Factors contributing to muscle wasting and dysfunction in COPD patients

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Abstract: Many patients with chronic obstructive pulmonary disease (COPD) suffer from exercise intolerance. In about 40% of the patients exercise capacity is limited by alterations in skeletal muscle rather than pulmonary problems. Indeed, COPD is often associated with muscle wasting and a slow-to-fast shift in fiber type composition resulting in weakness and an earlier onset of muscle fatigue, respectively. Clearly, limiting muscle wasting during COPD benefits the patient by improving the quality of life and also the chance of survival. To successfully combat muscle wasting and remodeling during COPD a clear understanding of the causes and mechanisms is needed. Disuse, hypoxemia, malnutrition, oxidative stress and systemic inflammation may all cause muscle atrophy. Particularly when systemic inflammation is elevated muscle wasting becomes a serious complication. The muscle wasting may at least partly be due to an increased activity of the ubiquitin proteasome pathway and apoptosis. However, it might well be that an impaired regenerative potential of the muscle rather than the increased protein degradation is the crucial factor in the loss of muscle mass during COPD with a high degree of systemic inflammation. Finally, we briefly discuss the various treatments and rehabilitation strategies available to control muscle wasting and fatigue in patients with COPD.

Keywords: COPD, muscle wasting, systemic inflammation, rehabilitation, muscle function

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and death throughout the world. The disease is mainly caused by smoking, but environmental pollution and α_1–antritrypsin deficiency may also cause the development of COPD (Petty 2006). In 2000 about 16 million people suffered from COPD in the USA alone (Mannino et al 2002) with the number of women suffering from this disorder increasing (Casaburi 2001). The disease is progressive, but the severity and progress can be moderated by actions such as smoking cessation, careful management of infections and appropriate rehabilitation (ATS/ERS 1999; Faulkner et al 2006).

One of the major problems of patients with COPD is exercise intolerance (Gosker et al 2000; Aliverti and Macklem 2001; Casaburi 2001). Although the disease is characterized by reduced maximal expiratory flow (ATS/ERS 1999; Faulkner et al 2006), FEV_1 in COPD correlates poorly with exercise capacity (Killian et al 1992; Gosselink et al 1996; Engelen et al 2000; Gosker, Lencer et al 2003). Likewise, in single and double lung transplants, exercise capacity did improve after surgery, but was still lower than normal (Ambrosino et al 1996) indicating that factors other than lung function alone limited exercise capacity (Evans et al 1997). Also in patients with COPD who did not undergo a lung-transplantation, evidence that the exercise intolerance is not only related to a reduced lung function, but also to skeletal muscle dysfunction is growing (Schols et al 1991; Gosselink et al 1996; Gosker, Lencer et al 2003). The importance of skeletal muscle dysfunction may increase over time

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as the deterioration in exercise capacity is uncoupled from the progression of airflow limitation (Oga et al 2005). It is important, therefore, to know how muscle function is affected, to identify the factors that contribute to the muscle dysfunction and the mechanism of muscle wasting in COPD so as to improve the management of the disease. Such knowledge may also have wider implications since COPD is one of a number of common disorders, including chronic heart failure (Gosker et al 2000) and cancer (Tisdale 2005), where muscle dysfunction and wasting are serious complications and may be brought about by similar underlying mechanisms. This review will focus on the changes in peripheral skeletal muscle structure, function and metabolism in COPD and discuss some of the potential underlying factors and mechanisms contributing to the observed muscle wasting and dysfunction.

The relation between muscle structure and function in COPD
Muscle weakness and loss of muscle mass

A loss of skeletal muscle mass is a common observation in patients with COPD and may not only lead to muscle weakness (Schols et al 1993; Gosselink et al 1996; Bernard et al 1998; Engelen et al 2000), but is also associated with an increased mortality of patients with COPD. Marquis and colleagues (Marquis et al 2002) reported that 50% of their patients with a FEV_1 predicted <25% and a mid-thigh cross-sectional area (CSA) <70 cm^2 died within 3 years, compared to only 12% of patients with a mid-thigh CSA >70 cm^2. Schols and colleagues (Schols et al 1993) found that about half of the patients with mild to severe COPD had a reduced body weight, which could be related to both a loss of muscle and adipose tissue. Since lean tissue depletion could even occur in overweight patients the prevalence of muscle wasting might be even higher (De Benedetto et al 2000).

Muscle atrophy occurs when the balance of protein synthesis and degradation shifts to net protein breakdown. Most of the research on muscle wasting in chronic diseases has focused on protein degradation pathways. For an extensive discussion of the molecular and cellular mechanisms involved in protein degradation, such as the ubiquitin-proteosome pathway, we refer the reader to several excellent reviews on this subject (Jagoe and Engelen 2003; Kandarian and Jackman 2006; Saini et al 2006).

