
Executive Summary

François Maltais, Marc Decramer, Richard Casaburi, Esther Barreiro, Yan Burelle, Richard Debigré, P. N. Richard Dekhuijzen, Frits Franssen, Ghislaine Gayan-Ramirez, Joaquim Gea, Harry R. Gosker, Rik Gosselink, Maurice Hayot, Sabah N. A. Hussain, Wim Janssens, Michael I. Polkey, Josep Roca, Didier Saey, Annemie M. W. J. Schols, Martijn A. Spruit, Michael Steiner, Tanja Taivassalo, Thierry Troosters, Ioannis Vogiatzis, and Peter D. Wagner; on behalf of the ATS/ERS Ad Hoc Committee on Limb Muscle Dysfunction in COPD

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Background: Limb muscle dysfunction is prevalent in chronic obstructive pulmonary disease (COPD) and has important clinical implications, such as reduced exercise tolerance, quality of life, and even survival. Since the last American Thoracic Society (ATS) and European Respiratory Society (ERS) statement on limb muscle dysfunction, important progress has been made in the characterization of this problem and on our understanding of its pathophysiology and clinical implications.

Purpose: The purpose of this document is to update the 1999 ATS/ERS statement on limb muscle dysfunction in COPD.

Methods: An interdisciplinary committee of experts from the ATS and ERS determined that the scope of this document should be limited to limb muscles. Committee members conducted focused reviews of the literature on relevant topics. A librarian also performed a literature search. An ATS methodologist provided advice to the committee, ensuring that the methodological approach was consistent with ATS standards.

Results: We identified important advances in our understanding of the extent and nature of the structural alterations in limb muscles in patients with COPD. Since the last update, studies have been published regarding mechanisms of development of limb muscle dysfunction in COPD and on the treatment of this condition. The clinical implications of limb muscle dysfunction have been delineated. Although exercise training is the most potent intervention to address this condition, other therapies, such as neuromuscular electrical stimulation, are emerging. Assessment of limb muscle function can identify patients who are at increased risk of poor clinical outcomes, such as exercise intolerance and premature mortality.

Conclusions: Limb muscle dysfunction is a key systemic consequence of COPD. However, there are still important gaps in our knowledge about mechanisms of development of this problem. Strategies for early detection and specific treatments for this condition are needed.

This Executive Summary is part of the full official Limb Muscle Dysfunction in COPD Update statement, which readers may access online at www.atsjournals.org/doi/abs/10.1164/rccm.201402-0373ST. Only the Executive Summary is appearing in the print edition of the Journal. The article of record, and the one that should be cited, is: An Official American Thoracic Society/European Respiratory Society Statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;189:e15–e62. Available at www.atsjournals.org/doi/abs/10.1164/rccm.201402-0373ST.

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Overview

Limb muscle dysfunction is an important systemic consequence of chronic obstructive pulmonary disease (COPD) because of its impact on physical activity, exercise tolerance, quality of life, and even survival. Although some mechanisms underlying development of limb muscle dysfunction have been identified (e.g., deconditioning), much needs to be learned about the impact of other potential contributors to this clinical manifestation of COPD. Limb muscle dysfunction can be prevented and improved, in part, with exercise training, but it is clear that novel therapies are needed to better address this problem.

The purpose of this document is to update the 1999 American Thoracic Society/European Respiratory Society (ATS/ERS) statement on limb muscle dysfunction. We intend to provide researchers and clinicians with recent advances in this field, with emphasis on the following areas: (1) structural and metabolic alterations found in limb muscles, (2) consequences and clinical evaluation of limb muscle dysfunction, (3) mechanisms of development of this comorbidity, and (4) treatment approaches to limb muscle dysfunction in COPD. Future research directions are also discussed.

Major conclusions of the statement include:

- Limb muscle dysfunction is prevalent in COPD. Muscle atrophy and weakness carry important consequences, such as difficulties in engaging in physical activity, exercise intolerance, poor quality of life, and premature mortality. Metabolic alterations in relation to structural changes within the lower limb muscle are also involved in exercise limitation.
- Lower limb muscle function is further compromised during COPD exacerbations. Patients experiencing exacerbations may be targeted for rehabilitative interventions aiming at preserving limb muscle function.
- Assessment of limb muscle function should be encouraged.
- Knowledge of the biochemical regulation of muscle mass will likely lead to development of specific therapy for muscle atrophy in COPD.
- Although physical inactivity is involved in the development of limb muscle dysfunction development in COPD, other mechanisms, such as inflammation, oxidative stress, nutritional imbalance, and hypoxemia, likely play a role.
- The most potent currently available treatment option for limb muscle dysfunction is exercise training, a key component of integrated COPD management.
- Neuromuscular electrical stimulation is emerging as a useful training modality in severely impaired COPD and during exacerbations.

