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Exercise training in chronic obstructive pulmonary disease

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Abstract—Exercise and activity limitation are characteristic features of chronic obstructive pulmonary disease (COPD). Exercise intolerance may result from ventilatory limitation, cardiovascular impairment, and/or skeletal muscle dysfunction. Exercise training, a core component of pulmonary rehabilitation, improves the exercise capacity (endurance and, to a lesser degree, maximal work capacity) of patients with COPD in spite of the irreversible abnormalities in lung function. Dyspnea and health-related quality of life also improve following pulmonary rehabilitation. The clinical benefits of exercise rehabilitation last up to 2 years following 8 to 12 weeks of training. Existing evidence-based guidelines recommend that exercise training/pulmonary rehabilitation be included routinely in the management of patients with moderate to severe COPD. Exercise training/pulmonary rehabilitation may be undertaken in an inpatient, outpatient, or home-based setting, depending on the individual needs of the patient and available resources. The type and intensity of training and muscle groups trained determine the expected outcomes of exercise training. Both high- and low-intensity exercise lead to increased exercise endurance, but only high-intensity training also leads to physiologic gains in aerobic fitness. The rationale for and outcomes of lower- and upper-limb training, as well as ventilatory muscle training, are reviewed, and the potential for anabolic hormone supplementation to optimize the benefits of exercise training is discussed.

Key words: chronic obstructive pulmonary disease, endurance, exercise, pulmonary rehabilitation, skeletal muscle, strength.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity, mortality, and health care use [1]. Exercise intolerance is one of the most troubling manifestations of COPD. Persons with mild stages of the disease may experience dyspnea during heavy exertion that is attributed to "slowing down with age." Patients with moderate and severe COPD commonly have difficulty performing such normal daily tasks as work, recreational exercise, hobbies, and self-care. Dyspnea, leg fatigue, and discomfort are the principal symptoms that limit exercise [2], and patients typically limit their activities to avoid these uncomfortable sensations. The resultant inactivity leads to progressive deconditioning that further increases the sense of respiratory effort related to

Abbreviations: AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation, ADL = activity of daily living, ATS = American Thoracic Society, BTS = British Thoracic Society, COPD = chronic obstructive pulmonary disease, CPET = cardiopulmonary exercise testing, CRQ = Chronic Respiratory Questionnaire, FEV_1 = forced expiratory volume in 1 s, HR = heart rate, HRR = heart rate reserve, IGF-1 = insulin growth factor-1, MWD = minute walk distance, NMES = neuromuscular electrical stimulation, NO = nitric oxide, PImax = maximal inspiratory pressure, PR = pulmonary rehabilitation, RV = right ventricle, SWT = shuttle walk test, Vd = dead space, VE = minute ventilation, VMT = ventilatory muscle training, VO_2max = maximal oxygen consumption, Vt = tidal volume, Wmax = maximal work load.

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any given task. Ultimately, patients often become progressively homebound and isolated, and may develop worsening depression and anxiety. Such depression is associated with significant disturbances in physical function [3]. Indeed, exercise capacity and health status also correlate with mortality [4].

Several coexisting factors contribute to exercise intolerance in COPD [5–8]. Importantly, however, it is possible to improve the exercise tolerance of the COPD patient, despite permanent impairment of lung function. Optimization of medical therapy, use of breathing strategies such as pursed-lips breathing and oxygen therapy (for hypoxemic persons) [9], anxiety management, slow deep breathing, and nutritional intervention [10] can all be beneficial. Exercise training, the focus of this review, has been proven conclusively to improve exercise tolerance for patients with COPD over and above gains made by optimizing medical therapy. It must be noted that many clinical trials demonstrating the benefits of exercise training have been undertaken in the context of comprehensive pulmonary rehabilitation (PR) programs. Although exercise training is the crucial core process in PR, the benefits of training noted in these trials cannot be viewed as separate from those derived from other important interventions included in PR, such as patient and family education, training with pacing, energy conservation and breathing techniques, anxiety and dyspnea management, reinforcement of cigarette abstinence, optimization of oxygen therapy, medical management, and nutrition. These additional processes aimed at long-term lifestyle modification likely enhance and maximize the benefits of exercise training [11,12]. As such, when possible, exercise training for patients with COPD optimally should be pursued initially in the setting of a formal PR program, in hopes that the helpful strategies learned will be continued long-term.

While the current clinical guidelines for PR for patients with chronic respiratory disease are referenced in this review, this article does not represent a new set of guidelines. Moreover, whereas the existing published guidelines for PR address some benefits of and recommendations for exercise training, they also provide a review of the behavioral, educational, and psychosocial aspects of PR and the outcomes tools used to measure exercise and other benefits derived from PR. In contrast, this manuscript provides an up-to-date, evidence-based review specifically focusing on the scientific rationale for and benefits of exercise training for patients with COPD. The multifaceted scientific basis of exercise intolerance in COPD is presented. Patient candidacy and clinical outcomes of exercise training for these patients are reviewed. Also, the rationale for selected approaches (type and intensity) of lower- and upper-limb and ventilatory muscle training are considered, based on existing medical literature. Finally, the use of anabolic hormone supplementation to optimize the benefits of exercise training is discussed.

CAUSES OF EXERCISE INTOLERANCE IN COPD

The principal factors contributing to exercise intolerance in COPD are as follows:

I. Pulmonary/ventilatory limitation
   A. Increased work of breathing from increased airways resistance/expiratory flow limitation
   B. Impaired lung emptying/dynamic hyperinflation
      1. Impaired tidal volume response to exercise
      2. Increased elastic load to inspiratory muscles
      3. Mechanical disadvantage of respiratory muscles (altered length-tension relationship)
   C. Other causes of respiratory muscle dysfunction
      1. Impaired nutrition
      2. Electrolyte disturbances
      3. Steroid myopathy
   D. Gas exchange abnormalities
      1. Increased dead space and ventilation/perfusion mismatch
      2. Diffusion impairment
      3. Hypoxemia

II. Cardiovascular limitation
   A. Increased pulmonary vascular resistance
      1. Hypoxic pulmonary vasoconstriction
      2. Vascular remodeling
      3. Loss of capillary surface area
   B. Right ventricle stroke volume limitation related to hyperinflation

III. Skeletal muscle dysfunction

IV. Nutritional impairment
   A. Cachexia
      1. Low fat-free mass, muscle atrophy
      2. Reduced respiratory muscle strength
   B. Obesity

V. Psychological factors
   A. Anxiety
   B. Fear

First, ventilatory limitation occurs for several reasons [5,13]. Increased airways resistance and expiratory flow limitation increase the work of breathing. Severe airflow obstruction can also lead to impaired lung emptying and higher end-expiratory lung volume that worsens during exercise (dynamic hyperinflation), as well as during hyperpnea of any other cause (e.g., anxiety). This hyperinflation limits the tidal volume (Vt) response to exercise [14], increases the elastic load to the inspiratory muscles, and leads to mechanical disadvantage of the respiratory muscles by forcing them into a shortened position (where the muscle length-tension relationship is altered). Indeed, the degree of hyperinflation is an important predictor of exercise capacity and dyspnea during exercise. The respiratory muscles may be further limited in their ability to generate inspiratory pressure by electrolyte disturbances, steroid myopathy, or loss of muscle mass due to impaired nutrition [15–17]. Ventilatory limitation to exercise also occurs as a result of gas exchange abnormalities that arise from excess physiologic dead space (dead space to tidal volume ratio, Vd/Vt), ventilation-perfusion (V/Q) mismatch, and reduction in diffusing capacity. Increased Vd/Vt leads to increased ventilatory demand for a comparable degree of work. Early onset lactic acidosis and other factors, such as hypoxemia, further exaggerate the increased ventilatory demand [13,18].

