CHAPTER 21

Rehabilitation in chronic obstructive pulmonary disease

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Pulmonary rehabilitation is a branch of medicine that requires a knowledge of both chest medicine and rehabilitation medicine; whereas chest medicine is a subspeciality of internal medicine, the scientific role of rehabilitation medicine were only discovered 1994 [1]. As a consequence, pulmonary rehabilitation remained an art for a long time, rather than science-based medicine. Nowadays the scientific evidence for the effectiveness of pulmonary rehabilitation is overwhelming [1–4]. Well designed studies have been conducted since the 1980s, so that statements on the efficacy of pulmonary rehabilitation programmes may now be made with a high degree of certainty [5–8]. More recently developed treatments for chronic obstructive pulmonary disease (COPD), such as transplantation and volume reduction surgery have further strengthened the interest in pulmonary rehabilitation [9]. At present, all the available evidence points to the fact that pulmonary rehabilitation appears as a well-established part of the treatment of COPD. Although most clinical trials are conducted in moderate-to-severe patients, significant effects can be anticipated in all stages of the disease, including mild disease [10] and very severe disease. Chronic oxygen therapy and ventilatory assistance, which are often considered part of pulmonary rehabilitation programmes, are discussed in Chapters 15 and 17, respectively, and will therefore not be addressed in the present chapter. The application of these interventions during exercise training, however, will be discussed.

Definition and rationale

Many organisations have proposed definitions of pulmonary rehabilitation [2, 3, 11–13]. These definitions are primarily applied to patients with COPD, although they are clearly also applicable to other patients, such as patients with interstitial lung disease, kyphoscoliosis, mucovisidosis or systemic disorders. A recent joint task force of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) defined pulmonary rehabilitation as follows.

"Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce healthcare costs through stabilising or reversing systemic manifestations of the disease" [6].

Eur Respir Mon, 2006, 38, 337–358. Printed in UK - all rights reserved. Copyright ERS Journals Ltd 2006; European Respiratory Monograph; ISSN 1025-448x.

This is a general definition which underscores that pulmonary rehabilitation is an essential part of the management of patients with chronic lung diseases. It is important that the intervention is quoted as "evidence based". In addition, it underlines the fact that the aim of the intervention is not to improve lung function, but rather to enhance the patients' active involvement in everyday life.

The present chapter will focus primarily on various aspects of rehabilitation in COPD patients, as most evidence is currently obtained for this patient category. In addition, currently COPD is the most frequent lung disease referred to pulmonary rehabilitation [14]. For the purpose of the present chapter, an operational concept of pulmonary rehabilitation will be used that is distinctly different from the definitions proposed by the American College of Chest Physicians, the National Institutes of Health, or the ERS and ATS task forces. This is done because these definitions are very general, comprising all possible aspects of treatment of COPD, and thus do not offer insight into how the selection of candidates for rehabilitation is performed in practice. Therefore, the present authors propose another concept that is more specific and indicates which patients with COPD are good candidates for pulmonary rehabilitation and which patients are not. The primary problem of patients with COPD is airflow limitation and slowing of expiratory flow [15]. The primary treatment for COPD patients is thus directed at improving airflow limitation by bronchodilators and anti-inflammatory agents. Since COPD is typically defined as not fully reversible airflow limitation, treatment with bronchodilators will often not result in a substantial effect. Therefore, despite optimal treatment with bronchodilators and anti-inflammatory agents, a functional deficit (impairment/disability/handicap or perhaps more modern impaired bodily function, reduced functional status and impaired participation) will often persist. This functional deficit is important for the patients and is associated with a reduced survival rate, worsened symptoms, reduced quality of life, reduced exercise capacity and increased medical consumption [2].

Indeed, recently mortality of COPD patients was best predicted using a composite score which also included, besides forced expiratory volume in one second (FEV_1), functional exercise tolerance (6-min walking distance), symptoms of dyspnoea (the Medical Research Council (MRC) scale) and the patient's nutritional status (body mass index) [16].

There is accumulating evidence that deconditioning and muscle weakness are important elements in this functional deficit [17–22]. Pulmonary rehabilitation programmes address this functional deficit with a multidisciplinary programme consisting of physiotherapy, exercise training, occupational therapy, education aimed at improving self-management and dietary measures. At present there is good evidence for the effectiveness of exercise training [4–6, 23–30].

It has been shown that nutritional interventions in combination with exercise training may increase fat-free mass (FFM) in subgroups of patients (see below) [31]. In specific subgroups of patients with a recent hospital admission for acute exacerbations, there is increasing evidence that programmes that enhance self-management may improve health-related quality of life and readmission rate [32, 33]. Although, intuitively and clinically, the other components of rehabilitation programmes may also be effective in certain patients, at present there is still little validated evidence for their efficacy in improving outcome variables in COPD patients. Moreover, there are no clear data on how COPD patients should be selected for these forms of therapy [13].

