Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

What We Know and Can Do for Our Patients

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Abstract

Skeletal muscle dysfunction occurs in patients with chronic obstructive pulmonary disease (COPD) and affects both ventilatory and nonventilatory muscle groups. It represents a very important comorbidity that is associated with poor quality of life and reduced survival. It results from a complex combination of functional, metabolic, and anatomical alterations leading to suboptimal muscle work. Muscle atrophy, altered fiber type and metabolism, and chest wall remodeling, in the case of the respiratory muscles, are relevant etiological contributors to this process. Muscle dysfunction worsens during COPD exacerbations, rendering patients progressively less able to perform activities of daily living, and it is also associated with poor outcomes. Muscle recovery measures consisting of a combination of pulmonary rehabilitation, optimized nutrition, and other strategies are associated with better prognosis when administered in stable patients as well as after exacerbations. A deeper understanding of this process' pathophysiology and clinical relevance will facilitate the use of measures to alleviate its effects and potentially improve patients' outcomes. In this review, a general overview of skeletal muscle dysfunction in COPD is offered to highlight its relevance and magnitude to expert practitioners and scientists as well as to the average clinician dealing with patients with chronic respiratory diseases.

Keywords: chronic obstructive pulmonary disease; skeletal muscle dysfunction; muscle wasting; ventilatory muscles; fiber switch

Skeletal muscle dysfunction is a major problem in many patients with chronic obstructive pulmonary disease (COPD). It affects both ventilatory and nonventilatory muscle groups, leading to worse outcomes, including increased mortality and hospitalization rates (1–3). Although not universally present in patients with COPD, muscle wasting is more prevalent in individuals with emphysema than in those with airway-type COPD (4), which is reminiscent of the historical description of the pink puffer emphysematous type mostly associated with body and muscle mass loss (5). Muscle dysfunction is also more significant in lower than in upper extremities (6, 7), which compromises the patients' ambulatory capacity and has devastating effects on their daily lives. Muscle integrity mirrors general well-being and nutritional status and thus indirectly associates with elements that are relevant to COPD outcomes such as susceptibility to infections, bone mineral density, or exacerbation rate.

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Despite its representing an important comorbidity, many healthcare providers have a poor understanding of skeletal muscle dysfunction, in part owing to overlapping and confusing definitions to describe the process and also the wrong perception that there are no useful interventions to alleviate it. In this short review, we describe these fundamental aspects to facilitate clinicians' better understanding of the topic and improve their day-to-day clinical practice. We first discuss the common features of ventilatory and nonventilatory muscles and later elaborate on the specific aspects pertinent to each group. We also introduce readers to the major controversies in the field; however, owing to space constraints, we defer the description of their more technical elements to good clinical guidelines and statements published over the last two decades (8–11). In the next section, we delve into the topic's complexities and clarify definitions to facilitate the reading later in the text.

Characteristics of COPD-associated Muscle Dysfunction

In general, the magnitude of muscle dysfunction correlates to the severity of lung disease (12); yet, there is variable expression of this process, with some patients with advanced COPD having relatively preserved muscle integrity and vice versa (12). With the same degree of airway obstruction, patients with the emphysematous phenotype have relatively more muscle wasting than patients with chronic bronchitis (4). We start by introducing important definitions used to characterize the process. Some of them are often applied interchangeably, but their precise use facilitates the understanding of the current literature and the process of muscle dysfunction. In general, there are three domains used to characterize muscle integrity: *1*) clinical/functional, which is used to appreciate muscle work, generally in the form of endurance and strength; *2*) metabolic, which refers to the ability of the muscle fibers to transform chemical energy into mechanical work generated by the myosin molecular motor (13) and is closely related to oxygen use, ATP generation, and intracellular calcium handling; and *3*) anatomical, which refers to the total amount of muscle mass available to generate work.

Although often overlapping (14), these domains can be disrupted in a relatively independent way. For instance, muscle mass may decrease without having a significant impact on force generation capacity, owing to relatively better-preserved metabolic efficiency, whereas metabolic and electrophysiological factors may come into play before muscle wasting develops (15). Thus, combinations of clinical/functional, metabolic, and anatomical disturbances may lead to unique signatures of muscle dysfunction.

