HIGHLIGHTED TOPIC | The Respiratory Muscles in Chronic Obstructive Pulmonary Disease

Comparative assessment of the quadriceps and the diaphragm in patients with COPD

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Caron MA, Debigaré R, Dekhuijzen PN, Maltais F. Comparative assessment of the quadriceps and the diaphragm in patients with COPD. J Appl Physiol 107: 952–961, 2009. First published April 9, 2009; doi:10.1152/japplphysiol.00194.2009.—Chronic obstructive pulmonary disease (COPD) and other chronic diseases such as heart failure are accompanied by skeletal muscle alterations that further enhance morbidity and mortality in affected individuals. Several studies have highlighted important structural and biochemical modifications in limb and respiratory muscles in COPD. Reviewing the similarities and differences between the two most studied muscles in COPD, the quadriceps and the diaphragm, may be helpful in providing important clues about the mechanisms underlying muscle changes associated with this disease. Although oxidative stress is present in both muscles, other muscle alterations are clearly distinct between the quadriceps and the diaphragm. For example, the oxidative metabolism varies in opposite directions, the diaphragm exhibiting increased resistance to fatigue while the quadriceps in COPD is characterized by premature fatigability. Differences in muscle phenotypic expression between the diaphragm and the quadriceps indicate that, in addition to systemic factors, the local microenvironment must participate in the reorganization seen in these two skeletal muscles in COPD.

chronic obstructive pulmonary disease; muscle dysfunction; cell signaling

IN NORMAL CONDITIONS, the limb and respiratory muscles are adequately equipped to fulfill their respective role in breathing and moving (21). Dysfunction of respiratory and limb muscles is recognized as a major systemic manifestation of chronic obstructive pulmonary disease (COPD) (1a) and of other chronic diseases affecting major organs such as the heart or the kidney (32). Historically, studies on respiratory and limb muscles have been conducted separately, the former by respiratory physiologists and the latter by exercise specialists. This may explain the paucity of studies in which the two muscle groups are directly compared. The recent development of molecular tools that can be used in both muscle groups and the growing availability of muscle specimens for research have encouraged a more integrated approach to the investigation of muscle alterations in COPD.

The aim of the present minireview is thus to describe the current state of knowledge on skeletal muscle cell alterations observed in patients with COPD. We felt that evaluating the similarities and contrasting the differences in the phenotypic expression of the quadriceps and diaphragmatic muscle changes could be useful in shedding light on the mechanisms of skeletal muscle alterations in COPD and to generate ideas for future research in this area. For example, because these two muscles are exposed to different levels of activation, inferences can be made about the respective role of local and systemic factors in skeletal muscle adaptation in COPD. It should be appreciated that this minireview is based on data obtained from clinically stable patients and that the quadriceps and diaphragmatic specimens from which the current information is derived most often originate from different studies and patients.

CLINICAL RELEVANCE OF MUSCLE DYSFUNCTION

Given its role as the primary inspiratory muscle and considering the increased work of breathing imposed on it (58), the diaphragm has been the topic of most publications on respiratory muscles in COPD. Observations made over the years have highlighted how the structure and function of the diaphragm are affected during the course of COPD (21, 46, 62, 82). This topic is clinically relevant because inspiratory muscle weakness is associated with dyspnea, hypercapnic respiratory failure (6), and even premature mortality in COPD (34). The study of...
limb muscle alterations linked to COPD has also been a
dynamic area of research since cachexia associated with this 
respiratory disease was formally reported more than 40 years 
ago (12, 73). Limb muscle dysfunction is a major concern in 
COPD because of its association with decreased survival (52,
77), poor functional status (49, 56), and low quality of life (56).
Of great interest, the pattern of limb muscle impairment in COPD 
is different from that seen in the diaphragm. While the processes 
underlying development of muscle dysfunction in COPD are still 
hotly debated, the components of such dysfunction have been, for 
the most part, well described in the past years and will be 
summarized in the next sections. The alterations reported in both 
muscle groups are summarized in Table 1.

Several factors are repeatedly mentioned in the literature to 
explain the development of skeletal muscle dysfunction in 
COPD such as aging, inactivity, oxidative stress, systemic 
inflammation, hypoxemia, and energy imbalance [for review, 
see Wagner (92)]. In the next sections, we will present the main 
alterations detected in the diaphragm and the quadriceps, 
compare their resemblances and/or differences, and, finally, 
discuss the underlying cellular signalization.