Aim

The aim of a pulmonary rehabilitation programme follows on from the above description. As with all other forms of medical treatment, this treatment may be directed at improving survival, symptoms, quality of life participation in daily life and reducing utilisation of healthcare recourses. The evidence available for each of these aims will be reviewed briefly.

Survival and utilisation of healthcare recourses

Several studies have analysed survival of COPD patients and pulmonary and systemic factors related to it. Briefly, the main determinant of survival across disease stages appears to be post-bronchodilator FEV_1 [34]. Additional determinants of survival are hypoxaemia, diffusing capacity, hypercapnia and pulmonary vascular resistance [35].

In a subanalysis of the Intermittent Positive Pressure Breathing trial, WILSON *et al.* [36] demonstrated an association between mortality and body weight, predominantly in patients with an FEV_1 >47% predicted. Other studies confirmed the association of reduced body weight and mortality in COPD [31, 37]. Several authors showed that mortality was higher in patients with a reduced FFM (often expressed as a function of height [2], as FFM-index) [38, 39]. Along the same lines, a recent study investigating the predictors of mortality concluded that mid-thigh cross-sectional area (related to muscle force and FFM) was a strong predictor of mortality, independent of the airflow obstruction [40]. Recently a composite score combining lung function, exercise capacity, body composition and symptoms was shown to predict survival more accurately [16].

These landmark studies have strengthened the idea that the systemic consequences of COPD are important factors in the prognosis and the morbidity of the disease. These studies also provide rationale for pulmonary rehabilitation to improve survival. Indeed, properly conducted pulmonary rehabilitation may increase walking distance, improve muscle function, reduce symptoms, and enhance nutritional status and FFM.

Several studies have claimed an effect of pulmonary rehabilitation on survival [11, 41]. All of these studies compared survival in patients involved in pulmonary rehabilitation programmes with historical controls. At present, however, none of the large prospective, randomised, controlled trials found a statistically significant effect on survival rate with pulmonary rehabilitation. A recent systematic review suggested a reduced relative risk for dying after pulmonary rehabilitation (relative risk reduction ~30%), but this did not reach statistical significance. As a consequence, the present conclusion is that it has not been satisfactorily demonstrated that pulmonary rehabilitation improves survival in COPD patients. It is important to note that ethical concerns may not allow for setting up of a study of sufficient size to demonstrate the effects of pulmonary rehabilitation. To do so, several thousands of patients should be offered pulmonary rehabilitation. Importantly, an equal number of patients should not be offered rehabilitation for a substantial amount of time, which would be unacceptable, given the effect of pulmonary rehabilitation of other relevant outcomes (see below).

It is important to realise that most studies have been conducted in stable COPD patients. A recent systematic review that focused on patients who underwent a rehabilitation programme immediately following an admission to the hospital due to a severe acute exacerbation suggested a statistically significant reduction in mortality [42]. It is clear that in this scenario, the mortality risk is significantly higher compared with the stable condition, and consequently the potential to improve survival is larger.

There is more direct evidence to support the effect of pulmonary rehabilitation on utilisation of healthcare recourses. One study, conducted in the 1980s [23], does not support this statement. However, there are two randomised controlled trials that show a benefit of multidisciplinary pulmonary rehabilitation on hospital days [25, 43, 44]. One large trial showed a benefit of a self-management programme, including home exercises and many components of regular pulmonary rehabilitation programme on hospital readmissions [32]. Additionally, there are many open studies comparing the utilisation of healthcare resources in the year prior to rehabilitation with the years following rehabilitation [12, 45–51], including data from a large study in the USA [14]. Furthermore, one trial showed a reduction in "mild" exacerbations, as assessed through diary cards [27]. In this trial, a similar, albeit nonsignificant, trend was seen for a reduction in hospital days. Hence, there is enough evidence to state that pulmonary rehabilitation may reduce utilisation of healthcare recourses. Since exacerbations are related to more rapid deterioration of lung function [52], it could be speculated that pulmonary rehabilitation may impact on disease progression. This tempting hypothesis, however, currently lacks support by strong data [53].