Coexisting cardiovascular limitation to exercise is common. In particular, increases in pulmonary vascular resistance (due to hypoxic vasoconstriction and/or structural abnormality of the pulmonary vasculature) and decreased right ventricular (RV) preload related to hyperinflation commonly lead to RV stroke volume limitation that impedes exercise capacity by limiting cardiac output [14,19].

Skeletal muscle dysfunction is another major factor that can contribute to exercise intolerance [18,20]. This is evidenced by the findings that (1) forced expiratory volume in 1 s (FEV_1) alone is a relatively poor correlate of exercise tolerance, (2) the perception of leg effort or discomfort is the main symptom that limits exercise in 40 to 45 percent of patients with COPD, and (3) exercise intolerance often persists after lung transplantation, when the patient's ventilatory limitation has been eliminated [18]. Nutritional (related to loss of muscle mass and/or obesity) and psychological factors such as anxiety also frequently impact exercise performance.

SKELETAL MUSCLE DYSFUNCTION: RATIONALE FOR EXERCISE TRAINING IN COPD

The existence of skeletal muscle dysfunction provides the basis of the scientific rationale for undertaking exercise training for patients with COPD. Skeletal muscle dysfunction in COPD is characterized by reductions in muscle mass and strength [21,22], atrophy of type I (slow twitch, oxidative, endurance) [23,24] and type IIa (fast-twitch, glycolytic) muscle fibers [25], reduction in fiber capillarization [26] and oxidative enzyme capacity [27–29], and reduced muscle endurance [20,30,31]. Both resting and exercise muscle metabolism are impaired [20,28,32,33], and patients develop lactic acidosis at lower exercise work loads than healthy persons [16,18]. This leads to an increased ventilatory requirement and early onset of muscle fatigue. The impaired skeletal muscle mass and strength in COPD is associated with reduced exercise capacity [34,35], and increased use of health care resources [36]. Importantly, low muscle mass is also a strong predictor of mortality in COPD [37–39], independent of the degree of lung function impairment. Moreover, improvements in muscle mass have been associated with improved survival [37].

Although the cellular and molecular mechanisms underlying cachexia and muscle loss are not completely understood, skeletal muscle dysfunction in COPD is caused by many coexisting factors [10,18,20,40]. Available data suggest that systemic inflammation, low anabolic hormone levels, reactive oxygen species, deconditioning, nutritional impairment, aging, and hypoxia likely play a role [20,41,42]. Importantly, inactivity and proinflammatory cytokines, common in COPD, can increase activity of the ubiquitin-proteasome pathway, a proteolytic pathway that causes muscle wasting [41]. All the anatomic and physiologic skeletal muscle abnormalities noted above may exist in the absence of steroid use. Steroid myopathy is an additional troubling cause of muscle weakness that can be superimposed on the other disturbances.

Importantly, in contrast to (and despite) irreversible abnormalities of lung architecture and airflow obstruction, the structural, metabolic, and physiologic skeletal muscle abnormalities noted in COPD can be improved or reversed by exercise training. In turn, exercise training/PR can restore the patient to the highest level of functional capacity possible for any existing degree of ventilatory impairment.

PATIENT CANDIDACY FOR EXERCISE TRAINING

The high costs of health care and the limitations on insurance reimbursement for exercise training mandate consideration of which patients with COPD are most likely to benefit. Patients with all degrees of severity of chronic airflow limitation, including those with severe reduction in FEV_1, can benefit from exercise training [43–45]. As such, all patients with moderate or severe COPD who experience disabling symptoms of dyspnea and/or leg fatigue despite optimal medical management should be considered potential candidates for exercise training/PR [11,12,46–49]. Persons with mild disease may continue to exercise to an extent sufficient to prevent deconditioning, and thus they are not routinely referred for PR. However, one general criticism of PR is that it has limited potential to affect disease outcome (such as hospitalizations or survival) when used principally for persons with advanced disease. On the other hand, successful realization of lifestyle modifications, such as long-term maintenance of aerobic fitness, smoking cessation, ideal body weight, and muscle mass have significant potential to impact overall functional status and rate of decline in lung function. Theoretically, therefore, relatively inactive persons and/or smokers (who have or are attempting to quit) with mild stages of COPD might be the most ideal candidates for PR. Berry and colleagues [45] recently demonstrated that patients with stage I (mild) COPD achieve benefits of training similar to those noted for persons with moderate to severe disease. It is not yet clear whether exercise training/PR implemented in early stage COPD can improve such disease outcomes as morbidity and mortality over the long term.

Persons with conditions wherein exercise is unsafe, or with conditions that would interfere with the rehabilitation program, should not undertake exercise training/PR. Absolute contraindications therefore include severe pulmonary hypertension with dizziness or syncope on exertion, severe congestive heart failure refractory to medical management, unstable coronary syndromes, or malignancy with bone instability or refractory fatigue. Relative contraindications include end-stage hepatic failure (where mental status impairment and overwhelming fatigue may occur), inability to learn, psychiatric instability or disruptive behavior, and lack of motivation. Persons with COPD and concomitant heart disease, particularly those believed at risk for arrythmia or sudden death, may be considered for cardiac rehabilitation as an alternative to PR. Cardiac rehabilitation shares many features in common with PR, but unlike PR is usually conducted with continuous telemetry monitoring during exercise.

Among persons with moderate to severe COPD, the factors that distinguish persons most likely to respond to exercise training are not completely understood. One study found that persons with severe COPD and severe dyspnea assessed by the Medical Research Council dyspnea score at baseline did not achieve significant improvements in walking distance following training [50], but several other studies have shown that even persons with severe dyspnea and disease can achieve gains in exercise tolerance with exercise training [44,51,52]. Therefore, one should not exclude patients with severe dyspnea from participating in exercise training on this basis alone. Patients with a greater degree of ventilatory reserve (minute ventilation measuring [VE]/maximum voluntary ventilation) achieve greater improvements in exercise capacity following training compared to patients with lesser reserve [53,54], particularly if they also have impaired peripheral muscle strength prior to training [54]. Inspiratory muscle strength (the maximal inspiratory muscle pressure a patient can generate during an inspiratory effort, or PImax) is another predictor of gains made with exercise training [54]. Additional research, particularly that providing newer insights into the molecular and cellular basis of muscle dysfunction [41], is needed to clarify the other factors that determine the likelihood of deriving benefit from exercise training.

