

Peripheral Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

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Abstract. Dysfunction of the quadriceps muscles is regularly observed in patients with severe Chronic Obstructive Pulmonary Disease. Besides symptoms such as dyspnea and fatigue, they are progressively disabled by impaired exercise performance. Whether or not chronic obstructive pulmonary disease is linked to a specific myopathic condition, or whether the peripheral muscle dysfunction is a secondary consequence of the disease itself, it has not been definitively established. Proposed causative factors for the related muscle dysfunction include coexisting heart disease, chronic inflammation, acidosis, hypoxemia, malnutrition, severe de-conditioning (as a result of dyspnea), certain medications (particularly corticosteroids) and chronic inactivity leading to muscle disuse. The focus of this review is to identify and evaluate the physiological, metabolic and structural mechanisms involved in peripheral muscle dysfunction in chronic obstructive pulmonary disease.

Keywords: Mechanism, Quadriceps muscle, Myopathy, Chronic obstructive pulmonary Disease, Peripheral, Muscle dysfunction.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most common respiratory conditions of adults in the developed world. COPD

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is currently the focus of intense research due to its steadily increasing prevalence, direct and indirect costs, and mortality. This progressive, generally irreversible condition is associated with clinically significant systemic alterations in biochemistry and organ function. As in other chronic inflammatory conditions, weight loss, muscle dissipates, and tissue depletion are commonly seen in COPD patients.

It has been firmly established, that there is a significant peripheral skeletal muscle disease in patients with COPD^[1]. The peripheral muscle dysfunction observed in COPD patients is characterized in parts by a marked reduction in quadriceps endurance^[2].

While the exact mechanisms involved in the dysfunction of the quadriceps muscles observed in some COPD patients have not been established, many researchers have proposed that disuse and consequent reconditioning are important factors in the development of quadriceps muscle weakness in COPD patients. Recent studies, however, have suggested that other factors such as systemic inflammation^[3], exposure to systemic corticosteroids^[4], malnutrition^[5], and hypoxia^[6], may also be involved in peripheral muscle dysfunction. In addition, oxidative stress, likewise resulting from an inability of the antioxidant system to cope with elevated oxidant production, has also been proposed to play an important role in altering peripheral muscle function in patients with COPD^[7].

Some investigators^[8] have found an association between reduced muscle mass and survival in COPD patients; independent of a reduction of FEV₁. This finding has served to accentuate the need to determine the mechanisms of and effective treatments for muscle dysfunction related to COPD.

Evidence of Peripheral Muscle Dysfunction

Prevalence

Muscle wasting is present in a large population of patients with COPD, but its prevalence can only be approximated as there are no simple techniques to measure muscle mass. It has been proposed that as much as 70% of COPD patients may be affected by peripheral muscle dysfunction^[9]. However, the true prevalence and the extent of muscle dysfunction are probably underestimated when extrapolated from body weight measurements. Since lean body mass, and an index of muscle

mass, may be reduced despite preservation of body weight and muscle weakness may occur in the presence of decreased fat free mass.

Reduction in Muscle Strength and Endurance

Peripheral muscle strength and endurance is decreased in COPD patients as compared with age matched healthy subjects. The degree of quadriceps weakness is related to disease severity. Bernard *et al.* compared thirty-four patients with COPD and 16 normal subjects of similar age and body mass index. The strength of three muscle groups ($p < 0.05$) and the right thigh muscle CSA, were evaluated by computed tomography (83.4 ± 16.4 vs. $109.6 \pm 15.6 \text{ cm}^2$, $p < 0.0001$), and were reduced in the COPD patients as compared to the healthy subjects. In the same study, the researchers related quadriceps strength significantly with the forced expiratory volume: the lower the FEV₁, the weaker the quadriceps muscle^[10].