Clinical/Functional Muscle Disruption

Muscle work is the result of movement generated through the application of force. Thus, lower muscle work is caused by less force generation capacity, which is due to lower strength, lower endurance, or both. Muscle strength is the ability to generate maximal force at a single time point such as weight lifting, and, compared with muscle endurance, it is relatively more dependent on muscle mass and cross-sectional area (8). In contrast, muscle endurance is the ability to generate submaximal force sustained over time, which, compared with muscle strength, is relatively more dependent on the fiber-type composition of the affected muscles and their oxidative capacity (16, 17). Identification of muscle dysfunction using strength and endurance is very useful for determining actual muscle work in the clinical setting. However, endurance is relatively more complicated to measure than strength, given that it is potentially confounded by the cardiopulmonary limitation on endurance exercises such as climbing stairs. A device known as a "dynamometer" can be used to measure isolated muscle strength and endurance, although detailed description of these determinations is beyond the scope of the present review and can be found elsewhere (9, 18, 19).

Metabolic Muscle Disruption

The muscle metabolic profile is partly influenced by the type of myosin heavy chain (MyHC) expressed by the fibers, which depend primarily on their motoneuronal innervation (20). Type I fibers express MyHC type I, are slow-twitch fibers, are innervated by slow motoneurons, have a predominantly oxidative metabolism, and are more fatigue resistant than type II fibers. Type II fibers express MyHC type II, are fast-twitch fibers, are innervated by fast motoneurons, depend more on anaerobic metabolism, and are more fatigable (20). Importantly, the fiber type is closely associated with its calcium sensitivity: Type I fibers are relatively more calcium sensitive than type II fibers and generate a greater fraction of their maximal force for a given amount of mobilized intracellular calcium (21, 22)

There are subtypes of type II fibers—IIa, IIx, and IIb (20)—that are in general less oxidative, calcium sensitive, and fatigue resistant than type I fibers. As discussed later in the text, fiber-type composition may change in COPD in a process known as "fiber switch" or "transformation," rendering the diaphragm metabolically more efficient and the lower extremity muscles less efficient (23). The process of fiber switch is contributed by two distinct phenomena: *1*) Some fibers undergo selective atrophy, which causes an increase in the relative abundance of the unaffected type (20, 23); and *2*) even in the absence of fiber atrophy, the expression of a given MyHC isoform's gene can be downregulated and a different one upregulated in the same fiber, resulting in a change of its metabolic profile (20). The process of fiber transformation is demonstrated by the presence of hybrid fibers expressing, in a single fiber, different MyHC isoforms that represent the transition occurring during different pathological states (24, 25). Other relevant factors that impact myofibers' metabolism are oxygen transport and use driven by cardiac output, capillary and mitochondrial densities, and the expression of oxidative enzymes (20, 26).

Anatomical Muscle Disruption

"Muscle anatomy" refers mostly to muscle size and total protein content, which can be decreased because of phenotypic variability, female sex, and other nonpathological factors (12, 27). Muscle anatomy can also be pathologically altered in atrophy, cachexia, and sarcopenia, all of which are possible in COPD. "Muscle atrophy," or "wasting," is a general term defining a reduction in the size of the muscle fibers that is usually a sign of net protein catabolism (8). Cachexia is a specific metabolic syndrome associated with an ongoing underlying disease, such as COPD, that is characterized by muscle wasting and weight loss (28). Sarcopenia is also a specific form

of muscle loss that occurs with advanced age and is not associated with weight loss (29).

Atrophy, cachexia, and sarcopenia are intertwined categories in patients with COPD, given that many of them are at an advanced age and can have heart failure, diabetes, cancer, and/or other conditions associated with different causes of muscle dysfunction (30). Few studies have addressed the trajectory of muscle loss in COPD (31, 32), and it is uncertain whether patients evaluated were actively losing muscle during the studies and thus were cachectic or instead had lower muscle mass without active catabolism and thus were simply atrophic (8).

