Peripheral muscle dysfunction and chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a systemic disease that includes significant adverse effects on muscle function, with varied changes to the structure and metabolism of the peripheral muscles. This review evaluates the evidence for the mechanisms that mediate these changes and the significance of the diminished muscle function.

Chronic obstructive pulmonary disease is now recognized to be a multi-system disease with major intrinsic abnormalities occurring in skeletal muscles. It was first so defined in 1999 following a joint statement from the American Thoracic and European Respiratory Societies (American Thoracic Society/European Respiratory Society, 1999).

Skeletal muscle dysfunction observed in the limbs of chronic obstructive pulmonary disease patients significantly reduce exercise tolerance. Exercise intolerance is an adverse prognostic factor contributing to poorer health, limited activity of daily living and reduced quality of life (Sin and Man, 2006; Rabinovich and Vilaro, 2010). The changes that occur in the muscles of chronic obstructive pulmonary disease patients are well described but the mechanisms which cause these changes are much debated.

This review outlines the pathophysiological (structural and enzymatic) adaptations of peripheral muscles in chronic obstructive pulmonary disease and discusses possible aetiological factors with particular reference to the clinical implications for both patients and their doctors.

Structural alterations of peripheral muscles in chronic obstructive pulmonary disease

Muscle typology

At a cellular level the human skeletal musculature is made up of two myosin heavy chain isomers: type I and type II. Type I fibres are slow twitch and low-tension fibres containing high quantities of oxidative enzymes, allowing them to be fatigue resistant. These fibres undergo aerobic metabolism, promoting muscular endurance. In contrast, type II fibres are fast twitch and high tension fibres, mainly working in anaerobic conditions, facilitated by the presence of glycolytic enzymes. These fibres are easily fatiguable, allowing human muscle to produce maximal force for a limited time period only, for example during sprinting. Type II fibres can be further divided into IIa (intermediate fibres – both glycolytic and oxidative capacities) and IIx (IIb) fibres (Montes de Oca et al, 2006).

In the vastus lateralis and tibialis anterior, which is part of the quadriceps muscle group, a reduction in type I and an increase in type II fibres was observed most frequently in patients with chronic obstructive pulmonary disease (Richardson et al, 2003; Allaire et al, 2004; Montes de Oca et al, 2006; Eliason et al, 2009). These studies suggest that a gradual transformation of peripheral muscle fibres occurs during the course of chronic obstructive pulmonary disease (I → I/IIa → IIa → IIa/x → IIx). In contrast, no difference of type I fibres between patients and controls was found by two similar cross-sectional studies examining the deltoid muscle, and no significant difference of type IIa and IIb fibres was found between groups (Gea et al, 2001; Hernàndez et al, 2003).

From the current literature it is not clear whether peripheral muscle dysfunction is a generalized phenomenon or whether only certain muscle groups are affected. This is discussed in greater detail later in the article.

Capillarity

Changes in capillarity have also been suggested as a mechanism for muscle dysfunction but research is mainly limited to the vastus lateralis and tibialis anterior muscles, with variable outcomes. A reduced number of capillaries per square millimetre and reduced capillary-to-fibre ratio have been found in some patients with chronic obstructive pulmonary disease (Jatta et al, 2009). Therefore, if capillarity abnormalities exist in peripheral muscles of patients with chronic obstructive pulmonary disease, oxygen transfer from haemoglobin to mitochondria may be altered, impairing adequate aerobic metabolism needed for everyday activity (Eliason et al, 2010).

Muscle mass

The cross-sectional area of the entire skeletal musculature is reduced in patients with chronic obstructive pulmonary disease (Allaire et al, 2004). The reduction in muscle mass is partially caused by muscle fibre atrophy, if no loss in overall fibre type numbers is present (Gosker et al, 2002b). Muscle atrophy is enhanced during acute exacerbations of chronic obstructive pulmonary disease, accelerating muscular dysfunction (Crul et al, 2010). Furthermore, muscle growth in patients with chronic