Symptoms

If pulmonary rehabilitation were to improve survival in COPD patients, and even if it did not improve survival of COPD patients, symptoms such as fatigue and dyspnoea still remain. There is a vast amount of literature showing that pulmonary rehabilitation improves symptoms in COPD patients [54–59]. Several studies have clearly demonstrated that after rehabilitation, dyspnoea is reduced at rest, during exercise and during daily living activities. Four studies are noteworthy in the present authors' opinion. Firstly, TOSHIMA *et al.* [60] studied 119 patients with COPD, randomly allocated to either an exercise training group (n=57) or an education group (n=62). These patients followed an 8-week outpatient-rehabilitation programme. In essence, the study showed that exercise capacity, measured as the endurance in a submaximal exercise, clearly increased in the training group, whereas no significant changes were observed in the education group. The study, therefore, clearly demonstrated that exercise training appears to be the active element of the rehabilitative treatment aimed at improving exercise capacity in COPD patients. The significance of improving exercise capacity is shown in a second study by O'DONNELL and WEBB [55]. They compared 23 elderly COPD patients following a rehabilitation programme with 13 control patients receiving the regular treatment for COPD. They studied the relationship between dyspnoea score and workload, and demonstrated that after a rehabilitation programme, there was a significant downward shift of the relationship between dyspnoea and workload downwards, such that at any given workload, dyspnoea was reduced. In addition, at a given work rate, symptoms of dyspnoea at isotime are significantly reduced [57, 61, 62]. A mechanism that may contribute to this downward shift is a significant reduction in ventilation at isowork, but also desensitisation to dyspnoea and enhanced inspiratory capacity at isowork [63]. Reductions in dyspnoea at isowork rate are equivalent after endurance and interval training [64].

These studies clearly showed that exercise-induced dyspnoea was reduced with pulmonary rehabilitation. In addition, several other instruments focusing on dyspnoea in daily life showed to be improved after exercise training. The study by O'DONNELL *et al.* [56] also demonstrated that after pulmonary rehabilitation, three classical dyspnoea scores, such as the Baseline Dyspnoea Index, the Oxygen Cost Diagram and the MRC Dyspnoea Scale, improved such that dyspnoea during daily living activities was also reduced. Probably the best evidence of improved dyspnoea in daily life is the systematic and clinically relevant improvement in the dyspnoea component of the chronic respiratory disease questionnaire, which specifically investigates dyspnoea during five activities with particular relevance to the individual patient [65]. Furthermore, nonrandomised studies suggested improvement of symptoms of dyspnoea using specific questionnaires assessing dyspnoea in daily life [66, 67]. It is clear that there is strong evidence that pulmonary rehabilitation improves symptoms, particularly dyspnoea. This is one of the effects of pulmonary rehabilitation which, at present, has been best documented.

Quality of life

Pulmonary rehabilitation clearly improves the health-related quality of life (HRQoL) in COPD patients (fig. 1). This contention is supported by all systematic reviews covering this topic since 1996 [4, 6, 73–76]. In a meta-analysis combining 23 trials available in medical literature, LACASSE *et al.* [65] found improvements in maximal exercise capacity and functional exercise capacity associated with improvements in HRQoL. More recently, a systematic review by TROOSTERS *et al.* [4] suggested that adding a pulmonary rehabilitation programme to the treatment of COPD patients yielded larger HRQoL benefits compared with adding another drug (fig. 1). For the feature dyspnoea, even the lower limit of the 95% confidence interval (CI) largely exceeded the minimally clinically important difference of 0.5 points (where the lower limit of the CI=0.73 points, mean 0.98 points), and the overall treatment effect was substantially larger than the minimum clinically important difference. At present, there appears to be conclusive evidence that pulmonary rehabilitation improves quality of life in COPD patients. This evidence may make it necessary to consider pulmonary rehabilitation in a large proportion of COPD patients who have reduced quality of life. Interestingly, the effects in HRQoL seems dissociated from the effects on functional exercise tolerance [77]. This may be due to a different time course of the training effects [77], or due to the fact that in some patients, effects on quality of life are obtained without apparent effects on physiological function [78]. This is likely to be due to the other components, such as psychological counselling, occupational therapy and education, which may enhance components of HRQoLwith-out physiological improvement.

Components of a rehabilitation programme

Patient education

Education programmes are often part of pulmonary rehabilitation programmes [57, 58]. However, education was usually only found to improve the patients' knowledge of

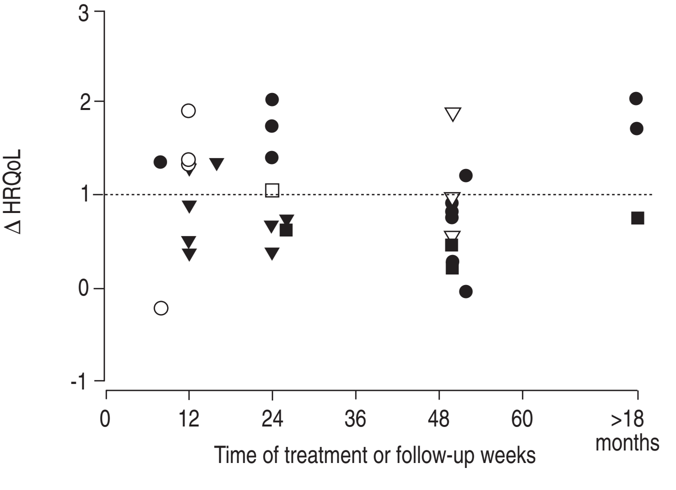

Fig. 1. – Effect of home- or community-based (○) [28, 68–70], outpatient (●) [25–27, 66, 68, 71, 72] or in-patient (□) [24] pulmonary rehabilitation compared with usual care on health-related quality of life (HRQoL), expressed as a fraction of the minimal clinically important difference (·········; 10 points for the Chronic Respiratory Disease Questionnaire, four points for the St. George's Respiratory Questionnaire) and different medication trials with inhaled corticosteroids (■), long-acting bronchodilators (▼) or combinations (▽). These trials are reviewed in an evidence-based review elsewhere [47]. Reproduced from [4] with permission.

