve aerobic capacity and muscle strength, and must progress as improvement occurs" (Spruit et al., 2013).

Endurance training. Exercise capacity has been reported to be reduced by 50-70% in patients with COPD compared with healthy age-matched subjects (Bolton et al., 2007; Couillard et al., 2002; Mercken et al., 2005; Rabinovich et al., 2001; Rodriguez et al., 2012). In addition, peripheral muscle endurance is severely impaired in COPD patients, with the magnitude of this decrease being highly variable (32-77%) (Maltais et al., 2014). Endurance training has been observed to elicit both central (e.g. enhancement of cardiac output via an increased stroke volume) and peripheral (e.g. increase in oxidative capacity and capillary density) adaptations in people with COPD (Morris, Walsh, Adams, & Alision, 2016). These adaptations contribute to the improvement of maximal and submaximal exercise capacity, and to the reduction of the absolute and relative energy cost of activities of daily living. COPD patients have been reported to experience improvements in maximal exercise capacity ranging between 16-29% after participating in an 8-week endurance training program (Bolton et al., 2007; Mercken et al., 2005; Rabinovich et al., 2001; Rodriguez et al., 2012), with the benefits being potentially greater for longer training programs. Although there is strong evidence in support of the implementation of endurance training in patients with mild-to-severe COPD (Lacasse, Martin, Lasserson, & Goldstein, 2007; McCarthy et al., 2015; Paneroni, Simonelli, Vitacca, & Ambrosino, 2017; Salman, Mosier, Beasley, & Calkins, 2003), there is not consensus on the most appropriate endurance exercise parameters (e.g. type of exercise, duration, intensity and frequency) that should be prescribed in PR programs.

In general, endurance training programs included in PR for COPD are usually conducted during 10 weeks (range: 3-16 weeks), with 2-3 sessions per week (range: 2-5 sessions), performing exercise on a cycle-ergometer or treadmill during 30-40 min (range: 20-45 min) at an average intensity of 60% of the peak power output (PPO) (range: 50 – 100% of PPO) (Zainuldin, Mackey, & Alison, 2011). When interval training is prescribed, a 1:1 - 1:2 work-to-rest ratio is used, with the duration of the exercise bout ranging from 20 s to 4 min (Zainuldin et al., 2011). However, a dose-response relationship has been reported to be difficult to establish in some cases because of the insufficient data and the heterogeneity across studies. There is evidence that supports the premise that the type of exercise should be focused on the skeletal muscles involved in the main activities of daily living in order to achieve greater benefits in functional performance and HRQoL. Thus, walking and cycling have been reported as more adequate activities for COPD management than swimming or paddling (Garvey et al., 2016). Furthermore, walking is considered to be the best training modality if the goal is to increase walking endurance (Leung, Alison, McKeough, & Peters, 2010). Although to our knowledge there are no studies comparing the effect of different training frequencies on the benefits derived from PR in people with COPD, all the selected guidelines agree in recommending 3 to 5 sessions per week (Garvey et al., 2016). In this line, a recent meta-analysis on the dose-response relationship of endurance training in sedentary older adults concluded that 3-4 sessions per week achieved the greatest benefits for cardiovascular fitness (Huang et al., 2016). On the other hand, exercising between 20 and 60 min has been suggested to be an adequate duration for exercise sessions in order to achieve substantial benefits, which might be partitioned in shorter bouts to cope with such recommendation in individuals with moderate to severe COPD (Garvey et al., 2016). Much debate exists in terms of the optimal intensity at which endurance exercise should be performed. A meta-analysis concluded that, despite the fact that it is difficult to draw absolute conclusions, high-intensity endurance training programs might provide greater benefits in submaximal exercise capacity than moderate- or light-intensity endurance training programs (Zainuldin et al., 2011). This fact could be due to the greater ability of high-intensity endurance training programs to elicit aerobic and anaerobic adaptations in skeletal muscle metabolism (Casaburi et al., 1991). In addition, a moderate positive relationship between endurance exercise intensity and changes in PPO per hour of training (r = 0.68) has been reported, suggesting a dose-response relationship (Morris et al., 2016). Therefore, based on the studies collected in the previous meta-analysis, a threshold target of 70-80% of PPO may be necessary to elicit physiological improvements leading to increased exercise capacity, although lower intensities (≈ 30-40% PPO) could be enough to induce a reduction in symptoms, and an improvement in HRQoL and performance in activities of daily living (Zainuldin et al., 2011).

