Chapter 7

Advances in Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease and Associated Conditions

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Additional information is available at the end of the chapter

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Abstract

Pulmonary rehabilitation (PR) is an evidenced-based, proven treatment as mentioned recent guidelines in patients with chronic obstructive pulmonary disease (COPD). Exercise training is a cornerstone of PR programs, Inspiratory muscle training, neuromuscular electrical stimulation (NMES) are effective in selected patients. Water-based rehabilitation and tai chi are well tolerated recent modalities. Although there is an absence of a specific PR protocol for special conditions, PR is recommended before and also after endobronchial volume reduction (EBVR), lung volume reduction surgery (LVRS), both before and after lung transplantation periods, before, after surgery, during the intensive care unit (ICU) period, the chemotherapy period and as a component of palliative care. After COPD exacerbation, it is recommended within 3 weeks of hospital discharge. Modifying PR programs while considering comorbidities might lead to greater improvement in outcomes. After PR, the important points are to follow prescribed home exercise programs, control programs in the PR center/unit, and being more active in daily living life for the purpose of preserving improvements. Tele-PR is an alternative to conventional modalities due to similar improvements. Although PR is effective, it is an underutilized resource. The awareness of PR should be increased in patients and among health professionals.

Keywords: PR, exercise capacity, quality of life, perioperative lung transplantation, EBVR

1. Introduction

Chronic obstructive pulmonary disease (COPD), a systemic progressive disease that results in reduced exercise capacity and quality of life, progressive dyspnea, and mortality. It causes health and economic burdens unless pharmacologic and nonpharmacologic treatments are optimized. One of the most important interventions is pulmonary rehabilitation (PR). It is a proven modality and is included in COPD treatment guidelines. The evidence-based benefits are improvement in exercise capacity and quality of life, recovery time after hospitalization, and survival; and reduction in perceived intensity of breathlessness, number of hospitalizations, and days in hospital; and enhancement of the effect of long-acting bronchodilators. Although most studies included patients with moderate-to-severe COPD and demonstrated evidence for these patients, PR is recommended for all patients who are symptomatic with reduced exercise capacity and quality of life, regardless of disease severity. PR is also an effective, feasible modality during the intensive care unit (ICU) period and early periods after exacerbation. The recommended time for PR is during the perioperative period in lung transplantation. Additionally, PR is required before endobronchial volume reduction (EBVR) and has shown to be beneficial before and after lung cancer surgery. This chapter outlines the pathophysiologies that give rise to indications for PR, the latest developments in PR, and PR modalities associated with COPD.

2. The definition of PR

PR is described as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior changes, that is designed to improve the physical and psychological conditions of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviors [1]."

3. Pathophysiologies indicated for PR

3.1. Exercise limitation

Exercise intolarence is one of the most important and common symptoms experienced by patients with mild-to-severe COPD and are related to reduced health-related quality of life. Exercise intolerance in patients with COPD is primarily due to impaired ventilatory mechanics, but it is also associated with gas exchange limitation, cardiovascular factors, peripheral skeletal muscle dysfunction and a combination of these [2, 3]. Additionally, anxiety and poor motivation are other factors of exercise intolerance. Although the exact association has yet to be found, it is thought that anxiety and depression contribute to exercise intolerance [4], due to the effect that these have on increased symptom perception [5, 6].

Ventilatory limitation: Multiple factors determine ventilatory limitation, which consists of abnormalities in ventilatory mechanics and ventilatory muscle function. Other reasons for ventilatory limitation are increased ventilatory demands as a result of changes in gas exchange, and discordance in the neuroregulatory control of breathing. The most important pathophysiology in patients with COPD is expiratory flow limitation. During exercise, air becomes trapped, which results in dynamic lung hyperinflation (DH) above the already increased resting volumes. Additionally, DH inhibits tidal volume expansion during exercise and contributes to cardiac dysfunction by increasing the positive intrathoracic pressures, which likely contribute to cardiac impairment [7].

Gas exchange limitation: Hypoxia is likely to limit exercise tolerance. Hypoxia increases pulmonary ventilation by enhancing output of peripheral chemoreceptors and production of lactic acid. Lactic acidemia results in increased pulmonary ventilation because of an increase in carbon dioxide production due to buffered lactic acid [8]. Above the lactic threshold, severe dyspnea correlates with increased work rates. Dyspnea may quickly increase. Furthermore, plasma norepinephrine and epinephrine also increase during exercise [9, 10].

