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Review

Skeletal muscle dysfunction in chronic obstructive pulmonary disease

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Abstract

It has become increasingly recognized that skeletal muscle dysfunction is common in patients with chronic obstructive pulmonary disease (COPD). Muscle strength and endurance are decreased, whereas muscle fatigability is increased. There is a reduced proportion of type I fibers and an increase in type II fibers. Muscle atrophy occurs with a reduction in fiber cross-sectional area. Oxidative enzyme activity is decreased, and measurement of muscle bioenergetics during exercise reveals a reduced aerobic capacity. Deconditioning is probably very important mechanistically. Other mechanisms that may be of varying importance in individual patients include chronic hypercapnia and/or hypoxia, nutritional depletion, steroid usage, and oxidative stress. Potential therapies include exercise training, oxygen supplementation, nutritional repletion, and administration of anabolic hormones.

Keywords: exercise, lung diseases, muscle, nutrition disorder, obstructive, rehabilitation, skeletal

Introduction

COPD is a chronic debilitating disease with disabling symptoms. Our ability to improve lung function pharmacologically in patients with COPD is quite limited. Surgical options (lung volume reduction surgery, lung transplantation) can produce substantial improvements in some patients, but are associated with significant morbidity and mortality, and are only indicated in a minority of patients. It has recently become apparent that skeletal muscle dysfunction is common in patients with COPD, and may play a role in reducing exercise tolerance. Therapeutic efforts to improve skeletal muscle function could lead to considerable benefits in such patients. The present review focuses on the evidence for skeletal muscle dysfunction in patients with COPD, as well as on potential mechanisms of and therapies to combat this dysfunction.

Skeletal muscle dysfunction

Strength

Muscle strength is decreased in patients with COPD as compared with age-matched control individuals [1–3]. Lower limb muscles are affected to a greater extent than are upper limb muscles [1–3]. The preferential reduction in lower limb strength may be due to a greater reduction in activity of the lower limbs in these patients. On average, quadriceps strength is decreased by 20–30% in patients with moderate to severe COPD [2,3]. However, there is considerable variability among patients, with some patients having relatively normal values, whereas others have a reduction in strength of more than 50%.

In one study [1], the cross-sectional area of the thigh was measured using computed tomography scanning. In that

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 s; MRS = magnetic resonance spectroscopy; Pi = inorganic phosphate; VO_2 = oxygen consumption.

study the reduction in strength was proportional to the reduction in thigh area (ie the reduction in strength was entirely due to muscle atrophy). A subgroup of patients who had previously received steroids did have a greater reduction in strength than in muscle mass. Further studies are required to determine whether patients with particular clinical characteristics will display a reduction in muscle strength that is out of proportion to their reduction in muscle mass. Quadriceps strength was significantly correlated with the forced expiratory volume in 1 s (FEV_1) [1]; the lower the FEV_1, the weaker the quadriceps muscle. Quadriceps strength also correlated with exercise capacity, both peak exercise capacity [1,3] and 6-min walking distance [3], independently of lung function. However, correlation does not represent causation.

Endurance

Several studies [4–6] have compared limb muscle endurance in patients with COPD and healthy control individuals. Measurement of endurance is particularly affected by motivational factors, and variability in measurements can be quite high. Two studies [4,5] examined quadriceps endurance. One study found a significant reduction in quadriceps endurance in patients with COPD [4], whereas the other did not [5]. This finding may reflect heterogeneity in skeletal muscle function between patients with COPD. However, the smaller number of patients evaluated in the negative study (six versus 17) may also be important. Small reductions in endurance of upper limb muscles (elbow flexors and adductor pollicis) have also been demonstrated in patients with COPD [5,6].

Fatigability

When normal individuals exercise vigorously the exercising muscle develops contractile fatigue. With contractile fatigue, the force generated by the muscle for a given neural input decreases. Patients with COPD become breathless when they exercise, and may stop exercise because of breathlessness before they stress the exercising muscle sufficiently to develop fatigue.