Introduction

Limb muscle atrophy and weakness are prevalent in COPD, affecting up to one-third of patients with COPD seen in specialized centers (1–3). Furthermore, this problem is not only confined to advanced disease; it may also occur in mild COPD (3). More than 10 years have elapsed since the first ATS/ERS statement on limb muscles in COPD (4). Since then, abundant evidence shows that limb muscle atrophy and weakness are strongly related to exercise intolerance, quality of life, and even premature mortality in COPD (1, 5–7). Another emerging message is that COPD exacerbations are associated with further decreases in quadriceps strength and mass (8–10). This finding is relevant because the preservation of muscle strength could become an important treatment goal during COPD exacerbation.

The involvement of limb muscles in COPD goes beyond simple issues of atrophy and weakness. Important morphological and metabolic alterations have been reported in this condition at rest and during exercise. These changes lead to premature use of glycolytic metabolism in the contracting muscles and promote muscle fatigue and exercise intolerance (11–13). Together, muscle atrophy and weakness as well as morphological and metabolic alterations are components of limb muscle dysfunction in COPD.

Limb muscle weakness and atrophy in COPD are likely of multifactorial origin, but little is known about the interplay and the relative role of the mechanisms underlying the phenomena. Molecular and biochemical mechanisms involved in muscle mass regulation in COPD are emerging (14–18). This line of research will, we hope, lead to development of specific therapies for muscle atrophy in COPD. As it stands now, exercise training remains the most potent therapeutic intervention to improve limb muscle function in COPD.

The primary objective of this document is to update current scientific and clinical knowledge on this topic and to provide guidance for future research directions. This document should be useful to scientists and also to clinicians, for whom we wish to raise awareness regarding the clinical relevance of limb muscle dysfunction.

Methods

The present document is intended to be a Clinical Statement. Methods involved in the production of this document are summarized in Table 1 and in the full document (online).
muscles are a separate topic. Limb muscle dysfunction is used in this document to reflect morphological and functional changes seen in limb muscles in patients with COPD with no implications on underlying mechanisms.

**Limb Muscles in Clinically Stable COPD**

Several structural changes of the limb muscles have been reported in patients with COPD. They are described in this section and summarized in Figure 1. In comparison to the quadriceps, upper limb muscles are relatively spared.

**Muscle Atrophy**

Using World Health Organization classification for body mass index (BMI), underweight in COPD is found in up to 30% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) class 4 COPD (2). Studies assessing body composition revealed that reduced muscle mass occurs in 4 to 35% of patients with COPD (2, 19, 20), this proportion being dependent on the criteria used to define low muscle mass (1, 2, 21). Low fat-free mass index (FFMI) is reported in 26% of patients with COPD with a normal BMI, underscoring the importance of assessing body composition to quantify precisely muscle atrophy (2). Even in the presence of a normal BMI, low FFMI is a strong predictor of mortality (1). Lower limb muscles are particularly vulnerable to atrophy in COPD (22, 23).

**Structural Alterations**

**Muscle fiber atrophy and fiber type shift.** All fiber types of the quadriceps are affected by the atrophying process (24), although some authors argue that the type IIX fibers are more specifically affected (25–27). A shift in quadriceps fiber type distribution, from type I to type IIX fibers, is a typical feature of advanced COPD (23, 24, 28, 29). This finding is inconsistent with normal aging, which is not associated with a shift toward type II fibers (30, 31). The proportion of type I fibers correlates inversely with disease severity (32, 33). The fiber type distribution shift in quadriceps and tibialis anterior (34) muscles is not observed in upper extremity muscles (35), indicating that muscle structural abnormalities are not homogeneously distributed among muscle groups.

**Changes in capillarization.** Total numbers of capillaries and capillaries per muscle fibers are reduced in limb muscles of COPD (24, 36). This is not a universal finding (37), perhaps because, in some studies, patients were involved in exercise training, which could improve muscle capillarization (38). However, reduction in the capillary to muscle fiber cross-sectional area has not been reported (39).