Cardiovascular factors: In patients with COPD, the cardiovascular system is influenced by various mechanisms. The most important is an increase in right ventricular afterload through elevated pulmonary vascular resistance from direct vascular injury [11, 12], hypoxic vasoconstriction [13], and/or increases in effective pulmonary vascular resistance due to erythrocytosis [14]. In the course of time, the overloaded right ventricle leads to right ventricular hypertrophy, which could result in right ventricular failure [15]. During exercise, pulmonary vascular resistance is rapidly increased due to breathing at lung volumes close to total lung capacity [16, 17]. Lung hyperinflation and excessive expiratory muscle recruitment are likely to reduce venous return and right ventricular preload in COPD [18, 19]. Moreover, during exercise, large intrathoracic pressure swings for the purpose of overcoming the increased elastic and resistive loads, may result in left ventricular dysfunction by increasing left ventricular afterload [20, 21]. These right ventricular effects can also compromise left ventricular filling through septal shifts that further reduce the ability of the heart to meet exercise demands [22].

Peripheral skeletal muscle dysfunction: Skeletal muscle dysfunction in patients with COPD is characterized by remarkably decreased muscle strength and endurance. The mechanisms are reduction in muscle mass and proportion of oxidative fibers, increases in the proportion of glycolytic fibers and muscle atrophy, and also a detoriation of oxidative metabolic capacity due to reductions in mitochondrial enzyme activities and capillary density. Additionally, systemic inflammation; malnutrition; corticosteroid use; hypoxemia; aging; smoking; the production of reactive oxygen and nitrogen species; enhanced protein degradation inside muscle fibers; increased activities of the proteasomal and lysosomal pathways; and activation of calpains and caspases contribute to muscle dysfunction. Therefore, patients with COPD enter into a vicious circle owing to disuse and inactivity due to the aforementioned mechanisms [23].

3.2. Body composition disorders

Unexplained weight loss occurs in about 50% of patients with severe COPD and 15% of patients with mild-to-moderate COPD [24, 25]. The main cause of weight loss in COPD is the reduction in skeletal muscle mass rather than loss of fat mass. Based on the reduction of fat mass or fat-free mass index (FFMI), nutritional abnormalities in COPD have been categorized into four types. Normal body mass index (BMI) with normal FFMI is normal, low BMI with normal or above-normal FFMI is defined as semistarvation, normal or above-normal BMI with low FFMI is defined as muscle atrophy, and low BMI with low FFMI as cachexia [26]. There are several reasons for weight loss in patients with COPD, even if during a stable period. In patients with stable COPD, there is an increased metabolic rate due to abnormal respiratory dynamics, chronic systemic inflammation, and drugs [27–31]. In malnourished mobile patients with COPD, although the basal metabolic rate is reduced, the resting energy expenditure is high. During exercise, inefficient muscle contractions due to increased consumption of adenosine triphosphate are added on. Also, there is an increase in the levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL) 1 in circulation. TNF-α and IL1 have been shown to contribute to weight loss even in healthy individuals [32].

3.3. Psychological status

Patients with COPD have a higher prevalence of depression and anxiety than the general population [33] and a higher risk for developing depression [34]. The etiology of the association between depression and COPD has not been revealed clearly. The most important risk factor for COPD is smoking. Depressed individuals are more likely to smoke [35], have a tendency to smoking [36, 37], and find smoking cessation more difficult [35, 38]. Conversely, smokers are more likely to be depressed [39], which could be caused by activation of nicotinic acetylcholine receptors [40], and the inflammatory effects of smoking [41]. Soluble tumor necrosis factor receptor-1 has shown to be associated with rates of depression in patients with COPD [42], but there is not exact relationship between TNF-α and COPD [43, 44]. Hypoxia is thought be an additional factor in the development of depression in COPD. Low arterial oxygen saturation has been shown to be associated with periventricular white matter lesions [45], which are found in patients with depression [46]. Other important risk factors are the severity of symptoms and reported quality of life [47]. Depression is found more frequently in support-bound patients with COPD [48].