Besides an increased rate of protein degradation, also a decreased rate of protein synthesis contributes to the muscle wasting in many chronic diseases (Rennie et al 1983). This

may be a consequence of systemic inflammation that often occurs in patients with COPD (Gan et al 2004). Indeed, recent studies indicate that the regenerative capacity of skeletal muscle is impaired in mice with elevated circulating tumor necrosis factor-α (TNF-α) levels (Guttridge et al 2000; Langen et al 2004, 2006). Furthermore, testosterone, an anabolic hormone, levels were lower in COPD patients (Casaburi 1998; Casaburi et al 2004; Van Vliet et al 2005). The lower testosterone levels were associated with muscle weakness (Van Vliet et al 2005). It has been speculated that chronic hypoxia (Aasebo et al 1993) and corticosteroid therapy (Kamischke et al 1998) contribute to low testosterone levels. It is equivocal whether insulin-like growth factor-I (IGF-1), which mediates muscle growth, is elevated or reduced in COPD patients (Creutzberg and Casaburi 2003). Also, human studies of myostatin, a hormone that is produced in the muscle and suppresses muscle growth by inhibiting satellite cell activity, are scarce and its role in muscle wasting in COPD is unknown (Jespersen et al 2006). Clearly, more studies are necessary to assess whether protein synthesis rates are affected during COPD.

Besides muscle wasting also other factors, such as a decrease in maximal neural drive to the working muscles (Rutherford et al 1986) may contribute to muscle weakness during COPD. Indeed, a reduced neural drive may well explain the decline in force generating capacity per muscle cross-sectional area (specific tension) in vivo without a change in in-vitro specific tension of isolated bundles from the same muscle (Debigare et al 2003). However, COPD patients who were matched for fat free mass index with control subjects did not show signs of muscle weakness or atrophy (Heijdra et al 2003; Degens et al 2005) indicating that the neural drive is maintained as long as fat free mass index is maintained.

Contractile properties and fiber type composition

During daily life most activities involve shortening contractions which require a sufficient power output from the muscle. Therefore, power output, which is the product of force and velocity, is more important during daily life than the ability of the muscle to generate isometric force. The loss of power in patients with COPD (Yquel et al 2006) as a result of a loss in muscle strength may be compensated for, to some extent, by the slow-to-fast transition in fiber type composition (Jobin et al 1998; Gosker, van Mameren et al 2002) and an increased proportion of hybrid fibers expressing more than one myosin heavy chain isoform (Gosker, van Mameren et al

2002). The slow-to-fast transition appears to be more marked during emphysema than in chronic bronchitis (Gosker, van Mameren et al 2002) and to be related to the severity of the disease in terms of FEV_1 (Satta et al 1997). Apart from a marked type IIX fiber atrophy and a slight increase in fibrosis and fat-cell replacement, which is not uncommon for skeletal muscle in the elderly, there are no myopathologic features in non-cachetic COPD patients (Gosker, Kubat et al 2003). Nevertheless, it is unlikely that the changes in fiber type composition during COPD, a disease that mostly becomes manifest after the age of 50, are just a reflection of the ageing process as normal ageing is, if anything, accompanied by a fast-to-slow rather than a slow-to-fast transition (Narici et al 1991; Degens and Alway 2006; Korhonen et al 2006). Although the changes in fiber type composition during COPD may be too small to affect the rates of contraction and relaxation during electrically evoked isometric tetani (Degens et al 2005), it remains to be established whether the fiber type transition is sufficient to cause a change in the shortening velocity during dynamic contractions. Nonetheless, as type II fibers are less efficient than type I fibers for force generation (Stienen et al 1996), the slow-to-fast-transition in fiber type composition may at least partly explain the reduced mechanical efficiency of COPD patients during one leg knee extensor exercise (Franssen, Wouters, Baarends et al 2002; Richardson et al 2004).

Metabolism and capillarization

Several studies have addressed the metabolic characteristics of muscles from COPD patients (Jakobsson et al 1990, 1995; Jobin et al 1998; Whittom et al 1998; Gosker, van Mameren et al 2002). The results of these studies are equivocal. Part of the discrepancies in the literature can be ascribed to differences in disease severity, medication (see section medication) and whether locomotor or other muscles have been studied. While the oxidative capacity of the vastus lateralis muscle of patients with moderate-to-severe COPD was significantly reduced (Jakobsson et al 1995; Gosker, van Mameren et al 2002), the oxidative capacity in the musculature of the upper extremity was not affected (Gea, Pasto et al 2001). Also, the mechanical efficiency was lower in leg muscles, while arm mechanical efficiency was not significantly affected (Franssen, Wouters, Baarends et al 2002). The different effect that COPD has on upper body and leg muscles was so marked that it is referred to as 'the compartment theory' (Gea, Orozco-Levi et al 2001). A simple explanation put forward for the differences between the two 'compartments' is the different degree of disuse they experience during

COPD (Gosselink et al 2000; Gea, Orozco-Levi et al 2001). Nevertheless, the glycolytic capacity was elevated in both the muscles of the leg (Jakobsson et al 1995) and the upper body (Gea, Pasto et al 2001). In advanced stages of the disease, however, energy metabolism becomes increasingly compromised as reflected by lower levels of glycogen, ATP and PCr in the quadriceps femoris muscle of patients with respiratory failure, but not in those without respiratory failure (Jakobsson et al 1990).