Mechanisms of Skeletal Muscle Dysfunction in Patients with COPD

The mechanisms of skeletal muscle dysfunction constitute an expanding area of research, and we introduce the readers to it in the following paragraphs. A more detailed description of these biological processes can be found elsewhere (33–36). There is consensus that no single cellular process leading to muscle wasting exists and that different phenomena converge in the COPD phenotype (37). Different muscle groups, such as the diaphragm, the lower extremities, the abdominal muscles, and the upper extremities, present variable and sometimes divergent characteristics (38), which suggests the nonsystemic nature of the process. However, the fact that muscle groups in different regions are exposed to variable loads makes possible the selective atrophy of some groups and not others despite common mechanisms. Controversy surrounds the role of inflammatory signals as potential drivers of COPD-associated muscle wasting (39), with some groups reporting its relevance (40) and others showing no role (41) or even some protective effect demonstrated by a negative correlation between local inflammation and muscle weakness (42). An issue that remains unclear is whether locomotor muscle dysfunction in COPD is driven by chronic immobility or if there is a distinct COPD myopathy (8). In support of the immobility hypothesis is the fact that many hallmarks of COPD muscle dysfunction resemble the ones associated with immobility, including atrophy, loss of type I fibers, lower oxidative enzyme activity, and others (43), as well as the fact that exercise can potentially restore a normal muscle phenotype to some extent (44). Behind the myopathy theory is evidence that some aspects of muscle dysfunction are poorly correlated with the level of physical activity of patients with COPD (45) and that even when matched by physical activity, COPD and healthy subjects display differences in muscle integrity (46).

Some basic mechanisms leading to muscle dysfunction are well established, whereas others are emerging as potential targets to interfere with this process. We define intrinsic mechanisms as the ones taking place primarily in the neuromuscular unit and leading to clinical/functional, metabolic, or anatomical disruption; extrinsic mechanisms as the ones originating in other structures, such as the chest wall; and mixed mechanisms as the ones combining the preceding categories.

Intrinsic Mechanisms

Net protein loss via catabolic activation. Different signals, including hypoxia, hypercapnia, smoking, malnutrition, and immobilization, eventually lead to accelerated intracellular protein degradation (47–49), which is the hallmark of muscle atrophy and occurs via two major mechanisms: the ubiquitin–proteasome (50) and lysosomal (51) pathways, which coexist in COPD and operate in a coordinated manner. Proteasomal degradation requires the regulated ubiquitin "tagging" of specifically targeted proteins, such as myosin (52), that are subsequently degraded by the 26S proteasome (52). This specificity is conferred by muscle-specific E3-ubiquitin ligases, such as MuRF1 (muscle-specific Ring finger 1 protein), atrogin 1, and NEDD4, which are upregulated in muscle biopsies from patients with COPD (50, 53, 54). Experimental interference with this mechanism prevents muscle loss in the context of chronic hypercapnia (48). Importantly, because the proteasome can degrade only proteins in monomeric form, the muscle sarcomere needs first to be destabilized and disassembled, which is accomplished by calcium-dependent proteases named *calpains* (55). Moreover, the autophagy–lysosomal pathway is induced in locomotor muscles of stable patients with COPD, and the degree of autophagy correlates with the severity of muscle atrophy and lung function impairment (51, 56).

Net protein loss via anabolic suppression. Two major signaling pathways control skeletal muscle growth: *1*) the insulin-like growth factor pathway, which induces muscle growth and is boosted during pulmonary rehabilitation (PR) (57, 58); and *2*) the myostatin–Smad3 pathway, which acts as a negative regulator of muscle growth (37, 54), and although it has been reported to be downregulated in noncachectic patients during PR (57), another group found no effect of exercise training on it (59). There is evidence of relative anabolic suppression of locomotor muscles compared with the diaphragm in patients with COPD (60), which is consistent with the adaptation of ventilatory muscles as described below. Also, there is evidence of subnormal testosterone levels in some patients with COPD, which could contribute to depressed anabolism and thus to wasting (61).

Calcium desensitization. As mentioned above, the fast-twitch fibers have a lower calcium sensitivity relative to the slow-twitch ones. Thus, slow-to-fast fiber transformation taking place in lower extremity muscles associates with lower calcium signaling efficiency (21, 22). Altered sarcoplasmic calcium reuptake compromising relaxation efficiency (62) and differential calcium sensitivity of contractile proteins (20) could also contribute to worse performance, although this has not been demonstrated specifically in patients with COPD.

Muscle injury, structural damage, and inadequate repair. Cycles of muscle injury and repair have been suggested in the context of COPD (63) and during eccentric/lengthening exercise (64) commonly used in rehabilitation protocols. Indeed, potential dysfunction of muscle stem cells (satellite cells), which are typically engaged after muscle injury, has been suggested as a contributor to suboptimal muscle repair (65–67).