their disease and did not necessarily improve self-management or change behaviour [79]. At present there are only a few structured studies on the effects of health education in COPD patients. These studies have largely failed to demonstrate any beneficial effect of education [23, 60, 80]. More recently, education has focussed more on enhancing self-management. Self-management is defined as any formalised patient education programme aimed at teaching skills needed to carry out medical regimens specific to the disease, guide health behaviour change and provide emotional support for patients to control their disease and live functional lives [32]. When patients at risk for hospital admissions follow these programmes they may result in significant long- and short-term reductions in hospital admission risk [32, 33]. It is of note, however, that in patients with significantly less risk for hospital admission, these programmes may be considerably less useful [81].

Smoking cessation is an important intervention in a rehabilitation programme. Improved appetite, reduced dyspnoea, a reduction in sputum production and improved pulmonary function are benefits of smoking cessation [76, 82, 83]. Individuals who smoke are also more prone to influenza infection [84]. The Lung Health Study [83] clearly demonstrated that smoking cessation improved pulmonary function. Smoking cessation, however, is difficult to achieve and only a few patients succeed in the long term. Nicotine replacement may slightly improve these results [85]. Psychological support may also be of benefit [86]. Unfortunately smokers are more likely to decline the invitation to take part in pulmonary rehabilitation [87].

Psychosocial support

Psychosocial support is another classical part of a rehabilitation programme focusing on restoring coping skills and learning stress management. The prevalence of psychosocial disorders in COPD patients is high [88, 89], with patients frequently exhibiting reactions such as depression, fear and anxiety associated with reduced functional capacity [90–92]. Neuropsychological benefits of pulmonary rehabilitation include significant reduction of depression, anxiety and improvement in general well-being [67, 93]. This improvement seems to be linked to continued participation in exercise programmes, since long-term benefits were seen only in patients who continued exercise training [94]. Psychotherapy, sometimes requiring a psychologist or psychiatric therapy, and psychopharmacological agents may, however, help patients to better cope with their disease process. At present very few controlled studies have been performed to identify the real benefit of psychosocial rehabilitation [93, 95, 96]. They virtually all showed beneficial effects.

Chest physiotherapy

The most commonly used technique to promote sputum expectoration is the forced expiratory technique [97, 98]. Postural drainage may also be of some benefit. The relevance of chest percussion and vibration which was recommended for many years has been questioned [99]. The effects of these techniques may be dependent upon the frequency at which vibrations and percussions are applied and this frequency may need to increase to 16 Hz [100]. Postural drainage should be reserved for individuals with large amounts of sputum of $>30\ mL\cdot day^{-1}$, when the problem is retention of secretions in the proximal airways [101]. It should be noted, however, that it is relatively difficult to measure sputum production. There is no evidence that postural drainage is useful for COPD patients with smaller amounts of sputum, either during acute exacerbations of COPD or with uncomplicated pneumonia [76]. The use of techniques, such as flutter breathing, lack validation in COPD. In cystic fibrosis, sputum rheology may change when the patient performs flutter breathing, but enhanced sputum production has not been shown [102]. One small study showed sustained bronchodilator effects of flutter breathing resulting in slightly improved exercise tolerance [103, 104]. However, the study needs replication before this technique should be widely applied. Pursed-lips breathing may be of benefit to selected patients to improve ventilation during exercise. It may result in slower breathing, enhancing the end expiratory lung volumes [105]; however, related improved exercise tolerance or reduction of symptoms is not guaranteed. Patients who are more likely to benefit from pursed-lips breathing are those with higher baseline breathlessness [106]. Diaphragmatic breathing seems of no benefit in patients with COPD, as it increases the work of breathing [107].

Exercise training

Impairment of exercise tolerance is a common problem in patients with COPD and, therefore, exercise training is an important component of all pulmonary rehabilitation programmes. There is substantial evidence demonstrating that exercise training is a mandatory component in pulmonary rehabilitation programmes [23, 60, 62]. Benefits of exercise training are largely related to the fact that the exercise capacity improves and, hence, at any given workload, a lower ventilatory requirement is necessary when blood lactate is reduced [30]. This allows the patients to perform activities of daily living with a smaller ventilation and consequently with fewer complaints.