Little work has yet been done on the capillarization of skeletal muscle in COPD (Jobin et al 1998; Whittom et al 1998; Richardson et al 2004). Although the number of capillaries per fiber might be reduced during COPD (Whittom et al 1998), the capillary supply per fiber CSA and total numerical capillary density was maintained (Whittom et al 1998). It seems that, at least anatomically, the microcirculation is intact in COPD patients (Richardson et al 2004). This is not an unequivocal finding, however, as Jobin et al (1998) found an almost 50% decrease in capillary to fiber ratio and capillary density, suggesting that a disproportionate loss of capillaries may occur during COPD.

Skeletal muscle fatigue

Muscle fatigue can be defined as the inability of a muscle to maintain a certain force or power output. As has been mentioned above exercise intolerance, as reflected by a low peak oxygen uptake, is a major symptom in patients with COPD (Oga et al 2007). It is likely that the increased load and oxygen need of the respiratory muscles during COPD and reduced venous return compete with an impaired delivery of oxygen to the limb muscles (Aliverti and Macklem 2001). However, under circumstances where the cardio-respiratory system is unlikely to be the limiting factor, such as during one-leg exercise, or exercise of a single muscle or muscle group, the capillarization and oxidative capacity of a muscle are important determinants of muscle fatigue resistance (Degens and Veerkamp 1994). Therefore, it is no surprise in light of these changes in the muscle as described above that an increased susceptibility to skeletal muscle fatigue has often been reported in COPD patients (Serres et al 1998; Allaire et al 2004; Coronell et al 2004; Van't Hul et al 2004; Saey et al 2005; Janaudis-Ferreira et al 2006). Other studies, however, do report an unaltered fatigue resistance (Gosker, Lencer et al 2003; Degens et al 2005; Franssen et al 2005).

Besides changes in the muscle itself that may cause an earlier onset of muscle fatigue, changes in fatigue resistance could also be caused by an altered central drive (central

fatigue) (Bigland-Ritchie et al 1978). To date, the central component in the development of muscle fatigue in COPD patients is poorly understood. However, it may play a role in the development of fatigue as systemic inflammation has been shown to cause feelings of tiredness (Spath-Schwalbe et al 1998). However, muscle fatigability has been determined largely with series of voluntary contractions (Serres et al 1998; Coronell et al 2004; Van't Hul et al 2004; Janaudis-Ferreira et al 2006), which makes it difficult to differentiate between central and peripheral factors. Using electrical or magnetic stimulation, however, one can exclude the contribution of central factors to the development of fatigue. As far as we know, only one study (Degens et al 2005) has assessed peripheral muscle fatigue using electrical stimulation in patients with COPD. In that study, neither differences in contractile properties nor fatigability were found. This indicates that there were no apparent differences in motivation between patients and controls matched for fat free mass index and physical activity level (Degens et al 2005). Although it is thus possible that the alterations in fatigue resistance observed in other studies may be related to a lower fat free mass index in patients with COPD and controls, the observation that muscle endurance was similar in wasted and non-wasted patients (Gosker, Lencer et al 2003; Franssen et al 2005) argues against this. However, in several studies it has been explicitly stated that the COPD patients were significantly less active than the controls (Serres et al 1998; Coronell et al 2004). Clearly, at least part of the decline in fatigue resistance often observed during COPD is attributable to a reduced physical activity level, but also smoking itself may reduce muscle fatigue resistance (Wüst et al 2006).

Factors underlying muscle dysfunction and wasting

Many factors have been suggested to induce changes in skeletal muscle structure and function in COPD. Here we will summarize the possible role of airflow obstruction, disuse, hypoxemia, malnutrition, oxidative stress and systemic inflammation in the adaptations of skeletal muscle of patients with COPD. Figure 1 summarizes how disuse, hypoxia and systemic inflammation may affect muscle wasting and dysfunction in COPD.

Airflow obstruction

In the GOLD classification the severity of COPD is determined as the degree of airflow obstruction as indicated by the percentage of the predicted FEV_1. Despite the fact that a low FEV_1 indicates a severe case of COPD no correlations between FEV_1 and skeletal muscle strength or fatigue have

been observed (Gosker, Kubat et al 2003; Gosker, Lencer et al 2003; Degens et al 2005). In terms of muscle fatigability, this is not surprising, as during muscle fatigue tests a relatively small muscle mass is recruited of which the oxygen requirement is well within the limits that can be provided by the affected lung. Although, the increased cost of breathing as a result of the obstructive airflow may well be a cause of exercise intolerance during COPD (Aliverti and Macklem 2001) and may cause structural changes in the respiratory muscles due to the continuous overload (Orozco-Levi et al 2001), it seems unlikely that the airflow obstruction *per se* will affect peripheral skeletal muscle structure or function.