Regarding the type of endurance training, both continuous and interval training have been reported to be equally effective to improve exercise and functional capacity, dyspnea and HRQoL when the total amount of work is matched (Zainuldin et al., 2011). However, the implementation of interval exercise might present some practical advantages to reach the previous recommendations on exercise intensity and duration. Time to exhaustion has been observed to be reduced to 5 and 13 min in COPD patients when intensities are set at 60-80% and 85-95% of PPO, respectively (Kortianou, Nasis, Spetsioti, Daskalakis, & Vogiatzis, 2010). Thus, a study that underwent two types of symptom-limited exercise tests in advanced COPD patients (forced expiratory volume in one second (FEV1) ≈ 40%) observed that the interval exercise protocol (30 s at 100% PPO + 30 s of unloaded pedalling until exhaustion) allowed a significantly longer exercise time (32-35 min *vs* 9-12 min) with lower metabolic (lactate: 3.9 *vs* 5.8 mmol·L^{-1}) and ventilatory responses (33 vs 38 L·min^{-1}) than the continuous exercise protocol (80% of PPO until exhaustion) (Vogiatzis et al., 2004). In addition, the participants reported lower symptoms of dyspnea and leg fatigue during the interval compared with continuous exercise at isotime (Vogiatzis et al., 2004).

Therefore, it seems that to achieve the goals of performing 20-60 min of endurance exercise at > 70-80% of PPO per session, interval exercise may be a more appropriate and comfortable strategy for patients with COPD. In this sense, several practical recommendations have been found in the literature (Kortianou et al., 2010): 1) The heavier the intensity of endurance exercise, the shorter the exercise bouts and the longer the rest intervals should be (e.g. for intensity close to 100% of PPO, 20-30 s of active exercise plus 30-40 s of active or passive rest might be appropriate); 2) during resting periods, pursed-lip breathing might help to increase tidal volume and reduce breathing frequency, leading to a reduction in end-expiratory lung volume and an increment in arterial saturation, reducing breathlessness during exercise; and 3) leg discomfort and dyspnea should be monitored and maintained between 5-6 and 3-4 points, respectively, in the 10-point Borg Scale of perceived exertion.

Finally, longer PR programs (up to 18 months) have reported more favourable effects on HRQoL in patients with COPD when compared with shorter PR programs (Beauchamp, Janaudis-Ferreira, Goldstein, & Brooks, 2011). Unfortunately, due to the small number of trials, the results for exercise capacity were less clear. It was suggested that while shorter exercise programs might improve exercise capacity in patients with COPD, longer exercise programs (> 6 months) may be necessary to induce long-term training effects and maintain exercise capacity unchanged 12-18 months after training (Beauchamp et al., 2011).