**Mitochondrial Function and Bioenergetics**

Mitochondrial functionality is altered in COPD limb muscles (38). Locomotor muscle oxidative capacity is reduced in COPD (40, 41), and this is consistent with type I to type IIX fiber type shift found in COPD (24, 28). Limb muscle metabolic profile of patients with COPD shows, at rest, low levels of ATP, inosine monophosphate, and phosphocreatine levels compared with age-matched healthy control subjects (41, 42). Half-time phosphocreatine recovery after cycling exercise is slower and phosphocreatine to inorganic phosphate ratio is lower in COPD than in healthy control subjects (43). In addition, intermediate markers of glycolysis as well as phosphofructokinase and lactate dehydrogenase activities are elevated in resting COPD muscles (41, 44, 45).

**Oxidative Stress**

Evidence of oxidative stress with higher levels of lipid peroxidation, oxidized glutathione, and protein oxidation and nitration is consistently found in the blood and limb muscles of patients with COPD (17, 27, 32, 46–64), particularly those with muscle atrophy (65). The development of oxidative stress in limb muscles of patients with COPD may result from enhanced inflammatory cell infiltration and cytokine production. However, there is no strong relationship between muscle oxidative stress and muscle inflammation in patients with COPD (17, 27, 52, 62, 64). Muscle oxidative stress may also be related to mitochondrial dysfunction. Interestingly, chronic cigarette smoke exposure also induces a significant increase in several oxidative stress markers in limb muscles of healthy smokers (17) and in limb muscles of animals chronically exposed to cigarette smoke (17, 66).

**Limb Muscle Function**

Strength and endurance are the two main defining features of muscle function; they can vary independently in such a way that one cannot be used to predict the other (67). Strength refers to the ability of the muscle to generate force; endurance is defined as the ability of the muscle to sustain a given task. Muscle weakness and reduced endurance are frequent in COPD. Quadriceps strength is reduced by an average of 20 to 30% in these individuals.
and weakness is found in patients with mild disease (3). Conflicting data exist about the rate of decline in quadriceps strength in patients with COPD, which was reported to be increased (8) or similar to the healthy aging population (81). Muscle weakness is not similar among muscle groups: strength of the upper limb muscle is better preserved than that of lower limb muscles (35, 70, 82). Muscle weakness is a direct consequence of reduced muscle mass (54, 68, 71, 83, 84), although during chronic or repeated exposure to systemic corticosteroids, strength loss out of proportion to muscle mass reduction can occur (68, 85).

**Muscle endurance and fatigue.** Volitional (57, 59, 67, 73, 86–89) and nonvolitional (90) quadriceps endurance is decreased in COPD. Magnitude of decrease is highly variable (range, 32–77%), probably because of differences in test procedures. Impaired quadriceps endurance is also present in patients with mild to moderate COPD, even in those with relatively normal physical activity (67). Impaired quadriceps endurance is the consequence of reduced oxidative capacity and oxidative stress (73), rather than reduced muscle mass (83). Endurance of the upper extremity muscles (69, 74, 91) is preserved in patients with COPD, providing additional indication about heterogeneity of muscle abnormalities in this disease.

Fatigue is defined as a failure of force generation after loaded muscle contractions that is reversible by rest (87, 92). Quadriceps fatigue can be objectively demonstrated in 48 to 58% of patients with COPD after cycling exercise (6, 72, 79, 93). Taking into account the amount of work performed, these patients exhibit greater susceptibility to fatigue than healthy individuals (72). The gastrocnemius and tibialis anterior of patients with COPD may also be more susceptible to fatigue during walking (80, 94). Susceptibility to muscle fatigue in COPD can be related to intrinsic muscle morphometric and metabolic derangements seen during exercise in this disease (11,13, 95–97). Insufficient oxygen delivery to contractile muscle may also contribute to premature lower limb muscle fatigue (98, 99).

**Limb Muscle Function during COPD Exacerbation**

Quadriceps strength often decreases during hospitalization for COPD exacerbation (10, 100, 101). Reduction in quadriceps

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**Figure 1.** Morphological and structural alterations reported in limb muscles in patients with chronic obstructive pulmonary disease (COPD). CS = citrate synthase; HADH = 3-hydroxyacyl CoA dehydrogenase.
force during hospitalization is associated with less improvement in walking time 1 month after discharge (100). Importantly, quadriceps force only partially recovered 3 months after hospital discharge (10). Muscle weakness has been associated with increased risk of hospital readmissions due to acute exacerbation (102). Muscle mass and strength maintenance may be compromised during an exacerbation, with activation of multiple atrophying biochemical pathways during this process (101, 103). Causes of muscle dysfunction during exacerbations may involve inflammation (10), impaired energy balance (104, 105), inactivity (100, 106), and systemic corticosteroid use (85).