Exercise training may improve oxidative capacity in peripheral muscles [64, 108, 109]. One study demonstrated that exercise training above the anaerobic threshold is more effective than training at lower intensity level [30]. Other studies support the contention that training at higher intenstity (*i.e.* >60% of the peak work rate) yields more favourable physiological training effects than training at lower intensities [110–112]. Suboptimal training intensity may have been one of the factors explaining why some programmes were unsuccessful in showing significant physiological training effects; it is clear that the training intensity is one of the factors that determines the success of a programme. Other patient-specific factors (*e.g.* systemic disturbance or disease stage) may also be factors linked to the overall success of training. Training should be conducted at high intensity, relative to the peak performance of the patient; thus, it may well be that this intensity is achieved at low absolute work rates [113]. Moreover, these effects were also present in patients with severe airflow limitation (FEV_1 <40% pred), who were often believed not to show a training response. It appears important to perform exercise testing before a training programme.

In order to fine-tune the training regimen, it is useful to determine the nature of the exercise limitation, *e.g.* cardiocirculatory, ventilatory, diffusion limitation, limitation in the pulmonary circulation, or peripheral muscle limitation. Subsequent exercise training may then be adapted to the individual needs of the patient. Since exercise physiology in COPD patients varies markedly, no consensus exists as to the best method of exercise training. Several methods have been shown to be successful, and these include endurance training, interval training and resistance training [114]. It remains questionable as to how training intensity should be modulated. In healthy subjects, training is normally targeted by means of percentage of maximal heart rate (60–90% pred) or the percentage of maximal oxygen uptake (50–80% pred) achieved [85]. Since, in COPD patients, exercise limitation will often not be related to cardiocirculatory factors, exercise physiology and training principles are likely to differ from normal subjects. Whether training should be based on the anaerobic threshold [30], a gas-exchange threshold [115] or on symptoms of leg fatigue or dyspnoea [116] remains to be determined. Programmes that used symptom scores (Borg rating 4–6) to increase training load gradually, but consistently, showed beneficial effects [26, 117, 118].

Including upper arm exercise, training may also yield significant effects. Some of the muscles used in the upper torso and arm positioning serve a postural function as well as a ventilatory function [119]. If the arms were trained to perform more work or if the ventilatory requirement for the same work were decreased, the capacity to perform activities of daily living could be improved. Several studies have demonstrated that arm training results in improvement in task-specific arm activities [120–123], even in critically ill patients [124].

An interesting recent study has suggested that dynamic hyperinflation, elicited by arm exercises, was reduced following arm exercise training [125]. It is noteworthy that some studies cast doubts as to the usefulness of unsupported arm exercises in addition to lower limb exercises [126]. This may well be true, as training effects appear to be highly specific, and upper limb mechanical efficiency is generally relatively better preserved than lower limb mechanical efficiency [127]. The clinical consequences of improved arm activities in COPD patients, however, remain largely unknown. Although no ideal duration has been established, 8 weeks is a common duration in many programmes, and should include at least 30-min sessions, 3–5 times a week, with the level of exercise being gradually increased [4, 6].

Muscle training

Specific skeletal muscle resistance training has become an increasingly important part of a rehabilitation programme. Two types of muscles may be trained: 1) ventilatory muscles and 2) peripheral muscles. In a meta-analysis of ventilatory muscle training, the effects of carefully designed inspiratory muscle training (monitoring pressures >30% of maximal inspiratory capacity) were reviewed [128]. This systematic review concluded that inspiratory muscle training did increase inspiratory muscle strength and endurance, and did reduce symptoms of dyspnoea. A related bonus towards improved exercise tolerance could not be confirmed in all trials; however, there was a tendency that studies including patients with respiratory muscle weakness at the beginning of the study did have an increase in exercise tolerance [128]. Hence inspiratory muscle training may be of benefit to patients who have functional limitations that are likely to be related to ventilatory muscle weakness or reduced ventilatory muscle endurance. Such limitations may include ventilatory limitations during exercise, hypercapnia and complaints of dyspnoea in disproportion to the ventilatory deficit [129]. In the context of pulmonary rehabilitation, there appears to be evidence that ventilatory muscle training in combination with whole-body exercise may enhance the effects of whole-body exercise on overall exercise capacity [130, 131]; however, not all studies had similar findings [132]. Therefore, whether ventilatory muscle training should be part of each pulmonary rehabilitation programme remains questionable. One research group has been particularly active in showing the effectiveness of respiratory muscle training. They suggested that expiratory muscle training had no benefits over inspiratory muscle training [133], and that inspiratory muscle training should be continued to maintain the benefits [134]. The same investigators recently also showed an effect on utilisation of healthcare recourses (*i.e.* fewer hospital days) in patients who underwent a long-term inspiratory muscle training programme [135].