Others. Alternative splicing of the gene codifying for the giant protein titin (68), oxidative stress (56, 69), and mitochondrial dysfunction (70) are reported to contribute to worse ventilatory and nonventilatory muscle work in COPD.

Extrinsic Mechanisms

Chest wall remodeling. In patients with COPD, the diaphragm chronically adapts to

the increased inspiratory load and reduced elastic recoil force of the lungs, leading to a relative preservation from anatomical and metabolic disruptions of the muscle. In fact, at very high lung volumes, the diaphragm from patients with COPD can generate more force than control subjects' (71). Despite that, from the clinical/functional standpoint, ventilatory dysfunction is very significant in COPD and is caused mainly by changes in the chest wall geometry. Hyperinflation leads to decreased length and area of apposition of the diaphragm with the rib cage (72, 73), and also to a chest wall bone configuration (74), which leads to less efficient ventilatory work. Studies of patients before and after lung volume reduction surgery showed increased postoperative diaphragm length and strength, as well as improved exercise capacity and maximum voluntary ventilation (75). These changes are also associated with chest wall remodeling resulting from bony thorax configuration (74). In contrast to the ventilatory muscles, extrinsic factors leading to peripheral muscle dysfunction have not been described in COPD.

Mixed Mechanisms

Interdependence of locomotor and ventilatory muscles during exercise. The interaction between locomotor and ventilatory muscle dysfunction in patients with COPD is relevant to the pathophysiology of the process (Figure 1). Indeed, the increased lactic acid production during exercise is a main factor associated with lower exercise tolerance (76). Because of slow- to fast-twitch fiber-type transformation in peripheral muscles, patients with COPD during acute exercise performance produce more lactic acid and CO_2 for a given exercise load, which requires increased compensatory work of breathing and could potentially exhaust ventilatory muscle capacity in a patient with very limited physiological reserve (77, 78). A summary of the general mechanisms contributing to muscle dysfunction is presented in Table 1.

Muscle Dysfunction and COPD Prognosis

Muscle dysfunction is associated with worse COPD prognosis, and two important elements suggest that it could indeed contribute to COPD outcomes. First, the association of survival of patients with COPD with their muscle integrity persists even after correcting for surrogates of pulmonary function (1–3). In other words, patients with similar lung function will be more or less likely to die in the long term based on the presence or absence of muscle dysfunction, respectively (1–3). Second, PR, which has a beneficial effect on muscle dysfunction, is associated with better outcomes without affecting the history of

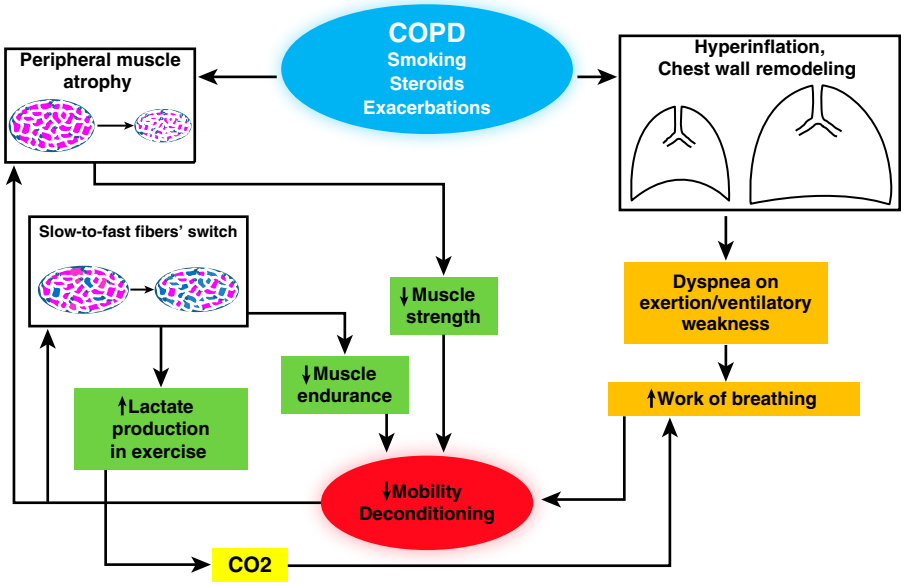

Figure 1. Pathophysiology of chronic obstructive pulmonary disease (COPD)-associated muscle dysfunction. Cigarette smoking and other factors, as well as exacerbations, are the main causes of COPD progression, which is associated with peripheral muscle atrophy and fiber switch. Hyperinflation and loss of elastic recoil lead to chest wall geometrical changes that cause diaphragmatic dysfunction. All these events contribute to immobilization and deconditioning, which further cause peripheral muscle dysfunction and deconditioning.

