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Advances in Comprehensive Pulmonary Rehabilitation for COPD Patients

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1. Introduction

Physical inactivity (lack of exertional pursuits) is the fourth leading risk factor for mortality worldwide and contributes to 6% of all deaths. Only hypertension, smoking, and diabetes are associated with greater mortality [1]. In addition, nearly 5% of worldwide mortality is caused by excessive weight [2]. Numerous prospective, observational studies suggest that the least active and unfit people are at the greatest risk for developing a variety of chronic diseases [3]. Physical inactivity has been identified as an independent risk factor for cardiovascular disease, diabetes, hypertension, obesity, osteoporosis, colon, breast and other cancers, depression, anxiety and other illnesses [4].

Chronic Obstructive Pulmonary disease (COPD) is the most common chronic lung disease and is the fourth leading cause of death in the world. COPD has a high impact on patients' wellbeing, health care utilization, and mortality [5] and causes a substantial and increasing economic and social burden [6, 7].

As COPD worsens and individuals experience increasing respiratory symptoms, a vicious cycle develops whereby activity declines, walking speed is reduced, fitness levels decline, and activities of daily living become too difficult to carry out, eventually causing disability and dependence [8]. Physical activity is reduced in severe COPD [9] but the level of activity in individuals with moderate COPD is less well studied. Hence, inactivity may not only be a manifestation of disease severity in COPD but may also contribute to disease progression [10]. In a recent study of the patterns of physical activity including the frequency, duration and intensity of episodes of physical activity, patients with COPD wore the SenseWear® armband

accelerometer for eight consecutive days [11]. With increasing COPD severity, time in physical activity, proportion of time performing activities, and frequency of activity decreased. These objective outcomes provide the best measures of physical activity [12].

COPD is characterized by inexorably progressive, non-normalizing airflow limitation and the severity of obstruction correlates with its morbidity and mortality [5, 13]. Based upon the presence of oxidative stress, increased levels of circulating cytokines, and multiple nonpulmonary manifestations, COPD is increasingly being recognized as a systemic disorder [5]. Furthermore, COPD does not manifest in a homogeneous manner and many different subgroups or phenotypes are being recognized. The polysystemic manifestations and heterogeneity of clinical and inflammatory profile presentations of COPD have led to an expanded classification in the most recent GOLD guidelines that incorporate clinical manifestations including effects on physical activity and healthcare utilization or risk in addition to physiologic impairment [5]. This multifactorial classification is used to stage COPD severity and to guide and monitor treatment [5]. In addition, the clinical course of patients with COPD is marked by repetitive exacerbations and abnormal inflammatory response which further contribute to a downward spiral of physical activity [5, 14].

Decreased caloric intake leading to nutritional depletion occurs in about 20-35% of outpatients with COPD and up to 70% of patients with acute respiratory failure or waiting for lung transplantation [15]. Cachexia, defined as weight loss with disproportional fat-free mass wasting, occurs in about one-third of patients with COPD eligible for pulmonary rehabilitation and represents a cause of increased mortality independent of ventilatory limitation [16].

2. Biochemical changes

Many of the major pathophysiologic derangements in advanced COPD have been attributed to systemic inflammation [17]. Previous studies show that systematic inflammation is induced by inflammatory cytokines, such as tumor necrosis factor (TNF- α), interleukin (IL-6) and IL-8 [18, 19]. Fat-free mass (FFM) depletion marks the imbalance between tissue protein synthesis and breakdown that occurs in COPD [20]. These inflammatory cytokines and endocrine hormones contribute to the reduction in exercise tolerance and poor quality of life caused by skeletal myopathy in COPD patients [21]. Skeletal muscle dysfunction plays an important role in the symptoms and impairments in strength, endurance, and maximal exercise capacity experienced by patients [22].