The inclusion of smokers in exercise training/PR programs is controversial [55]. Although the participation of a person who is still smoking can be discouraging to other patients who have already quit, the exercise training and PR process can lead to improvements in functional status, and it exposes the smoker to a supportive environment in which he or she may be inspired to quit. Few studies have evaluated clinical outcomes of exercise training/PR for current smokers. Some data suggest that active smoking leads to biologic changes that might limit the response to exercise training. For example, smoking maintains blood CO levels that reduce the O_2-carrying capacity of the blood and impairs O_2 extraction by the tissues [56]. It is unclear whether smoking limits the potential benefits of oxygen therapy in attenuating exercise-induced increases in pulmonary artery pressure. Smoking can also lead to

alterations in skeletal muscle fiber type (a reduced number of endurance fibers) and reduce oxidative enzyme capacity, even among healthy persons, and as such could contribute to the skeletal muscle dysfunction noted in COPD [57]. One small study found that current smokers were less likely to adhere to a 4-week PR program than ex-smokers [58]. On the other hand, Singh and colleagues demonstrated that current smokers achieved gains in exercise tolerance (shuttle walk test (SWT) distance and treadmill endurance) that were comparable to those made by nonsmokers following 7 weeks of training [59]. Likewise, Sinclair and colleagues showed no significant difference in gains in 12 min walking distance (MWD) between smokers and nonsmokers following training [60]. Therefore, active smoking is not an absolute contraindication to exercise training/PR. However, the inclusion of smokers in exercise training programs remains the subject of debate, and the long-term outcomes and cost-effectiveness of PR for active smokers as compared to nonsmokers is as yet unknown. Current clinical guidelines of the American Thoracic Society (ATS), the British Thoracic Society (BTS), and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) do suggest that any patient participating in PR who is smoking actively should be strongly encouraged to enroll in a smoking cessation program [11,12,49,55], and that smoking cessation should be an important component of the rehabilitation process.

CHOOSING THE SITE FOR EXERCISE TRAINING

Although disease severity does not inherently dictate candidacy for exercise training, the degree of physiologic and functional impairment does impact the optimal setting in which the training should occur. Exercise training and rehabilitation are effective in inpatient, outpatient, and home-based settings [12,61]. The advantages and disadvantages of each site are reviewed elsewhere [62]. Patients with severe functional impairment who need 24-hour medical and/or nursing intervention may benefit from inpatient rehabilitation [12]. Walking aids such as rollator walkers and gutter frames can assist in exercise training and improve exercise capacity for persons with very severe functional limitation [63,64]. Even ventilator-dependent patients who are stable medically may undergo rehabilitation with assistance from experienced staff. Outpatient, hospital-based individual or group training, usually undertaken two to three times a week, is the form of PR most widely used. However, the logistics of travel can limit program participation for some patients. While in some countries, patients who live too far to attend outpatient PR programs can undergo inpatient PR [65], this is not usually the case in the United States because of insurance limitations. Home-based or community/office-based rehabilitation can be used for patients with severe functional limitations who are not eligible for or do not have access to inpatient PR. Gains in exercise performance may be limited following home-based rehabilitation, depending on the nature of the training [66]. However, exercise training in the home may lead to better long-term maintenance of an exercise program because the lifestyle change occurs in a familiar environment [66,67].

CLINICAL OUTCOMES OF EXERCISE TRAINING

Improvements in Exercise Tolerance

Since exercise limitation usually begins with difficulty ambulating, most clinical trials of exercise training in COPD have focused on training the muscles of the lower limbs, alone or in combination with training the arms or respiratory muscles. Virtually all trials conducted over the last 40 years have shown that lower-limb training improves the exercise tolerance of patients with COPD [11,12,44,51,66–86]. Randomized, controlled trials have demonstrated consistently that lower-limb training of several types (treadmill, cycling, free walking, stair climbing, or a combination of these), undertaken in several settings, increases exercise endurance, and to a lesser extent, maximal work load (Wmax) [11,12,50,51,80,86–88]. Increases of up to 80 m (10%–25%) in walking distance [50,51,53,80,89–91], 10 min in treadmill endurance [87,92], 5 min (~70%) in cycle ergometry time at submaximal work loads [51,71,93,94], and 36 percent in Wmax [94] have been reported following 6 to 12 weeks of training. By way of example, Ries and colleagues compared the effects of 8 weeks of comprehensive PR (including the core process of twice-weekly cycle ergometry exercise training) to education and medical management alone in 119 patients with severe, stable COPD [87]. Patients who received exercise training achieved a 10.5 min increase in treadmill walking endurance, which was associated with a concomitant decrease in the symptoms of breathlessness and leg fatigue during exercise. These benefits were maximal at the completion of training and were maintained

over several months. Although the magnitude of benefits declined gradually over time, significant improvements over baseline persisted for 1 year following the training. Two recent meta-analyses of the effects of PR have confirmed the benefits of exercise training on exercise tolerance. In one, review of the results of 14 randomized controlled trials of PR demonstrated significant favorable effects of PR on exercise tolerance [95]. Cambach et al. analyzed clinical trials assessing the long-term effects of PR in patients with COPD or asthma and also demonstrated significant improvements in exercise endurance (measured by 6 MWD) and maximal exercise capacity up to 9 months postrehabilitation [89]. Short-term inpatient PR also leads to improvements in exercise tolerance for persons with COPD [52,96,97].

Other Benefits of Pulmonary Rehabilitation

In addition to gains in exercise tolerance, PR leads to significant improvements in dyspnea and health-related quality of life (QOL) [11,12,49,89,95,98]. Details regarding these gains and the tools used to measure these outcomes have been reviewed elsewhere [12,49,99–101]. Aerobic conditioning undertaken in PR also leads to reduced depression and improved cognition and neurobehavioral function for persons with COPD [102,103]. Some studies have noted benefits regarding return to employment [11]. Importantly, participation in PR can also lead to reductions in COPD exacerbations [104] and time spent in the hospital [96,105]. In turn, these benefits could ultimately impact disease survival. Finally, PR has been shown convincingly to be a cost-effective health care intervention, when one considers the cost of providing the program relative to the costs of health service use over time for persons who do not participate in rehabilitation [106]. Indeed, higher functional status following PR is a strong predictor of survival in persons with advanced COPD [107].

Current Clinical Guidelines for Exercise Training/ Pulmonary Rehabilitation

Based on the existing medical literature, an evidence-based guidelines report prepared and published jointly in 1997 by the American College of Chest Physicians and the AACVPR has led to the recommendation that exercise training be included routinely in the rehabilitation of patients with COPD [11]. The ATS [12] and BTS [49] Statements on Pulmonary Rehabilitation and the Global Obstructive Lung Disease Guidelines on management of patients with COPD [108] also support the position that any patient with moderate to severe COPD and exercise or activity limitation who lacks contraindications should undergo exercise training, particularly of the lower limbs. Persons who lack access to formal comprehensive PR or supervised exercise training should be given a home-based exercise program to follow. A recent study cautions, however, that the expected gains in endurance are less when patients are given only education and verbal advice and guidance about exercise, as compared to participating in a supervised exercise program [109]. The structure and duration of the program do affect program outcomes. The type of training and the target exercise intensity will be considered further in a later section. In general, existing guidelines recommend that exercise training for patients with COPD be undertaken at least 2 to 5 days per week, for at least 20 to 30 min per session [12] over an 8 to 12 week period [12,49]. Although exercise and education sessions are conducted twice weekly in many outpatient programs, one recent study cautions that twice weekly exercise may not be sufficient for some patients to achieve gains in walking distance and health status [110]. The recommendations for exercise training in the above-noted current clinical guidelines are summarized in the **Table**.