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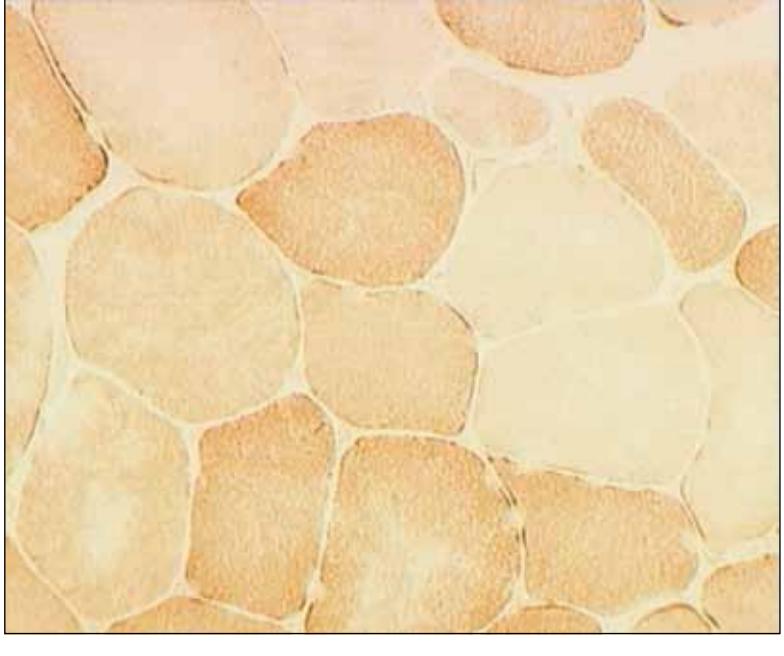
obstructive pulmonary disease is disturbed by the ubiquitin-mediated proteolytic pathways, producing negative regulators which promote muscle atrophy (Plant et al, 2010). This pathway is activated by factors such as cytokines, inactivity, acidosis or malnutrition (low insulin levels) (Debigare et al, 2001). Gosker et al (2002b) found type IIx fibres to be atrophied, with no differences found in type I and IIa fibres. In contrast, Whittom et al (1998) found type I fibre cross-sectional area to be reduced in patients with chronic obstructive pulmonary disease, although the type I fibres in their controls had a greater cross-sectional area than normally observed in healthy subjects, thus making the fibre cross-sectional area of patients look relatively reduced.

In addition, it has been suggested that muscle fibre atrophy is closely linked to body mass index, explaining why chronic obstructive pulmonary disease patients with muscle atrophy are typically underweight. Overall, the loss in peripheral muscle mass seems to contribute to muscle weakness and low functional capacity, consequently worsening patients' health status and exercise tolerance (Decramer et al, 2005). The concept of muscle disuse and atrophy is further discussed later in the article.

Enzyme status of peripheral muscles

Two categories of muscle enzymes have been studied: glycolytic (such as glycogen phosphorylase and lactate dehydrogenase) and oxidative enzymes (such as succinate dehydrogenase and creatine kinase), and three muscles have been examined: vastus lateralis, deltoid and anterior tibialis muscles.

Figure 1. Photomicrograph of type I and type II muscle fibres. The stain used highlights cytochrome oxidase activity essential for oxidative metabolism, so type I muscle fibres stain dark, as they contain a number of oxidative enzymes for aerobic metabolism. In contrast, type II fibres stain more lightly, because they contain more glycolytic enzymes. Type II fibres are further divided into type IIa (moderate stain) and type IIb fibres (pale stain).



Most studies have found oxidative enzymes to be reduced and glycolytic enzymes to be raised in the vastus lateralis in patients with chronic obstructive pulmonary disease (Jakobsson et al, 1995; Gosker et al, 2002a; Allaire et al, 2004; Eliason et al, 2010). However, no differences in the glycolytic and oxidative enzyme capacities were found in the deltoid and anterior tibialis muscle (Pouw et al, 2000; Gea et al, 2001).

The differences in enzyme status among the three muscles cannot be explained by variant anthropometrical characteristics of patients. Hence, Pouw et al (2000) proposed an explanation based on the structural and functional differences of the three muscles. The anterior tibialis muscle is regarded as a tonic (postural) muscle and primarily consists of type I fibres (oxidative), whereas the vastus lateralis has a low number of type I fibres (high type II – glycolytic) making it a phasic muscle, producing strength, power and locomotion. The deltoid muscle has both tonic and phasic properties, as a result of its combination of both type I and II fibres (both oxidative and glycolytic). Therefore, the fibre type arrangement of each muscle varies and may influence enzymatic capacities, confounding the results observed.

Figure 1 shows a photomicrograph of type I and II fibres, highlighting their individual enzyme compositions.

Aetiology of peripheral muscle dysfunction in chronic obstructive pulmonary disease

There are a number of potential aetiological causes of peripheral muscle dysfunction in chronic obstructive pulmonary disease. Some relate to the pathophysiology of chronic obstructive pulmonary disease, such as hypoxia, hypercapnia, oxidative stress, deconditioning and inflammation, while others are less directly linked to the disease process itself, for example glucocortico-steroid treatment and nutrition (Rabinovich and Vilaro, 2010).

Deconditioning and disuse

The one factor that is agreed among most researchers as a key cause of peripheral muscle dysfunction is disuse. Patients suffering from chronic obstructive pulmonary disease avoid high levels of physical activity in order to minimize exertion and associated symptoms of dyspnoea and muscle fatigue. The consequences of disuse are muscle fibre atrophy, reduced capillarity and oxidative enzymes, and muscle typology changes from IIa to IIb, with subsequent reduction of type I fibres (Jagoe and Engelen, 2003).