MUSCLE ATROPHY

Quadriceps. Depending on the severity of the disease and 
the population being studied, it is estimated that 4–35% of 
the patients with COPD have a reduced muscle mass (18, 78, 90).
Although lower limb muscle atrophy is more common in 
patients with low body weight, it can also be present in patients 
with normal body mass index (78), highlighting the importance 
of directly assessing muscle mass during the initial patients’ 
evaluation and follow-up visits. Quadriceps atrophy in COPD 
is associated with muscle weakness, poor exercise tolerance 
(7), and a decrease in quality of life (56). Of even more concern 
is the association between muscle atrophy and mortality. In 
patients with severe airflow obstruction, a reduction in 
midhigh cross-sectional area is associated with a mortality 
rate of 13 times higher than in patients with better preserved

Table 1. Alterations in diaphragm and quadriceps muscles in COPD

<table>
<thead>
<tr>
<th>Presence?</th>
<th>Description</th>
<th>Severity of airflow limitation</th>
<th>Presence?</th>
<th>Description</th>
<th>Severity of airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber CSA</td>
<td>Yes</td>
<td>[30% MHC content (66)</td>
<td>Mild to severe</td>
<td>Yes</td>
<td>[25–35% CSA (93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-60% CSA (46)</td>
<td>Mild to severe</td>
<td></td>
<td>Affects all fiber types (93)</td>
</tr>
<tr>
<td></td>
<td>Contractility defect</td>
<td>[Force generation of isolated skinned fibers (64)]</td>
<td>Mild to moderate</td>
<td>No</td>
<td>No difference in force generation of isolated fibers (19)</td>
</tr>
<tr>
<td>Fiber shift</td>
<td>Yes</td>
<td>Type II → type I (21, 46)</td>
<td>Mild to severe</td>
<td>Yes</td>
<td>Type I → type Ib (33, 40, 93)</td>
</tr>
<tr>
<td></td>
<td>Capillarization alterations</td>
<td>[Capillary contacts with every fiber type (21)]</td>
<td>Mild to severe</td>
<td>Yes</td>
<td>[Capillary contacts with type I and IIa fibers (93)]</td>
</tr>
<tr>
<td>Mitochondrial alterations</td>
<td>Yes</td>
<td>[Respiratory chain capacity (72, 95)</td>
<td>Moderate to severe</td>
<td>Yes</td>
<td>[Mitochondrial density (29)]</td>
</tr>
<tr>
<td></td>
<td>Shift in energetic metabolism</td>
<td>[Oxidative/glycolytic enzymatic ratio (21)]</td>
<td>Mild to severe</td>
<td>Yes</td>
<td>[Oxidative enzymes (HADH, CS) (35, 49, 50)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[Oxidative/glycolytic enzymatic ratio (35)]</td>
</tr>
</tbody>
</table>

Numbers in parentheses are Ref. nos. COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area; MHC, myosin heavy chain; HADH, 3-hydroxyacyl-CoA dehydrogenase; CS, citrate synthase.

Diaphragm. Changes in fiber cross-sectional area and myo-
sin content have also been reported in the diaphragm of 
patients with COPD. A 40–60% reduction in the cross-sec-
tional area of all muscle fiber types has been observed in 
patients with severe emphysema compared with non-COPD 
controls (46). More recently, Ottenheijm et al. (66) reported a 
30% loss in myosin heavy chain content in patients with only 
mild to moderate COPD, suggesting that reduction in diaphrag-
matic fiber cross-sectional area may occur earlier in the course 
of the disease than previously thought. Whether these changes

