RATIONALE FOR TRAINING THE SKELETAL MUSCLES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Skeletal muscle function is frequently impaired in patients with chronic obstructive pulmonary disease (COPD),
1 even in those persons affected by mild disease.2 Whether the abnormalities are mainly due to deconditioning are more related to a systemic effect of the disease, or, indeed, result from its treatment with corticosteroids is still a matter for discussion. The main abnormalities that are described are skeletal muscle weakness, atrophy, muscle damage, excessive cell death by apoptosis, and myopathy. This topic is discussed in more detail elsewhere in this book (see Chapter 49, “Peripheral Muscle Dysfunction in Chronic Obstructive Pulmonary Disease”).

Muscle weakness is associated with significant disability and can affect the overall prognosis. First, muscle weakness contributes to exercise intolerance in COPD.3,4 Second, patients with frequent hospital admissions show a greater degree of impairment of muscle strength than do patients who make less use of health care resources.5 Finally, patients with steroid-induced myopathy have a reduced survival rate.6 Recently, Marquis and colleagues7 have shown that reduced muscle bulk, as measured by midtigh cross-sectional area, is an important contributor to survival, even in patients with moderate COPD. These observations suggest that reversing skeletal muscle weakness should be a target of therapy for COPD. In this chapter, the extent to which muscle dysfunction can be improved, and the strategies by which to do so, are discussed.

EFFECT OF EXERCISE TRAINING ON SKELETAL MUSCLES

The effects of exercise training on physiologic outcomes and health-related quality of life in COPD have been well established in randomized controlled studies.8 Exercise training can be studied at the level of the intact muscle, at the level of the muscle fiber, and at the level of the molecular mechanisms of function of the muscle fiber.

Exercise training (see below) in patients with COPD enhances muscle strength and isolated muscle endurance. In addition to increased strength, increased muscle mass has been reported, especially when resistance training is added to the program. This suggests that hypertrophy can be achieved with exercise training in COPD, especially if these programs include a resistance training component. Whole body endurance, skeletal muscle endurance, and quadriceps fatigability improve considerably after exercise training, even when no specific resistance training is performed.2,9

APPROACHES TO SKELETAL MUSCLE TRAINING IN COPD

Exercise training is intended to restore skeletal muscle strength, muscle bulk, muscle endurance, muscular efficiency, muscle bioenergetics, and, at the cellular level, the oxidative capacity. In this chapter, the main focus is on the skeletal muscle. The effects of exercise training on other organ systems are not dealt with here, but adaptations of these systems also probably contribute to the effects of exercise training.

Exercise training programs generally consist of endurance training, interval training, and/or resistance training. The evidence suggests that the minimal time needed to achieve the clinically relevant benefits of exercise training in COPD is 8 weeks of three sessions/week. Sufficient stress on the working muscle is a prerequisite in order to achieve exercise training effects. Exercise training should be conducted at high workloads if physiologic benefits are the desired outcome.10 Owing to ventilatory constraints, it may be difficult to stress the working muscle of COPD patients sufficiently. This led to the early misconception that COPD patients were difficult, if not impossible,
to train. However, about two-thirds of patients referred to pulmonary rehabilitation derive significant physiologic benefits from exercise training. The different exercise training modalities are discussed below.

**Resistance Training** This form of exercise training consists of lifting adjusted weights. Generally, training intensity is set at 70% of the weight that a patient can lift once, over the full range of motion. From a review of the literature, McDonagh and Davies concluded that, to improve strength, a load of at least 66% of the maximum weight that can be lifted once (the one repetition maximum; 1RM) was required and had to be lifted at least 10 times. In addition, the higher the workload, the greater the training effect. Empirically, most training programs use 20 to 30 repetitions. Although the training modality was introduced in 1945, there have been few studies in which this intervention has been attempted in COPD patients. The interesting aspect of this form of exercise training is that relatively small muscle groups are put to work. This allows the imposition of relatively high workloads, without exceeding the ventilatory capacity of the patient. The findings of studies on COPD and other chronic diseases have unanimously confirmed that weight-lifting results in improved muscle strength. There has been only one investigation of the effect of resistance training on muscle cross-sectional area in COPD strength. There has been only one investigation of the effect of resistance training on muscle cross-sectional area in COPD patients, and the results showed an added effect of resistance training on whole body endurance compared with a relative increase in the proportion of type I and IIa muscle (oxidative) fibers and a relative decrease in the number of type IIb fibers, which is consistent with the improved oxidative capacity.