Peripheral muscle training has gained increasing interest since the mid 1990s. Muscle weakness is an important systemic consequence of COPD in a significant number of patients. Several factors contribute to the observed skeletal muscle weakness. Among others, these include inactivity [136], repeated exacerbations [137], systemic inflammation, hypoxia and endocrine disturbances. Indeed, in many patients, hypogonadism was shown by very low circulating testosterone levels [138–140]; reduced testosterone levels have been associated with muscle weakness [140]. There are at least four well-designed studies showing that in COPD patients, muscle weakness is an important factor in exercise limitation. These studies demonstrated that exercise is commonly limited by complaints of muscle weakness and muscle fatigue [141], or that relationships between exercise capacity and peripheral [17, 19] or ventilatory muscle force [142] were present. One intervention study [22] convincingly showed that skeletal muscle fatigue is a factor limiting cycling exercises in a substantial number of patients, whereas in other studies, ventilatory factors were the dominant limiting factor. Moreover, there are two randomised studies demonstrating that improving peripheral muscle force in COPD patients improves exercise capacity and improves their quality of life [143, 144]. Several studies showed that the addition of resistance training to conventional endurance training may result in significantly more increment in muscle force [117], without compromising the endurance effects of training [145]. Others have shown comparable effects of endurance and resistance training [146]. The present authors believe that at present, there is sufficient evidence to incorporate peripheral muscle training into all pulmonary rehabilitation programmes. Replacing endurance exercise training by peripheral muscle training in patients in whom ventilatory or diffusion limitation severely limits exercise capacity is at least an intriguing idea, since the ventilatory stress during resistance training is relatively low [147]. One recent study has shown that the admistration of the anabolic hormone testosterone, aimed at restoring testosterone levels in hypogonadal men, may amplify the effect of a resistance training programme (fig. 2; [138]). This study would need confirmation in a larger trial, but the results are promising in showing the benefits of both resistance training and testosterone replacement in a selected group of patients.

Nutritional support

Weight loss in COPD is a common finding; ~20–30% of COPD patients are underweight [148, 149]. Moreover, depletion in FFM, which indicates loss of predominantly muscle mass, may be present despite normal body weight. It has been shown in several retrospective studies that weight loss [37, 150] and low body weight [151] are related to reduced survival rate, and two studies have even showed that weight gain is related to improved survival [31, 37]. More recently, three studies, one in Canada [40], one from the Netherlands [39] and one from Denmark [152], showed that depletion of FFM is particularly related to reduced survival rate, independent of body weight. Conversely, COPD patients are also commonly overweight. Although being overweight is not associated with increased mortality rate in patients with COPD, hypocaloric regimens are sometimes indicated in these patients in order to improve functional status. They should be combined with exercise/reactivation in order to compensate for the accompanying loss of FFM. In underweight patients, it would be logical to give caloric supplements to reverse weight loss or improve nutritional status. It should be noted, however, that undernutrition in these patients is not simply the result of reduced food intake alone, but is also related to increased energy requirements [153]. An increased resting metabolic rate, resting energy expenditure (REE) [154], as well as an increased total daily energy expenditure (TDE), have been shown [155]. The presence and underlying causes of an increased REE and TDE appear to be (partly) independent. Whereas the latter has been related to an increased oxygen consumption for activities [155], an increased REE has been related to persistent slow grade inflammation [156, 157]. Three placebo-controlled randomised trials in clinically stable in-patients showed a

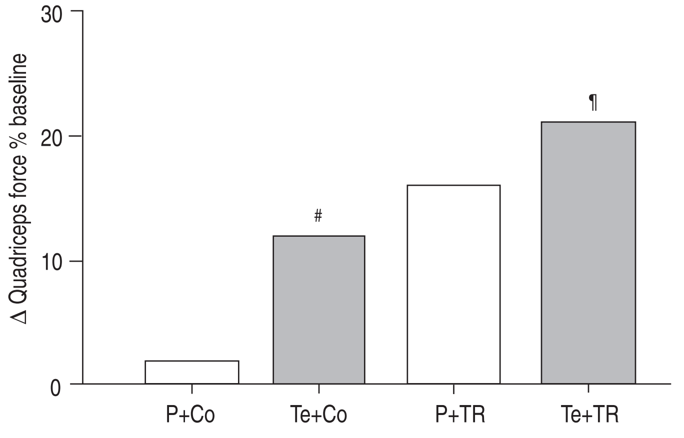

Fig. 2. – Effect of resistance training (TR) and testosterone (Te) replacement therapy (■) or placebo (P; □) on leg press; one repetition maximum. #: response to intervention significantly different from placebo plus no training group; ¶: response to intervention significantly different from nontraining groups. Co: control. Adapted from [138].

significant effect of oral nutritional support after 4 and 8 weeks on body weight, body composition and functional performance [158–160]. Over a short course of an exacerbation, nutritional supplements did increase calorie and, particularly, protein intake, but this did not result in short-term functional benefits [161]. To date, studies in COPD outpatients have been disappointing. This poor treatment response may be attributed, at least partly, to an inadequate assessment of the energy requirements [155] and to the observation that patients were taking the supplements instead of their normal meals.