Resistance training. Exercise training in COPD has traditionally focused on endurance training alone. However, due to the strong evidence on the potential benefits of resistance training in COPD (Iepsen et al., 2015a, 2015b; Liao et al., 2015; O'Shea, Taylor, & Paratz, 2004; Puhan, Schunemann, Frey, Scharplatz, & Bachmann, 2005; Strasser, Siebert, & Schobersberger, 2013), current recommendations strongly support the implementation of resistance training as a part of PR in patients with COPD (Garvey et al., 2016; Spruit et al., 2013). Resistance training programs have been demonstrated to provide greater gains in upper- and lower-body strength than endurance training programs (O'Shea et al., 2004), although in a more recent meta-analysis the difference did not reach statistical significance (Iepsen et al., 2015b). In addition, a positive effect on HRQoL after strength training has been reported when compared to a control group (O'Shea et al., 2004), although no differences were observed when compared to an endurance training group (Iepsen et al., 2015b). It is likely that the benefits of exercise training on HRQoL are not influenced by the type of exercise training. Moreover, it seems that it makes no (statistically significant) difference to perform resistance or endurance training in terms of adaptations in muscle strength, functional aerobic capacity, and peak oxygen uptake or peak workload attained during a graded incremental exercise protocol in COPD patients (Iepsen et al., 2015b). However, a meta-analysis including 11 randomized controlled trials and 331 participants with COPD concluded that when the two forms of exercise training were combined (i.e. concurrent training), the intervention provided greater adaptations in muscle strength than an exercise program including endurance training alone (Iepsen et al., 2015a). In another meta-analysis including 18 randomized controlled trials involving 750 participants with COPD, combined endurance and resistance training greater improvements in leg press strength (weighted mean difference (WMD) of 12.3 kg, 95% CI 6.0 to 18.7 kg) and pectoral muscle strength (WMD of 4.5 kg, 95% CI 2.5 to 6.4) than endurance training alone (Liao et al., 2015). In addition, a positive effect on the St George Respiratory Questionnaire total scores (a questionnaire designed to evaluate health impairment in patients with COPD) was reported in the concurrent training group compared with the endurance training group (WMD of -7.4, 95% CI -12.6 to 2.3) (Liao et al., 2015). Collectively, these findings indicate that the combination of resistance and endurance training provides greater benefits in muscle function and HRQoL than endurance training alone in patients with COPD.

In regard to the potential benefit of resistance training on respiratory function in patients with COPD, a meta-analysis including a total of 14 randomized controlled trials and 305 participants with COPD found a non-statistically, neither clinically, significant improvement in absolute or percentage-of-predicted FEV1 (0.08 L and 2.71%, respectively; both $p > 0.05$) resulting from PR programs including resistance exercise (Strasser et al., 2013). By contrast, there was a statistically significant improvement in forced vital capacity with resistance training (0.37 L), and a positive trend was observed regarding peak ventilation ($3.77\ L\cdot min^{-1}$; $p = 0.08$) (Strasser et al., 2013). Although the mechanisms for these adaptations remain unclear, the improvement in lung function with resistance training has been suggested to be due to the potential functional improvement of expiratory muscles (i.e. abdominal wall and internal intercostals). In addition, the improvement in lung mechanics (e.g. reduced physiological dead space/tidal volume ratios) (Clark, Cochrane, & Mackay, 1996), as a consequence of increased strength and the use of the abdominal muscles leading to a higher position of the diaphragm in the chest, might lead to the enhancement of lung function. Actually, resistance training has proven to enhance inspiratory muscle function, with a 16% increment in maximal inspiratory pressure (Ramirez-Venegas, Ward, Olmstead, Tosteson, & Mahler, 1997).