Resistance training may also impact on markers of systemic inflammation. Recently, it was hypothesized that systemic inflammation and overexpression of tumor necrosis factor-α (TNF-α) may play a role in the onset of muscle weakness. In addition, apoptosis, seen in the quadriceps muscle of low body mass index (BMI) COPD patients, may also be influenced by the presence of TNF-α. It was convincingly shown, in an intriguing study by Greiwe and colleagues, that myocytes of frail elderly subjects produced TNF-α and that resistance training reduced TNF-α expression. Similarly, Conraads and colleagues showed reduced concentrations of circulating TNF-α receptor levels after combined endurance and resistance training in subjects with CHF. What happens to the increased TNF-α expression observed in skeletal muscle from COPD patients after resistance training remains to be studied. Both high- and low-intensity resistance training may have protective effects against oxidative stress. These findings are of the utmost importance to patients with COPD. If resistance training in subjects with COPD could have similar effects, that is, reduction in systemic inflammation and protection against oxidative stress, this therapy would be able to modify the pathogenesis and onset of muscle weakness in COPD, especially in fragile, low-BMI patients.

Recently, the question of whether neuromuscular electrostimulation could be a way to stimulate the skeletal muscle adequately was investigated in two studies. Electrical stimulation was delivered with the use of bipolar interferential current or low-frequency current (symmetric biphasic). The results of both studies suggest that this form of exercise may be a useful tool for improving muscle strength and endurance capacity.

**Whole Body Exercise Training** The most common type of clinical exercise training in COPD and other chronic diseases is dynamic exercise training. This form of exercise training is generally performed on cycle ergometers and treadmills. Some investigators have also used free walking as a mode of exercise. In the latter case, the intensity is,

---

*Resistance training (or strength training) consists of small muscle group training by lifting weights. This form of training should be distinguished from whole body exercise on ergometers. For this latter form of exercise, we use in this chapter “endurance training” or “interval training.”*
However, poorly controlled. The upper limbs can be trained with the use of specific arm ergometers. As with resistance training, the goal of this form of exercise training is to provide a training stimulus to the working muscle with the added benefit of also generating adaptations of the cardiovascular and respiratory systems. Exercises should be performed for at least 30 minutes, three times per week, if the goal is to improve exercise capacity. In addition, physiologic improvements are only achieved when the training is performed at high intensity. Initially, it was believed that the training intensity needed to be above the lactic threshold, but later publications reported clear physiologic training effects, even in the absence of lactic acid production (measured in the blood), provided that a high relative workload (>60% of the maximal workload) was imposed. It is recommended that training intensity be targeted at 60 to 70% of the peak work rate of the patient. Careful design of the incremental exercise test is, however, critical since the choice of the increments may determine the duration of the exercise test and the achieved peak power. The correct training intensity can be confirmed by using symptom scores (Borg rating) of about 4/10 to 6/10. This level of respiratory sensation is associated with an exercise intensity of about 80% of the peak exercise capacity. It was confirmed in a recent study that dyspnea ratings for a given relative work rate do not change throughout a 6-week training program. Adopting this strategy, we showed statistically and clinically relevant effects of exercise training. There are some important limitations to these tools; for example, patients may experience a "learning curve" in using the Borg scores for symptoms and may quickly become desensitized to dyspnea.

Patients with more severe disease may also have more difficulty in meeting the criterion of 30 minutes of continuous exercise. Training programs can be adjusted without the focus of the high training intensity being lost. Cutting the 30 minutes into shorter intervals of high-intensity exercise has been reported to result in similar training effects to those of endurance training. Even periods as short as 30 seconds of high-intensity exercise alternating with rest have been used as a training modality. Use of this modality may indeed result in lower symptom scores during exercise training. Further research, however, needs to be focused on the effects of these programs on the skeletal muscles. Most of the effects described below have been studied with the use of endurance training at high intensity.