Duration and Maintenance of Benefits

One criticism of the PR process has been the limited duration of benefits achieved. However, several recent trials have confirmed the presence of training benefits up to 2 years following PR [87,91,104,111]. For example, Troosters and colleagues [91] demonstrated persistence of improvements in 6 MWD, Wmax, maximal oxygen consumption (VO_2max), and QOL 18 months after a combined multimodality endurance and strength training program. The randomized-controlled trial conducted by Guell and colleagues [104] showed improvements in 6 MWD, with reduced dyspnea and improved QOL (measured by the Chronic Respiratory Questionnaire (CRQ) [112]) that persisted 2 years following a 12-week program of daily supervised exercise, breathing retraining, and chest physiotherapy for persons with moderate to severe COPD.

The tendency for exercise endurance to decline gradually over time has, however, raised questions regarding the optimal means of maintaining the gains of exercise training. It is well known that the effects of training are lost among healthy persons if exercise is discontinued

Table.
Evidence-based guidelines for exercise training in COPD.

Training/Candidacy	ACCP/AACVPR*	ATS†	BTS‡
Lower-Limb Training	Recommended as part of PR: optimal specific prescription not defined	Endurance and strength training recommended: • 20–30 min • 2–5× per week • intensity 60% VO_2max where possible	Endurance and strength training recommended: • 20–30 min • 3–5× per week • intensity 60–70% VO_2max where possible • maintain O_2 saturation >90%
Upper-Limb Training	Strength and endurance training recommended as part of PR	Strength and endurance training recommended as part of PR	Strength and endurance training may be included in PR
VM Training	Evidence does not support routine use in PR; may be considered in some patients with decreased respiratory muscle strength and breathlessness	Role in PR unclear	Nonessential
Patient Candidacy	Any patient with stable disease of the respiratory system and disabling symptoms	Patients with chronic respiratory impairment who are dyspneic or have decreased exercise tolerance or experience restriction in activities	All patients with chronic lung disease whose medical management is optimized and whose lifestyle is adversely affected by chronic breathlessness

ACCP = American College of Chest Physicians
AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation
ATS = American Thoracic Society
BTS = British Thoracic Society
VM = ventilatory muscle
PR = pulmonary rehabilitation
VO_2max = maximal oxygen consumption

*American College of Chest Physicians and American Association for Cardiovascular and Pulmonary Rehabilitation. Pulmonary rehabilitation: joint ACCP and AACVPR evidence-based guidelines. Chest 1997;112(5):1363–96.
†American Thoracic Society Statement. Pulmonary rehabilitation—1999. Am J Respir Crit Care Med 1999;159:1666–82.
‡British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. Thorax 2001;56:827–34.

[113]. Several factors influence the continuation of exercise after PR, including motivation, family/social support, logistics of the living environment, and disease stability. Persons whose disease is clinically stable who continue to exercise following training may be most likely to maintain improvements in exercise tolerance [114]. However, maintenance of exercise is often interrupted by COPD exacerbations, which can lead to worsening functional impairment. Further research into maintaining exercise gains following PR should also address the best means of preventing functional decline and maintaining exercise performance in the face of exacerbations [114].

Another question that warrants further study is whether the frequency and/or severity of exacerbations affects the long-term outcomes following PR. In this regard, the question of whether patients benefit from sequential, repeat outpatient PR programs has been addressed [115]. In one study, successive, yearly PR led to repeated short-term gains in exercise tolerance and reduction in yearly exacerbations, but did not result in additive long-term gains in exercise tolerance [115]. It is still unclear whether reduction in exacerbation frequency that results from repeated participation in PR programs could alter the disease outcome, such as by improving survival.

Formal exercise maintenance programs are an alternative strategy that can help maintain the benefits of the initial rehabilitation. However, outcomes of such maintenance programs have been variable [90,92,116], and to date no formal clinical practice guideline has been established. In a study by Swerts and colleagues [116], continued participation in a supervised exercise program over an additional 12 weeks was needed to maintain gains in

walking endurance made initially in PR for a period up to 1 year. In a randomized trial, Ries and colleagues found that patients who, following PR, underwent a 12-month maintenance program (of weekly telephone contact and monthly supervised reinforcement sessions) had better maintenance of exercise tolerance and health status, with reduced hospital days during the intervention period, compared to persons in the control study group who did not participate in the maintenance program [117]. There were, however, no long-term differences between the two groups resulting from completion of the maintenance program. Other studies have failed to show any better preservation of exercise tolerance or QOL following participation in a maintenance program [90,118,119]. Thus, at present, there is no conclusive indication that a structured maintenance program of exercise and/or psychosocial support affects the long-term outcome following PR/exercise training.

Program Duration

The optimal duration for exercise training/PR is also not known. The potential for achieving greater overall gains in exercise tolerance (and other factors such as smoking cessation, dietary adherence, anxiety, and dyspnea management) with a longer program must be weighed against the issues of adherence to the program and the potential for higher program costs. In one randomized-controlled trial [120], patients with severe COPD who underwent a 7-week course of PR showed no significant differences in endurance from those who attended a 4 week course, although improvements in dyspnea and health status were greater in those who had 7 weeks of rehabilitation [120]. In another trial [121], 18 months of exercise led to greater improvements in walk distance, stair-climbing rate, performance of an overhead task, and self-reported disability, compared to a traditional 12-week exercise program. However, the true impact of the noted additional benefits on day-to-day activities is not known, and the cost-effectiveness of a longer intervention has not been measured. With regard to cost and program duration, the study by Clini et al. [97] demonstrated that a short, intensive inpatient PR program (conducted in Italy), with up to 12 sessions held 5 days per week, led to comparable gains in exercise tolerance at a lower cost, compared to a longer outpatient program (exercise three times per week for ~8 weeks). The decreased cost was attributable to fewer total sessions and the elimination of transportation costs. It is not clear whether a similar cost result could be achieved in a hospital setting in the United States, given the strict criteria for admission to inpatient rehabilitation and the different health care reimbursement climate. Nevertheless, it is clear that shorter programs of 2 to 3 weeks that include a sufficient number and type of training sessions can also lead to improved exercise tolerance [97,98]. Patient gender may also influence the desired program duration [122].

Importantly, the health status questionnaires used currently to assess the effect of exercise training/PR on the performance of activities of daily living (ADLs) may not fully reflect how training-induced gains in walking endurance (treadmill or SWT) or measured improvements in peak work load or VO_2max translate into functional performance of ADLs. To this end, efforts are under way to develop physical activity monitors that can assess more thoroughly the degree of activity before versus after exercise training [123].