Consequences of Limb Muscle Dysfunction in COPD

The most troublesome consequence of muscle dysfunction is its association with reduced life expectancy (1, 5, 7) (Figure 2). Muscle atrophy (1, 5) and quadriceps weakness (7) are predictors of mortality in subjects with COPD: (1) mid thigh muscle cross-sectional area less than 70 cm² as assessed by computed tomography scanning is associated with fourfold increase in mortality after adjusting for age, sex, and FEV₁ (5); (2) FFMI less than 16 kg/m² in men and less than 15 kg/m² in women is associated with 1.9-fold increase in mortality after adjusting for age, sex, and FEV₁ (1); and (3) a quadriceps strength (kg) to BMI (kg/m²) ratio less than 120% is associated with increased mortality; each 10% increment of this ratio is associated with a 9% reduction in mortality (7). These indicators stress the importance for clinicians to carefully monitor body composition and muscle strength in patients with COPD. Muscle atrophy and weakness are also associated with reduced quality of life (107) and greater healthcare resource use (108). Quadriceps strength is a strong predictor of exercise capacity in patients with pulmonary diseases (109): a twofold increase in muscle strength is associated with 1.4- to 1.6-fold increase in work capacity (110). One explanation for this is the influence of muscle strength on leg effort perception during exercise (110), the main limiting symptom in an appreciable portion of patients with COPD (111) (Figure 2). Premature leg fatigue reduces the ability of bronchodilators to produce improvement in exercise tolerance (6, 112). Perturbation in muscle energy metabolism during exercise seen in COPD is also relevant to whole-body exercise capacity, as it is associated with premature fatigue (11, 13, 95–97) and increased ventilatory requirements during exercise (46, 113, 114), imposing an additional burden on already overloaded respiratory muscles.

Figure 2. Relationships between muscle mass and strength and clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). A mid thigh muscle cross-sectional area (MTCSA) < 70 cm² (A) (5), a low fat-free mass index (FFMI) defined as an FFMI < 16 kg/m² in men and < 15 kg/m² in women (B) (1), and a reduced quadriceps strength defined as a quadriceps strength (kg) to body mass index (BMI, kg/m²) ratio < 120% (C) (7) are predictors of mortality in COPD after adjusting for traditional mortality risk factor such as age and FEV₁. The strength of the quadriceps is a significant contributor to exercise capacity in COPD (D) (110). All panels adapted by permission from the indicated references.
Etiology of Limb Muscle Dysfunction in COPD

Several factors have been hypothesized to initiate and/or promote changes in limb muscles of patients with COPD (Table 2). Together, they have the ability to activate various biochemical pathways initiating or enhancing alterations in fiber type expression, contractile proteolysis, metabolic alterations, and regenerative defects in limb muscles.

Disuse versus Myopathy
One important question is whether limb muscle dysfunction simply reflects years of physical inactivity or whether some COPD-specific myopathy (115–119) can be invoked. Against the hypothesis of COPD myopathy are observations that many functional and cellular findings in COPD are identical to those of disuse and that limb muscle function and oxidative profile can be improved with training (115, 118, 120–124). The fact that full recovery of muscle function is unusual does not necessarily indicate a myopathy, because intensity and/or duration of training may be insufficient to correct alterations that have developed over several decades (119, 125, 126). On the other hand, several observations favor the existence of a myopathy in patients with COPD. Muscle structure and function are poorly related to the degree of physical activity (127–129). Disparities in muscle function and/or structure remain when patients with COPD are compared with control subjects having similar degree of physical activity (116, 130). Muscle typology does not improve to the same extent after exercise in COPD (24, 131, 132) compared with healthy subjects (133–135).

Mechanisms of Limb Muscle Dysfunction in COPD

Inflammation. Through transcriptional activities of nuclear factor-kappa B (NF-kB) and forkhead box O (FOXO) (136), production of proinflammatory cytokines during the inflammatory response can enhance ubiquitin proteasome system activity, apoptosis (137), and macroautophagy occurrence (138), which have all been linked to muscle atrophy development (139, 140). Increased expression of E3-ligases Atrogin-1, muscle ring finger protein 1 (MuRF-1), and neural precursor cell expressed developmentally down-regulated protein 4 (Nedd4) is observed in quadriiceps of patients with COPD (14, 15). Despite these convincing arguments supporting a role for inflammation, data supporting its presence in quadriiceps of patients with COPD are equivocal (45, 52, 141–144), even in established muscle atrophy and during periods of acute exacerbation when inflammatory bursts should be expected (103).