The great heterogeneity observed across trials in some cases, and the insufficient data in other cases, have prevented the establishment of dose-response relationships in relation to both intensity and volume of resistance training for COPD management. In general terms, resistance training programs in patients with COPD usually incorporate 2-3 sessions per week (in non-consecutive days), in which on average, a total of six exercises (range: 3-9 exercises) per session are performed targeting the trunk, upper limb and lower limb skeletal muscles, including 2-4 sets of 6-12 repetitions per exercise at intensities ranging between 50-90% of one repetition maximum (1RM) (O'Shea et al., 2004; Strasser et al., 2013). The common dose at the end of the intervention has been reported to be 9 sets per muscle group per week (range: 2-12 sets) (Strasser et al., 2013). In most cases, resistance training is administered by means of weight machines, although free weights can also be used, or a combination of both (O'Shea et al., 2004). In addition, training duration is typically 12 weeks (range: 6-26 weeks) (O'Shea et al., 2004; Strasser et al., 2013). Importantly no adverse events in any of the studies reviewed were reported (Iepsen et al., 2015a, 2015b; Liao et al., 2015; O'Shea et al., 2004), although as noted in these review works, no major adverse events should be expected as a consequence of exercise training when the type of training and level of intensity are adjusted individually. Attending to the evidence from two meta-analyses on the dose-response relationship of resistance training in the general older population, high-intensity resistance training (> 75-80% of 1RM) has been found to be superior to moderate- and light-intensity resistance training for the enhancement of maximal muscle strength (Csapo & Alegre, 2016; Steib, Schoene, & Pfeifer, 2010), although this effect was substantially smaller when training protocols were matched for mechanical work (Csapo & Alegre, 2016). In addition, training twice a week produced similar effects in muscle strength to training three times a week, but it had a higher effect than training once weekly (Steib et al., 2010). Another meta-analysis confirmed the previous findings and added that performing 2-3 sets per exercise of 7-9 repetitions at 70-79% of the 1RM with an inter-set rest interval of at least 60 s provided the greatest adaptations in muscle strength in healthy older adults (Borde, Hortobagyi, & Granacher, 2015). Furthermore, resistance training interventions lasting 50-53 weeks were found to be superior to achieve greater gains in muscle strength compared to shorter interventions (Borde et al., 2015). Training to failure was not observed to generate greater muscle adaptations than not training to failure, with training volume as a more important feature to achieve morphological muscle adaptations in older adults (da Silva et al., 2018). This fact matches with the preference of patients with COPD to increase resistance or load rather than increase the number of repetitions per set until exhaustion (Ries, Ellis, & Hawkins, 1988). Finally, supervised training has been found to be superior to unsupervised training in improving measures of dynamic steady-state balance and measures of muscle strength/power in healthy older adults (Lacroix, Hortobagyi, Beurskens, & Granacher, 2017). Even small amounts of supervised sessions within mainly unsupervised interventions seem to have a beneficial extra effect (Lacroix et al., 2017). In general, the previous results obtained from the meta-analyses including older adults (i.e. not specifically with COPD) might help in optimizing the exercise parameters included in resistance training programs in COPD patients, although most of the previous recommendations are in consonance with the general characteristics of the resistance training programs reported in patients with COPD (O'Shea et al., 2004; Strasser et al., 2013). On the other hand, exercise intensity has not been found to influence functional adaptations in older people (Steib et al., 2010). Actually, muscle power and maximal angular velocity of movement are key determinants of functional performance in older adults (Alcazar, Rodriguez-Lopez, et al., 2018; Byrne, Faure, Keene, & Lamb, 2016), and high-velocity resistance training or power training have been reported to be superior to traditional resistance training to increase muscle power (Steib et al., 2010) and functional performance in older people (Straight, Lindheimer, Brady, Dishman, & Evans, 2016; Tschopp, Sattelmayer, & Hilfiker, 2011) independent of training intensity. The main difference between power training and traditional resistance training is that, in the first case, concentric repetitions are performed as fast as possible. This characteristic has demonstrated to decrease cardiovascular loading (Lamotte, Fleury, Pirard, Jamon, & van de Borne, 2010) and increase muscle oxygenation (Tanimoto & Ishii, 2006) during resistance exercise in comparison with traditional resistance training, which makes power training a potentially more suitable approach for patients with COPD. Both power training and testing have been reported to be safe in aging populations (Alcazar, Guadalupe-Grau, Garcia-Garcia, Ara, & Alegre, 2018; Porter, 2006). In any case, future studies should evaluate the effects of high-velocity resistance training or power training in patients with COPD.

Considerations for concurrent training programs

Concurrent training (combining continuous or interval endurance training and resistance training) has been demonstrated to be feasible and safe in patients with COPD (Bolton et al., 2007; Guadalupe-Grau et al., 2017). Since the current guidelines recommend the implementation of both endurance and resistance training (i.e. concurrent training) within PR in COPD (Garvey et al., 2016; Spruit et al., 2013), there are several aspects that should be considered in order to optimize training adaptations. In terms of training frequency, concurrent training performed twice a week was observed to promote similar adaptations when compared with three times per week in previously trained elderly men (Ferrari et al., 2016). The exercise sequence within the sessions (i.e. performing endurance prior to resistance training *vs* resistance prior to endurance training) has been found to influence the benefits derived from concurrent training. While the intra-session exercise sequence had no influence in maximal and submaximal endurance adaptations (Cadore et al., 2018), the implementation of resistance prior to endurance training three times per week elicited superior adaptations in lower-body muscle strength, muscle quality and rectus femoris neuromuscular economy in older adults (Cadore et al., 2012; Cadore et al., 2013). However, another study found no differences between exercise sequences regarding muscle adaptations (muscle strength and power, functional performance, electromyographic activity, and rectus femoris echo intensity) when it was performed twice a week (Wilhelm et al., 2014). Although there is evidence indicating a positive effect derived from performing resistance prior to endurance training, great heterogeneity exists across studies with people older than 50 years old (Murlasits, Kneffel, & Thalib, 2018). Thus, we could follow the recommendation of implementing resistance prior to endurance training in older people and people with COPD, although more studies are needed in order to strengthen this evidence. Another way to avoid a possible interference effect of endurance training on resistance training-induced muscle adaptations would be to perform both type of exercises on alternate days (Cadore & Izquierdo, 2013). In this sense, even a minimum dose of one session per week of resistance training and one session per week of cycle endurance training has been reported to promote positive and substantial adaptations in muscle strength, power and endurance in older adults (Cadore & Izquierdo, 2013).