We measured quadriceps twitch force (a measure of fatigue) before and after high-intensity cycle exercise to the limits of tolerance in a group of patients with moderately severe COPD [7]. We found a significant reduction in twitch force after exercise in 11 out of 19 patients. Thus, the majority of patients displayed contractile fatigue of the quadriceps muscle (the primary working muscle during stationary cycling) despite their having a severely reduced exercise capacity (the peak oxygen consumption [VO_2] averaged 51% of predicted). In a subsequent study we measured potentiated quadriceps twitch force (a more sensitive index of contractile fatigue [8]) in a group of patients with COPD of varying severity. Potentiated twitch force fell in 17 out of 21 patients after exercise [9]. Thus, most patients with COPD will develop contractile fatigue of the exercising muscle after exercise to the limits of tolerance. Patients with severe disease (FEV_1 <40% of predicted) were as likely to develop exercise-induced quadriceps fatigue (seven out of nine) as those with milder disease (10 out of 12) [9].

Healthy elderly individuals also develop exercise-induced quadriceps fatigue after cycle exercise to the limits of tolerance [10]. The degree of exercise-induced quadriceps fatigue was not significantly different between the healthy elderly and the patients with COPD, even though the patients with COPD exercised at a significantly lower workload. These results suggest that the quadriceps muscle is more fatigable in patients with COPD than in healthy elderly persons.

Muscle fiber type

In general, biopsies of the quadriceps muscle in patients with COPD have shown a reduced proportion of type I fibers and an increase in the proportion of type II fibers as compared with normal individuals [11–15]. Type I fibers are slow-twitch fibers, develop a relatively small tension, have increased oxidative capacity, and are resistant to fatigue. Type IIb fibers are fast-twitch fibers, develop high tensions, depend primarily on anaerobic glycolytic metabolism, and are highly susceptible to fatigue. Type IIa fibers are intermediate in character. The increased proportion of type II fibers was of type IIb in most studies, but an increase in type IIa fibers with no change in type IIb fibers has also been reported. This shift in fiber proportion should help to preserve strength, but at the cost of increased fatigability and reduced muscle endurance. However, the relative proportion of fiber types had no independent effect on exercise capacity [12,13]. In addition to the shift in fiber type, there is a reduction in cross-sectional area of type I and type IIa fibers (ie muscle atrophy is present) [11].

Muscle capillarity

Muscle capillarity is an important component of skeletal muscle oxidative capacity. The number of capillaries/mm^2 was significantly lower in patients with COPD than in healthy control individuals [14]. The ratio of capillary to fiber was also significantly lower in patients with COPD in one study [14], but this ratio did not reach statistical significance in another [11]. The ratio of capillary to fiber did not improve following a physical training program [11].

Muscle metabolism

Several studies in which the quadriceps muscle was biopsied [16,17] showed a reduction in oxidative enzyme capacity in patients with COPD as compared with control individuals. Citrate synthase (an enzyme that is involved in the citric acid cycle) and, to a lesser extent, 3-hydroxyacyl coenzyme A dehydrogenase (an enzyme that is involved in β-oxidation of fatty acids) are both significantly reduced in patients with COPD. Citrate synthase activity significantly

correlated with peak VO_2, independently of lung function [18]. In one study [16], phosphofructokinase (a glycolytic enzyme that is involved in anaerobic metabolism) was significantly increased in patients with COPD, but this finding was not confirmed in a subsequent study [17]. Cytochrome oxidase (the terminal enzyme in the mitochondrial electron transport chain) activity was significantly increased in patients with COPD and resting hypoxemia [19]. It had been believed that all oxidative enzymes would respond in a qualitatively similar fashion to deconditioning, training, etc. However, these results suggest that different oxidative enzymes may be regulated differently in patients with COPD.

Cellular bioenergetics can also be measured *in vivo* in humans by ^{31}P magnetic resonance spectroscopy (MRS). The ratio of intracellular phosphocreatine to inorganic phosphate (Pi) is closely related to that of ATP to ADP, and is believed to be a useful measure of mitochondrial phosphorylation potential. Intracellular pH can also be measured using ^{31}P-MRS. Recovery times for phosphocreatine after exercise have been used to assess mitochondrial density and function. A number of studies have utilized this technology in patients with COPD. However, in many of the studies patients were chronically hypoxic or had chronic hypercapnic, hypoxemic respiratory failure. The muscles usually studied are those in the forearm or calf, because these are the easiest muscles to position within the coil. More recently, technology has evolved that permits assessment of the quadriceps muscles during and after exercise. However, the ability to measure precisely the same area of the muscle with no pollution of the signal from adjacent muscles before, during, and after exercise is probably not as good for the quadriceps muscle as it is for the calf or forearm muscles. It should be remembered that lower limb muscles are particularly susceptible to deconditioning, and appear to be more impaired than upper limb muscles in patients with COPD.