Disuse

The physical activity level of patients with COPD is lower than that of the average population (Pitta et al 2005, 2006b) and during and after a period of exacerbations patients become even less active (Pitta et al 2006a). This is thought to be a consequence of the so-called dyspnea spiral: patients do not exert themselves too much in order to avoid the occurrence of dyspnea, which in turn causes a decline in fitness and an earlier occurrence of dyspnea and so on (Serres et al 1998). It is therefore not surprising that disuse contributes significantly to the alterations in skeletal muscle structure and function during COPD (Degens and Alway 2006). In fact, in a patient group compared with a physical activity level matched control group, no differences in muscle strength, fatigue resistance and contractile properties were detected (Degens et al 2005). However, disuse alone is inadequate to explain all the changes occurring in skeletal muscle structure and function. For instance, Gosker et al (Gosker, Engelen et al 2002) showed that atrophy mainly occurred in type IIX fibers, whereas disuse would cause atrophy of each fiber type, with type I fibers being affected the most (Degens and Alway 2006). Also, a 12-weeks physical-rehabilitation program did not entirely reverse the effects of COPD in terms of capillarization and fiber type distribution (Whittom et al 1998).

Hypoxemia

Due to the difficulties with breathing and impaired oxygen uptake, patients with severe COPD may have a decreased hemoglobin oxygen saturation level (hypoxemia), which may result in local tissue hypoxia. The abundance of the transcription factor hypoxia-inducible factor-1α (HIF-1α) increases during hypoxia (Raguso et al 2004) and may induce a down-regulation of oxidative enzymes and an upregulation of glycolytic enzymes (Hoppeler et al 2003). In addition, it has been shown in cardiomyocytes that hypoxia inactivates
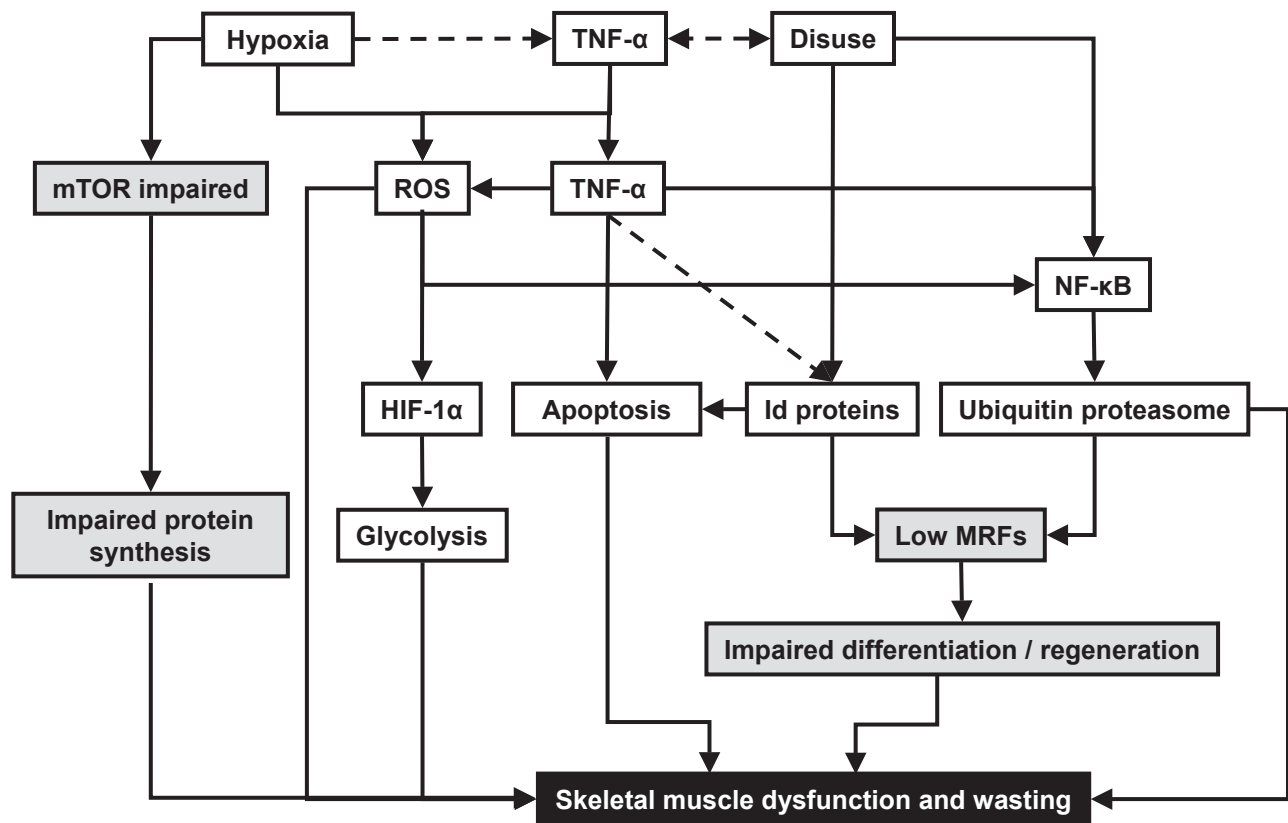
Figure 1 Pathways by which hypoxia, disuse and systemic inflammation contribute to muscle dysfunction and wasting during Chronic Obstructive Pulmonary Disease. Grey shaded boxes indicate impaired regeneration or protein synthesis; black shaded box represents the end result of the pathways in terms of muscle dysfunction and muscle wasting. Solid lines indicate observed relations; dotted lines indicate possible relations. TNF-α: tumor necrosis factor - α; mTOR: mammalian target of rapamycin; ROS: reactive oxygen species; HIF-1α: hypoxia-inducible factor - 1α; NF-κB: nuclear factor - κB; Id proteins: inhibitor of differentiation proteins; MRFs: myogenic regulatory factors (such as MyoD).