Oxidative stress. In COPD, systemic (56) and local (27, 48, 49) oxidative stress has been reported at rest, during acute exercise bouts (54, 56), and during acute exacerbation (145, 146). Oxidative stress levels are directly related to quadriiceps force and endurance in patients with severe COPD (17, 52, 53, 57, 59). Oxidative stress could alter the integrity of proteins, enhancing their degradation (147). Direct oxidative stress exposure (148) or indirect production of reactive oxygen species through inflammatory response (149, 150) induces proteolysis and increases expression of ubiquitin-proteasome components. Induction of NF-kB (149) and FOXO (151) transcriptional activities or p38 kinase activity (18, 152) by oxidative stress are believed to regulate proteolytic signaling.

Table 2: Etiologies of Limb Muscle Atrophy, Weakness, and Susceptibility to Fatigue

<table>
<thead>
<tr>
<th>Factors leading to muscle atrophy and weakness</th>
<th>Mechanisms Involved</th>
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<tr>
<td>Disuse</td>
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<td>Inflammation</td>
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<td>Oxidative stress</td>
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<td>Hypoxemia</td>
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<td>(158, 254–256)</td>
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<td>Hypercapnia</td>
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<td>degradation (163,</td>
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<td>Low levels of anabolic hormones and</td>
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<td>protein synthesis</td>
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<td>Impaired energy balance</td>
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<td>protein synthesis</td>
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<td>Corticosteroids</td>
<td>Reduced muscle</td>
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<td>growth factor-1 levels (178)</td>
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<td>Vitamin D deficiency</td>
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<td>muscle weakness,</td>
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<td>Factors leading to muscle susceptibility</td>
<td>Reduced motor output</td>
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<td>Central fatigue—afferent feedback from</td>
<td>Changes in muscle</td>
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<td>muscle fatigue</td>
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<td>Reduced O2 delivery (impaired cardiac</td>
<td>Preferential use of</td>
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<td>output, blood flow competition between the</td>
<td>glycolysis and</td>
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<td>respiratory and limb muscles, reduced</td>
<td>accumulation of muscle</td>
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<td>capillarity)</td>
<td>metabolites associated with muscle fatigue</td>
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<td>Muscle metabolic alteration (reduced</td>
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<td>oxidative enzyme activity, reduced</td>
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**Hypoxia.** Hypoxic conditions decrease muscle mass (153, 154). Patients with COPD having reduced arterial P_O2 (155) or O₂ delivery (156) tend to have lower body mass than those with preserved oxygenation. Biochemical mechanisms involved in the negative muscle mass regulation by hypoxemia are complex and involve hypoxia inducible factor-1 signaling cascade (157, 158). Both inflammatory response (159) and increased production of reactive oxygen species (59, 160) as a reaction to hypoxia have been hypothesized to link hypoxia to cellular signaling yielding muscle atrophy. Hypoxemia also may also compromise muscle oxidative capacity and capillarization (161).

**Hypercapnia.** Increase in cellular CO₂ content in chronic hypercapnia may worsen in exacerbated patients. Consequently, tissue pH decreases (162) and acidosis can alter contractile protein synthesis and degradation (163). In muscle tissue, acidosis increases expression of genes encoding proteins of the ubiquitin-proteasome pathway (164) and impairs insulin/IRS/AKT signaling (165).

**Low levels of anabolic hormones and growth factors.** Low testosterone levels have been reported in COPD (166–170). However, association of limb muscle function indices with serum testosterone levels in COPD is inconsistent across studies (166, 169). Myostatin, a transforming growth factor-β (TGF-β) family member that acts as a negative regulator of limb muscle growth (171, 172), may be elevated in blood and muscles in COPD (16, 173, 174).

**Impaired energy balance.** Muscle atrophy may result from disturbed balance between energy expenditure and dietary intake, which may affect muscle protein synthesis rate, thus creating an imbalance between protein synthesis and breakdown. Altered appetite regulation, oxidative stress, and systemic inflammation may all contribute to loss in muscle tissue in COPD (175).

**Corticosteroids.** Although short-term exposure to systemic corticosteroids does not appear to compromise limb muscle strength and function (176), chronic or repeated exposure can potentiate muscle atrophy and weakness (85, 177). Corticosteroids decrease protein synthesis and simultaneously promote protein degradation (178). These actions on protein synthesis are believed to occur through inhibition of key hypertrophic biochemical pathways. Muscle protein degradation in the context of corticosteroids exposure is related to activation of ubiquitin-proteasome and lysosomal systems, two major proteolytic pathways (178).