In one study of the quadriceps muscle in normoxic patients with COPD [20], the Pi : phosphocreatine ratio was higher and intracellular pH lower in patients with COPD than in age-matched control individuals at the same absolute work rate. Similarly, the half-time for phosphocreatine recovery was significantly longer in the patients with COPD. These results provide further support that oxidative metabolism in the exercising muscle is impaired in patients with COPD. The increased Pi : phosphocreatine ratio and decreased intracellular pH during exercise were observed in previous studies in the forearm and calf muscles [21–25]. A prolonged half-time for phosphocreatine recovery was observed in some [22,24,25], but not all previous studies [23].

Blood lactate levels start to increase at very low work rates in patients with COPD [26,27]. Because blood flow to the leg is within normal limits in patients with COPD [27], the increase in lactate is due to an increase in net lactate output across the leg, probably because of increased lactate production within the exercising muscle. Oxygen delivery to the exercising leg is also not impaired in patients with COPD [27], suggesting that the increase in lactate production is due to an intrinsic muscle abnormality (reduced oxidative capacity) that results in early activation of anaerobic glycolysis.

Mechanisms of skeletal muscle dysfunction

Disuse

Patients with COPD tend to reduce their level of physical activity because exertion causes unpleasant sensations. A vicious cycle can result, with reductions in physical activity producing more deconditioning, and more impairment in skeletal muscle function leading to more symptoms at lower levels of work. Inactivity produces a number of structural and biochemical changes [28–30]. Muscle mass decreases and type IIa fibers tend to convert to type IIb. A reduction in the proportion of type I fibers with prolonged inactivity has been reported [31]. Oxidative enzyme concentration, the number and density of mitochondria, and the number of capillaries all decrease [28–30]. Reductions in oxidative capacity and muscle atrophy are common in patients with COPD. Deconditioning is almost certainly an important factor in the skeletal muscle dysfunction that is observed in patients with COPD.

Medications

Short courses of high-dose corticosteroids are used to treat acute exacerbations in patients with COPD. Low-dose oral corticosteroids have been used chronically to treat some patients with COPD, although the efficacy of this approach is hotly disputed. Steroid-induced myopathy has been well described, and may be more common than was initially appreciated. Histologically, both myopathic changes and generalized fiber atrophy are seen [32]. In one study [32], survival of patients with steroid-induced myopathy was significantly lower than that in a matched group of patients with COPD and a similar degree of airflow obstruction. In a provocative study [33], the average daily dose of steroids was measured for 6 months in a group of patients with COPD or asthma. Only one patient was receiving daily steroids. The other patients received bursts of steroids for exacerbations of their disease. The average daily dose of steroids was only 4.3 mg (range 1.4–21.3 mg). Eight out of 21 patients had significant quadriceps weakness, as defined as a reduction in quadriceps force below the normal range. An average daily dose of steroids that exceeded 4 mg/day was more common in patients with quadriceps weakness than in those without. The average daily dose of steroids explained 51% of the variance in quadriceps force measurements. The results of this study were interpreted as indicating that bursts of steroids might cause peripheral

muscle weakness. An alternative explanation is that patients with repetitive exacerbations are sicker, and therefore weaker than those without exacerbations.

Hypoxia

Chronic hypoxia adversely affects skeletal muscles. With prolonged exposure to high-altitude hypoxia, glycolytic enzyme (which is active in anaerobic metabolism) activity increases, whereas oxidative enzyme activity decreases [34]. Hypoxia also increases oxidative stress, which can adversely affect muscle performance [35]. In animals, hypoxia leads to a reduction in muscle fiber diameter [36]. Muscle fiber cross-sectional area is decreased in mountain climbers undergoing prolonged hypoxia (greater than 6 weeks) [37].