TYPE AND INTENSITY OF TRAINING

The optimal type and intensity of training for patients with COPD remains the subject of debate. While all types of training can improve exercise performance, different outcomes can be expected depending on whether the patient undertakes aerobic endurance versus strength training, whether high- or low-intensity training is chosen, and whether upper-limb and/or respiratory muscle training is pursued in addition to lower-limb training. No single exercise formula can be considered ideal for all persons. The exercise program must be individually tailored to meet the needs and goals of the patient, using resources available.

Aerobic Versus Strength Training

In general, aerobic fitness (endurance) training improves one's ability to sustain an exercise task at a given work load. Walking, running, cycling, stair climbing and swimming are examples of endurance training exercise. In contrast, strength training involves bursts of activity over a shorter period, such as occur during weight lifting. Each of these forms of training can be undertaken at high or low intensity; that is, at high or low percentages of the patient's individual maximal work capacity for the given task. Many clinical trials of exercise training in COPD, such as the study by Ries and colleagues [87],

have used aerobic endurance exercise such as cycling as the principal or sole mode of exercise training. As reviewed above, lower-limb aerobic fitness training leads to gains in exercise endurance, and to a lesser degree, gains in maximal work load [11,12,49,87]. Fewer studies have evaluated the impact of strength training as a sole exercise modality for persons with COPD. Resistance training improves leg strength and walking distance in healthy elderly persons [124]. Simpson and colleagues demonstrated a 73 percent increase in cycling endurance time at 80 percent of maximal power output following 8 weeks of weight lifting training of the upper- and lower-limb muscles of patients with COPD [125]. Of note, there was no concomitant improvement in 6 MWD. In another study, weight training of the upper and lower limbs led to improved muscle function and treadmill walking endurance in patients with mild COPD who had impaired isokinetic lower-limb muscle function prior to training [126], and the noted improvements in muscle strength correlated with improvements in muscle endurance. The relative advantages and disadvantages of high- versus low-intensity strength training for persons with COPD are as yet unknown. Safety, especially prevention of muscle tears, is of paramount importance, particularly for persons on chronic steroid treatment who may be at risk for muscle rupture (e.g., biceps) when exposed to a high-intensity load. Clearly, such rupture can lead to prolonged, if not permanent, additional functional disability. A recommended approach for strength training prescription has been reviewed recently [127].

Since both aerobic fitness/endurance training and weight training can be beneficial and are safe for patients with COPD (when administered properly), most rehabilitation programs currently use both types of training. The best way to combine these training strategies is, however, still unclear. Spruit and colleagues compared the effects of dynamic strength exercise to those of endurance training (walking, cycling, and arm cranking) during a 12-week rehabilitation program in 48 patients with severe COPD [128]. Significant improvements in muscle force and torque, 6 MWD, Wmax, and health-related QOL were noted for patients in both groups, and the two training types led to a similar magnitude of gains. However, the substantial intersubject variability raised questions as to whether some subjects may have derived benefit more from one versus the other form of training. Bernard and colleagues conducted a randomized trial of 12 weeks of aerobic endurance training, alone or in combination with strength training, in 36 patients with moderate to severe COPD [68]. Whereas muscle strength increased to a greater degree in the combined training group, the addition of strength training to aerobic endurance training did not lead to greater improvements in peak work rate, 6 MWD, or QOL assessed by the CRQ. More recently, Ortega and colleagues also compared the effects of 12 weeks of strength training, endurance training, or a combination approach in 47 patients with COPD [129]. Greater improvements in submaximal exercise capacity were noted among persons who had endurance training as part of their regimen, and greater improvements in muscle strength were found in subjects whose regimen included strength training. Overall, similarly to the study by Bernard [68], there was no clear noted additive or synergistic effect of combination therapy on exercise performance as compared with either modality alone, and the training effects were consistent with the type(s) of training undertaken.

Although to date there exist no clear proven benefits of combined modality training, there likely are subgroups of individuals that might benefit particularly from this approach. Also, the ability to perform day-to-day activities may be a more important outcome to detect beneficial effects, as compared to a limited profile of program-based, standardized strength and endurance tests. However, as noted, a limited number of tools exist to accurately assess and quantitatively measure ADL performance. Thus, since both interventions are generally safe, it is reasonable to include both aerobic and strength training in the exercise program of most persons with COPD.

High- Versus Low-Intensity Aerobic Fitness (Endurance) Training

Assessment of Exercise Intensity: Identification of Target Work Load

In general, high-intensity exercise is considered to be that which takes place at greater than 60 percent of the patient's VO_2max or Wmax, whereas lower intensity exercise is conducted at lower work rates. Historically, several methods have been used to define the exercise intensity used in clinical trials of exercise training in COPD. The use of target heart rate (HR) may not be a reliable indicator of consistently chosen target work rate in this patient population. The HR at estimated lactate threshold varies as a percentage of predicted peak HR, and percentage of heart rate reserve (HRR) [130], and a

specific HR achieved during training may correlate to variable work rates, depending on the severity and stability of the cardiopulmonary disease over time. Cardiopulmonary exercise testing (CPET), wherein the work rate is measured directly, is the most direct means of assessing exercise intensity [131]. However, comprehensive CPET is not mandated in all patients prior to PR, and it is not available at all centers. The incremental SWT [132] is an acceptable noninvasive alternate field test that can be used to guide training intensity. Performance in this test correlates well to VO_2max measured during an incremental CPET. Thus, a specific target training work load can be derived from the maximal speed achieved during the SWT [49]. Persons with very advanced disease and severe functional impairment who are unable to perform standardized walk tests or CPET can be exercised to the tolerable limits of dyspnea and/or leg fatigue.

Assessment of Physiologic Changes Following Training

A separate issue is how to measure whether physiologic changes associated with improved aerobic fitness have occurred following training. CPET is the standard means of measuring VO_2max, Wmax, and lactate threshold, and of comparing values before and after exercise training [133]. Muscle biopsies can be used to detect structural and metabolic changes following training, but are usually conducted for this purpose only in a research setting. More recently, it has been appreciated that biomarkers such as exhaled nitric oxide (NO) may be of use in assessing the physiologic response to exercise training. Exhaled NO has been identified as a marker of physical fitness in healthy subjects [134]. Increases in exhaled NO have also been associated with improvements in exercise tolerance following PR for persons with COPD [135,136]. The routine clinical utility of this measure is as yet unknown.

Outcomes of High-Intensity Endurance Training

High-intensity exercise must be undertaken for the patient to gain significant physiologic improvements in aerobic fitness. Characteristic physiologic changes indicating improvements in aerobic fitness following exercise training include increased muscle fiber capillarization, mitochondrial density and oxidative capacity of muscle fibers, and delay of the onset of anaerobic metabolism during exercise (i.e., ability to exercise to a higher work rate before reaching the anaerobic/lactate threshold). These factors in turn lead to reduced ventilatory requirement for a given exercise task, increased VO_2max and decreased HR for a given oxygen consumption (VO_2). The demonstration of improvements in one or more of these variables following exercise training in patients with COPD is evidence of physiologic improvement in aerobic fitness.