The outcome of enteral nutrition in COPD may be limited by post-prandial dyspnoea, satiety and potential adverse effects of energy or nutrient load on the ventilatory system. Nutrition and ventilation are intrinsically related because oxygen is required for optimal energy exchange. It was suggested that standard formulae, which are usually rich in carbohydrates (50–60% nutritional supplements energy), would induce greater ventilation as a result of a higher respiratory quotient. Several randomised controlled studies compared the acute effects of high (50–100% nutritional supplements energy) and low carbohydrate (30% nutritional supplements energy) content, respectively, on immediate post-prandial energy metabolism at rest and during exercise in clinically stable COPD patients [162–165]. Adverse effects have indeed been demonstrated with high carbohydrate formulae, but only in studies that used high amounts of oral nutritional supplements (ONS; 916 kcal) that exceed the energy content of a normal meal and would therefore be difficult to incorporate into the daily pattern of meal consumption without affecting spontaneous food intake. ONS could also have acute adverse effects on intake of normal food by delaying gastric emptying time. One study showed adverse effects of a high-fat ONS compared with a standard ONS on gastric emptying time [166], and another study showed increased post-prandial dyspnoea after 250 kcal of a high-fat ONS compared with an equicaloric amount of high carbohydrate (= standard) ONS [167]. A more recent study showed the positive effects of small-sized carbohydrate- and protein-rich ONS on weight gain after 8 weeks when compared with normal-sized supplements of a similar macronutrient composition [168]. Hence, based on the available evidence, it can be concluded that in clinically stable COPD patients, it seems more relevant to consider portion size and daily distribution of ONS than macronutrient intake in order to avoid potential acute adverse effects of nutritional supplementation and to enhance compliance and efficacy of enteral nutrition.

As muscles are an important target in pulmonary rehabilitation, a combination of nutritional support with specific muscle stimulation, either by exercise or with supportive anabolic agents, appears a relevant option. Growth hormone has received considerable attention, as improved respiratory muscle function has been reported in COPD patients after 3 weeks of intramuscular administration [169]. A more recent study using a similar regimen, but in a placebo-controlled fashion, has shown a significant increase in FFM in the treated patients, but no associated functional improvement [170]. In a large clinical trial, SCHOLS *et al.* [171] investigated the physiological effects of a daily nutritional supplement either alone or in combination with anabolic steroids (nandrolone decanoate) for 8 weeks, as an integrated part of a pulmonary rehabilitation programme. All patients participated in a standardised general physical training programme, with particular attention to exercise in relation to daily activities, cycle ergometry, treadmill walking and swimming. A significant weight gain was seen despite a daily supplementation, which was smaller than in most previously reported studies. Nutritional support and exercise combined not only increased body weight, but also resulted in a significant increase in FFM and respiratory muscle strength. In the group additionally treated with a short course of anabolic steroids, the weight gain was similar to the group with nutritional support only, but a larger increase in FFM and a larger improvement in respiratory muscle strength were also present [171]. This observation is in keeping with other studies that administered anabolic steroids to COPD patients [138, 172, 173]. Despite an overall significant treatment effect of nutritional supplements in this trial [174], a substantial proportion of nonresponders was noticed. A *post hoc* survival analysis in this patient group revealed a significantly lower survival in the nonresponders compared with the responders [31]. Recently, STEINER *et al.* [175] found no additional benefit of nutritional supplements to exercise training, although, surprisingly, the authors reported some benefits, although only in patients who were not underweight at the outset of the study. Nutritional modulation of energy and substrate metabolism by so-called "nutriceuticals" are not yet widely recommended, but showed promising preliminary results. Polyunsaturated fatty acid replacement, for example, has been shown to improve exercise capacity in one randomised controlled study [176]. Creatine supplements resulted in enhanced FFM, muscle strength and skeletal muscle endurance, when added to classical pulmonary rehabilitation [177]. In summary, nutritional therapy offers not only supportive care, but also provides the potential for direct intervention through an improvement in muscle strength. In some patients, energy supplementation in combination with an anabolic stimulus (training, anabolic steroids, or specific nutrients) will be sufficient to obtain functional improvement. It can be envisaged that better patient selection for these adjunct therapies will be crucial to further breakthroughs in this field of research.