Hypercapnia

Short-term exposure to hypercapnia results in skeletal muscle weakness, but no change in fatigability [38,39]. In acute hypercapnic respiratory failure marked derangements in energy metabolism are seen, with marked reductions in ATP and phosphocreatine concentrations [40,41]. Acute hypercapnia also contributes to intracellular acidosis in patients with acute respiratory failure [41]. The effects of chronic hypercapnia need to be delineated.

Nutrition

Nutritional depletion is common in patients with COPD. A commonly used definition of nutritional depletion is a body weight less than 90% of ideal body weight. Using this definition, 35% of patients entering a pulmonary rehabilitation program were nutritionally depleted [42]. Body weight can be divided into fat and fat-free mass. Patients can be nutritionally depleted with a reduced fat-free mass, despite having a body weight within normal limits (due to an increased proportion of fat mass). Approximately 10% of patients meet this criteria [42].

A prolonged period of under-nutrition results in a reduction in muscle strength and endurance [43–45]. Undernutrition results in a reduction in muscle mass and fiber atrophy [43,46]. Type II fibers are affected to a greater extent than are type I fibers [43,46]. Glycolytic and oxidative enzyme activity are both reduced [46,47]. Muscle bioenergetics may also be impaired; high ADP levels and reduced phosphocreatine levels after contraction have been reported in food-deprived animals [47,48].

Oxidative stress

Oxidative stress may also contribute to the skeletal muscle dysfunction that is observed in patients with COPD. Increased plasma concentrations of lipid peroxidation products have been observed in patients with COPD during acute exacerbations [49]. The main source of these oxygen free radicals is mitochondria [50,51]. However, another source is immune cells activated by inflammation. Elevated tumor necrosis factor-α levels have been observed in patients with COPD and weight loss [52,53]. Susceptibility of a tissue to free radicals depends largely on the antioxidant status of the tissue [50]. The antioxidant status of skeletal muscle may be impaired by disuse or chronic hypoxia, or both.

Therapy

Exercise training

Deconditioning from disuse is believed to be a major contributing factor in the skeletal muscle dysfunction that is observed in patients with COPD. Therefore, exercise training in this setting should be helpful. In normal individuals, an endurance training program produces a number of morphologic and physiologic changes within the exercising muscle that increase its aerobic capacity [28]. These changes include an increase in mitochondrial number, increased muscle capillarization, and an increase in muscle oxidative enzyme activity. After intense training the proportion of type I fibers increases, whereas type IIb fibers can transform to type IIa [54]. In order for an endurance-training program to produce these results, exercise must be above a critical minimum intensity (the minimum intensity has not been precisely defined, but exercise at 50–60% of maximal VO_2 is clearly above it), and must be of sufficient duration and frequency [55].

It was formerly believed that patients with COPD could not perform exercise at a sufficient intensity (ie above the critical minimum intensity) to produce physiologic adaptations within the exercising muscle. In a previous study [56], muscle oxidative enzyme activity did not change after exercise training in a group of patients with COPD. However, the patients exercised at a relatively low intensity, even for patients with COPD. When patients with COPD underwent a more intensive training regimen an increase in oxidative enzyme activity was observed after training, clearly showing that patients with COPD can exercise sufficiently to undergo adaptations in the exercising muscle [57].

In a study that employed ^{31}P-MRS in the quadriceps muscle [20] an improvement in cellular bioenergetics was observed after pulmonary rehabilitation. For the same duration and intensity of submaximal exercise, the Pi : phosphocreatine ratio decreased and intracellular pH increased as compared with before rehabilitation. Similarly, the half-time of phosphocreatine recovery decreased after pulmonary rehabilitation. These improvements in bioenergetic state are consistent with an improved mitochondrial oxidative capacity. Quadriceps endurance has been assessed in patients with COPD by performing repeated dynamic contractions until exhaustion at different power outputs. After pulmonary rehabilitation endurance time was significantly increased at all power outputs, indicating that quadriceps endurance was improved after

rehabilitation [58]. We measured quadriceps fatigability before and after pulmonary rehabilitation in 21 patients with COPD [9]. Quadriceps contractile fatigue was assessed by measurement of quadriceps twitch force during supramaximal magnetic stimulation of the femoral nerve before and after constant load cycle exercise. For the same duration and intensity of exercise, the degree of exercise-induced quadriceps fatigue was significantly decreased after pulmonary rehabilitation. Thus, pulmonary rehabilitation resulted in increased fatigue resistance in the quadriceps muscle.