Couillard *et al.* reported that quadriceps endurance was significantly reduced in patients with COPD when compared with the healthy control subjects ($p < 0.01$). They measured quadriceps endurance in 25 subjects, 12 with COPD and 10 healthy subjects with sedentary lifestyles, by repeated knee extensions of the dominant leg. Biopsies of the vastus lateralis were done 48 hrs before and after exercise, as well as muscle oxidative stress was measured by lipid peroxidation and oxidized proteins. Muscle antioxidant was evaluated by peroxidase glutathione activity. Forty-eight hours post exercise, only patients with COPD had a significant increase in muscle lipid peroxidation ($p < 0.05$) and oxidized proteins ($p < 0.05$), whereas increased peroxidase glutathione activity was only observed in healthy control subjects ($p < 0.05$). Both increases in muscle lipid peroxidation and oxidized proteins were significantly and inversely correlated with quadriceps endurance capacity in COPD ($p < 0.05$). Their findings led them to conclude that quadriceps exercise increased oxidative stress, but not antioxidant activity in patients with COPD. Furthermore, the increase in oxidative stress was correlated with a decrease in quadriceps endurance^[11].

In a study assessing the relevance of quadriceps endurance in patients with COPD, Coronell *et al.* confirmed reduction in quadriceps strength finding. Thus, even normal weight and clinically stable patients

with COPD have marked impairment in the endurance of the quadriceps muscle, regardless of physical activity and even when airflow obstruction is mild-to-moderate. They proposed that muscle endurance is irrespective of muscle strength and that it is related to an increased susceptibility to peripheral muscle fatigue as task failure was associated with a decrease in f_{EMG} and transitory loss of strength in the exercised thigh^[12]. Differences in diagnostic methods and study populations are likely the cause of variations in findings.

Increased Muscle Fatigue

Onset of muscle fatigue, a reversible post-exercise fall in quadriceps strength; as measured by quadriceps twitch force before and after exercise to the limits of tolerance in patients with moderately severe COPD occurs earlier as compared with healthy control subjects.

In one study, Mador *et al.* conducted with a 29 subject population; 8 patients with severe COPD (FEV₁, 26% predicted), 11 patients with mild-to-moderate COPD (FEV₁, 50% predicted), and 10 healthy subjects in which they evaluated quadriceps fatigability. They reported that maximum voluntary contraction of the right quadriceps achieved a force of 44 kg in patients with severe COPD; 49 kg in patients with mild-to-moderate COPD, and 58 kg in healthy subjects. Three sets of 10 maximum voluntary contractions of the quadriceps achieved greater fatigability (measured as the decrease in potentiated twitch force during magnetic stimulation of the femoral nerve) of the quadriceps in patients with severe COPD than in patients with mild-to-moderate COPD, or the healthy subjects. The fall in twitch force in patients with mild-to-moderate COPD was not significantly different from healthy subjects^[13].

Changes in Muscle Fiber

Mador and Bozkanat reported changes in fiber type, reduced capillarity, decreased oxidative enzyme capacity, and altered cellular bioenergetics in patients with COPD, thus cited these as factors in the reduction in muscle endurance. They proposed deconditioned as the primary mechanism of the muscle dysfunction and cited hypoxia or hypercapnia, nutritional depletion, and steroid use as possible related factors. The researchers hypothesized that COPD may also produce a systemic inflammatory response that may adversely affect skeletal

muscle function and recommended additional research focusing on this concept^[14]. Sato *et al.* reported that the diameter of Type I and (to a greater degree) Type II fibers were smaller than those of control subjects, and correlated with amount of weight loss and reduction in percent predicted FEV₁ changes; they premised probably resulted from chronic hypoxemia^[15].

Changes in Muscle Capillarity

Muscle oxidative capacity is related to muscle capillarity. Jobin *et al.* found that the number of capillaries/mm² and the ratio of capillary to fiber to be significantly lower in patients with COPD than in healthy control individuals^[16]. Whitton *et al.* in their study reported that the number of capillary contact for Type I, IIa, and IIb fibers was significantly reduced in COPD compared with normal subjects ($p < 0.05$). However, while the capillary to fiber ratio tended to be reduced in patients, this difference did not reach statistical significance ($p = 0.15$), nor did the ratio of capillary to fiber improve following a physical training program^[17].