At the cellular level, muscle mass maintenance relies on a 
tight balance between protein synthesis and degradation, as 
illustrated in Fig. 1. The mechanisms ensuring this regulation 
have been described in several animal models of muscle 
atrophy and act as a template to nourish research and reflection 
in human diseases associated with cachexia. Several signaling 
pathways are involved in the control of atrophy and hypertro-
phy processes [for review, see Sandri (74)]. The ubiquitin-
proteasome complex (degradation) and the insulin-like growth 
factor (IGF)-1/phosphatidylinositol 3-kinase (PI3K)/Akt path-
way (synthesis) interact together, mainly through Akt, to reg-
ulate both protein degradation and synthesis processes (9).
ubiquitin-proteasome pathway is involved in both normal and pathological protein degradation. In a healthy cell, the bulk of intracellular proteins are degraded through this pathway, ensuring normal protein turnover (44). In support of the key role of the ubiquitin-proteasome pathway in protein degradation, upregulation of this pathway has been reported in several chronic and inflammatory conditions in which muscle atrophy is present (43). When phosphorylated by IGF-1, the kinase activity of Akt is upregulated, promoting protein synthesis and cell survival. In addition, Akt also reduces protein degradation by favoring the exclusion of Forkhead box-containing protein O (FoxO) transcription factors from the nucleus (86). The relevance of this Akt-FoxO interaction resides in the fact that, once confined to the cytoplasm, FoxO loses its ability to upregulate the expression of genes implicated in contractile protein breakdown such as Atrogin-1 and MuRF-1 (75, 86). Quadriceps. Increased mRNA expression of Atrogin-1 and MuRF-1, two muscle-specific ubiquitin ligases (E3 ligases) frequently upregulated during the muscle atrophy process (8, 28, 96), was recently reported in the quadriceps of patients with COPD compared with healthy subjects (23). Unexpectedly, this study also reported a higher level of phospho-Akt and of phospho-4E-BP1 (transcriptional repressor eukaryotic initiation factor 4E binding protein-1), a downstream effector of Akt, in patients with COPD and atrophied quadriceps muscles compared with healthy controls (23). As the upregulation of...
Akt and downstream effector pathway promotes protein synthesis, this apparently paradoxical observation suggests that the IGF-1/PI3K/Akt pathway may be ineffective to preserve muscle mass and indicates that another mechanism foiling the positive effects of the IGF-1/PI3K/Akt signaling pathway on muscle mass should be invoked to explain muscle atrophy in COPD. Apart from a defect in the protein translation machinery, increased transcriptional activity of FoxO1 is one such potential mechanism explaining the presence of muscle atrophy despite accentuated Akt kinase activity (97). A gene expression analysis of the quadriceps showed both FoxO1A and FoxO3A mRNA overexpression in patients with COPD and muscle atrophy compared with healthy controls (20). Consistent with this finding, FoxO1 mRNA level is also increased when assessed in the quadriceps of patients with COPD (23). Based on these observations, we suggest that FoxOs could play a role in the atrophy process in COPD by counterbalancing the muscle hypertrophying IGF-1/PI3K/Akt pathway. FoxO activity can be modified in several ways according to the specific posttranslational modification it is subjected to (phosphorylation, acetylation, ubiquitination, binding protein partner) [for review, see Calnan and Brunet (13)]. This has yet to be evaluated in COPD to further elucidate the role of FoxO in the cachectic process in this disease. Apart from these data, little is known about the regulation of IGF-1/PI3K/Akt in patients with COPD. A decrease in peripheral blood IGF-1 level has been reported (84) whereas exercise training seems to elicit a positive hypertrophic response, increasing IGF-1 mRNA expression in the quadriceps (91).

Finally, increased apoptosis levels have been reported in the quadriceps of patients with COPD, pointing to an overactivation of this normal cellular process in this disease possibly contributing to the atrophying process (1). However, another study showed no increase in either necrosis or apoptosis levels in quadriceps of patients with COPD (30). Although attractive in itself, the actual contribution of apoptosis to skeletal muscle atrophy remains controversial.

**Diaphragm.** Despite increased diaphragmatic activity from which we would predict a tendency toward hypertrophy, the proteasome is also overactivated in the COPD diaphragm (65), reaching three times the activity level measured in control subjects. Furthermore, an elevation in mRNA expression of Atrogin-1 and increased diaphragmatic caspase-3 activity was reported in these patients (65). Caspase-3 activation is one of the initial and rate-limiting steps required for the degradation of actomyosin complexes into small fragments that are suitable for proteasomal degradation (24). Although not yet confirmed, it is tempting to suggest that the upregulation of the ubiquitin-proteasome pathway and caspase-3 activity is responsible for the 30% reduction in myosin heavy chain content in the diaphragm previously described (66). Nevertheless, this causal relationship remains to be proved.