The effects of cycle ergometer or whole body exercise training on peripheral muscles have been well studied in COPD patients, and the evidence for its usefulness is strong. The aim of implementing dynamic endurance training is to improve the skeletal muscle endurance capacity. This goal is met through an improvement of the overall oxidative capacity of the skeletal muscle and a reduction in fatigability. No improvements are seen in the oxygen delivery to the working skeletal muscles with exercise in contrast to what is observed in healthy controls. In a well-designed study by Sala and colleagues (Figure 28-1), the effects of endurance training on skeletal muscle oxidative capacity were clearly shown in healthy subjects and patients with COPD. From the results of this study, it can be concluded that patients with COPD are able to restore the extraction ratio of the lower limbs after exercise training, which is indicative of improved oxidative capacity at submaximal work loads. Peak oxygen consumption (VO2), however, cannot increase to a large extent as patients with ventilatory constraints may not be able to increase their peak oxygen delivery to the same degree as healthy subjects. The results of Sala and colleagues also confirm that endurance training in patients with COPD improves oxidative capacity. This was demonstrated by the increased intramuscular pH, a better preserved intramuscular phosphocreatine (PCr) pool—indicated by a lower inorganic phosphate concentration (\([P_i]/[PCr]\) ratio—at submaximal work rates after training, and a faster [Cr] recovery time.

The improved oxidative capacity of skeletal muscles after endurance training may be mediated by many factors. Maltats and colleagues showed an increased concentration of citrate synthase and 3-hydroxyacyl-CoA dehydrogenase, two enzymes important in oxidative phosphorylation, reflecting the oxidative capacity of the skeletal muscle. In addition, these investigators showed a specific increase in the cross-sectional area of oxidative muscle fibers type I and IIa. An improved oxidative capacity of the skeletal muscle will lead to less rapid onset of lactate accumulation and will result in a reduction of minute ventilation (and hence dyspnea) for an identical level of oxygen consumption. Lactate production is not a prerequisite for the achievement of training effects. Frequently, patients with severe COPD are

**FIGURE 28-1** Overview of training effects. All effects of exercise training are displayed as a percentage of the initial value. Effects are displayed for healthy control subjects and COPD patients (FEV1 \(43 \pm 9\%\) of predicted). Peak work rate (\(W_p\)), peak VO2 (\(VO_{2p}\)), peak ventilation (\(V_{Ep}\)), and peak oxygen delivery to the leg (\(O_2\) leg) are unchanged in COPD after training. Submaximal ventilation (\(V_{Es}\)) tended to decrease. A training effect in terms of oxidative capacity of the muscle is evidenced by increased peak oxygen extraction ratio (\(O_2\) Ep), calculated as (arterial oxygen content — femoral venous oxygen content)/arterial oxygen content, reduced lactate level at submaximal isowork (\(L_s\)), ratio of inorganic phosphate/phosphocreatine (\([P_i]/[PCr]\)) and time to replace half of the available phosphocreatine (\(PCr_{rec}\)). *p < .05, #p = .12, one tail). Adapted from Sala E et al. [34]
limited by ventilatory factors during an incremental exercise test, without demonstrating significant lactate production. These patients may, however, also benefit from dynamic exercise training. The physiologic effect of endurance training in patients not producing lactate can be appreciated from faster oxygen uptake kinetics, and reductions in fatigability of the quadriceps muscle.

It is important to acknowledge that in patients with COPD, as in healthy subjects, training effects are specific. One of the important benefits to patients is the improved mechanical efficiency achieved by practice. Therefore, patients will achieve a higher power output, even without improving peak VO\(_2\). Generally, the effects of exercise training on peak work rate are 20 to 25%, whereas peak VO\(_2\) improves by 10 to 15%. We analyzed data from 22 patient groups from 16 independent studies (total \(n = 498\)) in which the effect of exercise training in COPD was investigated. The effects found in each of these studies for VO\(_{2\text{peak}}\) and peak work rate are summarized in Figure 28-2. The mean change in peak work rate, weighted for the number of subjects studied, was 20 ± 41%, and the mean change in peak VO\(_2\) was 8 ± 25%. This analysis again shows the improved mechanical efficiency as in all studies the change in peak work rate is larger than the change in peak VO\(_2\).