Bronchiectasis, permanent damage and widening of one or more of the large connecting bronchi (airways), may occur in nearly one third of individuals with COPD [22]. Individuals with bronchiectasis have elevated levels of proinflammatory cytokines that are associated with decreased fat-free mass, increased proteolysis and worse respiratory function [22-24]. This chronic inflammation increases the levels of oxidative stress [25, 26]. Circulating (plasma) and intracellular biomarkers of oxidative stress are increased in patients with bronchiectasis compared with control subjects [25].

Decline in nutritional status is directly related to lung function outcomes and has been proposed as a predictor of morbidity and even mortality in patients with chronic respiratory diseases independent of the ventilatory limitation [15]. Furthermore, malnutrition is accompanied by a loss of diaphragmatic and structural skeletal muscle mass, as well as humoral and cellular dysfunction [15]. Anabolic stimulation through a combination of nutritional support and exercise appears to be the best approach to improving functional status [27]. A multicenter study of stable COPD patients with a body mass index of 22 kg/m² and a fat-free mass index of 16 showed that the consumption of oral nutritional supplements, rich in proteins (with 50% of whey protein) produced a significant improvement in quality of life [28]. A subsequent Cochrane Database meta-analysis showed that undernourished patients with COPD improved with nutritional supplementation [29]. Malnourished patients who received supplementation had significantly better maximum inspiratory pressures and maximum expiratory pressures [29].

Thus, impaired skeletal muscle function is a potentially remediable systemic manifestation of COPD [30]. These findings have implications for identification of drug targets aimed at improving muscle function in COPD [30]. Except for markers of myogenesis, molecular responses to resistance training are not tightly coupled to lean mass gains [30].

3. Management of comprehensive pulmonary rehabilitation

Pulmonary Rehabilitation (PR) has become a cornerstone in the management of patients with stable COPD in recent years [31]. Systematic reviews show large and important clinical effects of PR in these patients [32]. PR improves anxiety and depression in patients with COPD [33]. PR also reduces the number and duration of hospitalizations [34, 35]. In addition, physical training and chest physiotherapy in respiratory disease have long-term, durable benefits [36-38]. The components of PR vary widely but a comprehensive program includes smoking cessation, education, nutrition counseling, and exercise training [5].

3.1. Educational and nutritional management

All patients enrolled in PR should receive educational and nutritional interventions as part of an integrated care plan that seeks to achieve a normal nutritional status, either through natural diet or supplements [15, 39]. Nutrition depletion occurs by multiple mechanisms including energy imbalance, disuse atrophy of the muscles, hypoxemia, systemic inflammation and oxidative stress [15]. Each of these mechanisms may represent targets for nutritional intervention.

Patients with COPD are best managed through multimodal therapies delivered through an integrated healthcare system [40]. Dietary supplementation with whey may potentiate the effects of exercise training on exercise tolerance and quality of life in patients with COPD [41]. Use of a nutritional supplement containing anti-inflammatory whey peptide with exercise therapy in stable elderly COPD patients increased body weight, reduced markers of systemic inflammation, and improved exercise levels and respiratory health [17].

There is a clear need for adequately powered and controlled intervention and maintenance trials to establish the role of nutritional supplementation in the enhancement of exercise performance and training and wider management of the systemic features of COPD [40]. Hence, combination therapy, nutritional, pharmacologic, and physical training, may produce weight gain, increases in lean mass, respiratory muscle strength, exercise capacity, lung function, and respiratory health while reducing morbidity and mortality. Physiotherapy, occupational therapy, and medical treatment are individually adjusted to each patient's needs and requirements with the goal of improving current quality of life and these targets should be re-adjusted when patients opt for palliative care [42].