Other potential interventions. Neuromuscular electrical stimulation (NMES) has been presented as a useful training modality that might be included in PR programs for COPD patients (Maltais et al., 2014; Spruit et al., 2013). NMES consists in the depolarization of motor neurons (inducing muscle contraction) by the application of an electrical current through electrodes placed on the skin located over the targeted muscles. NMES has demonstrated to augment lower-limb muscle function when compared with a non-exercise control group (Bax, Staes, & Verhagen, 2005). However, volitional training seems to be superior to NMES when the participants do not present limitations to perform volitional resistance exercises (Bax et al., 2005). Otherwise, in case of immobilization due to injury, illness or disability (e.g. COPD-related exacerbation requiring hospitalization), NMES may be more effective than volitional training (Bax et al., 2005). Thus, a meta-analysis demonstrated that NMES improved quadriceps muscle strength, exercise capacity and 6-min walking distance (6-MWD) performance in moderate-to-severe patients with COPD (Chen et al., 2016). By contrast, NMES did not improve HRQoL in these patients (Chen et al., 2016). Therefore, NMES might be recommendable in severely disabled patients with COPD, unstable patients, during exacerbations, and in general, in those cases in which the tolerance to volitional exercise training is severely compromised (Maltais et al., 2014). NMES may also be applicable for home use (Neder et al., 2002) or as an adjunct to volitional resistance training. The methodological considerations for the use of NMES are beyond the scope of the present manuscript, so the interested readers are referred to other review works on the topic (Bergquist et al., 2011; Maffiuletti, 2010; Maffiuletti et al., 2018).

Respiratory muscle training has been postulated as another beneficial form of training for patients with COPD (Spruit et al., 2013). The main goal of respiratory training is to enhance inspiratory and/or expiratory muscle strength and endurance, in order to reduce dyspnea, increase exercise capacity and improve HRQoL. To do this, inspiratory and expiratory muscles are subjected to airflow restriction (e.g. with the use of an external device), or different breathing techniques may be performed to strengthen respiratory muscles. The evidence obtained from the literature points out that respiratory muscle training programs are typically performed 2-7 days/week during 1-52 weeks at an intensity of 30-80% of maximal inspiratory capacity (Beaumont, Forget, Couturaud, & Reychler, 2018; Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; Holland, Hill, Jones, & McDonald, 2012; Neves et al., 2014; O'Brien, Geddes, Reid, Brooks, & Crowe, 2008). The evidence points out that inspiratory muscle training (IMT) programs are effective to significantly improve maximal inspiratory capacity [WMD of 12.0 cmH_20, 95% CI 10.0 to 14.0] (Beaumont et al., 2018). In addition, clinically and statistically significant improvements in the baseline-transition dyspnea index and functional exercise capacity (6-MWD performance) were derived from inspiratory muscle training when compared to a non-exercise control group [WMD of 2.3 points, 95% CI 1.7 to 2.9; and WMD of 42.7 m, 95% CI 16.9 to 68.5, respectively]. However, these gains were not accompanied by neither statistically nor clinically significant improvements in HRQoL (Beaumont et al., 2018), and no significant differences were found when IMT was compared to a PR incorporating exercise training (O'Brien et al., 2008). Adding IMT to exercise training enhanced maximal inspiratory capacity further than exercise training alone [WMD of 8.6 cmH_2O, 95% CI 2.6 to 14.7], but not significant differences were observed in terms of exercise capacity and dyspnea (Beaumont et al., 2018; O'Brien et al., 2008). In addition, several breathing techniques (e.g. diaphragmatic breathing, pursed-lip breathing and ventilation feedback training) have been found to be effective in improving exercise tolerance (ranging from 35 to 88 m in 6-MWD test) without any impact in dyspnea and HRQoL in severe to very severe COPD patients (Holland et al., 2012). However, the addition of breathing techniques to exercise training did not provide additional benefits for dyspnea, exercise tolerance or HRQoL compared to exercise training alone (Holland et al., 2012). Therefore, breathing exercises may be useful for individuals who are not able to take part in exercise-based pulmonary rehabilitation programmes (Holland et al., 2012).