4. Content of PR programs

4.1. Exercise training

Exercise training is a cornerstone of PR programs. Exercise training is shown to be the best approach for increasing muscle strength, is likely to improve motivation for exercise, reduce mood abnormalities [49, 50], decrease symptoms [51], and improve cardiovascular function [1]. As recent major guidelines recommend, the main components of exercise training programs for patients with COPD are endurance and resistance training, which should be included in PR programs. Although none of the guidelines make clear, specific, and accurate recommendations for whole exercise training, they agree on endurance training at least 3 to 5 times weekly >60% of the maximal work rate. However, there is no consensus of initial workloads or in increasing the exercise load or program duration; the duration of exercise is recommended for at least 20 minutes and a target program duration of up to 12 weeks [52].

Inspiratory muscle training (IMT): Respiratory muscle training is a part of rehabilitation in selected patients with COPD. Respiratory strength has been found to correlate with improved pulmonary function, reduction of dyspnea severity, improved exercise tolerance, and enhanced functionality and quality of life [53, 54]. IMT is thought to contribute to contraction of the diaphragm by increasing type II fibers [55], which results in reduced inspiratory time [56] and subsequently increased expiratory time. Hyperinflation is expected to eventually diminish [57]; therefore, IMT is thought to impact on dyspnea without any significant change in inspiratory pressure [58, 59].

Neuromuscular electrical stimulation (NMES): NMES is one of the recent rehabilitation modalities that involve passive stimulation of contraction of the peripheral muscles through the application of an electric current via electrodes placed on the skin over the targeted muscles by depolarizing motor neurons. It aims to elicit beneficial training effects without causing dyspnea in patients who are unable to participate in PR programs. The stimulation-pulse duration is usually 250–400 μs, and stimulation frequency ranges from 8 to 120 Hz. Intensities range from 10 to 100 mA, and these are gradually increased throughout the entire stimulation according to the patient's individual tolerance. In a meta-analysis published in 2016, it was found that NMES improved quadriceps strength and exercise capacity; however, there was no statistically significant improvement in the degree of health-related quality of life in patients with moderate-to-severe COPD [60]. In several studies, it has been reported that NMES had an impact on the increase in type II fiber cross-sectional area with a decrease in type I fiber cross-sectional area of the muscle, and on the decrease in muscle oxidative stress in patients with COPD. Owing to the fact that NMES has a low impact on ventilation, heart rate, and dyspnea, it could be applied during periods of exacerbation, and during admission to the ICU for acute COPD exacerbation [61, 62].

Recent exercise training approaches: Besides conventional exercise trainings, there have been a few papers published recently about alternative exercise training modalities in patients with COPD. According to these studies, water-based rehabilitation [63] and tai chi were found as well tolerated and enjoyable [64, 65].

4.2. Other interventions

PR programs should be comprehensive and individualized according to patients' needs. Other interventions are breathing strategies, bronchial hygiene techniques, psychological and nutritional recommendations and support if needed, and education of patients and care givers. Body composition abnormalities, especially malnutrition, have already been found to increase risks of mortality among patients with COPD. A significant improvement has been shown in pulmonary function in patients with COPD who have a higher fat, lower carbohydrate diet than the traditional high-carbohydrate diet [66]. Omega-3 polyunsaturated fatty acids (PUFA) have been shown to have an antiinflammatory effect and be effective in patients with COPD [67]. It is also important to relapse any deficiency of vitamin D due to the association with early progression, myopathy/muscle weakness, and the immune-modulatory effect of vitamin D [27].

5. Outcomes and response to PR

It has been demonstrated that PR is the most effective therapeutic approach for improving dyspnea, health status, and exercise tolerance [68]. It is also one of the most cost effective therapeutic strategies. Additionally, it reduces hospitalizations among patients who have had recent exacerbations [69]. Improvements are seen among all grades of COPD severity, but recommendations are stronger in moderate-to-severe COPD. In some studies, improvements of outcomes were seen regardless of baseline lung function, dyspnea, and exercise capacity [70].

5.1. Exercise capacity

Various exercise tests are used for evaluating exercise capacity, the mechanisms of main disruption, and the response to PR. Some are also strong independent prognostic factors in patients with COPD. There are several laboratory-based exercise tests that use either maximal incremental or constant workload protocols to evaluate exercise performance after PR. Field tests are more widely used and more practical to perform. The six-minute walk test (6MWT), incremental and endurance shuttle walk test (ISWT, ESWT) are standardized and have also been used in PR and various clinical trials. In COPD, endurance tests [constant work rate exercise test (CWRET) and ESWT] are more responsive to interventions than other types of tests. The cycle ergometer CWRET has been used more widely than ESWT. By using CWRET, the work rate, inspiratory capacity, and isotime responses, which verify potential mechanisms of improvement or deterioration, are accurately measured [71].