the transcription factor peroxisome proliferator-activated receptor α (PPARα) and thereby decreases the expression of genes involved in fatty acid oxidation (Huss et al 2001). These changes in transcriptional regulation of the expression of metabolic genes during hypoxia may result in an increased glycolytic and a reduced oxidative capacity similar to what is observed during COPD (Hoppeler et al 2003; Raguso et al 2004).

Chronic hypoxia may be linked with muscle wasting and weakness. Just 8 weeks at altitudes greater than 5000 m has been shown to cause as much as a 10% reduction in muscle mass and peak power (Ferretti et al 1990; Hoppeler et al 1990). Although a decrease in fiber CSA is associated with exposure to hypoxia (Hoppeler et al 1990; MacDougall et al 1991), other confounding factors such as a decreased food intake, due to an hypoxia-induced expression of leptin, together with detraining may contribute to muscle wasting during hypoxia (Westerterp and Kayser 2006).

Hypoxia has been shown to impair the mTOR pathway, which is involved in transcription of DNA and translation of mRNA into protein (Proud 2004b) and may, as a conse-

quence, contribute to muscle wasting during COPD. In addition, it has been reported in cell culture studies that hypoxia inhibits myoblast differentiation by degradation of MyoD, a myogenic transcription factor, via the ubiquitin proteasome pathway (Di Carlo et al 2004). Clearly, such an effect in vivo will have a negative impact on the regenerative potential of skeletal muscle. Moreover, hypoxia may also induce inflammation (Orth et al 2005), causing muscle atrophy through inflammatory pathways (see below and Figure 1).

In addition to these relatively long-term effects, there is evidence that hypoxia might acutely affect the contractile apparatus. Indeed, single fibers isolated from bundles exposed to hypoxia for 30 min exhibited a marked force loss which was attributable to a reduced fraction of strongly attached cross bridges, while reoxygenation completely reversed the contractile dysfunction (Ottenheijm, Heunks, Geraedts et al 2006). In addition to muscle weakening, hypoxia has also been shown to reduce the maximum shortening velocity, power output, force frequency relation and endurance in muscle bundles (Machiels et al 2001; Zhu et al 2005), possibly through nitrotyrosylation of proteins (Ottenheijm,

Heunks, Geraedts et al 2006) and the presence of reactive oxygen species (ROS). Although in vitro there seems to be a clear effect of acute hypoxia on skeletal muscle function this is not necessarily the case in vivo. In the electrically stimulated human quadriceps muscle no change in contractile properties, strength or fatigue resistance could be detected during acute exposure to hypoxia (Degens et al 2006). The discrepancy between in vitro and in vivo observations might be caused by absence of oxidative stress in vivo (Dousset et al 2002). It is possible that hemoglobin and myoglobin, absent in the in vitro situation, scavenge nitric oxygen (NO) and ROS, so that the detrimental effects of these substances are attenuated, at least for a limited period (Ordway and Garry 2004). Indeed, in chronic hypoxemic COPD patients oxidative stress is enhanced (Koechlin et al 2005).

Hypoxia itself, however, can not fully account for all the observed changes in skeletal muscle as many patients with COPD suffering from muscle wasting and dysfunction do not exhibit hypoxemia. In addition, hypoxia may even protect the nucleus from apoptosis (Riva et al 2001), whereas an elevated occurrence of apoptosis in skeletal muscle has been observed in depleted patients with COPD (Agusti et al 2002; Degens et al submitted).

Malnutrition

Many patients with COPD suffer from semi-starvation, possibly caused by elevated levels of circulating leptin, which negatively affects dietary intake and consequently muscle mass and function (Engelen et al 1994; Casaburi 2001; Franssen, Wouters, Schols 2002; Schols 2003a). Moreover, the basal metabolism in COPD is increased as a consequence of extra work required for breathing and/or the presence of systemic inflammation. Hypermetabolism in combination with a decreased appetite often leads to a negative nutrition balance and ultimately weight loss (Schols 2003b).