In contrast to lower limb muscles respiratory muscle biopsies have revealed an opposite adaptation – increased type I fibres, reduced type II fibres and increased oxidative enzyme activity – attributable to the increased workload in chronic obstructive pulmonary disease (Vogiatzis and Zakynthinos, 2009). The fact that upper limb muscles show similar changes to respiratory muscles supports the theory of deconditioning as a cause of upper limb weakness, as upper extremity muscles do not suffer from

the reduced activity seen in the lower limbs (Hernàndez et al, 2003). Seymour et al (2010) found that 32% of UK chronic obstructive pulmonary disease hospital outpatients had reduced quadriceps strength. Resistance training may improve this weakness, even during an acute exacerbation of chronic obstructive pulmonary disease (Troosters et al, 2010).

A debate exists within the literature as to whether a myopathy instead of a deconditioning effect is present in peripheral muscles of patients with chronic obstructive pulmonary disease (Wagner, 2006). However, if a myopathy exists one would expect to find a homogenous pattern of structural and metabolic changes among all peripheral muscle groups, which is not evident from the research.

Hypoxia

Hypoxia has several negative effects on peripheral muscles, contributing to muscle wasting by inhibiting anabolic hormones, altering mitochondrial enzyme capacities (especially the oxidative component), initiating oxidative stress by enhancing inflammation, altering both muscle capillarity and typology, and inhibiting protein synthesis while stimulating proteolysis (Jagoe and Engelen, 2003).

Reversing hypoxia by administering supplemental oxygen to exercising patients with chronic obstructive pulmonary disease enhances exercise tolerance (Richardson et al, 2003). Nonetheless, enzyme status in chronic obstructive pulmonary disease patients did not change after oxygen therapy, suggesting that other mechanisms are also involved in peripheral muscle dysfunction (Jakobsson et al, 1995).

Systemic inflammation

Some degree of systemic inflammation is consistently present in patients with chronic obstructive pulmonary disease, which is supported by finding increased levels of pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukin-6 (Wouters, 2002; Sin and Man, 2006). These cytokines cause peripheral muscle weakness by inhibiting the actions of insulin growth factor, enhancing proteolysis, promoting skeletal muscle apoptosis and altering repair mechanisms. The origin of this inflammatory response remains unknown, but smoking has been implicated (Barnes and Celli, 2009).

Oxidative stress

Two sources of oxidative stress have been identified:

1. Mitochondria, producing oxygen free radicals
2. Tumour necrosis factor alpha produced by macrophages and monocytes.

Oxygen free radicals can induce protein degradation contributing to muscle mass loss and myocyte damage (Aliverti and Macklem, 2001; Debigare et al, 2003).

Exercise contributes to an enhanced antioxidant status, reducing the rate of muscle mass loss in chronic obstructive pulmonary disease. However, as chronic obstructive pulmonary disease patients commonly avoid exercise they lose this protection against oxygen free radicals (Debigare et al, 2003).

Anabolic hormones

Normal musculature growth requires a steady state of anabolic hormones, especially growth hormone and testosterone. Growth hormone stimulates the liver to produce insulin growth factor, resulting in protein synthesis, inhibition of proteolysis and therefore contributing to muscle growth. Testosterone also promotes protein synthesis in humans. Levels of both these hormones are reduced in patients with chronic obstructive pulmonary disease, resulting in muscle mass loss, muscle dysfunction and exercise intolerance (Debigare et al, 2003; Jagoe and Engelen, 2003).

Hypercapnia

Linked with hypoxia, hypercapnia is present in some patients with severe chronic obstructive pulmonary disease. In patients with acute respiratory failure hypercapnia leads to intracellular acidosis, which subsequently alters enzyme function and stimulates proteolysis (American Thoracic Society/European Respiratory Society, 1999; Debigare et al, 2001).

Clinical consequences of muscle fatigue

Muscle dysfunction in patients with chronic obstructive pulmonary disease has significant consequences for the patient and the clinician responsible for care must be aware of these effects. In studies from the UK and Netherlands approximately a third of chronic obstructive pulmonary disease patients attending outpatients had some muscle dysfunction. Lower limbs are particularly affected leading to significant exercise limitation (Bernard et al, 1998). The inability to exercise not only affects patients' peripheral muscle composition but also compromises cardiac fitness, leading to an overall deterioration in symptoms and quality of life (Decramer et al, 2005; Rabinovich and Vilaro, 2010).