Selection of candidates and programmes

Although the effects of pulmonary rehabilitation have now been established, there is at present no unanimity as to which COPD patients constitute good candidates for pulmonary rehabilitation programmes. It is important to note that studies are by definition performed in selected patients. Few studies have attempted to identify those patients who would benefit most from pulmonary rehabilitation. Obviously patient motivation is crucial to be adherent to the proposed therapy. One study suggested that patients lacking social support were more likely to drop out from a rehabilitation programme, or were less likely to accept the invitation to participate [87]. Once enrolled in a multidisciplinary programme, no strong psychosocial predictors for nonadherence or training effects were found [67], and selection of the "best" candidates for exercise training remains difficult. In a study using discriminate analysis, only 30% of the variability in the training effect could be explained from baseline measures [73]. Data from ZuWallack *et al.* [178] have shown that a smaller 12-min walking distance and a greater FEV1 were significantly predictive of improvement in the 12-min walking distance after a 6-week outpatient rehabilitation programme. A study by Maltais *et al.* [113] demonstrated that increases in maximal oxygen uptake, maximal load and reductions in exercise ventilation were significant and of similar magnitude in patients with an FEV1 <40% and >40% pred. The decrease in lactic acid for a given work rate reached statistical significance only in those patients with an FEV1 >40% pred. The significance of FEV1 in selecting candidates for a training programme thus appears limited. As clear evidence is available demonstrating that a training programme improves quality of life in COPD patients [4, 65], patients with low quality of life appear to be good candidates. Moreover, since muscle weakness [17, 19] and early onset muscle fatigue [22] are related to exercise capacity and to utilisation of healthcare recourses [20], peripheral and ventilatory muscle weakness should also be considered in the selection of candidates. Recently, a study by Plankeel *et al.* [179] confirmed that patients with ventilatory limitation could reach significant improvements in functional exercise tolerance (despite less improvement in peak oxygen consumption). Combining the different pieces of evidence available, it appears that patients with severe complaints of dyspnoea, with reduced quality of life and with clear peripheral muscle weakness would constitute ideal candidates for exercise training [76]. A programme for these patients would consist of endurance training, peripheral muscle training and dietary measures if they are overweight or underweight. The need for other elements in rehabilitation programmes, such as education, psychosocial support, occupational therapy or chest physiotherapy is not yet clearly established. Furthermore, from pre-transplant rehabilitation programmes and from programmes in preparation of volume reduction surgery, it appears that patients with more severe ventilatory limitation with FEV1 20–40% pred may also constitute an indication for pulmonary rehabilitation [9] if presenting with severe complaints of dyspnoea, clearly reduced quality of life, and severe peripheral muscle weakness. Peripheral muscle weakness is important in determining exercise limitation in these patients. Although, intuitively, it would appear that exercise training in these patients would result in smaller benefits, several studies addressing this issue have found clear effects of exercise training [9, 108, 113, 180]. It appears logical to perform peripheral muscle training in these patients because peripheral muscle training does not cause as much dyspnoea as whole-body exercise and may allow substantially greater loads on the peripheral muscles. An alternative would be to offer interval-type training instead of endurance training. More recent advances like neuromuscular electrical stimulation [181, 182], and noninvasive mechanical ventilation [183–185] may be promising future avenues in well-selected patients. Well-organised centres for rehabilitation should provide a multidisciplinary team with a medical supervisor; their recommendation for electing patients would usually be that optimal therapy is already installed in nonsmoking patients or that patients are actively involved in a smoking-cessation programme. Patients should, on selection, undergo a full clinical, physiological, psychological and social evaluation to determine the type of rehabilitation programme optimally suited for their individual needs.

Summary

Pulmonary rehabilitation programmes are increasingly popular, especially in chronic obstructive pulmonary disease (COPD) patients. It is now clearly established that these programmes improve exercise capacity, reduce symptoms and improve quality of life in COPD patients. At present, there is no conclusive evidence that these programmes would improve survival or reduce medical consumption, although suggestive evidence is present.

Pulmonary rehabilitation programmes are, by definition, multidisciplinary and consist of exercise training, peripheral muscle training, ventilatory muscle training, chest physiotherapy, occupational therapy, education, and psychosocial and nutritional support. The elements that are best supported by evidence available in the literature are exercise training, peripheral muscle training and nutritional support.

At present, there is little evidence available in the literature to select the best possible candidates for rehabilitation. It appears intuitively logical to select patients with poor exercise capacity, peripheral muscle weakness and those associated with severe symptoms and poor quality of life. Prospective studies attempting to identify the best possible candidates for rehabilitation still need to be performed.

Keywords: Exercise training, muscle training, nutritional intervention, quality of life, survival, utilisation of healthcare resources.

Acknowledgements. The authors acknowledge the support of the Fonds voor Wetenschappelijk Onderzoek, Vlaanderen, Belgium. T. Troosters is a postdoctoral fellow of the Fonds voor Wetenschappelijk Onderzoek.

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