Table 1. General Mechanisms Contributing to Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

Signals and stimuli that initiate the muscle loss and wasting processes
1. Immobilization
2. Malnutrition
3. Smoking
4. Infections/exacerbations
5. Hypoxemia
6. Hypercapnia
7. Corticosteroids
Intrinsic cellular processes that mediate muscle dysfunction
1. Ubiquitin–proteasome pathway
2. Lysosomal–autophagy pathways
3. Anabolic suppression
4. Calcium desensitization
5. Muscle injury
6. Oxidative stress and mitochondrial dysfunction
Extrinsic processes that lead to muscle dysfunction
1. Hyperinflation-associated diaphragmatic dysfunction (diaphragm)
2. Bony thoracic remodeling (diaphragm)
3. Lactate hyperproduction and lower exercise tolerance

Different signals, including immobilization, malnutrition, and smoking, activate cellular processes leading to net protein loss in skeletal muscle and also alter the chest wall geometry, compromising ventilatory muscle function.

the pulmonary disease (79, 80). It is important to emphasize that although skeletal muscle wasting is associated with lower COPD survival, PR's beneficial effects on skeletal muscle have not been associated with overall lower mortality (81). The reason for that disconnect is unclear but could be due to heterogeneous responses to PR among different patient groups (8) or to other factors. In the following subsections, we summarize clinical evidence supporting the relevance of muscle dysfunction and recovery to the prognosis of COPD, and we clarify the significance of weight changes in relation to muscle mass and patients' outcomes.

Effects of Clinical/Functional Disruption and Recovery on COPD Outcomes

Peripheral muscle weakness. Peripheral muscle weakness, defined as poor muscle strength (3), is associated with increased mortality (3). Similarly, underperformance in 6-minute walk distance (6MWD) (82) and on the handgrip strength test (83) also predicts mortality. Recovery of muscle force in the context of PR is associated with improved symptoms, limb muscle function, exercise capacity, quality of life, and other outcomes (84–86).

Ventilatory muscle weakness. Ventilatory muscle weakness has consistently been demonstrated in patients with COPD, leading to reduced maximum inspiratory pressure and transdiaphragmatic pressure (9, 87, 88). During an exacerbation, ventilatory muscle dysfunction is a predictor of generalized muscle weakness (89) and of mechanical ventilation requirements (90). Indeed, ventilatory support with noninvasive ventilation can prevent intubation and reduces length of hospital stay and mortality (91, 92).

Effects of Metabolic Disruption and Recovery on COPD Outcomes

Peripheral muscle metabolic disruption. In quadriceps muscles of patients with COPD, the relative number of type I fibers decreases compared with type II fibers (93), a phenomenon known as "slow- to fast-twitch fiber transformation," which is associated with worse lung function (94, 95), exercise capacity (96), and functional performance (17, 97) as well as mortality (98). Indeed, PR associates with higher expression of the relatively more oxidative types I and IIa fibers (94, 99).

Metabolic disruption in ventilatory muscles. In contrast to peripheral muscles, diaphragm muscles of patients with COPD undergo fast- to slow-twitch fiber transformation (33, 100), which is associated with increased oxygen consumption (101, 102) and resistance to fatigue (88); yet, the force generation capacity of individual fibers seems to be subnormal (100, 103). Indeed, inspiratory muscle training in the context of PR is associated with a higher proportion of type I fibers and the size of type II fibers in accessory ventilatory muscles (104).