On the other hand, the addition of activity counselling to PR improved the levels of physical activity in patients with COPD in comparison to PR alone, leading to significant increases that exceeded the minimal important difference for daily steps in COPD (Lahham, McDonald, & Holland, 2016).

Flexibility training has also been indicated as an additional training mode to be integrated in PR programs (Garvey et al., 2016; Spruit et al., 2013). However, it is also acknowledged that there is no evidence supporting the implementation of flexibility training in the management of COPD (Garvey et al., 2016; Spruit et al., 2013), and thus, its inclusion as a component of PR might be considered futile, or at least questionable in the majority of patients with COPD.

There might be other potential adjuncts to exercise training that may maximize its effects (Spruit et al., 2013). For example, an optimal pharmacological dose (e.g. bronchodilators) (Casaburi, Kukafka, Cooper, Witek, & Kesten, 2005) or the application of noninvasive positive pressure ventilation (Corner & Garrod, 2010) during exercise might reduce the work and/or unload the respiratory muscles and change the primary focus of exercise limitation from dyspnea to leg fatigue, increasing the ability of the individuals to sustain a higher exercise intensity. By contrast, the administration of oxygen and helium-hyperoxic gas mixtures has been reported to bring inconsistent results (Spruit et al., 2013). On the other hand, anabolic hormonal supplementation in combination with exercise training in those patients presenting low levels of anabolic steroids (i.e. testosterone and its analogs) may improve adaptations in muscle mass and strength, with no adverse events when low doses are prescribed in the short term (Casaburi et al., 2004). However, more research is needed in order to confirm such findings and extend the exercise recommendations to other therapies that in combination with exercise might potentiate its benefits.

Further considerations on the implementation of PR in people with COPD

PR is one of the most cost-effective treatment interventions available for patients with COPD (Rochester et al., 2015) and it is associated with a substantial reduction in hospitalizations and healthcare costs (Griffiths et al., 2000; Griffiths, Phillips, Davies, Burr, & Campbell, 2001; Group, 2004; Raskin et al., 2006). Its cost-effectiveness is superior to some of the main pharmacological options (such as Tiotropium, LABA and triple therapy) (Zoumot, Jordan, & Hopkinson, 2014). Despite this high level of evidence, implementation of PR in people with COPD is very low (Johnston & Grimmer-Somers, 2010). It has been reported that only 1-9% of eligible patients with COPD attend a PR program each year (Calle Rubio et al., 2017; Yohannes & Connolly, 2004). The main reasons for this problematic situation are the non-participation of referred patients in PR programs and the non-referral of eligible patients to PR programs by healthcare professionals. Thus, a systematic review observed that the percentage of referred participants who did not attend PR at all ranged from 8 to 50% (Keating, Lee, & Holland, 2011). In addition, among those patients who did initiate the PR program, 10-32% dropped-out and did not complete the program (Keating et al., 2011). The main barriers reported by the patients who did not attend and/or complete the PR program were difficulties with transportation, mobility, distance and location of programs, and the disruption to already established personal activities or routines (Keating et al., 2011; Thorpe, Johnston, & Kumar, 2012). The lack of perceived benefit and the influence of the participant's doctor were also reported by some patients among other barriers to participation in a PR program (Keating et al., 2011; Thorpe et al., 2012). None of the common physiological and clinical variables (e.g. dyspnea or disease severity) showed a consistent association with non-attendance and/or completion of the PR program (Keating et al., 2011). However, the problem does not seem to be just the attendance and completion of PR programs by the referred patients, but also the referral of patients by healthcare professionals. Despite strong evidence and international recommendations acknowledging the benefits derived from the implementation of PR at any stage of the disease, including from stable patients to patients just discharged from the intensive care unit after respiratory failure (Bailey et al., 2007; Morris et al., 2008), the median referral rate has been reported to be as low as 17% (Milner, Boruff, Beaurepaire, Ahmed, & Janaudis-Ferreira, 2018). The main healthcare professional perceived barriers to referral were: low knowledge of, or disbelief in, the benefits of PR; low knowledge of the referral process; low knowledge of patient eligibility criteria; low awareness of PR; and the belief that it would be too difficult to achieve a behaviour change in patients or that patients would not take responsibility of their disease (Milner et al., 2018). In regard to this problematic situation, an official American Thoracic Society/European Respiratory Society policy statement has recently been published, to which those readers interested in enhancing implementation, use and delivery of PR are referred to (Rochester et al., 2015). Overall, the improvement of the knowledge of the benefits of PR and exercise training in COPD patients among healthcare professionals might enhance PR referral, while the implementation of home-based exercise training programs (Liu et al., 2014) or the use of NMES at home (Chen et al., 2016) might be indicated in COPD patients unable to attend the PR facilities.