It is clear that exercise training can improve skeletal muscle function in patients with COPD. Exercise training (pulmonary rehabilitation) was shown to improve endurance exercise capacity and quality of life in patients with COPD [59,60]. Further studies are required to determine whether improvements in skeletal muscle function are responsible for the improvements in endurance exercise capacity and quality of life after pulmonary rehabilitation. In addition, the methodology of exercise training needs to be further studied. Some studies [26,61] have shown that (for the same total work) exercise at high intensity produces more benefits than exercise at lower levels of intensity. These results differ from those obtained in normal individuals. In normal persons, as long as the work intensity is above a critical minimum intensity, it is the total work performed and not the intensity of exercise that determines the training response [62]. Whether the addition of strength training and/or upper limb training provides any additional benefits when added to lower limb endurance training requires further study [63]. In one study [64], the addition of strength training did not provide any further benefits.

Oxygen therapy

Hypoxia reduces exercise performance in patients with COPD. Possible mechanisms include reduced oxygen delivery to the exercising muscle and increased ventilatory requirements. Exercise performance improves in hypoxemic patients with COPD when supplemental oxygen is administered [65,66]. As described above, chronic hypoxia can adversely affect skeletal muscle function. It has not yet been determined whether the effects of chronic hypoxia can be reversed by long-term oxygen therapy.

In one study [67] an increase in the creatine phosphate/creatine phosphate + creatine ratio (measured from quadriceps muscle biopsy) was observed after long-term oxygen therapy in patients with COPD, suggesting a possible improvement in skeletal muscle energy metabolism. The same investigators did not observe any change in oxidative enzyme activity after long-term oxygen therapy [15]. During exercise, acute administration of supplemental oxygen to hypoxemic patients with COPD improved aerobic metabolism, as measured using MRS [24,68]. Long-term oxygen therapy could also help by allowing patients to be more active, thereby reducing the effects of deconditioning. However, in one study [69] patients with COPD who desaturated during exercise were randomized to receive supplemental oxygen or air during exercise in the context of a formal pulmonary rehabilitation program. Exercise performance and quality of life improved in both groups, with no significant differences between the groups.

Steroids

Because oral steroids have a deleterious effect on skeletal muscle function, their use should be avoided whenever possible. The efficacy of chronic oral steroid therapy in stable patients with COPD is controversial at best. If chronic oral therapy is contemplated, it should be clear that simpler, less toxic therapeutic options have failed. Chronic therapy should only be continued if a clear unambiguous response to a trial of therapy is observed. The majority of patients will not show such a response [70]. In contrast, administration of steroids during an acute exacerbation is beneficial [71]. Two weeks of therapy was just as effective as 8 weeks of therapy, indicating that a prolonged taper of steroid dosage is not required. The long-term effects of short bursts of high-dose steroids require further study.

Nutrition

Because nutritional depletion has been associated with a poorer outcome in patients with COPD [72,73], nutritional repletion has been attempted. The results of this intervention have not been encouraging. In a recent meta-analysis [74], nutritional support had no significant effect on weight gain, anthropometric measures, FEV_1, respiratory muscle strength, or 6-min walk distance. It was often difficult to increase caloric intake substantially in outpatients with COPD because many of the patients tended to decrease their spontaneous intake of food in proportion to the degree of supplementation. In one study [75], patients were fed enterally via percutaneous gastrostomy. Caloric intake was greater than two times the resting energy expenditure. Patients gained weight, but the majority of weight gained was fat and there was no significant change in lean body mass. These results demonstrate that nutritional support alone is not usually successful in increasing lean body mass in patients with COPD.

Recent evidence [52,53] suggests that, in some nutritionally depleted patients with COPD, weight loss may be related to a systemic catabolic response induced by inflammation. In such patients, it is believed that nutritional support will not address the underlying problem, and therefore will not be effective. In a relatively large study [76], nutritional supplementation was administered while patients underwent an inpatient pulmonary rehabilitation program. Despite relatively modest nutritional supplementation, patients increased weight and, to a lesser extent,

fat-free mass as compared with a control group. Despite the positive results for the group as a whole, many patients did not gain weight with this approach. Unfortunately, limb muscle strength and quality of life were not measured. Inspiratory muscle strength was measured and did not significantly improve in the nutritionally supported group. Distance walked in 12 min improved in all groups (all of the patients were undergoing an exercise training program). There was no significant difference in the degree of improvement between the patients who were nutritionally supported and the control group who were not. The combined effects of nutritional supplementation and exercise training in nutritionally depleted patients with COPD require further study.