The ISWT is a significant predictor of survival, readmission, and is usually sensitive to PR in patients with COPD [72]. In a recent meta-analysis of nine trials, a mean improvement of 38 m was found [68]. After recovering from a stay in the ICU, ISWT was found to improve by a mean of 64 m after rehabilitation [72]. ESWT duration was found as moderately correlated with FEV1, but not with muscle mass or strength in patients with COPD [73]. ESWT is responsive to PR improving by 100–400 s. [71]. According to a meta-analysis of rehabilitative interventions in COPD, the mean effect of rehabilitation on 6MWD was 44 m when treatment and control groups were compared [74].

Peak oxygen uptake (V′O2peak) shows the highest oxygen uptake during incremental exercise tests by achieving the subject's limit of tolerance. With good subject effort, V′O2peak is closely reflective of the subject's "maximum" V′O2, the gold standard index of aerobic capacity [75]. There is very little information about what constitutes a minimal clinically important difference (MCID) in V′O2peak. In the National Emphysema Treatment Trial (NETT), 4 ± 1 W was considered the symptoms-anchored MCID in patients with severe COPD [76], with a V′O2peak change of $\sim 0.04 \pm 0.01$ $L \cdot min^{-1}$. In several studies including patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2–4 COPD V′O2peak has been shown to moderately significantly increase after lower limb endurance muscle training. After PR in patients with COPD, V′O2peak was found to be in the range 0.1–0.5 $L \cdot min^{-1}$ or ~10–40% of baseline, with a mean improvement of ~11% [77, 78].

5.2. Health-related quality of life daily living activities

In a recent study, it was aimed to determine the responsiveness of St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), COPD Clinical Questionnaire (CCQ), and Hospital Anxiety and Depression Scale (HADS) to PR in 419 patients with COPD, and also estimate the MCID for CAT, CCQ, and HADS. It was demonstrated that SGRQ, CAT,

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CCQ, and HADS were responsive to PR in patients with moderate-to-very-severe COPD. The calculated MCID ranges were −3.0 to −2.0 points for CAT; −0.5 to −0.3 points for CCQ; −1.8 to −1.3 points for HADS-A, and −1.7 to −1.5 points for HADS-D [79].

6. PR in special conditions

6.1. Before and after transplantation

Lung transplantation is a recommended intervention in patients with advanced-stage pulmonary disease who are unresponsive to pharmacologic and nonpharmacologic treatment. Factors such as chronic respiratory failure, cardiovascular risk factors, muscular and nutritional conditions, which are likely to influence the prognosis for a successful lung transplantation, usually accompany advanced chronic respiratory disorders. Therefore, PR is an important approach that modifies and controls potential risk factors. PR plays an important role for the maintenance of exercise tolerance and physical functioning [80] both before and after the lung transplantation because common extra pulmonary manifestations could be persistent or deteriorate. As such, PR is recommended both before and after lung transplantation. Although there is an absence of a specific PR protocol for patients for lung transplant, it was shown to improve maximal and functional exercise capacity, quality of life, and skeletal muscle function [81].

Before transplantation: The role of PR in preoperative patients is essential for quitting smoking, improving body composition, optimizing medical treatment, and restoring patients' independence for functioning, relieving symptoms, decreasing disability, and improving quality of life by increasing their participation in social and physical activities. It has been shown that the rate of success in lung transplantation was linked to exercise capacity and resting carbon dioxide in arterial blood values [82]. Those parameters were also found to predict hospital stay after surgery and mortality. Additionally, pretransplant PR was also found to be associated with decreased posttransplant ICU days, mechanical ventilation, and chest tube days and survey [83]. Multidisciplinary, comprehensive PR must be individualized and the modality and intensity of training must be selected for each patient. The duration of training can vary from 6 weeks to 6 months [84]. The program should consist of education (including the following topics: bronchial hygiene, breathing control techniques, relaxation, education about COPD, and education of relatives and energy conservation), exercise training (upper and lower limb aerobic exercise, resistance training, flexibility, inspiratory muscle training), psychological support, and nutritional support. The intensity of exercise is dynamically increased according to the progress of each individual patient.