While proteolysis is clearly accentuated in the COPD diaphragm, its physiological meaning and implications are still unclear. In the quadriceps, a reasonable chain of events would be that hypertrophy/atrophy imbalance in the favor of the latter would lead to fiber atrophy and muscle weakness. However, diaphragm weakness could mostly be related to chest-wall configuration and muscle fiber length/tension issues rather than to fiber atrophy and intrinsic weakness (82), suggesting that increased diaphragmatic proteolysis may not solely reflect an atrophying process. Due to chronic shortening and reconfiguration of the chest wall, the diaphragm in COPD undergoes important structural modifications (16), including either a possible shortening (60) or a loss (25) in sarcomeres that could require the activation of the proteolytic machinery to clear the protein debris. On the other hand, a 30% reduction in myosin heavy chain content was observed in patients with only mild to moderate COPD (66). Marked changes in chest-wall configuration and muscle fiber length/tension relations are not likely to occur in this early stage of disease. Consequently, it can be questioned whether the activation of the muscle proteolysis pathway observed in the diaphragm in COPD is the result of muscle reorganization or a true maladaptive muscle atrophy phenomenon. Very little is known concerning the protein regeneration status in the diaphragm of COPD patients (57, 62). Recent data from our laboratory suggest that the ubiquitin-proteasome pathway is more activated in the quadriceps than in the diaphragm and that this activation is concomitant with a lower anabolism and an amplified catabolism in the limb muscles compared with the diaphragm (22). We are only beginning to understand the regulation of muscle protein balance in skeletal muscles of patients with COPD. In pursuing this quest, comparative studies of the diaphragm and the vastus lateralis should be instrumental in clarifying whether skeletal muscle dysfunction in COPD is of local or systemic origin.

**CONTRACTILITY**

**Quadriceps.** As expected from the documented quadriceps atrophy and reduction in muscle fiber dimension, patients with COPD exhibit a reduction in muscle strength (7, 37). In these individuals, the reduction in quadriceps strength is in proportion to that of muscle mass, suggesting a preserved contractile apparatus (7). In vitro contractility studies on quadriceps muscle bundles in patients with COPD and healthy controls gave credence to this notion (19).

**Diaphragm.** Since the landmark study of Similowski and colleagues (82), it has widely been accepted that diaphragmatic weakness in COPD was the result of chest wall reconfiguration and hyperinflation leading to chronic diaphragmatic fiber shortening and a suboptimal length/tension relationship. When normalized for a given lung volume, diaphragmatic strength of patients with COPD is not inferior to that of healthy controls (82). At variance with these physiological data, invasive evaluation of diaphragm function indicates that the force generation of isolated skinned diaphragm fibers is already reduced in mild COPD compared with controls with normal lung function (64), although this finding may not be universal (87). These somewhat discrepant findings between clinical and basic sciences may be related to different patients’ characteristics and/or to variations in experimental conditions among studies. Loss of myosin heavy chain content and alteration in titin function, a structural muscle cell protein that can also act as a stretch sensor and induce muscle remodeling and gene expression, are likely explanations for diaphragmatic weakness in COPD (64). Reduced calcium sensitivity may also contribute to poor force generation as suggested by in vitro experiments performed on single skinned diaphragm muscle fibers of patients with COPD demonstrating a reduced calcium sensitivity of these fibers compared with those from healthy controls (66). What remains unclear, however, is the relative contribution of
the changes in diaphragmatic configuration vs. the alterations in diaphragmatic contractile properties to diaphragmatic weakness. This area of investigation may have important potential therapeutic implications for the treatment of diaphragmatic weakness in COPD (62, 63).