Although prior reviews did not provide evidence for the usefulness of nutritional supplementation therapy, more recent analyses concluded that nutritional supplemental therapy increased weight, fat free mass, exercise tolerance, and hand grip strength in undernourished patients with COPD [29, 43, 44]. High calorie nutrition therapy and L-carnitine supplementation may be beneficial whereas no effect is observed with additional creatine [45]. The duration and type of exercise may also affect PR results. Although both low and high intensity exercise training are beneficial for patients with COPD, higher intensity lower extremity exercise yields better physiologic improvement than lower intensity exercise [46]. PR programs that are 12 weeks or longer produce enhanced and more durable results than shorter programs [43, 46]. The benefits of PR tend to wane gradually over 12 to 18 months [43, 46].

3.2. Importance of exercise training

There are two different types of Physical Exercise Training for COPD patients: endurance and interval type training [47]. Endurance or continuous programmes include constant load and incremental load training. However, patients with symptoms of severe dysnea during exercises were incapable of performing high-intensity (70 to 80 % of the peak work rate) continuous type training. Interval training is recommended as an alternative to continuous training in patients with severe symptoms of dyspnoea during exercise due to an inability to sustain continuous training at the recommended intensities. During interval training short exercise bouts (30-180 seconds) are performed at high intensity (at least 70-80% of peak work rate). Recommended frequency of training is the same as with continuous training [47]. Finally, there is evidence that regular physical activity contributes to the primary and secondary prevention of several chronic diseases and is associated with a reduced risk of premature death [48].

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level [49]. Exercise therapy is defined as a subcategory of physical activity in which planned, structured, and repetitive bodily movements are performed to maintain or improve one or more attributes of physical fitness [49]. Physical fitness refers to the ability to carry out daily tasks with vigor and alertness without undue fatigue and with ample energy to enjoy leisure time pursuits and to meet unforeseen emergencies [49].

Physical activity is the strongest predictor of all-cause mortality in patients with COPD [50]. Nowadays, lack of physical activity is associated with the burden of chronic disease [51]. The

low levels of Physical Activity (PA) generally observed in people with COPD may be due in part to the difficulties they experience as they attempt to perform daily activities that they need and want to perform [14]. Importantly, physical inactivity is potentially reversible [52].

There is strong evidence that community physiotherapy benefits health by promoting physical activity [8, 53]. Exercise prescribed by a physiotherapist can target directly any impairments contributing to activity limitations and requires the active participation of subjects in an individualized physical exercise program [53]. Exercise training can produce significant improvement in health related quality of life, exercise capacity, respiratory muscle strength, and exertional dyspnea in patients with COPD who have normal exercise capacity [54]. Hence, enrollment in a comprehensive Pulmonary Rehabilitation Program (PRP) that includes exercise training and dietary supplementation may benefit patients with COPD. PRP may be supported by motivational counseling [55]. Furthermore, physical activity is an attractive outcome measure for interventional studies in patients with COPD.

Both physical activity and daily exercise improve the health of COPD patients [10]. It is necessary to avoid a sedentary lifestyle and encourage them to perform physical activity and exercises [10]. The performance of regular physical activity by patients with COPD reduces the risk of both hospital admissions and all-cause and respiratory mortality [10]. It appears that patients with COPD have a significantly reduced duration, intensity, and number of daily physical activities when compared with healthy control subjects [56]. Hence, the recommendation that COPD patients be encouraged to maintain or increase their levels of regular physical activity should be considered in future research [10]. A Spanish research group developed a novel alternative to formal PRP that includes a walking training circuit in the city of Catalonia [57] that has been replicated in other cities such as Navarre [58] (Figure 1).



Figure 1. Walking circuits from “Walking Guide for COPD patients” [58]

3.3. Oxygen therapy

Oxygen therapy is one of the therapies currently available to reduce COPD mortality [59]. Long-term oxygen therapy (LTOT) reduces pulmonary hypertension and improves survival in patients with COPD and resting hypoxemia (arterial partial pressure of oxygen ≤ 55 mmHg) [60].

The use of oxygen supplementation during exercise training for individuals with COPD is unclear [61]. Supplemental oxygen during exercise training improves functional outcomes such as symptoms, health-related quality of life, and ambulation [61]. However, there are no significant differences in maximal exercise outcomes, functional exercise outcomes (six-minute walk test), shuttle walk distance, health-related quality of life, or oxygenation status [61, 62].