After transplantation: Although pulmonary functions are improved after transplantation, limited exercise capacity is persistent due to different mechanisms. Persistent limited exercise capacity is not only associated with ventilatory or cardiovascular factors [85, 86], skeletal muscle dysfunction is the main problem. Skeletal muscle changes include impaired oxidative capacity, lactate threshold changes, and a lower proportion of type I muscle fibers [87]. A sedentary life style both before and after transplantation contributes to skeletal muscle weakness [88]. Hospitalizations due to infections or acute rejections and the use of immunosuppressive medication further impact muscle function in lung recipients [89]. It was found that V′O2 peak was 45–52% predicted in patients after lung transplantation for up to 2 years. Patients stop exercise because of leg fatigue, rather than dyspnea [90]. Additionally, maximal cycle-work capacity correlates better with isokinetic cycling work capacity than with pulmonary function after lung transplantation [91]. PR should be started in the ICU with positioning of the patient, ventilation of all lung lobes, and mobilization of secretions by managing cough. Deep breathing exercises should be initiated because tachypnoea and pursed-lip breathing persist postoperatively and old breathing patterns must be overcome. Sitting and mobilization out of bed should then be performed. After all chest drains have been removed, walking or cycle ergometry should performed. Muscle strength and function, and endurance training should focus on lower extremities, and weights can be limited to 3 kg initially for upper extremities [92]. After discharge, patients should be referred to PR center/units as soon as possible. Although there is no consensus on optimal exercise training and education programs, aerobic and strength exercise training of the lower and upper extremities 2–3 times per week for 6–8 weeks, are recommended. The intensity of exercise can be increased according to patient tolerance. High-intensity aerobic exercise training at 60–80% of maximal work capacity has been found to be correlated with physiologic improvements in patients with stable COPD. Hence, high-intensity training is preferred. Interval training could be applied in patients who cannot sustain continuous high-intensity. Stretching, flexibility, and chest-mobility exercises may also be an important component of exercise after LVRS or transplantation [1, 82, 93]. Education of patients and care givers is also an important issue.

6.2. Lung volume resection surgery (LVRS)

Similar recommendations are valid for LVRS, which is not usually an effective intervention for exercise intolerance and functional disability. Baseline skeletal muscle dysfunction, time needed to achieve postoperative improvement in lung function (peak benefits are usually seen 6–12 months after surgery), and inactivity/immobility associated with the perioperative period are factors that reduce exercise capacity. Several studies compared the benefits of LVRS and several-weeks'–duration comprehensive PR in patients with severe emphysema. PR was found to significantly improve exercise tolerance, health status, and dyspnea, without significant changes in lung function as compared with PR and LVRS, even if highly selected patients showed significantly better improvement in lung function [94–97], exercise capacity [95–97], and quality of life [96, 97].

6.3. Endobronchial volume reduction (EBVR)

Endobronchial volume reduction interventions result in improved spirometric measures and 6MWD at 6 months, only if in correctly selected subjects. PR is recommended before and after EBVR, which is indicated in the presence of persistent dyspnea despite maximal medical therapy and PR, and reduced exercise capacity (6MWD ≥140 m after rehabilitation) [97].

6.4. Lung cancer

In patients with lung cancer, exercise limitations can be due to the effects of the cancer, coexisting morbidities, and/or the effects of treatment and surgery. Cancer-related anemia, and muscle atrophy and dysfunction contribute to limited exercise capacity. Inactivity due to cancer and its comorbidities further compound this situation. In the pre- and postoperative period, quitting smoking, optimizing COPD medical treatment, educating patients, prophylaxis for thrombosis, and PR are the recommended approaches that decrease risks. PR is an effective and feasible intervention before and after surgery, during the chemotherapy period, and as a component of palliative care. Even though PR consists of an exercise program for lower and upper extremities, breathing, airway clearance techniques, oxygen therapy, bronchodilator optimization, and self-management training similar to other conditions, it should also be individualized and multidisciplinary in patients with cancer.