**SHIFT IN FIBER-TYPE DISTRIBUTION**

At least six signaling pathways may be involved in the fiber typing reorganization occurring in the quadriceps and diaphragm in COPD (Fig. 1). FoxO1 is one potential target since its overexpression in mice induces an increase in type II-fiber proportion (41). Although this pathway could be relevant for the quadriceps, it would be difficult to invoke its involvement in diaphragm fiber-type shift toward preponderant type I fibers. A second potential pathway is peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α). This transcriptional coactivator is able, when expressed in mice, to induce transformation of type II into type I fibers by enhancing, among others, the expression of troponin I and myoglobin, two proteins present in type I fibers (47). In relation with this finding, reduced quadriceps PGC-1α mRNA levels were reported in patients with COPD (71). The status of PGC-1α in diaphragm is currently unknown, but this protein could be implicated in the fiber-type shift observed in this tissue. Calcineurin, a calcium-dependent phosphatase, is able to induce expression of type I fiber-specific genes (15) while the administration of the specific calcineurin inhibitor cyclosporine A to rats results in an increase in type II fiber proportion (15). These data indicate that an imbalance in the cellular regulation of calcineurin could play a role in the fiber-type shift occurring in the vastus lateralis muscle in COPD; however, this has yet to be investigated. Finally, mitogen-activated protein kinase (MAPK) signaling could also be involved in the fiber reorganization in COPD. A type I phenotype is observed when the extracellular signal-regulated kinase (ERK) signaling is inhibited in C2C12 muscle cells (81). Also, overexpression of MAP kinase phosphatase-1 (MKP1) in type IIx fibers results in the synthesis of type I and IIa myosin heavy chains (81).

The investigation of the cellular signaling involved in the opposite fiber-type shift occurring in the quadriceps and the diaphragm could offer a promising opportunity to unravel the mechanisms of skeletal muscle adaptation in COPD and initiate novel therapeutic avenues to modulate fiber-type proportion in this disease.

**Quadriceps.** A shift in fiber-type distribution of the lower limb muscles is a common feature in COPD. Compared with healthy controls, a decrease in the proportion of oxidative type I fibers in favor of glycolytic type IIx is observed in the quadriceps of patients with COPD (33, 40, 93). This finding is not consistent with normal aging, which is rather associated with a decline in type II fibers (42). The proportion of type I fibers correlates with disease severity (33, 93), a finding further supported by the absence of modification in the different fiber types in mild to moderate disease (21). The shift in fiber-type distribution reported in the quadriceps is not seen in upper extremity muscles such as the deltoid (26). The notion that only certain peripheral muscles exhibit a shift in fiber-type distribution may have potential implications for the mechanisms of skeletal muscle dysfunction in COPD since it suggests that local factors (i.e., inflammation, oxidative stress, activity level, etc.) are involved in the muscle phenotypic changes seen in this disease.

**Diaphragm.** A different portrait can be drawn concerning the fiber-type distribution of the respiratory muscles. The fiber-type distribution shifts in opposite direction in the diaphragm compared with the quadriceps, as an increase in the proportion of type I fibers is reported in the former muscle in patients with severe emphysema (46). The fiber-type profile of the diaphragm found in patients with advanced COPD may represent an adaptation to the chronic increase in work of breathing faced by this muscle as disease severity progresses, a situation not dissimilar to what is observed when skeletal muscles undergo long-term endurance training (38). Cross-sectional studies suggest that the fiber-type shift occurs earlier in the natural course of COPD in the diaphragm than in the quadriceps (21), indicating that the respiratory muscles may show greater plasticity than limb muscles.

**CAPILLARIZATION AND MITOCHONDRIAL ALTERATION**

**Quadriceps.** Muscle capillarization is one key component of the O$_2$ transport and utilization chain. Adequate capillarization ensures a proper distribution of O$_2$ throughout muscle tissue, allowing optimal O$_2$ utilization by the cellular machinery and mitochondria to ultimately optimize muscle performance. An insufficient capillarization along with the resulting impairment in O$_2$ transport is proposed as one muscle adaptation contributing to exercise intolerance in COPD. One study showed that the capillary-to-fiber ratio tended to be reduced in vastus lateralis of patients with COPD; however, when taking into account fiber cross-sectional area, the ratio was identical between subjects with COPD and matching controls (93). It was nevertheless reported that capillary contacts with oxidative type I and IIa fibers were diminished in COPD (93).