Oxidative stress

Reative Oxygen Species (ROS) and free radicals are elevated in patients with COPD both during rest and exercise (Couillard et al 2002, 2003; Gosker, Bast et al 2005; van Helvoort, Heijdra, Thijs 2006). The mitochondrial electron transport chain and neutrophils are an important source of ROS (Zhang et al 1990). Also hypoxia, cigarette smoke, sepsis and an increased cost of breathing (Heunks and Dekhuijzen 2000) cause an increased generation of ROS and reactive nitrogen species in the lungs and respiratory muscles, spilling into the circulation. There is evidence that an abnormal oxidative stress response to submaximal and maximal exercise may be more severe in muscle-wasted than non-muscle-wasted patients with COPD (van Helvoort, Heijdra, Thijs 2006). Oxidative stress may acutely affect skeletal muscle function via inhibition of the activity of the sodium/potassium pump (Comellas et al 2006), sarcoplasmic reticulum function, myosin ATPase and mitochondrial respiration (Zhang et al 1990), and in the long run may also cause muscle wasting and dysfunction in both respiratory and peripheral muscle (Langen et al 2003; Koechlin et al 2004, 2005 Ottenheijm, Heunks, Geraedts et al 2006).

Systemic inflammation

A common feature in many chronic diseases including COPD is the presence of systemic and/or local inflammation (Gan et al 2004). In patients with COPD the lung is thought to be the main source of inflammatory cytokines. It has been shown that resistive breathing may cause the respiratory muscles also to produce inflammatory cytokines and thereby to contribute to the development of cachexia in patients with COPD (Vassilakopoulos et al 2004). The negative correlation between muscle strength and a marker of systemic inflammation during an exacerbation (Spruit et al 2003) suggests that inflammation is indeed an important factor in muscle adaptations during COPD (Degens and Alway 2006).

Inflammatory cytokines may also have central actions leading to "sickness behavior", a loss of motivation and thus contribute to tiredness and the downward spiral of inactivity (Spath-Schwalbe et al 1998). For instance, acute administration of IL-6 to otherwise healthy trained runners seriously impaired exercise performance (Robson-Ansley et al 2004), but the effect may be mediated by an altered (serotonergic) activity in the brain increasing the sensation of generalized fatigue (the central fatigue hypothesis), rather than peripheral factors (Polkey 2003).

In the remainder of this section we will concentrate mainly on the effects of TNF-α on skeletal muscle tissue, as most research has focused on this cytokine. Cachectin, or TNF-α, has long been known to induce muscle wasting (Beutler and Cerami 1986). In a transgenic mouse model that over-expresses TNF-α in the lung, not only circulating TNF-α levels, but also the expression of TNF-α in the muscle were increased; the latter was thought to be the result of TNF-α inducing its own expression via a positive feed back loop (Langen et al 2006). One can imagine, that in particular during exacerbations, when the inflammation is aggravated (Papi et al 2006), this is a serious complication.

TNF-α may also have acute effects on skeletal muscle function. For instance, systemic administration of TNF-α to dogs caused diaphragm weakness after only three hours (Wilcox et al 1994). Since then, it has been shown in vitro that exposure of single muscle fibers to TNF-α decreased the force generating capacity (Li et al 2000; Reid et al 2002), possibly through the generation of ROS or reactive nitrogen species. It should be noted, however, that in these studies supraphysiological doses of TNF-α were applied and it remains to be determined whether physiological levels of TNF-α have similar effects.

Chronically elevated systemic inflammation increases the activity of the ubiquitin proteasome pathway via activation of nuclear factor – κB (NF-κB), a factor that plays an important role in muscle atrophy (Debigare et al 2001; Kandarian and Jackman 2006). The ubiquitin proteasome pathway is an ATP-dependent protein degradation pathway where proteins are labeled by ubiquitin for subsequent degradation in the proteasome. Although the activation of the ubiquitin-proteasome pathway is apparent in many other chronic diseases, including cancer (Khal et al 2005), it is not known whether activation of the ubiquitin-proteasome pathway also plays a role in peripheral skeletal muscle wasting during COPD. Only recently it has been shown that the ubiquitin-proteasome pathway is activated in the diaphragm in patients with mild-to-moderate COPD (Ottenheijm, Heunks, Li et al 2006) leading to a loss of myosin, and thereby force generating capacity (Ottenheijm et al 2005).