**Vitamin D deficiency.** Vitamin D deficiency is highly prevalent in COPD compared with age-matched smoking control subjects (179), and it is suggested that vitamin D deficiency could contribute to limb muscle dysfunction (180, 181). However, published evidence is unconvincing in this regard (182, 183). In one study, genetic polymorphisms in the vitamin D receptor associated with quadriceps strength (184), indicating that the vitamin D pathway may affect muscle independent of serum levels.

**Smoking.** Cigarette smoking is unlikely to be the main mechanism involved in limb muscle dysfunction in COPD because, in several studies, smoking history was matched in patients with COPD and healthy control subjects. However, smoking by itself may be associated with muscle atrophy and weakness in otherwise healthy subjects (3, 64, 81, 185–188). Smoking is also associated with decreased type I fiber cross-sectional area, reduced type I fiber proportion, reduced cytochrome oxidase activity, increased lactate dehydrogenase activity, and higher level of protein oxidation in the quadriceps (189–191).

### Assessment of Limb Muscle Function in COPD

The existing relationships between limb muscle mass and strength and important clinical outcomes in patients with COPD (see previous section on the consequences of limb muscle dysfunction) suggest that assessing body composition and limb muscle strength in the clinical evaluation of COPD can identify patients who are at increased risk for exercise intolerance and premature mortality. Bioelectrical impedance and dual-energy X-ray absorptiometry provide reasonably accurate assessment of body composition (192). Learning about limb muscle status may help clinicians understand the mechanisms of exercise limitation in a given patient. Limb muscle strength assessment is also useful to prescribe adequate loads for resistance training. One strategy could be to evaluate body composition and quadriceps strength at the time of referral to the exercise laboratory for assessment of dyspnea and/or exercise tolerance. Some exercise laboratories implemented this practice several years ago (110).

Various methodologies exist to measure muscle strength (193), including handheld dynamometry (70, 194), the one-repetition measurement (the maximum value that a patient can move over the full range of motion) (195, 196), and hydraulic resistances (68, 197). They are discussed more completely in the full document (online).

We favor using strain gauges to measure isometric maximal quadriceps strength; this methodology could be implemented in clinical practice to provide reliable and reproducible measurements (198, 199) (Figure 3). The maximal voluntary contraction force has historically been reported in kilograms, because weights are used to calibrate the apparatus. Force could also be reported in Newtons, the product of force in kilograms and gravitational pull (9.81 m/s²). Maximal voluntary contraction force is typically reported as the best of three reproducible maneuvers. Isometric muscle force can also be assessed on specifically built computerized dynamometers (e.g., Cybex or Biodex), but these devices are expensive and not widely available. One current limitation of assessment of quadriceps strength is that there are no widely accepted reference values. This could be circumvented by expressing quadriceps strength in kilograms as a percentage of BMI (7). Another limitation of volitional assessment of strength is its dependence on patient cooperation. Nonvolitional assessment of limb muscle strength involves electrical or magnetic stimulation of a peripheral nerve (6, 78). This technique is currently practiced only in research laboratories.

### Effects of Interventions on Limb Muscle Function in COPD

The effects of interventions designed to improve limb muscle mass and function are summarized in Table 3.

### Exercise Training

Exercise training is the only intervention that can be indisputably recommended for treatment of limb muscle dysfunction in COPD. Rehabilitative exercise training improves limb muscle function and
morphology in patients with COPD (93, 125, 126, 200–203). Endurance exercise training (either of interval or constant-load modality) improves the cross-sectional area (CSA) of all fiber types within the vastus lateralis muscle (24, 33, 204, 205). In addition, endurance training has been reported to modify quadriceps muscle fiber type distribution in favor of type I fibers (204–206). These morphological and typological adaptations in limb muscle fibers are not different across GOLD classes 2 to 4 (33). Exercise training also shifts muscle energy metabolism from glycolytic to oxidative metabolism (41, 43). Phenotypical changes within limb muscles are accompanied by positive adaptations in muscle mass regulating pathways (132, 196, 205, 206). Resistance exercise, alone or in combination with aerobic exercise, also helps to improve muscle mass and strength in COPD (197, 201, 203, 207).