Although the mean effects of endurance and interval training are undisputed, about one-third of patients may not respond as expected to this intervention; the reasons for this are not yet understood. It is possible that these patients have less muscle weakness before starting the exercise training, are more ventilatory limited, or are less compliant with therapy. These variables, however, allow prediction of training response for only about 40%. Other variables may therefore further explain the poor response to exercise training. Rabinovich and colleagues studied the effect of endurance training on skeletal muscle reox capacity and observed that some patients (especially those with a low BMI) have impaired muscle reox capacity after a daily exercise training program. These patients become more susceptible to oxidative stress after exercise training. It remains largely unstudied whether exercise training increases oxidative stress in selected patients. In addition, further studies are required to investigate the role of antioxidants in preventing oxidative stress.

**Effect of Combining Resistance and Dynamic Training Modalities** Exercise programs that combine resistance and dynamic training modalities may improve muscle strength and general exercise capacity, however, the literature in this area is still sparse. The results of two studies, in particular, have confirmed the additive effect of a program combining resistance and endurance training in patients with COPD. Consequently, exercise training in patients with COPD should include endurance or interval dynamic exercises and resistance training. A 40-minute program consisting of endurance (20 min) and resistance (20 min) training proved to be superior to 40 minutes of exercise training in each of the modalities separately.

**TRAINING THE UPPER LIMBS IN PATIENTS WITH COPD** Although most research has been focused on the effects of lower limb exercise training, it is important to recognize that COPD patients may encounter problems in carrying out the activities of daily living with the upper limbs. Carefully conducted research, however, has revealed that the upper limb muscles (ie, shoulder girdle) may suffer less from the deconditioning generally seen in the lower limbs and that the mechanical efficiency of upper limb activities is relatively well preserved compared with the mechanical efficiency observed in healthy subjects. Despite these relatively favorable conditions, COPD patients report excessive symptoms during upper limb activities. The main reason is the coupling of respiration to the muscles involved in upper limb movement. Upper limb exercises do impact on the breathing pattern. This is even more the case during unsupported arm exercises, where relatively more load is shifted toward the diaphragm. Hence, at isoventilation, more dyspnea is reported during upper limb exercises compared with lower limb exercise in COPD patients, especially during unsupported upper limb exercises. Upper limb exercise training programs can be used to reduce dyspnea during upper limb activities. Lower limb exercise training will not improve upper limb performance, so that, if improving upper limb performance is the aim of the training program, specific upper limb exercises should be included. Exercise programs including upper arm exercises reduce the ventilatory requirements for arm elevation. Martinez and colleagues suggested that unsupported arm exercises are to be preferred over ergometer training as an exercise modality as they mimic more accurately the activities of daily living.
STRATEGIES FOR “DIFFICULT-TO-TRAIN PATIENTS”

In recent years, efforts have been made to improve the outcome of exercise training in patients who are difficult to train. Generally, the methods used can be placed into two categories: (1) methods that enhance training intensity and (2) methods that stimulate muscle growth. These are summarized in Table 28-1.

Some of these methods are briefly discussed below, but the evidence to support these strategies is limited, and the interventions should be restricted to particular patient subgroups. Proper patient selection seems to be key to the efficient use of resources.

METHODS TO ENHANCE TRAINING INTENSITY

Since there seems to be a dose–response effect of exercise training, enhancing training intensity should result in increased training effects. Owing to the severe mechanical limitations of the ventilatory system, it may be difficult to achieve high workloads in some patients. Indeed, Richardson and colleagues showed, in a small group of very severe COPD patients (forced expiratory volume in 1 second [FEV1] 0.97 L), that the skeletal muscle had considerable metabolic reserve and that it could cope with higher metabolic loads when the ventilatory limitation was alleviated with the use of 100% oxygen or a helium–oxygen gas mixture.