Changes in Muscle Metabolism

Biopsies of the quadriceps muscle have shown a reduction in oxidative enzyme capacity in patients with COPD as compared with control individuals. Citrate synthase and 3-hydroxyacyl coenzyme A-dehydrogenase are both significantly reduced in patients with COPD. Cytochrome oxidase activity was significantly increased in patients with COPD and resting hypoxemia^[18].

Despite normal blood flow and oxygen delivery to the lower limbs in COPD patients, blood lactate levels start to increase at a very low work rate in patients with COPD. This increase is due to an increase in net lactate output across the leg. Probably because of the increased lactate production within the exercising muscle, possibly due to an intrinsic muscle abnormality (reduced oxidative capacity) that results in early activation of anaerobic glycolysis^[19].

Indications of Greater Lower Limb Involvement

Several studies have found that the muscles of the lower limbs are involved to a greater extent than those of the upper limbs, and that the

extent of the involvement of the lower limbs is a more accurate predictor of disease severity.

Marquis *et al.* studied the mid thigh muscle cross sectional area and compared it to the body mass index as a predictor of mortality in COPD patients. It was concluded that the mid thigh muscle area was a strong predictor of mortality in patients with COPD^[20].

Gea *et al.* examined the deltoid muscles of COPD patients and found that the effect on these muscles was different to, in fact almost the opposite of, the effect observed in the quadriceps. Reporting that oxidative capacity appeared to be preserved or even increased in the deltoid muscles of COPD patients. They proposed that local factors in addition to systemic factors are essential in determining the phenotype of each skeletal muscle in patients suffering from chronic obstructive pulmonary^[21]. The seemingly disproportionate involvement of the muscles of the lower limbs may be due to the fact that; activities related to gait development are usually avoided by patients with COPD due to the sensation of dyspnea, as well as the predominance of upper-limb use in the performance of daily activities.

Risk Factors, Causes and Mechanisms

It has long been accepted that chronic obstructive pulmonary disease (COPD) patients experience exercise intolerance and muscle wasting^[22]. However, it has yet to be established whether this is primarily due to muscle dysfunction or muscle disuse^[23]. Literature has put forward that muscle dysfunction is common in COPD patients and have proposed inactivity, acidosis, hypoxemia, chronic inflammation, malnutrition, coexisting heart disease, severe deconditioning, and medications (*i.e.* corticosteroids) as possible mechanisms^[24]. Comorbidity and ageing are other external factors which could possibly exacerbate ability to define the relationship between the lung impairment and alterations in the peripheral muscles in COPD patients.

Hypercapnia

Exercise capacity is reduced in hypercapnic patients with severe stable COPD; band related to lower ventilation during exercise^[25]. Short-term exposure to hypercapnia results in skeletal muscle weakness, but no change in fatigability^[26].

Oxidative Stress

Oxidative stress occurs with exercise in patients with COPD in their systemic circulation, particularly during exacerbations of their disease and has been related to skeletal muscle dysfunction. Muscle oxidative stress is associated with reduced quadriceps endurance^[27]. Couillard *et al.* studied eleven COPD patients (FEV_1 1.15 ± 0.4 L (mean $\pm$ SD)) and twelve healthy age-matched subjects with a similar low quantity of physical activity performed endurance exercise localized to a peripheral muscle group; the quadriceps of the dominant leg. They found that quadriceps exercise induced systemic oxidative stress in chronic obstructive pulmonary disease patients, and that vitamin E levels were decreased in these patients at rest. In addition, they concluded that the expected increase in antioxidant defenses after exercise was compromised in these individuals^[28]. Maltais *et al.* performed muscle biopsies on the skeletal muscles of nine COPD patients during exercise (age = 62 ± 5 yr, mean $\pm$ SD, FEV_1 $40 \pm 9\%$ of predicted) and in nine normal subjects of similar age (54 ± 3 yr). It was concluded that in COPD the increase in arterial Lactic acid (La) during exercise is excessive, the oxidative capacity of the skeletal muscle is reduced, and that these are interrelated^[29]. Sue *et al.* reported the onset of the anaerobic threshold at low levels of incremental exercise in two-thirds of patients with moderate to severe COPD, suggesting an increased reliance on anaerobic metabolism in patients with COPD. A premise supported by noted histochemical and morphological changes seen in the skeletal muscle of COPD patients^[30].