Vascular endothelial growth factor (VEGF) is crucial for angiogenesis. The promoter of the VEGF gene contains a hypoxic response element and can be upregulated by several factors such as hypoxia-inducible factor (HIF), among others (10). HIF-1α, a HIF subunit, is normally targeted by the E3 ligase von Hippel-Lindau protein (pVHL) and degraded by the ubiquitin-proteasome system (54). pVHL mRNA expression is increased in skeletal muscle of subjects with mild to moderate COPD but not in more advanced disease (39). The repercussion of this pVHL upregulation could be an insufficient quantity of VEGF and therefore an inadequate angiogenesis near certain oxidative fibers. Using a human antibody array, Barreiro and colleagues (5) have found that VEGF protein level is decreased in quadriceps of COPD patients compared with healthy controls. The available information thus indicates that the angiogenesis process may be abnormal at the limb muscle level in COPD.

Along with abnormal muscle capillarization, Gosker et al. (29) reported a reduced mitochondrial density in the vastus lateralis of patients with COPD compared with age-matched controls, whereas Picard et al. (67) showed that the respiratory function of individual mitochondria is preserved. Another important observation resides in the fact that mitochondria isolated from vastus lateralis of COPD patients produce more oxidative stress than those isolated from controls (67, 68). Increased release of reactive oxygen species (ROS) could have
important implications by promoting muscle protein degradation through the ubiquitin-proteasome pathway (27).

Diaphragm. In the diaphragm, the number of capillary contacts tends to be greater for each fiber type in patients with COPD than in controls (21). The overall mitochondrial respiratory chain capacity is increased and has a higher efficiency in patients with moderate (95) and severe (72) COPD than in controls with normal lung function. Together with the observed changes in oxidative enzyme activities and fiber-type shift observed in the diaphragm, greater diaphragmatic mitochondrial function in COPD may be a reflection of an endurance training-like effect resulting from the increased work of breathing seen in COPD. No differences in the accumulation of lipofuscin inclusions, a surrogate of cellular oxidative damage, were observed between diaphragm samples from patients with COPD and healthy subjects (21). However, with more sensitive research tools, diaphragmatic oxidative stress was reported in patients with severe COPD as confirmed by the presence of increased levels of protein carbonylation and of superoxide anion in mitochondria and membrane compartments (3, 51). Catalase activity is 90% higher in the diaphragm of patients with COPD compared with non-COPD subjects (94). Moreover, malondialdehyde levels, a marker of lipid peroxidation, are significantly lower in the COPD diaphragm compared with controls. This indicates that the COPD diaphragm attempts to adapt to a higher ROS production by increasing antioxidant defenses that seems to protect, at least partially, against oxidative damage (94).

METABOLIC ALTERATIONS

Quadriceps. A number of metabolic alterations occur in the skeletal muscle of patients suffering from COPD. First, the activity of oxidative enzymes such as 3-hydroxyacyl-CoA dehydrogenase (HADH) (35, 49, 50) and citrate synthase (49, 50) is reduced in the vastus lateralis of patients with moderate to severe COPD. Cytochrome c oxidase, an enzyme of the electron transport chain, is also decreased in these individuals (35), although the current literature is not in full agreement in this regard (68, 76). Glycolytic enzymes are not unambiguously affected in the presence of COPD (35). However, when oxidative-to-glycolytic enzymatic ratios are considered, predominance of a glycolytic metabolism appears to be a common feature in the quadriceps of patients with COPD (35). This metabolic pattern of the lower limbs differs from what is seen in the upper extremity muscles in which an increased citrate synthase and lactate dehydrogenase activity is observed in severe COPD patients (26). These observations corroborate the putative importance of local factors in the development of muscle dysfunction in COPD.

Diaphragm. Consistent with the greater proportion of type I fibers, an increase in oxidative enzyme activities combined with a decrease in glycolytic enzyme activities is seen in the COPD diaphragm, resulting in a clear predominance of oxidative metabolism in this muscle (21, 45). This observation further indicates that some skeletal muscle adaptations such as energy metabolism in COPD are probably more dependent on local than systemic factors.

The COPD-associated metabolic alterations observed in the quadriceps and the diaphragm are in accordance with the fiber-type switch observed in these tissues. Since type I fibers have a more oxidative metabolic profile than type II fibers, a variation in their proportion should reasonably be accompanied with a parallel variation in the oxidative enzyme activities. Variation in enzyme activities within each fiber type may also contribute to alter the metabolic profile of the skeletal muscles in COPD. As each single fiber expresses oxidative and glycolytic enzymes in different proportions, type IIX fibers could, in the diaphragm for example, express more oxidative enzymes in COPD patients and therefore contribute to their reported increase. Giving weight to this hypothesis, the oxidative enzyme activity is lesser in type IIX fibers from the quadriceps of patients with COPD than in healthy controls (31).