Anabolic hormones

Anabolic hormones are important mediators of muscle growth. Deficiencies in anabolic hormones lead to muscle wasting. Because anabolic hormones can be exogenously supplemented, this is an important area of research. Two hormone systems that are known to effect muscle – growth hormone and anabolic steroids – have been studied in patients with COPD.

Growth hormone exerts its effects primarily by increasing levels of insulin-like growth factors. In growth hormone-deficient adults, administration of growth hormone increases muscle mass and strength, and improves exercise performance [77,78]. Administration of growth hormone to healthy elderly individuals increases muscle mass, but not muscle strength or endurance [79,80]. Two controlled studies [81,82] examined whether administration of growth hormone would increase the benefits of exercise training in patients with COPD. In both studies, the group that received growth hormone plus exercise training increased lean body mass, whereas the group that received exercise training alone did not. In one study [82] muscle cross-sectional area was measured, and increased in the growth hormone group. Despite the increase in muscle mass, no significant change in maximal inspiratory muscle strength was observed [81,82]. The only measure of peripheral muscle strength obtained was handgrip strength, which did not change with exercise training in either the growth hormone or control group [81]. There were no significant differences between groups in the improvements after training in peak exercise capacity, whereas the improvements in endurance exercise were not significantly different between groups in one study [82], and were significantly less in the growth hormone group in the other [81]. Growth hormone is extremely expensive, and the data to date do not support its use in patients with COPD.

In hypogonadal men, testosterone replacement increases muscle mass and strength [83,84]. Although anabolic steroids have been used by competitive athletes for years to enhance performance, the effects of these agents in eugonadal men remained controversial. Recently, it was unambiguously shown [85] that anabolic steroids will increase muscle size and strength in healthy eugonadal men. Elderly men with mildly depressed testosterone levels may respond to anabolic steroids by increasing body weight and muscle strength [86].

Low testosterone levels are relatively common in patients with COPD [87]. The effects of anabolic steroids in patients with COPD with low testosterone levels have not been evaluated. Two studies [76,88] evaluated the effects of anabolic steroids in patients with COPD undergoing pulmonary rehabilitation [76,88]. In one of the studies the patients received nutritional supplementation in addition to anabolic steroids. In both studies, there was a significant increase in weight and lean body weight with anabolic steroids as compared with a control group. Maximal inspiratory muscle strength increased significantly in the anabolic steroid group in one study, but not in the other. Measurements of limb muscle strength were not performed. In the one study in which these parameters were measured [88], peak exercise capacity and 6-min walk distance were not significantly improved in either the anabolic steroid or the control group after pulmonary rehabilitation. Improvements in peripheral muscle strength usually do not result in an improvement in endurance exercise performance. When strength training was added to an endurance exercise program in patients with COPD the limb muscles did become stronger, but this increase in strength did not result in any additional improvement in exercise performance or quality of life [64].

Conclusion

Skeletal muscle dysfunction is very common in patients with COPD, and may play an important role in limiting exercise performance in these patients. Muscle strength and endurance are both decreased and the muscle is more easily fatigued. Muscle atrophy is largely responsible for the reduction in muscle strength. Changes in fiber type, reduced capillarity, decreased oxidative enzyme capacity, and altered cellular bioenergetics have all been documented in patients with COPD, and can potentially explain the reduction in muscle endurance. Mechanistically, deconditioning is of major importance. Other factors that are probably important in individual patients include hypoxia or hypercapnia, nutritional depletion, and steroid use. COPD may also produce a systemic inflammatory response that may adversely affect skeletal muscle function, but more work is required to substantiate this hypothesis. Exercise therapy has been shown to improve skeletal muscle function. Other potential therapies, such as oxygen supplementation, nutritional repletion, and administration of anabolic steroids, require further study.

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