For many years, the efficacy of exercise training was questioned, since persons with severe FEV_1 impairment were thought to be too ventilatory-limited to achieve gains in aerobic fitness [137]. Subsequent studies have shown convincingly, however, that many (although not all) patients with severely impaired lung function can tolerate moderate- to high-intensity endurance training and can achieve significant physiologic gains in aerobic fitness [44,71,79,94,138,139]. For example, Casaburi [71] compared the effects of cycle ergometry training (45 min/day for 8 weeks) at a high-intensity work load (mean 71 W) to those following training at a low-intensity work load (mean 30 W) in 19 patients with moderate COPD (FEV_1 56 ± 12% predicted). Training led to reductions in lactate production and VE requirement for identical work rates in both groups, but the magnitude of physiologic improvement was much greater in the subjects trained at the high work rate. Also, cycle endurance time increased by 73 percent in the high-intensity group, and by only 9 percent in the low-intensity group. Maltais et al. also demonstrated physiologic gains in aerobic fitness following 12 weeks of exercise training (30 min/day, 3 days/week) at a work rate corresponding to 80 percent of the VO_2max in persons with severe COPD (FEV_1 36 ± 11% predicted) [44]. Similar improvements in physiologic parameters of aerobic fitness following high- but not low-intensity endurance training have been confirmed in several additional studies [139–142].

Importantly, whereas moderate- to high-intensity exercise is needed to make gains in aerobic fitness, it is not always necessary that the exercise intensity be so high that the patient reaches anaerobic threshold [79,82]. Improvements in VO_2max and maximal treadmill work load and reduced symptoms of dyspnea and fatigue can occur following moderate- to high-intensity exercise, even among persons who do not reach anaerobic threshold [82]. Moreover, not all patients can tolerate high-intensity exercise at the outset of training. It likely is important, however, that such patients exercise to the maximum intensity tolerated to achieve gains in aerobic fitness. Those who do can achieve gains in the maximum intensity of exercise tolerated over time. This was demonstrated by Maltais and

colleagues [79], who evaluated 42 patients with severe COPD (mean FEV_1 38 ± 13% predicted) at baseline and after 12 weeks of cycle ergometer endurance training. Although the intended target training intensity was 80 percent of Wmax, the actual average tolerated training intensity by week 2 was only 24.5 ± 12.6 percent Wmax for this group of patients. However, by week 12, the same patients were able to exercise, on average, at 60 ± 22.7 percent of Wmax. Patients not only achieved significant increases in Wmax from training, but also made significant improvements in VO_2max and had reductions in VE and arterial lactate concentration for exercise at a given work rate following training.

Interval training (alternating periods of high- vs. low-intensity exercise or rest) is another option for persons who cannot sustain extended, continuous periods of high-intensity exercise. Two recent studies have confirmed the efficacy of interval training in improving exercise tolerance [143,144]. Importantly, interval exercise more closely resembles the type of exercise output required for ADLs than does continuous high-intensity exercise. The physiologic response to interval training depends on the precise structure, i.e., nature and intensity, of the program, and on the study population chosen. Physiologic gains in aerobic fitness can occur.

Moderate- to high-intensity training likely leads to improved aerobic fitness, at least in part by enhancing the activity of skeletal muscle oxidative enzymes. Maltais and colleagues found reduced activity of the oxidative enzymes citrate synthase and 3-hydroxyacyl Co A dehydrogenase before training in 11 persons with severe COPD. The activity of these enzymes increased significantly after high-intensity exercise training, and the noted improvement correlated to the reduction in lactic acid during exercise [44]. Moreover, reductions in ventilatory requirement following training are associated with increased Vt and lower respiratory rate, with a resultant decrease in Vd/Vt [94]. Reduction in the activity of the proteolytic proteasome pathway of metabolism is another mechanism by which physical training may lead to improved muscle function [145].

It is important to consider whether any detrimental effects of high-intensity training exist for persons with COPD. A few studies have addressed this issue. To determine if high-intensity exercise leads to diaphragmatic fatigue, twitch diaphragmatic pressure was measured during cervical magnetic stimulation before and at sequential intervals after high-intensity cycling exercise (to the time of intolerable symptoms) in 12 patients with moderate to severe COPD [146]. Of the 12 subjects, only two developed evidence of contractile diaphragmatic fatigue, whereas the majority of patients tolerated high-intensity exercise without adverse effect. However, in a different type of study, Orozco-Levi found that the diaphragm muscle in patients with COPD may be susceptible to sarcomere disruption, and this effect can be exacerbated by threshold inspiratory loading [147]. It is not clear whether such injury could be induced by high-intensity exercise. Quadriceps fatigue has been reported following high-intensity exercise [30]. One further study cautions that, although endurance exercise improves muscle redox potential in healthy persons, moderate intensity training can lead to reduced muscle redox capacity in patients with severe COPD [148]. Such an effect could potentially lead to worsened, rather than improved, skeletal muscle function in some patients, by virtue of exaggerating oxidative stress. Further work is needed to clarify which patients are at greatest risk for this potentially detrimental training effect, and which are likely to improve oxidative enzyme capacity following training. Identification of persons who may be at risk of diaphragm fatigue and exaggerated oxidative stress or other detrimental training effects, and an understanding of the impact of these effects on exercise tolerance and functional status long-term, would be useful in designing optimal exercise strategies for individuals.

Finally, it must be noted that improvement in the physiologic parameters of aerobic fitness following high-intensity exercise is not absolutely necessary to achieve improvements in exercise tolerance. This is important, since (1) high-intensity exercise may lead to a greater degree of dyspnea/leg fatigue and may therefore be less likely to be incorporated into the patient's routine lifestyle; (2) some persons cannot tolerate high-intensity exercise, and (3) as noted, some may develop deleterious muscle effects. Moreover, it has not been proven conclusively that aerobic fitness (with such physiologic gains as increased VO_2max and decreased lactate, VE, etc.) results in better improvement in day-to-day functional capacity than lower intensity exercise (which does not lead to these physiologic training effects).

Outcomes of Low-Intensity Training

It has been demonstrated clearly that lower intensity exercise also leads to improved exercise tolerance, even in the absence of measured physiologic gains in aerobic

fitness. For example, striking gains in treadmill endurance without increases in VO_2max were noted in the randomized-controlled trial of outpatient PR conducted by Ries et al. [87], as well as in another study evaluating the effects of low-intensity isolated peripheral muscle exercise in 48 patients with severe COPD [149]. Low-intensity multimodality exercise training also led to increased exercise tolerance for patients undergoing inpatient PR [52]. Gains in endurance and/or strength may be seen following such low-intensity exercise training. Two recent studies have directly compared the clinical benefits of high- versus low-intensity exercise training [141,150]. In these trials, gains in exercise endurance were noted following both types of training, although the magnitude of gain was greater among the patients who had higher intensity exercise. However, the study by Normandin [150] found that the low-intensity training group had greater increases in arm endurance, and both groups achieved comparable reductions in overall dyspnea, functional performance, and health status.