QUADRICEPS AND DIAPHRAGMATIC DAMAGES AND REPAIR

Muscle damage occurs in a variety of situations and is mainly characterized by transient structural cell damage, regional disorganization of the myofilaments, and muscle weakness. Lengthening contractions are most damaging to muscles. On cell damage a complex and coordinated sequence of cellular events is initiated to restore muscle function. Satellite cell activation, replication, and fusion are key events in the regenerative process (17). In addition to mechanical stresses, other mechanisms such as loss of intracellular calcium homeostasis and oxidative stress are hypothesized to contribute to the development of muscle injuries. Recently, supporting evidence demonstrating disturbed calcium cycling in vastus lateralis from patients with severe COPD has been published (36).

Quadriceps. Little information exists on the level of muscle damage and regeneration in the quadriceps muscle of patients with COPD. In one study, increased sarcomere disruption and myofibrillar degeneration were reported in the vastus lateralis of patients with COPD compared with healthy subjects (59). In a second study, a slight increase in fatty cell replacement and fibrosis was observed in muscle specimens from patients with COPD compared with healthy subjects (30). No signs of muscle damage and regeneration have been observed in this group of patients (30).

Diaphragm. Mounting evidence apparently confirms increased muscle damage and regenerative processes in the respiratory muscles of individuals affected by COPD. Increased diaphragmatic sarcomere disruptions were reported in patients with COPD compared with healthy subjects (61). Moreover, it was observed that diaphragm myofibrillar structures of these patients were more prompt to develop structural abnormalities during an inspiratory loading test (61). Autopsy studies confirmed the presence of an accentuated number of injured diaphragmatic myofibers in patients with COPD than in healthy subjects (80).

The presence of satellite cell activation and mechanogrowth factor (MGF) (53) as well as embryonic and neonatal myosin heavy chain (57) in diaphragmatic muscle samples from patients with COPD is suggestive of an undergoing regenerative process. Although this response seems to be appropriate to induce muscle repair, its effectiveness still needs to be evaluated since an incomplete or defective regenerative process could contribute to the progression of muscle atrophy.

POSSIBLE IMPLICATIONS

Respiratory and limb muscle impairment is associated with important clinical consequences such as exercise intolerance,
poor quality of life, and even premature mortality. Given all these consequences, the development of specific treatments for skeletal muscle impairment appears as a priority. This will benefit not only the field of COPD, but several chronic diseases associated with skeletal muscle dysfunction. Currently, the clinical approach to skeletal muscle dysfunction is nonspecific, the use of exercise being the most commonly employed intervention to treat both limb and respiratory muscle dysfunction (48) despite the fact that the level of activity markedly differs between the two muscle groups. Although combining resistance and aerobic exercises are recommended in patients with COPD, the optimal training prescription has not been established. An important consideration is that these individuals seem to respond differently to exercise training compared healthy subjects (69, 70).

What have we learned from the comparison between the quadriceps and the diaphragm? First there are important differences in the phenotypic changes between these two muscles, the most obvious being the opposite direction of the shift in fiber-type distribution. A hypothetical integrated model explaining diaphragm and quadriceps muscle changes in COPD is presented in Fig. 2. According to this model, we suggest that local factors, such as the degree of muscle activity, are crucial in modulating the phenotypic expression of COPD-associated changes in these muscles (46).

Conversely, muscle changes such as oxidative stress and activation of the ubiquitin-proteasome pathway are seen both in the diaphragm and the quadriceps. It can be speculated that these biochemical modifications may find their origin at the systemic level. Low-grade systemic inflammation and/or tissue hypoxia reported in COPD may induce oxidative stress and activate the catabolic cascade within the diaphragm and the vastus lateralis (11, 88). Even if systemic factors are involved in diaphragmatic and quadriceps oxidative stress and proteolysis, the level of local activation may also modulate the expression of these muscle changes. For example, the high level of metabolic diaphragmatic activity may stimulate the production of ROS and the creation of oxidative damage (3) eventually leading to increased proteolysis in this muscle (62, 65). In the quadriceps, the presence of oxidative stress may be related to other mechanisms such as mitochondrial uncoupling between the citric-acid cycle and the respiratory chain (68) that does not seem to be present in the diaphragm, which is known to exhibit a more efficient oxidative profile.