Besides activating the ubiquitin proteaseome pathway TNF-α induces apoptosis, or programmed cell death, in skeletal muscle cells and myoblasts (Bazzoni and Beutler 1996; Stewart et al 2004). The loss of myonuclei may cause an increase of the myonuclear domain, the volume of cytoplasm associated with a single myonucleus, beyond a sustainable size and consequently be followed by muscle fiber atrophy (Allen et al 1999). Apoptosis may indeed play a role in muscle wasting during COPD in particular in patients with a low body mass index (Agusti et al 2002; Plataki et al 2006). In addition, TNF-α induces expression of Id proteins in astrocytes (Tzeng et al 1999) and Id proteins in turn can induce apoptosis both via alteration of gene transcription and binding to regulators of apoptosis (Florio et al 1998). Although a link between TNF-α and Id protein expression has not been investigated in other cell types, Id proteins themselves have been shown to induce apoptosis in many cell types, including neonatal cardiomyocytes and myoblasts (Yokota and Mori 2002). It is therefore tempting to speculate that altered Id expression also plays a role in the development of apoptosis during COPD and impaired regenerative capacity. This has not yet been investigated in patients with COPD, but both the elevated expression of Id2 protein and apoptotic factors in the diaphragm and soleus of the emphysematous hamster (Alway et al 2004) hint to this possibility.

As mentioned above, it is possible that the primary problem of muscle atrophy during COPD is a decreased regenerative capacity. Myogenic regulatory factors, such as MyoD, play an important role in satellite cell differentiation and hence regenerative capacity of the muscle (Charge et al 2004). Both in transgenic mice overexpressing TNF-α in the lung (Langen et al 2006) and in mice treated with TNF-α (Guttridge et al 2000; Langen et al 2004), the regeneration of skeletal muscle from disuse atrophy is delayed. This decline in regenerating capacity was possibly related to an accelerated breakdown of MyoD by the ubiquitin proteasome pathway (Langen et al 2004). Interestingly, MyoD becomes more prone to degradation by the ubiquitin proteasome pathway when it forms dimers with inhibitors of differentiation (Id) proteins (Reid 2005). Elevation of these proteins may thus contribute to the reduced abundance of MyoD protein but not mRNA in the soleus and diaphragm of emphysematous hamsters (Degens et al 2004), indicating MyoD breakdown rather than reduced transcription. No studies have so far investigated whether alterations in MyoD and Id expression also occur in skeletal muscle from patients with COPD and whether they also suffer from an impaired skeletal muscle regenerative capacity.

Rehabilitation and medication

Here we only briefly discuss several of the more common potential treatments that target skeletal muscle wasting during COPD. For a more extensive discussion we refer the reader to other reviews that specifically address this issue (Spruit et al 2004; Hansen et al 2006).

Exercise training

As disuse is considered an important factor contributing to muscle wasting and dysfunction it is not surprising that many studies have addressed the efficacy of exercise training on skeletal muscle structure and function in patients with COPD (Serres et al 1998; Franssen et al 2005; Gosker, Schrauwen et al 2005).

Endurance training improves exercise tolerance in patients with moderate and severe COPD, with the effect being largely influenced by the intensity of the training; a low intensity produces less of an effect than high intensity

training sessions (Casaburi 2001). This improvement in exercise tolerance is accompanied by at least a reduction of the percentage of type II fibers, muscle hypertrophy and an increase in oxidative capacity (Whittom et al 1998; Casaburi 2001; Vogiatzis et al 2005).

Strength training is effective in increasing muscle mass and strength and is associated with an improved quality of life in patients with COPD (Casaburi 2001). Combined strength/endurance training results in the benefits that each of the programs separately would achieve, ie, not only an increase in submaximal exercise capacity, but also improvements in lean body mass and strength (Ortega et al 2002). Moreover, interval training might also be preferred above constant-load exercise as it minimizes leg discomfort and ratings of dyspnea, without compromising the benefits of the endurance training program (Vogiatzis et al 2005).

This response to training represents a normal response of the muscle to increased use (Salmons and Henriksson 1981). The beneficial effects of exercise may, at least partly, be brought about by an increase in the expression of myogenin (Siu, Donley et al 2004), a reduction of the occurrence of apoptosis (Siu, Bryner et al 2004), and suppression of the muscle specific ubiquitin ligase atrogin (Leger et al 2006). Furthermore, endurance training may attenuate systemic inflammation (Garrod et al 2007) and it is thus possible that the beneficial effects of training are partly mediated via a reduction in inflammation. So far, it is not clear whether all patients would benefit from exercise programs as for instance in some elderly people the hypertrophic response is attenuated, indicating a reduced plasticity at old age (Welle et al 1996; Degens and Alway 2006). This attenuated response has been shown to be related to elevated baseline levels of soluble TNF-receptors in the elderly (Bruunsgaard et al 2004). This would imply that chronic patients with a significantly elevated systemic inflammation may have reduced improvements in response to exercise training, particularly when one considers that the inflammatory and oxidative stress response is augmented in muscle-wasted patients (van Helvoort, Heijdra, Dekhuijzen 2006). Supporting the notion that exercise may loose its effectiveness when systemic inflammation is present, is the observation that the cellular protein breakdown in patients with a low fat free mass does not decline after an exercise training regime (Bolton et al 2006).