An important question is whether the response to exercise training is normal in COPD. Muscle angiogenic and molecular response to training may be blunted in COPD (208, 209); whether this is entirely explained by an insufficient training intensity is uncertain. Gene expression response after endurance training in patients with COPD differs from that seen in healthy sedentary subjects (210). Qualitatively, genes associated with oxidative stress, ubiquitin proteasome, and cyclooxygenase pathways are distinctly induced in COPD, potentially reflecting specific molecular response of muscle to exercise and suggesting additional mechanisms for exercise limitation (210). The occurrence of oxidative (61) and nitrosative (53) stress at the muscle level has been reported after exercise training; cachectic patients seem to be more prone to this effect (211). However, the functional significance of these observations is unclear (209), and exercise training is a safe and effective intervention to treat limb muscle dysfunction in COPD.

The magnitude of response to pulmonary rehabilitation in COPD is highly variable among patients (212), and there seems also to be a genetic component to this phenomenon (213, 214). Patients developing quadriceps contractile fatigue during training sessions show greater training effects in terms of functional exercise capacity and health-related quality of life than those who do not (215). This argues in favor of training intensity being an important determinant of exercise training outcome (62, 113, 216).

Exercise training early after an exacerbation. Several interventions to prevent or counteract muscle impairment during episodes of exacerbation have been considered (217). Resistance training initiated during the second day of hospitalization may counteract limb muscle dysfunction: quadriceps force increased by 10%, and 6-minute walk distance improved at discharge (9). This was associated with a more favorable anabolic/catabolic balance in muscle (9). Moreover, 1 month after discharge, functional status and muscle force remained better in the group that trained during the exacerbation (9).

Figure 3. Standard operating procedure for isometric quadriceps strength assessment. During the maneuver, vigorous encouragement of the patient is needed. Patient is positioned in a standardized fashion (typically sitting with knees and hips in 90° flexion or, less often, supine [3]). Maximal voluntary contraction force (reported in kilograms or Newtons) can be reliably assessed as the best of three reproducible maneuvers. Maximal voluntary contraction is recorded as the maximal force that can be maintained for 1 full second.
**Neuromuscular stimulation.** Transcutaneous neuromuscular electrical stimulation can be particularly useful for severely disabled patients with COPD (218, 219), as the load on the cardiopulmonary system is low (220). Indeed, it may even be considered for home use (221) and in patients who are unstable (222). Increase in midthigh muscle and type II fiber CSA, decrease in fiber type I CSA, change in fiber type distribution in favor of type I fibers, decreased muscle oxidative stress, along with a more favorable anabolic to catabolic balance have been reported (222–224). Larger trials are needed to clarify the optimal stimulation parameters (frequency, intensity, and duration of stimulation) and in which population this training option should be offered.

**Other Interventions**

Several interventions have been investigated for their ability to improve limb muscle mass and function (Table 3). These interventions have not reached widespread clinical application because of uncertain efficacy and potential of adverse effects.

Nutritional supplementation has been investigated in COPD (225, 226). As body weight gain is associated with improved prognosis in COPD (227), efforts should be made to establish appropriate treatments for the underweight patients. A caveat is that weight gain may predominantly consist of fat mass with little effect on limb muscle mass and function (226, 228). Combination of nutritional intervention with an anabolic stimulus, such as exercise training, is warranted to ensure that nutritional intervention impacts muscle mass and function (229). Patients with COPD are vulnerable to nutritional depletion during an acute disease exacerbation. Adequate nutritional support, especially in patients with already impaired energy balance, is also important (105, 230). Although some improvement in FFM and in muscle strength can be achieved with nutritional intervention, particularly when coupled with an anabolic stimulus (229), nutritional interventions are not widely used because of equivocal benefits (231). Well-designed randomized controlled trials are needed to address this question.

A variety of anabolic drugs and bioactive nutrients have been tested with the hope of improving muscle mass and strength in COPD. None of them can be recommended as routine treatment. Testosterone supplementation and its analogs are able to improve muscle strength (233–236), but this does not necessarily translate into improved functional capacity. Also, the potential of adverse events, including carcinogenesis and virilization, has limited the application of this intervention in clinical practice. Growth hormone and its analogs (237–241), megestrol acetate (242), creatine (243–246), L-carnitine (247), antioxidants (57, 248–250), and vitamin D supplementation (183, 251; alone or in combination with exercise training, have been tested in COPD. The role of these therapies is uncertain, and additional studies are warranted.

**Suggestions for Future Research**

Despite progress made since the first ATS/ERS Statement on limb muscle in COPD, much remains to be learned about this important systemic consequence. In the context of a worldwide epidemic of obesity, the diagnosis of muscle atrophy may become more difficult as clinicians are likely to be misled by normal or increased BMI, believing that this implies normal muscle mass. Although muscle atrophy is less prevalent when BMI is normal or increased, there is still an appreciable portion of patients who expresses muscle atrophy and weakness (1).