COPD patients with low fat-free mass (FFM) have lower levels of oxidative stress with supplemental oxygen [63]. Patients with COPD are able to achieve a higher work rate during exercise training, which positively affects training results after several weeks [64]. It is generally recommended that COPD patients who are already hypoxaemic at rest should use oxygen during exercise, aiming at a rather arbitrary oxygen saturation of $> 90\%$ [64]. A review of the effect of oxygen in COPD patients with or without desaturation during exercise training concluded that hyperoxia has no clear effect on the results of exercise training in COPD patients with or without documented desaturation during exercise [64]. Only one study demonstrated a significant, and clinically relevant, improvement in higher work load during rehabilitation [65]. In conclusion, more studies are needed to define the role of supplemental oxygen in PR; for instance, on the oxygen concentration, intensity of exercise programmes, and its effects in different COPD phenotypes.

4. Measuring and improving the physical activity level in COPD patients?

Exercise tolerance is a well accepted clinical marker in COPD and provides information about disease stage, prognosis, functional capacity, and the effects of treatment [66]. The assessment of physical activity in healthy populations and in those with chronic diseases is challenging. Furthermore, physical activity is most accurately measured using objective tools such as accelerometer-based activity monitors [67]. In addition, other outcomes must be included, such as quadriceps and grip strength [68].

Physical activity monitors are frequently used to estimate levels of daily physical activity [69]. These devices use piezoelectric accelerometers, which measure the body's acceleration, in one, two or three axes (uniaxial, biaxial or triaxial activity monitors). The signal can then be transformed into an estimate of energy expenditure using one of a variety of algorithms, or summarized as activity counts or vector magnitude units (reflecting acceleration) [69]. With the information obtained in the vertical plane or through pattern recognition, steps or walking time can also be derived from some monitors [69].

A systematic review identifies the available activity monitors that have been appropriately validated for use in assessing physical activity in these groups [70]. Forty monitors were tested

in validation studies; 12 uniaxial, 3 biaxial, 16 triaxial accelerometers and 9 multisensor devices [70]. Furthermore, a recent study evaluated the validity and usability of six activity monitors in COPD patients against the double labelled water indirect calorimetry method [71]. The Actigraph GT3X and DynaPort MoveMonitor best explained the majority of the total energy expenditure variance not explained by total body water and showed the most significant correlations with activity energy expenditure [71].

Moreover, the Dynaport MiniMod and Actigraph GT3X discriminate best between different walking speeds [69]. Overall, these findings should guide the choice of valid activity monitors for research or for clinical use in patients with chronic diseases such as COPD. In a recent comparison, two types of accelerometer: the DynaPort and the Actiwatch were used in order to assess the level of physical activity [12] and compared with a multisensory armband device (SenseWear, BodyMedia; Pittsburgh, PA) [9]. The main finding of this pilot-study was the significant reduction in physical activity observed with each patient. The study provides evidence for a gradual reduction in daily physical activity levels with increasing GOLD stage, although the correlation between physical activity and lung function is weak [9].

5. Does the choice for inspiratory or expiratory muscle strength or endurance training matter?

COPD alters muscle structure and/or functional. Strength and endurance are the two main functional properties of both respiratory and peripheral muscles and reduction in either strength or endurance leads to muscle dysfunction. Strength mainly depends on muscle mass, and endurance is related to muscle fiber aerobic properties [72]. Muscle weakness is a relatively stable condition related to the loss of muscle strength which requires long-term therapeutic measures (training and/or nutritional interventions). In contrast, muscle fatigue is a temporary dysfunction related to endurance [73]. Many COPD patients experience muscle dysfunction and reduced muscle mass, primarily as a result of chronic immobilization [74]. Over the last decade, the potential use of resistance training for COPD has gained increasing attention.