Although oxidative stress and activation of the ubiquitin-proteasome pathway are seen in the diaphragm and the quadriceps, caution is warranted before concluding that the extent of the involvement of these biochemical processes is similar between the two muscles. In this regard, it should be appreciated that our comparative assessment of the quadriceps and diaphragm in COPD is almost exclusively based on quadriceps and diaphragmatic data that were obtained independently from each other. This approach may be potentially biased due to heterogeneity and lack of control for confounding factors in study populations, which stresses the need for further studies in which both muscles are sampled within the same subjects.

What are the therapeutic implications of the above discussion? Although exercise training is the current therapy of choice for limb muscle dysfunction in COPD, possible new avenues should be explored to optimize the benefits. First, there is a need to define what is the optimal training regimen as it may be argued that intense exercise training may have some detrimental effects on the vastus lateralis by amplifying the degree of oxidative stress and catabolism (4, 69). The activation of the muscle proteolysis pathway in the vastus lateralis and the diaphragm suggests that inhibiting the ubiquitin-proteasome system may be an interesting therapeutic target in both muscle groups. Enhancing muscle fiber calcium sensitivity with pharmacological agents like levosimendan is an exciting area of research for respiratory and limb muscle weakness in patients with COPD (89). Testosterone supplementation, alone or in combination with a resistance exercise regimen, increases lean body mass in patients with COPD (14). Further and longer-term studies on anabolic supplementation will need to

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**Fig. 2.** Interactions between systemic factors, activity level, and mitochondrial function in the phenotypic expression of diaphragmatic and quadriceps changes in COPD. The diaphragm and quadriceps in COPD are exposed to a systemic environment characterized by oxidative stress, low-grade inflammation, intermittent to chronic hypoxemia, and low anabolic hormone levels that influence their morphology and function. For example, the particular systemic milieu depicted here would favor the atrophying process in both muscles. The marked difference in the level of activation between the diaphragm and the quadriceps modulates the effects of systemic factors on the muscles, in part by dictating the nature of mitochondrial adaptations seen locally. Reactive oxygen species (ROS) production is increased in the diaphragm due to an increased mitochondrial activity. At the quadriceps level, ROS production is also enhanced but in relation with mitochondrial uncoupling, the result of a chronic decrease in the level of activity. This model could explain why oxidative stress has been reported in both muscles despite vastly different levels of muscle activation. Increased ROS production and the resulting oxidative stress could then trigger the proteolysis cascade and the atrophying process in both muscles (through IGF-1/PI3K/Akt, proteasome, FoxO). The level of muscle activity influences the signaling pathways (MAPK, calcineurin, VEGF) involved in the distinct fiber-type distribution, capillarization, and energy metabolism found in the diaphragm and in the quadriceps. CSA, cross-sectional area.
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be conducted in this population. Finally, myostatin inhibition is an appealing strategy since this protein represses muscle mass (55). Little is currently known concerning myostatin status in skeletal muscle of COPD patients, but this research avenue is worth further investigation considering the effectiveness of this protein in repressing muscle hypertrophy (79).

CONCLUSION

In summary, this minireview presented an overview of the major diaphragm and quadriceps alterations described in COPD and the underlying signaling implicated in these processes. Some muscle alterations in COPD appear early in the disease and are remarkably heterogeneous in terms of direction and amplitude when the diaphragm and quadriceps are compared; this is particularly the case for the fiber-type distribution, which goes in opposite direction in these two muscles. This indicates that, in addition to systemic factors, local factors must participate in the reorganization seen in skeletal muscles in COPD. On the other hand, the diaphragm and the quadriceps show some interesting and intriguing similarities. For example, both muscle groups exhibit a greater propensity toward oxidative stress and the activation of the ubiquitin-proteasome pathway. Underlying the profound changes seen in muscle tissue of these patients is a complex set of intricate molecular signaling that need to be accurately portrayed. Such knowledge is essential to better understand the underlying causes and to develop novel effective therapeutics that will preserve or improve muscle functions and consequently the well-being of patients with COPD.

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