There are some recommendations for future research:

1. If the question about presence of disuse versus specific COPD-related myopathy is to be answered, patients with COPD should be matched with control subjects having a similar degree of physical activity, as assessed with activity monitors.
2. Widely accepted normative values for quadriceps muscle strength should be determined.
3. There is a need to know more about the onset of limb muscle dysfunction in COPD. A focus on patients with mild disease would be of interest. Longitudinal studies will be important to understand when the muscle pathological processes start and how they evolve over time.
4. Investigation of molecular mechanisms involved in initiation and development of limb muscle dysfunction is a key issue.

**Table 3: Effects of Treatments for Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mass</th>
<th>Strength</th>
<th>Exercise Tolerance</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>√ (201)</td>
<td>√ (200, 201)</td>
<td>√ (205)</td>
<td>?</td>
</tr>
<tr>
<td>Oxygen</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Nutrition alone</td>
<td>No (269)</td>
<td>No (269)</td>
<td>No (269)</td>
<td>?</td>
</tr>
<tr>
<td>Nutrition with exercise training</td>
<td>√ (228, 229, 270)</td>
<td>√ (229, 270)</td>
<td>√ (228, 229, 270)</td>
<td>?</td>
</tr>
<tr>
<td>Nutrition with exercise training and anabolic hormone supplementation</td>
<td>√ (271)</td>
<td>√ (271)</td>
<td>√ (271)</td>
<td>?</td>
</tr>
<tr>
<td>Testosterone</td>
<td>√ (196)</td>
<td>√ (196)</td>
<td>No (196, 233)</td>
<td>?</td>
</tr>
<tr>
<td>Growth hormones</td>
<td>√ (240)</td>
<td>No (240)</td>
<td>No (240)</td>
<td>?</td>
</tr>
<tr>
<td>Gherlin</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Megestrol</td>
<td>No (242)</td>
<td>?</td>
<td>No (242)</td>
<td>?</td>
</tr>
<tr>
<td>Creatine</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Vitamin D alone</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Vitamin D with exercise training</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

√: Studies support that the treatment has a favorable effect on the outcome; No: studies support that the treatment has no favorable effect on the outcome; ?: there are no supporting data for a treatment effect on the outcome.

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for development of specific and safe therapy for this problem.

5. Clinical trials are warranted to evaluate to which extent treatment of limb muscle function affects clinical outcomes (exercise capacity, quality of life, and survival) in COPD

6. Large and multicenter studies in thoroughly phenotyped patients will be instrumental in understanding specific risk factors for developing limb muscle dysfunction and evaluating treatment for this condition.

7. Whether muscle abnormalities can be completely normalized with exercise training is a question that should be addressed specifically in an adequately powered clinical trial.

8. In the context of increasing prevalence of (abdominal) obesity in COPD, emphasis should be placed on possible biochemical cross-talk between fat and muscle. For example, it may be that limb muscle dysfunction influences prevalence of metabolic syndrome.

This statement was prepared by an ad hoc subcommittee of the ATS Assembly on Pulmonary Rehabilitation and the ERS Scientific Group 01.02 “Rehabilitation and Chronic Care.”

Members of this committee were as follows:

FRANÇOIS MALTAIS, M.D. (Chair)
MARIE DE CRAMER, Ph.D., M.D. (Co-Chair)
ESTHER BARRERO, M.D., PH.D.
YAN BURELLE, Ph.D.
RICHARD CASABURI, P H.D., M.D.
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FRITS FRANSSEN, M.D., PH.D.
MARC DECRAMER, P H.D., M.D. (Chair)
ANNEMIE M. W. J. SCHOLS, P H.D.
GÉRARD SCHAUDIN, P H.D.
GHISLAINE GAYAN-RAMIREZ, P H.D.
JOEL COMTE, M.D.
HARRY R. GOSSER, Ph.D.
PAUL GOSSELINK, Ph.D.
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WIM JANSENS, Ph.D., M.D.
MICHAEL I. POLKEY, Ph.D.
JOSEP ROCA, M.D.
DIDER SAË, P.T., Ph.D.
ANNEMIE M. W. J. SCHOLS, Ph.D.

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CONCLUSIONS

Limb muscle dysfunction is a clinically relevant systemic manifestation of COPD, because it influences important clinical outcomes. This comorbid condition can be treated with exercise training. Future research should allow a better understanding of mechanisms involved in development of skeletal muscle dysfunction, with the hope for development of specific therapies.

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