Recently, two studies have reported the effects of transcutaneous neuromuscular electrical stimulation (NMES) on the exercise tolerance of patients with COPD. In one, improvements in muscle strength and endurance, whole body exercise endurance, and dyspnea were noted following NMES [151]. Compliance with the regimen was excellent and, notably, subjects were able to continue the training regimen despite the occurrence of intermittent disease exacerbations. Similarly, Bourjeily-Habr and colleagues demonstrated that transcutaneous electrical stimulation of the lower-limb muscle led to improved quadriceps and hamstring muscle strength with associated improvements in distance completed in the SWT [152]. Importantly, in both of these studies, the noted benefits were achieved even without conventional concomitant strength or endurance training. Transcutaneous electrical muscle stimulation may be particularly beneficial for patients with very severe disease who are unable or unwilling to participate in a conventional exercise training program.

The mechanisms by which exercise tolerance/endurance improves following low-intensity exercise, wherein no specific improvements in aerobic fitness are noted, are not fully elucidated. However, gains in peripheral or respiratory muscle strength [153–157], increased mechanical efficiency of performing exercise due to improved neuromuscular coupling and coordination, reduction in hyperinflation/improved lung emptying, reduced anxiety and dyspnea, and improved motivation may all play a role [158,159]. Different combinations of mechanisms likely result in the improvements noted in individual persons.

Upper-Limb Training

Relatively few studies examine the use of upper-limb exercise training for patients with COPD. The studies evaluating the rationale for and outcomes of arm training for COPD patients have been reviewed elsewhere [11,12,159]. In brief, arm training has been studied because patients with moderate to severe COPD, particularly those with mechanical disadvantage of the diaphragm due to lung hyperinflation, have difficulty performing ADLs that involve the use of the upperlimbs. Also, arm elevation is associated with high metabolic and ventilatory demand [160–162], and activities involving the arms can lead to irregular, shallow, or dyssynchronous breathing [163,164]. Celli et al. have postulated that an altered breathing pattern may result from de-recruitment of accessory respiratory muscles from their work as muscles of inspiration to contribute to arm activity [164,165]. Upper-limb exercise may cause a shift in the load of breathing to the mechanically disadvantaged diaphragm, with resultant ventilatory limitation during arm activities [166]. Although skeletal muscle dysfunction plays a significant role in exercise limitation of the lowerlimb, the dyspnea experienced during arm exercise is likely more related to the above-noted patterns of muscle use, and is less likely primarily dependent on inherent skeletal muscle dysfunction of the upperlimb. Indeed, studies of the anatomical and physiologic derangements of skeletal muscle in COPD have demonstrated that upper-limb muscles are affected to a lesser degree than lower-limb muscles [22,167,168]. This is likely due to the patient's tendency to eliminate first those activities that involve the muscles of ambulation, leading to overall deconditioning. In contrast, arm activities are still required for maintenance of self-care and independent living, even if they induce uncomfortable symptoms of dyspnea and fatigue. Nevertheless, improvements in upper-limb strength or endurance resulting from training could lead to improved overall functional capacity and ability to perform ADLs.

Upper-limb muscle training may consist of endurance training (via arm ergometry [supported exercise], or unsupported, arm-lifting exercise), or strength training (weight lifting) [169]. Reported benefits of upper-limb training in COPD include improved arm muscle endurance

[170] and strength [125], reduced metabolic demand associated with arm exercise [171], and improved sense of well-being [77]. In general, benefits of upper-limb training are task-specific; that is, improvements are noted only in performance of the types of tasks for which the muscle groups were trained [169,172]. Since upper-limb training is generally safe, does not necessarily require use of specialized equipment, and is easily incorporated into most exercise programs, the AACVPR/ACCP Joint Evidence-Based Guidelines Panel [11] and the ATS Statement on Pulmonary Rehabilitation [12] recommend that upper-limb training be included routinely as a component of the rehabilitation of patients with COPD. Further study is needed to determine whether routine use of arm training, particularly when combined with lower-limb training, can lead to consistent improvements in overall endurance and the ability to perform ADLs.

Respiratory Muscle Training

Since respiratory muscle dysfunction plays an important role in exercise limitation for COPD patients, inspiratory muscle training has also been investigated, in hopes that gains in respiratory muscle strength and endurance might lead to improved exercise tolerance and decreased dyspnea. The relative advantages and disadvantages of resistive loading, threshold respiratory muscle training, and isocapnic hyperventilation have been reviewed [159]. Threshold-type ventilatory muscle training (VMT) is generally the most easily quantitated mode of training because of the ability to set and standardize the training load. Pursed-lips breathing and diaphragmatic breathing are additional techniques used to optimized ventilatory function at rest and during exercise for persons with COPD. Of note, diaphragmatic breathing can increase the work of breathing, inspiratory loading, and dyspnea in some persons [173,174]. It is most likely detrimental in persons with severe hyperinflation, poor diaphragmatic movement during inspiration, and little increase in Vt when using the diaphragmatic breathing technique [175]. On the other hand, persons with COPD with a relatively low-Vt, rapid respiratory rate breathing pattern, whose Vt increases with diaphragmatic breathing, may benefit from the use of this technique.

Clinical outcome studies of VMT have yielded conflicting results. In general, existing data suggest that the training undertaken must be sufficient to result in an improvement in PImax if improvement in ventilatory muscle or overall exercise endurance is to be expected [11]. A training load of at least 30 percent of the pretraining PImax is necessary to improve muscle strength [11,176]. Some recent studies have used a training load of up to 60 percent of pretraining PImax. It is still unclear whether there is additional clinical advantage to training at this higher intensity [177]. VMT usually requires the use of the muscle-training device 15 to 30 min per day, 5 or more days per week, for at least 2 to 6 months. When an adequate training load is delivered, VMT can lead to improvements in inspiratory muscle strength (measured by PImax) [177–184], respiratory muscle endurance [177–180,183,185,186], and reduction in ventilatory demand at a given level of exercise [187]. Some studies have also demonstrated that VMT leads to improvements in exercise endurance (assessed by distance in MWD or incremental SWT) [187,188], and gains in maximal exercise capacity [189]. Perception of dyspnea, both at rest and during exercise, decreases [178,186,188], and health-related QOL improves [188] following VMT. Conflicting results have been reported when VMT is added to exercise training of the limbs: some studies have demonstrated that VMT in combination with general exercise training leads to greater improvements in exercise endurance (e.g., timed walk distance) compared to exercise training alone [185,190], while others have not [78,180].