Oxygen acutely improves peak exercise performance in selected COPD patients. It is generally accepted that oxygen supplements reduce ventilatory requirements, both at rest and during exercise. In addition, oxygen supplementation clearly increases oxygen delivery, especially in hypoxic patients. The consequence of this is that higher work rates can be achieved for the same level of ventilation. Therefore, the use of oxygen breathing may improve training intensity and therefore may impact on the training effect. Although the theoretical concept seems appealing, data are scarce concerning the benefits of oxygen supplementation in exercise training. To the best of our knowledge, three studies have been published so far. None has shown beneficial effects of oxygen supplementation. However, the patients studied by Rooyackers and colleagues were only mildly hypoxic at maximal exercise, and in the study by Garrod and colleagues, only a short-term exercise training program was applied, at very low work rates (unloaded pedaling). Exercise intensity with the use of oxygen supplementation was carefully investigated in a recent double-blind prospective exercise training study; the results confirmed higher training intensities and more pronounced training effects in the group that received oxygen. As a clinical guideline, we suggest that oxygen supplementation be used in those patients in whom the capacity for high-intensity training is clearly increased. Very often, it is claimed that oxygen should be administered to maintain oxygen saturation above an arbitrary certain level (89 to 90%). This concept, however reasonable it may appear, is not evidence based as brief periods of hypoxemia have not been shown to result in adverse effects, and training with hypoxemia may even be beneficial for the muscle if an adequate training stimulus can be provided.

A second way to unload the ventilatory system is through the application of noninvasive mechanical ventilation (NIMV). When properly applied, ventilatory help with techniques such as proportional assist ventilation (PAV) or bilevel positive airway pressure (BiPaP) increases the exercise capacity of COPD patients and may be effective in preventing diaphragmatic fatigue during high-intensity exercise. Indeed, a higher training load can be achieved in patients with severe COPD when PAV is used, resulting in more pronounced training effects. In patients with less severe disease, however, application of NIMV does not result in enhanced training effects. Since the application of NIMV is time-consuming and adjustment of the ventilator settings to the needs of the patient during variable exercise is difficult, this intervention will probably be restricted to highly selected patients.

A last, and potentially appealing, way to reduce the work of breathing, and hence improve ventilatory capacity, is through the breathing of gas mixtures of lower density than air. An often-used mixture is helium 79%/oxygen 21% (Heliox, HeO2). This combination of gases increases peak exercise performance for whole body exercise, resulting in a possible enhanced training effect. This strategy has been investigated in only one study, and no significant effects were found. In this study, HeO2 was administered at a maximal flow rate of only 10 L/min, and training was only conducted twice a week for 6 weeks. Despite these limitations, the authors showed a trend for more improvement when HeO2 was administered during exercise training (37 ± 33% in the group breathing room air vs 72 ± 51% in the group breathing HeO2, p = .07). This study warrants confirmation in a setting where HeO2 is delivered in an unrestricted manner during high-intensity exercise training three times a week and for a sufficient period of time (> 8 weeks).

It should be noted that the above-mentioned strategies are only relevant in selected patients. These options should be considered only after the less invasive and more traditional approaches have been exhausted. In particular, ventilatory capacity in COPD patients may also be improved by optimizing medication (including instructions on how to use inhaler devices correctly and enhancing compliance with medications). Although some drugs have only limited impact on FEV1, they may substantially reduce dynamic

---

Table 28-1 Interventions That Can Be Used to Increase Training Intensity or May Stimulate Muscle Growth or Muscle Function

<table>
<thead>
<tr>
<th>Increasing training intensity</th>
<th>Stimulating muscle growth or muscle function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal bronchodilatation</td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Growth hormone, insulin-like growth factor-I</td>
</tr>
<tr>
<td>Helium–oxygen</td>
<td>Nutritional supplements</td>
</tr>
<tr>
<td>Noninvasive mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Pursed-lips breathing</td>
<td></td>
</tr>
<tr>
<td>Arm bracing</td>
<td></td>
</tr>
<tr>
<td>Reduction in amount of working muscle</td>
<td></td>
</tr>
</tbody>
</table>
hyperinflation during exercise and hence improve exercise performance.86 Pursed-lip breathing,87 and the adoption of a leaning-forward posture with arm bracing, is yet another low-cost intervention that, in selected patients, may improve the ability to cope with high-intensity exercises. It is obvious that these relatively simple and low-cost interventions should be explored first, before more complex, labor-intensive interventions are attempted.

**METHODS TO STIMULATE MUSCLE GROWTH**

Several investigators have tried to restore muscle function by giving nutritional supplements or anabolic stimulants to patients. These strategies should only be used as an adjunct to a pulmonary rehabilitation program in which exercise training is offered. Supplements that have been used in COPD are growth hormone, anabolic steroids, and nutritional supplements (including creatine supplements).