Even though surgical procedures have improved and patients are highly selected, morbidity and mortality rates are still increasing as a consequence of cardiopulmonary complications after surgery. Limited exercise capacity as a modifiable risk factor is the best independent predictor of postoperative complications. Multidisciplinary preoperative PR improves exercise capacity and postoperative recovery, and reduces hospital stay and pulmonary infections [98]. During the chemotherapy period, symptoms such as fatigue, breathlessness, and quality of life are likely to deteriorate. Exercise training improves fatigue, aerobic capacity, muscular strength, and physical and functional activity in patients with cancer, even though they are undergoing chemotherapy [99]. Breathing techniques and medications that result in reduced inflammation and opened airways in combination with exercise training have recently become a part of supportive care for patients undergoing chemotherapy and radiation therapy [100]. PR plays a role in the management of terminal cancer. Exercise training modalities include walking with/without assistance or device, passive or active strengthening exercises, continuous passive motion, passive or active range of motion, NMES, and pain management interventions such as massage and heating pads [101]. Oxygen therapy has an important role in palliative care because it both treats hypoxemia and reduces the sensation of dyspnea. Additionally, education about mobilization with assistive devices, environmental modification, energy conservation, and work simplification techniques are also beneficial. These interventions have been investigated and were shown to be effective in cancer-related fatigue in several studies [102–104]. In another study, it was shown that exercise training decreased anxiety, stress, depression, and there were improvements in pain, fatigue, shortness of breath, constipation, and insomnia in patients with cancer, even at advanced stages [105].

6.5. Exacerbation of COPD

COPD exacerbations are known to deteriorate life quality, disease progression, and mortality. The British Thoracic Society (BTS) recommends the initiation of PR within 1 month of hospital discharge after exacerbation, consisting of a minimum of twice-weekly supervised sessions lasting between 6 and 12 weeks [106]. Exercise should combine progressive muscle resistance and aerobic training [106]. Systematic reviews have shown that quality of life and daily functioning were improved with large and important clinical effects of PR [107, 108]. According to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines of management of COPD exacerbations, PR added to medical treatment during hospitalization increases mortality [109]; however, NMES and resisted quadriceps exercises performed during hospitalization during exacerbation have been shown to improve muscle strength without increasing systemic inflammation. PR that is started within 3 weeks of discharge following a COPD exacerbation reduces hospital admissions, improves quality of life, and also increases exercise capacity when implemented within 8 weeks of discharge. Although the best approach is indistinct and further investigations are necessary, a combination of regular exercise with breathing technique training has been shown to be superior [109].

6.6. PR in the intensive unit care

In the ICU, skeletal muscle mass is lost at a rate of 5% per week. This neuromuscular weakness has been found to be correlated with the duration of mechanical ventilation, and associated with functional disability and decreased quality of life for up to 5 years after hospitalization. Mobilization and rehabilitation of critically ill patients might improve physical functioning and decrease duration of mechanical ventilation and ICU length of stay [110, 111]. A meta-analysis was published in 2017 that consisted of studies with PR programs containing patient mobilization, walking, standing, breathing exercises, in-bed supine cycle ergometry, passive-active range of motion (ROM), and NMES. It was shown that early mobilization and physical rehabilitation of critically ill patients seemed to be safe, with a low risk of potential safety events, even if as a usual care. Although the definition of safety assessments was heterogeneous, it was emphasized that the awareness and implementation of existing recommendations should be increased [112].

6.7. Patients with hypercapnia

Hypercapnia is an indicator of alveolar hypoventilation due to an overload on the ventilatory pump that is greater than its capacity. In patients with COPD, diminished ventilatory response usually results in chronic retention of carbon dioxide. Chronic respiratory failure is frequently seen in the end stage of the progression of COPD. In the BTS guidelines, it is mentioned that patients with chronic respiratory failure gain as much benefit as those without chronic respiratory failure from PR with level 3 evidence [106]. A study showed that pCO2 levels were significantly more reduced in patients with COPD with pursed-lip and diaphragmatic breathing exercises during hospitalization period than in a control group. It was suggested that respiratory exercise training was quite effective in reducing pCO2 levels. As the guidelines recommend, patients with COPD should be referred for PR regardless of having chronic respiratory failure [113].