COPD Exacerbation

Peripheral muscle weakness is enhanced during an acute exacerbation of COPD. CXCL8 and IGF-I may be involved in the development of peripheral muscle weakness in hospitalized, and in stable patients with COPD^[31].

Systemic Inflammation

Microscopically, skeletal muscles show accelerated apoptosis, increased oxidative stress^[32], and inflammatory changes such as acute-phase reactants and cytokines^[33]. Supporting the premise that local inflammatory and oxidative factors may be involved in the pathological and physiological changes in the skeletal muscles in patients with COPD.

Sin and Man claim that several factors point to systemic inflammation playing a role in peripheral muscle dysfunction in COPD, including: a clear inverse linear relationship between FEV₁ and CRP, the association between systemic inflammation and reduced muscle strength. Plus exercise tolerance, health status, and the fact that inhaled corticosteroids, which down regulate airway inflammation, may also modulate systemic inflammation in COPD^[34]. Broekhuizen *et al.* concurred reporting that serum CRP levels were inversely related to the distanced achieved in the 6 min walk test, independent of other factors such as age, sex, and smoking history^[35].

Several studies have found that C-reactive protein (CRP) levels are elevated in clinically stable COPD patients^[36,37], supporting the premise that systemic inflammation is involved in COPD related peripheral muscle dysfunction.

Andreas *et al.* proposed that COPD is the consequence of neurohumoral activation, namely inflammation, cachexia, effects on ventilation, and skeletal muscle dysfunction. These initiate a self-perpetuating cycle that contributes to the pathogenesis of COPD, which involves respiratory muscle dysfunction as well as systemic inflammation^[38].

There are some questions as to whether the proposed systemic inflammation would be a mechanism of muscle dysfunction, or if the muscle dysfunction results in systemic inflammation. Sin and Man premised that while it is tempting to ascribe systemic inflammation to muscle dysfunction, it is possible that muscle dysfunction (and perhaps the local oxidative stress and the inflammatory load within muscles) can promote systemic inflammation^[39].

Diagnosis of Muscle Dysfunction

Muscle function is evaluated based on strength and endurance. Muscle strength testing evaluates the capacity of the muscle to develop maximal force, whereas muscle endurance testing evaluates the muscle's ability to maintain a certain force in time. The assessment of peripheral muscle dysfunction is generally made by either a neurologist and or a pathophysiologist who will assess the type and extent of the muscle pathology. Initial assessment determines the presence, if any, of neurogenic, myopathic, or inflammatory abnormalities by muscle biopsy.

Measurements of muscle energetic have become more assessable with P-magnetic resonance spectroscopy^[31] and muscle biopsy to determine muscle enzymes and fiber typing; however, these tools are not available for routine clinical evaluation. More practical field tests include the incremental and endurance shuttle walk test equivalents of laboratory examination and the 6 min walk test^[40]. Magnetic stimulation techniques can be used to evaluate the quadriceps muscles. Muscle strength can be measured through isometric maximum voluntary contraction. Quadriceps twitch force (QTW) is a non volitional measurement has been found to give a more sensitive measurement of muscle fatigue.

Polkey *et al.* proved that fatigue of the quadriceps muscle can be detected with serial measurements of QTW during magnetic stimulation of the femoral nerve^[41].

Mador *et al.* measured QTW before and after high intensity cycle exercise to the limits of tolerance in a group of patients with COPD as to determine whether quadriceps fatigue could be detected. It was found that QTW fell significantly after high intensity cycle exercise to the limits of tolerance in a group of patients with moderate to severe COPD^[42].