A Cochrane Database Systematic Review showed that breathing exercises over four to 15 weeks improve functional exercise capacity in people with COPD compared to no intervention; however, there were no consistent and clear effects on dysnoea or health-related quality of life [75].

Muscle strength can be measured by the maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) [76]. Inspiratory muscle training (IMT) provides breathing training together with resistance loading produced by a valve and is regarded as a mixture of strength and endurance training. IMT may improve inspiratory muscle strength, endurance, functional exercise capacity, dyspnoea, and quality of life. A question to be taken into account in the planning of a respiratory muscles training protocol in COPD patients would be to determine which is more important, inspiratory muscle strength training or endurance training. A meta-analysis showed that inspiratory muscle endurance training was less effective than respiratory muscle strength training [76]. Both types of training (strength and endurance) significantly

improve the endurance of the muscles, but only strength training was able to significantly improve the MIP, the MEP and functional exercise capacity [76].

Although many resistance devices are available, the Threshold-IMT® is frequently used and produces loads of 7-41 cm H₂O. The devices produce a range of resistance levels, with lower resistance levels offered by the Threshold Inspiratory Muscle Trainer (Phillips Respironics, Murrysville, PA) and higher resistance levels offered by the POWERBreathe® (HaB International Ltd, Southam, Warwickshire, UK) and the PowerLung® (PowerLung, Houston, TX). The POWERBreathe® is only for inspiratory muscle training and has three models. The Light POWERbreathe® produces loads of 17-98 cm H₂O, the medium device delivers loads of 23-186 cm H₂O, and the heavy device achieves loads of 29-274 cm H₂O. The PowerLung® is for inspiratory and expiratory muscles training and has four models that produce varying levels of resistance [72].

The Orygen-Dual Valve® was designed and patented by researchers of Barcelona and allows both simultaneous and sequential dual training work (expiratory and inspiratory muscles) (Figure 2) [72]. The Orygen-Dual Valve® is a relatively cheap, portable, and easy to use piece of equipment that provides workloads up to 70 cm H₂O at a rate of 15-20 breaths/min [72].



Figure 2. Martín-Valero, R. makes the rehabilitation programme with Orygen-Dual Valve®

High-intensity inspiratory muscle training improved inspiratory muscle function in subjects with moderate-to-severe COPD, producing significant reductions in dyspnoea and fatigue [77]. In addition, a 4-week supervised high-intensity respiratory training program in patients with COPD demonstrated functional improvements [78, 79]. The Orygen-Dual Valve® makes

the rehabilitation programme more efficient than usual training as it requires fewer resources in terms of time and staff, and allows patients to acquire skills for further training outside the Hospital [68]. Furthermore, the hi-IMT achieves this result in a shorter time, which is an advantage for improving the efficiency of rehabilitation programmes within the public health system [72]. The training must be supervised by a therapist once a week during the first month.

The addition of high-intensity IMT to aerobic exercise produced incremental benefits in muscle weakness, cardiopulmonary function, and health-related quality of life in a randomized study of patients with chronic heart failure [80]. A multicenter randomized controlled trial is currently underway to determine whether the addition of IMT to a general exercise training program improves the distance walked in six minutes, health related quality of life, daily physical activity, and inspiratory muscle function in individuals with COPD and reduced inspiratory muscle strength [81].

6. What are the views and perceptions of people with COPD regarding a pulmonary rehabilitation?

Individuals with COPD people who complete a course of PR believe that ongoing structured exercise with professional and peer support assists them with continued regular exercise [82]. However, patients with COPD often encounter potential barriers to PR attendance including difficulties with travel to exercise venues, fluctuating health status with respiratory symptoms that impede physical activity, and psychological emotional effects including feelings of embarrassment [82, 83].