Noninvasive mechanical ventilation (NIMV): Noninvasive mechanical ventilation (NIMV) reduces breathlessness and increases exercise tolerance by reducing the acute load on the respiratory muscles. According to these mechanisms, the effect of NIMV on PR outcomes has been investigated in several studies in which NIMV was applied during exercise training or at night. In a review of the Cochrane Database in which the effect of NIMV was investigated during exercise training as a part of PR, it was shown that NIMV during exercise training improved exercise capacity of the lower limbs, and enabled exercise at higher training intensities. There was no definite evidence about quality of life and none of the studies investigated the effect of NIMV during exercise training on physical activity [114]. It has also been shown that exercise tolerance and quality of life were improved in patients with severe COPD using nocturnal NIMV after PR, presumably through resting the respiratory muscles at night [115]. As a recommendation of the ERS/ATS guidelines, NIMV could be an adjunctive therapy to unload the respiratory muscles for the purpose of increasing the intensity of exercise training in selected patients with severe chronic respiratory disease who have a suboptimal response to exercise [1].

6.8. Comorbidities

The most common comorbidities associated with COPD are cardiovascular disease, orthopedic problems, metabolic disease, depression, and anxiety. It is expected that comorbidities may effect the outcomes of PR as an impact on COPD outcomes such as quality of life, health care costs, and mortality rate. Various comorbidities such as anxiety and depression, cardiovascular disease, metabolic disease, and osteoporosis affected PR outcomes in some studies [116–121]; a meta-analysis could not be performed according to the heterogeneous results. Only four studies investigated the influence of the number of comorbidities on PR outcomes. Three of which showed that the number of comorbidities was not related to PR outcomes [117, 119, 120]. A study showed that metabolic disease negatively influenced 6MWT distance, whereas cardiac disease negatively influenced the St. George's Respiratory Questionnaire [118]. A prior study of patients with COPD with osteoarthritis and neurologic problems who were assigned to water-based exercise training reported a greater improvement in outcomes compared with land-based exercise training [121]. Previous studies have identified that patients with psychiatric problems experienced a lesser improvement in dyspnea [117], and patients with metabolic disease demonstrated a greater improvement in dyspnea after PR compared with controls [118]. A study was published in 2017 that included 165 patients with COPD with exercise limitations. Comorbidity was classified as cardiac, metabolic, orthopedic, behavioral health problems, or other diseases. Comorbidities were found to have no effect on the maximal incremental exercise test and constant workload cycle endurance time after PR. Patients with cardiac disease were found to have greater improvements in dyspnea scores than those with no cardiac disease, and patients with orthopedic problems had a smaller but clinically significant improvement in dyspnea after PR [122]. Modifying PR programs with consideration to comorbidities might lead to greater improvement in outcomes, but how to structure programs according to comorbidities is still to be determined.

7. Follow-up programs of PR and Tele-PR

The best and the most effective follow-up program have not been found. After PR, the important points are to follow prescribed home exercise programs and follow-up programs in the PR center/unit, and to be more active in daily living life for the purpose of preserving improvements. Accordingly, family members have a role that is as important as that of the PR center staff in encouraging and motivating the patients. In a cohort of patients with COPD who completed a 10-week comprehensive PR program, a structured follow-up home program was prescribed and the patients were monitored for 1 year. At the 1-year follow-up evaluation, only the patients who continued with the home program had maintained the improvements of the initial PR program in endurance capacity, and psychological and cognitive functioning [123, 124]. Despite the clear benefits of PR, it is often an under-utilized resource. Limited access and poor adherence result in <5% of eligible people with COPD receiving PR each year. Although the traditional models of inpatient and outpatient PR are suitable for many patients, alternative models may also be effective and may improve patient access, particularly in regions or healthcare systems where traditional models of PR are not feasible. For example, tele-rehabilitation, which links expert rehabilitation healthcare providers with others at a remote site or with patients in their homes, also has the potential to improve access [125]. A recent study showed that home-based maintenance tele-rehabilitation was equally as effective as hospital-based, outpatient, maintenance PR in reducing the risk for acute exacerbations of COPD and hospitalizations with lower risk for emergency department visits. It was suggested that tele-rehabilitation was likely to be an effective alternative strategy to hospital-based, outpatient, maintenance PR. In addition, it had a potential economic advantage compared with standard PR [126]. Tele-PR has been developed to improve patients' participation and treatment adherence, but the most important point is awareness. The awareness of PR should be increased in patients and among health professionals.

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