Clinicians should be aware that muscle fatigue not breathlessness or hypoxia can be the main determinant of reduced exercise tolerance (Gagnon et al, 2009). Patients with the emphysema phenotype seem particularly vulnerable to muscle weakness and the degree of impairment correlates well with the diffusing capacity of the lung (Engelen et al, 1994). Killian et al (1992) studied 417 subjects, observing that exercise intolerance in 43% of patients with chronic obstructive pulmonary disease and 35% of healthy subjects was caused by leg fatigue. In comparison, only 26% of chronic obstructive pulmonary disease patients and 22% of healthy subjects reported dyspnoea to be the main limiting symptom. Quadriceps strength in chronic obstructive pulmonary disease patients correlates significantly with 6-minute walk distance, a test that contributes to survival prediction and is a better correlate than oxygen desaturation (Gosselink et al, 1996).

The challenge to the clinician is to recognize the critical role of muscle dysfunction in the chronic obstructive pulmonary disease patient and then to manage this aspect of the condition appropriately. There are a number of potential strategies that predominantly address the potential aetiological factors that predispose to muscle dysfunction. First do no harm – although inhaled steroids have an important place in the management of chronic obstructive pulmonary disease the catabolic effect of systemic steroids should be avoided wherever possible in such patients, particularly as a long-term strategy. Addressing hypoxia in order to maximize muscle function not just dyspnoea may be critically important during exercise. It is logical to consider that promoting adequate nutrition may reduce muscle mass loss.

Malnutrition may be in some part responsible for muscle wasting, as a result of inadequate muscle proteogenesis and gluconeogenesis (Debigare et al, 2001). Supplementation of essential amino acids improves nutritional status and muscle activity (Dal Negro et al, 2010) whereas studies investigating caloric nutritional supplementation have not shown benefit (Ferreira et al, 2005). Smoking cessation may reduce systemic inflammation and there are hopes that recently developed drugs such as the phosphodiesterase-4 inhibitors (for example roflumilast) which exhibit systemic anti-inflammatory properties may block mediators implicated in muscle dysfunction (Gross et al, 2010). As yet the evidence base for any of these strategies remains weak.

In contrast recognition that skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease contributes to both exercise intolerance and poor health status has raised awareness of the potential benefits of pulmonary rehabilitation (Troosters et al, 2005). These multidisciplinary programmes are designed for patients suffering from chronic respiratory illnesses, aiming to reduce dyspnoea and other symptoms such as muscle fatigue (i.e. muscle deconditioning) (American Thoracic Society/European Respiratory Society, 2006; Troosters et al, 2007).

Exercise training is a vital part of pulmonary rehabilitation, partially reversing peripheral muscle dysfunction and thereby improving muscle strength (Panton et al, 2004; McKeough et al, 2006). Quadriceps strength and muscle cross-sectional area are positively linked to both percentage forced expiratory volume in 1 second of predicted value and peak maximal oxygen consumption the importance of strengthening the quadriceps muscles in patients with chronic obstructive pulmonary disease (Bernard et al, 1998). The combination of strength and endurance training in pulmonary rehabilitation programmes is greatly beneficial to patients. Strength exercises improve activities such as maintenance of balance and rising from a chair, whereas endurance exercises help walking.

Both the National Institute for Clinical Excellence (2004) and the World Health Organization's Global Initiative for Chronic Obstructive Lung Disease association recognize pulmonary rehabilitation as an important and essential component in managing patients with chronic obstructive pulmonary disease (Troosters et al, 2005; Global Initiative for Chronic Obstructive Lung Disease, 2009) which should be considered in all suitable patients with significant functional limitation.

Conclusions

Alterations in peripheral muscle typology, capillarity, muscle mass and metabolic enzyme status have been linked to a distorted oxidative capacity, contributing to exercise intolerance in patients with chronic obstructive pulmonary disease. Multiple causes are believed to contribute to these changes. Muscle dysfunction is as important as breathlessness in limiting exercise capacity in chronic obstructive pulmonary disease patients with reduced quadriceps muscle mass correlated to lower life expectancy and poorer quality of life. Exercise capacity is already reduced in patients suffering from even mild to moderate chronic obstructive pulmonary disease (Eliason et al, 2009). Recognition of this important manifestation of chronic obstructive pulmonary disease by clinicians provides greater understanding of the basis for patient symptoms and an opportunity to intervene therapeutically to specifically address the factors that may contribute to abnormal muscle function in these patients. **BJHM**

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Conflict of interest: none.

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KEY POINTS

- Alterations in peripheral muscle typology, capillarity, muscle mass and metabolic enzyme status have been found in patients with chronic obstructive pulmonary disease.
- Peripheral muscular abnormalities distort the oxidative muscular capacity, resulting in exercise intolerance.
- Clinicians should remember that muscle weakness is the significant factor limiting exercise tolerance in many patients with chronic obstructive pulmonary disease. Pulmonary rehabilitation programmes may greatly benefit these patients, improving both exercise capacity and quality of life.

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