It remains unclear which patients will benefit most from VMT. Since VMT is generally safe and noninvasive, requires simple equipment, and can be undertaken independently by the patient in the home setting, it is reasonable to offer VMT for persons who remain symptomatic with dyspnea and exercise limitation despite peripheral muscle strength and/or endurance training [11]. Patients with respiratory muscle weakness (e.g., due to malnutrition/cachexia, generalized debility or corticosteroid use) may benefit the most [178]. It is less clear whether persons with normal respiratory muscle strength and normal respiratory mechanics, or who have inherent normal muscle strength but decreased PImax due to impaired respiratory mechanics caused by hyperinflation may benefit from VMT. Indeed, the diaphragm of COPD patients has a higher degree of neurological activity than that of healthy persons [15], and the diaphragm of patients with severe COPD and hyperinflation has a histologic and metabolic profile of trained, rather than deconditioned muscle [191,192]. In addition, there are other morphological adaptations that occur as a result of chronic diaphragm shortening [15]. Collectively, these changes may lead to a chronic “spontaneously trained”

state of the diaphragm. Ramirez-Sarmiento and colleagues recently evaluated external intercostal and vastus lateralis (control) muscle fiber type, as well as inspiratory muscle strength and endurance before and after supervised inspiratory muscle training at 40 to 50 percent of PImax versus sham training in a group of patients with severe COPD [193]. Study patients were not malnourished, hypoxemic, or taking corticosteroids, and they had no significant comorbid metabolic, neuromuscular, or orthopedic disease. Those included for study had hyperinflation evidenced by elevated residual volume percent predicted and normal baseline inspiratory muscle strength. Inspiratory muscle training led to improvements in inspiratory muscle strength and endurance that were associated with a 38 percent increase in the proportion of type I (slow-twitch, oxidative, fatigue-resistant) endurance fibers and a 21 percent increase in the size of type II (fast-twitch, glycolytic) fibers in the external intercostal muscle. Thus, even persons with normal baseline inspiratory muscle strength can, after selected training regimens, achieve improved respiratory muscle function after VMT. It is not clear as yet, however, how and whether such improvements translate into improved ability to perform ADLs and/or affect health-related QOL. Further investigation is needed to identify the subgroups of patients and training regimens most likely to yield optimal benefit from VMT.

ADJUNCT MEASURES TO OPTIMIZE THE BENEFIT OF EXERCISE TRAINING

Several strategies exist that can complement and augment the benefits of exercise training in selected COPD patients. The role of supplemental oxygen and noninvasive assisted ventilation as adjuncts to training are reviewed in this issue and elsewhere [194]. Nutritional support can be an important adjunct intervention to improve exercise performance for COPD patients, since malnutrition and cachexia, as well as obesity with relatively low muscle mass, are common coexisting afflictions [194–196]. Finally, in recent years, tremendous interest has arisen in the potential role of anabolic hormone therapy in improving the skeletal muscle dysfunction and exercise limitation associated with COPD. The rationale for use of these interventions is based on several findings. First, as mentioned, low muscle mass in COPD correlates with decreased strength and exercise endurance, as well as increased use of health care resources [34–36], impaired QOL, and reduced survival [195]. As such, interventions that could increase muscle mass have the potential to improve exercise performance and QOL. Second, anabolic hormones such as testosterone, growth hormone, and insulin growth factor-1 (IGF-1), the major mediator of growth hormone's anabolic action on muscle [18], are important for muscle growth and development. Testosterone and IGF-1 levels are lower in some patients with COPD than in healthy persons [18]. Third, androgen supplementation leads to improved lean body mass and muscle strength, both in eugonadal and hypogonadal men without COPD (reviewed by Casaburi [18]). Thus far, short-term therapy appears relatively safe in older men. The safety of androgen or growth hormone administration to women is less clear and requires further study. Testosterone administration to females can lead to masculinization, disturbances of lipid balance, and mood changes, and its effect on breast cancer risk is not fully clear [18].

To date, there exist only a small number of clinical outcome studies of anabolic hormone replacement/supplementation in COPD. In one study, 4 months of treatment with oxandrolone (an anabolic agent used to assist weight gain for persons with other medical conditions) was well tolerated and led to significant increases in body weight and lean body mass in patients with involuntary weight loss and moderate to severe COPD [197]. These gains were associated with improved 6 MWD in approximately half the study subjects. Schols and colleagues evaluated the effects of caloric supplementation versus supplementation plus low-dose nandrolone decanoate or placebo in 217 patients with COPD [198]. All patients also participated in an exercise training program. Among patients with nutritional depletion, nutritional intervention alone led to a predominant increase in fat mass. Addition of nandrolone led to increases in fat-free mass that were associated with a slight increase in respiratory muscle strength. There was no noted increase in 12 MWD in this study. Similarly, 27 weeks of oral treatment with the anabolic steroid stanozolol in addition to inspiratory muscle and cycle ergometer exercise training led to an increased body weight and lean body mass in 10 nutritionally depleted patients with COPD, but the noted weight gain did not result in improved 6 MWD or maximal exercise capacity [199]. Moreover, in a fourth trial, 3 weeks of daily administration of growth hormone also increased lean body mass but did not improve muscle strength, 6 MWD, or maximal exercise capacity in 16 patients with

COPD attending a PR program [200]. Thus, overall, clinical outcomes of anabolic hormone supplementation have been disappointing, in that they have failed to demonstrate significant improvements in exercise capacity despite improvements in lean body mass. However, further work is needed to clarify the potential role of these treatments for patients with COPD since (1) selected subgroups may benefit more than others, and (2) we may not as yet have identified the optimal anabolic hormone regimen and type of concomitant training program needed to achieve benefits. Finally, the potential roles for novel treatment strategies such as IGF-1 or pharmacologic agents that could alter muscle lactate production or affect phosphocreatine synthesis remain to be investigated [194]. Further understanding of the cellular and molecular basis of muscle and weight loss, the role of systemic inflammation and other factors leading to muscle dysfunction in COPD should help elucidate future useful strategies for improvement of exercise capacity for persons with COPD.

CONCLUSIONS

There are several causes of exercise intolerance in COPD. Skeletal muscle dysfunction plays an important role in the symptoms and impairments in strength, endurance, and maximal exercise capacity experienced by COPD patients. As is true for healthy persons, exercise training for patients with COPD improves exercise capacity by optimizing muscle function and conditioning, Strikingly, significant gains are typically made in exercise training in spite of irreversible abnormalities in lung function. Aerobic (endurance) and strength training of the lower-limb and upper-limb and respiratory muscles is beneficial. High-intensity endurance training leads to physiologic gains in aerobic fitness for persons who can tolerate it, but both high- and low-intensity training lead to gains in exercise endurance, even for persons with advanced disease. Exercise training should be considered for all persons with COPD who experience exercise intolerance despite optimal medical therapy and who lack contraindications to training. When possible, this should ideally be initiated in the context of a formal pulmonary rehabilitation program. The type and intensity of exercise chosen depends on the individual patient's limitations and needs and the resources available. Anabolic hormone supplementation may have a role in optimizing the benefits of exercise training, but further study is needed to clarify the optimal means of combining this with exercise training and to establish which patients are most likely to benefit from this intervention. The existing published guidelines for pulmonary rehabilitation have been referenced in this evidence-based review article, as they offer additional discussion of the current recommendations for exercise, as well as recommendations on the educational, behavioral, and psychosocial facets of pulmonary rehabilitation for patients with COPD and other forms of respiratory disease.

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