Tateishi *et al.* have proposed that spatially resolved (SR) spectroscopy will assist in the study of the dynamics of muscle oxygenation in COPD patients^[43]. Other methods to assess exercise tolerance include incremental and steady-state cardiopulmonary exercise testing (CPET). The CPET is the gold standard for measuring exercise tolerance and gas exchange during exercise.

Consequences of Peripheral Muscle Dysfunction

The importance of research into COPD related peripheral muscle dysfunction was established in the relation between peripheral muscle dysfunction and patients' quality of life plus the predicted length of survival.

Jagoe *et al.* reviewed and interpreted current literature as to concluded that muscle wasting in chronic obstructive pulmonary disease was associated with impaired skeletal muscle function, worse quality of life and very poor prognosis^[44].

Bernard *et al.* found that low muscle mass in COPD was associated with weaker peripheral muscles and impaired functional status^[45].

Typically COPD patients progressively limit their activity because of exertion related dyspnea. Inactivity due to related dyspnea leads to deconditioning, and deconditioning leads to muscular weakness and inefficiency, which then requires more effort by the heart and lungs for the same level of muscular effort. This leads to increased inactivity and thus to greater deconditioning. In addition, muscle disuse has a negative effect on antioxidant status and, thus, enhances the risk of oxidative damage.

Marquis *et al.* reported that the mid thigh muscle area was a strong predictor of mortality in this cohort of patients with COPD, and proposed that assessment of body composition in the clinical evaluation of patients with COPD may prove to be useful in predicting outcome in these individuals^[46].

Conclusion

Obviously, with the number of contrasting findings and the diversity of proposed mechanisms, a great deal of further research is needed before the causes and optimum treatment for COPD related peripheral muscle dysfunction can be established. One possible factor in the contrasting findings may be related to the lack of established criteria for a control group, which should include a group of subjects with a sedentary life style comparable to that of deconditioned COPD patients. Although, a few studies have used control group subjects who for one reason or another also have impaired muscle function due to inactivity. Many previously done studies have used only 'healthy subjects' as a control group, which would mean that factors related to inactivity could not reasonably be expected to be equal. Moreover, it may exacerbate the researchers ability to properly evaluate factors. In addition, few of the studies have been done on larger groups of patients (over 100), separated into subgroups by disease severity and then further by tested quadriceps strength and endurance, and followed up for a longer period of time. Further research into mechanisms such as systemic inflammation and hormone replacement is necessary, but deconditioning cannot be annulled as a factor in the observed muscle dysfunction.

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الاختلال الوظيفي للعضلات الطرفية في داء الرئة الانسدادي المزمن

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المستخلص. عادة ما نجد و بشكل دوري ضعفا في عضلات الفخذ في المرضى الذين يعانون من الداء الرئوي الانسدادي المزمن بالإضافة إلى الأعراض الشائعة مثل الزلة التنفسية والتعب العام في الجسم وبشكل يتطور نحو الأسوأ في الأداء الوظيفي للجهد العضلي. إن ارتباط الداء الرئوي الانسدادي المزمن أو عدم ارتباطه بحالات اعتلال عضلي محدد أو أن الاختلال الوظيفي للعضلات الطرفية هو نتيجة المرض نفسه هو أمر لم يثبت بشكل محدد بعد. إن العوامل المسببة المقترحة لخاصية الاختلال الوظيفي لهذه العضلات التي تحصل في هذا المرض تشمل التالي: الأمراض القلبية المرافقة، حالة الالتهاب المزمن فيه، إحمضاض الدم الحاصل، نقص الأكسدة، سوء التغذية، بعض الأدوية المستخدمة خاصة الكورتيكوزون، عدم القدرة على ممارسة الحياة والعيش بسبب الزلة التنفسية المرافقة مما يؤدي إلى الخمول وعدم استخدام العضلات. إن هذا البحث يركز على تحديد وتقييم الآليات الطبيعية الفيزيولوجية والاستقلابية والبنوية التي تسبب الاختلال الوظيفي للعضلات الطرفية في الداء الرئوي الانسدادي المزمن.