Impressive results have been achieved with the use of anabolic steroids (testosterone,88 nandrolone decanoate,89 and oxandrolone90) in patients with COPD. Although the focus of studies has been on patients with low BMI, low testosterone levels were not an inclusion criterion. In addition, the studies involved regular exercise training, but no specific strength training was included. Typically, anabolic steroid treatment is used to improve skeletal muscle strength, in combination with strength training.91 Casaburi and colleagues used testosterone in patients with low baseline testosterone levels.92 These authors showed a benefit of anabolic steroids in combination with resistance training in improving muscle strength but not exercise performance. Similar observations were made in healthy elderly patients,93 where testosterone administration in combination with resistance training led to a mean change in muscle cross-sectional area compared with resistance training alone (4.51 ± 1.69 cm² vs 0.61 ± 1.41 cm²). In this study, testosterone administration and megestrol acetate (an appetite stimulant) ingestion, without resistance training, could not prevent the loss of skeletal muscle cross-sectional area induced by megestrol (−4.44 ± 1.66 cm²). Therefore, in selected patients, anabolic steroids or testosterone may be useful agents for the restoration of skeletal muscle strength when resistance training is performed.

Another intervention that can be used together with exercise training is administration of growth hormone. The administration of growth hormone in growth hormone-deficient patients results in enhanced breakdown and oxidative utilization of fat but, more importantly, in muscle hypertrophy through up-regulation of insulin-like growth factor-I (IGF-I).94 This growth factor induces muscle regeneration through myoblast proliferation.95–97 In healthy elderly subjects, however, growth hormone does not provide additional beneficial effects over a regular strength training program.98,99 Growth hormone, independently of resistance training, resulted in a greater predominance of muscle (glycolytic) fiber type IIx without altering the functional outcomes (ie, cross-sectional area and muscle strength). In addition, the results of this study showed a large number of side effects. In underweight COPD patients and patients with CHF,100 this strategy also proved to be largely ineffective in increasing muscle strength or exercise capacity.101,102 It is of note that in ~60% of patients suffering from cardiac cachexia, growth hormone resistance has been reported.103 Hence, administration of growth hormone will lead to less pronounced increases in the levels of autocrine IGF-I and may cause only minimal muscle proliferation. The local application of IGF-I to old muscle effectively counteracts immobilization-induced atrophy.104 This strategy merits further investigation as it bypasses the possibly blunted IGF-I response to growth hormone supplementation. Other interventions, such as interleukin-15 (IL-15) treatment, are currently under investigation. IL-15 may be a potent promoter of myofibrillar protein accumulation and may be effective in preventing atrophy. In vitro and animal model studies105,106 are needed to examine the proinflammatory action of IL-15 before experiments in humans can be conducted.

Finally, nutritional supplements such as creatine, or amino acids such as L-carnitine and glutamate, have not been studied extensively in COPD patients. These supplements have been used in healthy subjects, in conjunction with exercise training, with variable success.107,108 It remains to be determined whether these supplements are useful in COPD patients. There are theoretical backgrounds for supplementation with creatine and protein supplements. COPD patients have low levels of intramuscular substrate109 and may lack specific amino acids.110 Although this opens a window of opportunity for the use of nutritional supplements in COPD patients, in combination with exercise training, our preliminary experience with creatine supplements has been rather disappointing.111

**SUMMARY**

Skeletal muscle weakness and reduced oxidative capacity are clear hallmarks of the systemic impact of COPD. Impaired muscle function, unlike airflow limitation, can be partially reversed. This leads to clear improvements in exercise capacity, activities of daily living, and health-related quality of life. Exercise training is a potent therapy for the restoration of muscle function in COPD patients, but programs should be adapted to individual needs. Endurance training, interval training, and resistance training should all be considered when these programs are being developed. In all of these programs, the targeted muscle should be stressed at high intensity. In selected patients, exercise therapy can be supported by oxygen supplementation, NIMV, and/or neuromuscular electrical stimulation. In addition, anabolic stimulants (growth hormone, IGF-I, or anabolic steroids) may be useful in selected patients, but patient subgroups for these therapies need to be better defined.

**REFERENCES**