Many qualitative studies of PR in patients with COPD have been performed over the past decade to determine the impressions and opinions of PR participants. There are two main theories that have been used to analyse qualitative research [88, 89]. The first one is known as the grounded theory approach [90] and the second theory is the interpretative phenomenological analysis framework [88, 89, 91]. Qualitative research uses data collected from focus groups [82, 92], semi-structured interviews [87, 93, 94] or a combination of both methods [92, 95]. Some studies use triangulation research [96] or embed a qualitative study in a randomized controlled trial in order to explore patients' views on self-management [97]. The main areas of research were: the effect of people's health status on exercise adherence [82], pain [85], and social relationships, such as social integration and social support [86].

It is necessary to increase strategies for self motivation among individuals with COPD [87]. Encouraging health behaviours is a key feature relating to PR participation including physical activity and smoking reduction or cessation [55]. Telephone delivery of health-mentoring is feasible and acceptable to individuals with COPD in primary care and may improve PR participation [55]. Telemonitoring of individuals with COPD enhanced self-management by improving patients' knowledge about their disease [97].

7. Occupational therapy in COPD

Patients with COPD may benefit from occupational therapy as well as physical therapy. However, there are few studies evaluating occupational therapy for individuals with COPD. A qualitative study suggested that occupational therapy may reduce breathlessness, improve mental outlook, and increase the confidence of individuals with COPD [84].

In the future, occupational therapists may be able to assess and provide rehabilitation interventions for patients with COPD [98]. Incorporation of occupational therapy in PR may increase patients' knowledge of COPD, elevate their sense of control, promote re-engagement in activities, reduce anxiety, and improve social engagement [98].

Theoretical and clinical occupational therapy supports a rehabilitation model based on continued participation in activities that are considered essential in the life of the person [99]. The respiratory symptoms of patients with COPD have an impact on activities of daily living. Occupational therapy interventions in patients with COPD aim to develop specific strategies to perform basic activities of daily living, and leisure activities, so that they involve the least possible waste of energy [100]. Through energy saving techniques, Occupational Therapy aims to reduce the patient's subjective respiratory distress. In activities of daily living training, patients learn to work efficiency and also learn economies of movement, minimizing the energy cost of dressing, personal hygiene, home care, leisure activities, shopping, and other activities related to the patients' work [100]. Although simple, energy saving techniques require a learning process that is difficult to achieve outside of a multidisciplinary rehabilitation program [100].

Research into COPD's psychological effects on patients' ability to perform daily activities provides a wholistic approach to COPD and its consequences. The Occupational Therapy framework provides a basis for the design of a comprehensive PR intervention that addresses all aspects of a patient's life. Recent research shows that optimization of occupational performance improves the welfare of individuals with COPD [101]. Members of the patient's social network should not be excluded from these plans and interventions. Application of a family psychoeducational program based in training and information about COPD pathology including risk factors, habits that facilitate disease progression, specific strategies for handling the problems of daily life, and how to face the difficulties in occupational performance for each stage of the disease may empower the patient's friends and family to assist with rehabilitation [102]. An initial interview with the patient, family, and friends is the initial step to developing a comprehensive PR program that includes all members of the patients' social network [103].

8. Conclusion

In conclusion, a multidimensional therapeutic approach is recommended for developing a comprehensive pulmonary rehabilitation program for patients with COPD. Critical elements of PR include optimization of pharmacologic and nonpharmacologic management, exercise,

physical activity, ventilatory support, nutritional, and occupational therapy interventions. In addition, there is a need for new models for pulmonary rehabilitation which allow all program components to be delivered at home, with proven clinical outcomes and low costs [104]. It is possible that undertaking pulmonary rehabilitation within the home environment may promote more effective integration of exercise routines into daily life over the longer term with greater adherence to exercise [104]. In fact, home-based exercise programs achieve equivalent clinical outcomes and are cost effective compared with hospital-based programs. The decentralization of pulmonary rehabilitation increases the options for its provision and may assist in overcoming the most frequently identified barriers to pulmonary rehabilitation [104].

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