Nutrition

Nutritional support has been shown to result in functional improvements and decreased mortality in depleted patients (Schols 2003b). One of the benefits of nutritional support is

an increase in muscle strength (Efthimiou et al 1988), which will inevitably improve the quality of life of the patient. Combination of nutritional support and exercise training may be the best approach to obtain functional improvements in patients with COPD (Schols 2003a). For detailed information about the effects of nutrition of muscle performance in patients with COPD and other chronic diseases, the reader is referred to some excellent reviews on this subject (Schols 2003b; Engelen et al 2005).

Oxygen therapy

Oxygen supplementation is often used to reduce dyspnea experienced by severe hypoxemic COPD patients. Oxygen supplementation may not only increase the exercise capacity (Aliverti and Macklem 2001), but also reduce the normal exercise-induced elevation in systemic inflammation and oxidative stress in muscle-wasted patients with COPD (van Helvoort, Heijdra, Heunks 2006). An additional benefit of supplemental oxygen during exercise is that patients can exercise at higher work loads (Emtner et al 2003) and thereby augment the improvement in exercise tolerance.

Long-term oxygen supplementation only benefits hypoxemic, but not normoxemic patients with COPD by increasing survival and attenuating the progression of pulmonary hypertension (Zielinski 1999). However, to our knowledge no studies have addressed the direct or long-term effects of oxygen therapy on skeletal muscle adaptations in COPD patients.

Medication

Anabolic hormone, such as testosterone, supplementation has been suggested to treat muscle wasting and dysfunction during COPD (Casaburi et al 2004; Hansen et al 2006). Combination of strength training and testosterone supplementation appeared to give additive effects on lean body mass and strength in patients with COPD (Casaburi et al 2004). However, the long-term (side and beneficial) effects of hormone replacement remain to be established. The observation that IGF-I is only positively related to muscle strength when IL-6 levels are low but not when IL-6 levels are high (Barbieri et al 2003) suggests that the effectiveness of testosterone replacement (which probably acts in part through an effect on IGF-1) may be attenuated in patients with high levels of systemic inflammation.

Since systemic inflammation plays an important role in the progression of the disease anti-inflammatory drugs have been used to attenuate the disease progression and the concomitant observed muscle wasting (Hansen et al

2006). Corticosteroids are often prescribed to minimize the inflammatory reaction, in particular following exacerbations. Unfortunately, corticosteroids also induce the activity of the ubiquitin proteasome pathway (Tisdale 2005) and prolonged treatment with corticosteroids results in a 'steroid myopathy', characterized by a preferential type II fiber atrophy (Decramer et al 1996). The vitamin D analogue α-calcidol, already widely used for the treatment of osteoporosis, has proved successful in reducing circulating TNF-α levels and the release of cytokines by macrophages and improving muscle power in patients with rheumatoid arthritis (Scharla et al 2005). No studies have so far addressed the efficacy of α-calcidol in the treatment of muscle weakness (and/or osteoporosis) in COPD.

One could also consider to provide supplementation with IGF-I, or inhibitors of TNF-α, but IGF-I may increase the chance of getting cancer and TNF-α inhibitors increase the risk of sepsis and infection (Hansen et al 2006). Therefore, factors downstream, such as the ubiquitin proteasome pathway, or factors involved in satellite cell differentiation, may be better targets. In this context it is worthwhile to note that Id proteins may be an interesting target as they play a role in muscle wasting and their inhibition is also a potential target in the treatment of cancer (Benezra et al 2001).

Drugs that inhibit NF-κB, which is downstream of the TNF-receptor and an upstream regulator of MuRF1, a ubiquitin ligase, appear to be effective in attenuating muscle wasting during cachexia (Tisdale 2005). Indeed, there are clear indications for further drug developments such as with inhibitors of the ubiquitin-proteasome pathway and apoptosis (Libera and Vescovo 2004; Tisdale 2005; Hansen et al 2006). As suggested by Tisdale (2005), it is advisable to combine inhibitors of protein degradation with stimulators of protein synthesis by, for instance, an increased intake of amino acids, such as leucine, that stimulate the mTOR pathway (Proud 2004a).

In clinical settings, it seems that a combination of multiple strategies results in the best functional improvements. Clearly, however, more studies are needed to determine the best combination of therapies in terms of cost-effectiveness, benefit and patient compliance (Schols 2003a).

Summary and conclusion

In this article, we present an overview of the changes in muscle structure and function in COPD and the factors contributing to these changes are discussed. Muscle wasting should be considered as a serious complication in COPD and has important implications for survival. One notable feature

of the literature is the great diversity of muscle symptoms in patients with apparently similar degrees of lung disease. Whether this indicates a difference in the nature of the disease or of the genetic susceptibility to muscle complications remains an important question. There is no doubt, however, that continued research into the question of muscle wasting and decreased skeletal muscle fatigue resistance in COPD will eventually lead to the development of specific treatments for cachexia, such as targeting the ubiquitin proteasome pathway, cytokine inhibition, administration of anabolic factors as well as life style changes, such as exercise and nutrition. The clinical approach to cachexia in COPD and other chronic diseases should change dramatically in the near future.

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