CONCLUSIONS

PR has been demonstrated to improve limb muscle dysfunction, exercise capacity and quality of life, and reduce healthcare use in COPD patients. Exercise training is considered as the cornerstone of PR, and its inclusion in PR programs has demonstrated to increase the benefit derived from PR. Therefore, supervised exercise training is recommended in patients with COPD at any stage of the disease (figure 1). Exercise should be addressed to both upper- and lower-body muscles, acknowledging that lower-limb muscles have a greater influence on exercise capacity and quality of life in COPD patients. High-intensity endurance training is recommended on a basis of 3-5 sessions per week and 20-60 min per session, with interval endurance training being a more feasible approach to reach such recommendations in people with COPD. On the other hand, high-intensity resistance training is recommended on a basis of 2 sessions per week, performing 2-3 sets of 7-9 repetitions per exercise with an inter-set rest interval of at least 60 s. The combination of endurance and resistance training (i.e. concurrent training) has been observed to enhance the training-induced adaptations in muscle function and quality of life. In this sense, performing resistance prior to endurance training within the training sessions might obtain greater adaptations. Other potential adjuncts to concurrent training exist, such as NMES, respiratory muscle training and physical activity counselling, which might maximize the benefits derived from exercise and/or facilitate the participation of COPD patients in PR programs. Finally, the application of educational programs targeting healthcare professionals in order to improve the general understanding of the benefits of PR in COPD management might improve the referral and implementation of PR programs in patients with COPD.

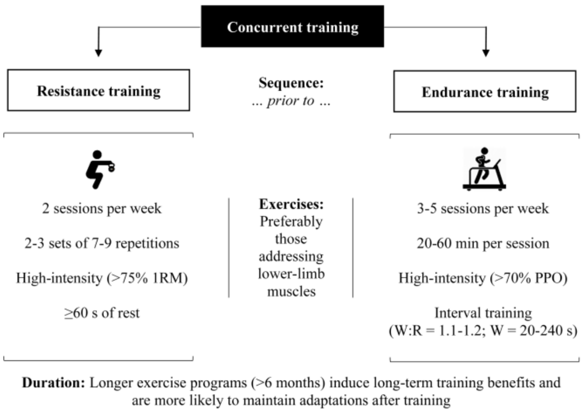

FIGURE 1: Summary of the current evidence-based recommendations for the prescription of supervised exercise training programs in patients with chronic obstructive pulmonary disease. Exercise training programs should be adjusted to the individual characteristics and requirements of each subject. In general, training load must exceed loads encountered during daily life to improve aerobic and muscle function. Therefore, some subjects may benefit from less strenuous exercise programs than those based on the recommendations given in the present figure. These recommendations may be updated by novel evidence presented in future studies. *Note*: 1RM, one

repetition maximum; PPO, peak power output; W:R, work-to-rest ratio; W; work or exercise bout.

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