Effects of Anatomical Disruption and Recovery on COPD Outcomes

Peripheral muscle wasting. Peripheral muscle wasting has been associated with worse prognosis. Indeed, computed tomography–measured midthigh muscle cross-sectional areas in stable patients with COPD correlated with mortality and was a better predictor than body mass index (BMI) (1). Also, smaller pectoralis muscle area was associated with higher disease severity as measured by Global Initiative for Chronic Obstructive Lung Disease stage and lower resting oxygen saturation, BODE score (based on BMI, airflow obstruction, dyspnea, and exercise), quality of life score, and exercise capacity (12). A recent report indicated that lesser erector spinae muscle mass is associated with worse dyspnea score, higher BMI, worse emphysema, lower FEV_1, and higher mortality (105). During COPD exacerbations, there is an accelerated loss of locomotor muscle mass (106, 107) that is often associated with immobilization (108) and fails to recover to the preexacerbation baseline, similar to what is observed with pulmonary function (109) and the degree of emphysema (110). Indeed, lesser quadriceps mass at the time of exacerbation predicts higher chances of need for readmission and death (111), and in-hospital rehabilitation starting on the second day of admission attenuates the muscle mass decline observed during exacerbations (112).

Ventilatory muscle wasting. Ventilatory muscle wasting is relatively less relevant than wasting of peripheral muscles. Both autopsy- (113) and ultrasound-based studies (114) indicate that diaphragmatic mass of patients with COPD remained similar to that of healthy control subjects, which may be due to the reported greater firing rate of diaphragm motor unit potentials (70) leading to a hypertrophic signal (33, 100) that compensates the ongoing atrophy (114). In contrast, low intercostal muscle mass predicts future COPD exacerbations (115).

Effects of Body Weight on COPD Prognosis

Lower BMI is a predictor of higher mortality in COPD (116). That effect is independent of lung function and is partially determined by skeletal muscle mass (117). Although there is agreement that underweight patients with COPD have worse outcomes (116, 118), the effect of obesity-driven higher BMI is a subject of controversy (119). An analysis of outcomes in patients who were followed for 8 years after hospital admission for an acute exacerbation showed that overweight was a predictor of survival (120); however, a recent analysis of 3,600 patients from the COPDGene study indicated that obesity was associated with worse outcomes, including quality of life, dyspnea, 6MWD, and severe exacerbations (121). These associations were even stronger when obesity was analyzed as a dose-dependent response (121). Moreover, muscle lipid content correlated with decreased oxidative enzyme activity (122), exercise capacity (96), and lower survival (98), and fat content of intercostal muscles was associated with COPD exacerbation rates (115). Thus, although weight loss is associated most of the time with muscle wasting, weight gain is not necessarily indicative of adequate muscle performance and or mass.

Treatment of Skeletal Muscle Dysfunction in Patients with COPD

In general, the cornerstones of treatment of COPD-associated muscle dysfunction are rehabilitation-based exercises, optimized nutrition, and electrical stimulation. We summarize the evidence and controversies surrounding these measures in the following subsections.

Pulmonary Rehabilitation

Exercise training, which is a formal component of PR, is the most significant currently available intervention for treating

muscle dysfunction in COPD (84). Training of the ambulatory muscles is a mandatory component of PR (123). The reported magnitude of muscle recovery after PR has been variable, ranging from modest or nonrecovery (124) to very robust improvement (44), and that variability can be due to different tolerance to exercise (8), genetic and epigenetic factors, regenerative potential, and oxidative metabolism (125). Also, some evidence indicates that localized training focused on specific muscle groups could be more beneficial than exercise targeting multiple groups (126).

Exercise protocols in PR. The ideal rehabilitation program should *1*) tailor the training protocol to the specific patient's requirements to accommodate comorbid conditions and avoid exercise-induced muscle injury, particularly in regard to eccentric/lengthening exercises (64); *2*) exceed the loads typically encountered by the patient during his or her daily life; and *3*) progress and become more challenging as improvement occurs (81). There are basically two types of exercises: resistance/strength and endurance exercise. Endurance exercise in the form of cycling or walking is a common modality of PR (81). Typically, endurance and strength training of the lower and upper extremities is combined with ventilatory muscle training. In the latter case, inspiratory (80, 127), and less commonly expiratory (128), muscle training led to improvements in dyspnea and other quality-of-life parameters. Details on the technical aspects of PR can be found in excellent resources (81), and a summary of its exercise training principles is presented in Table 2.

Table 2. Basic Aspects of Exercise in Pulmonary Hypertension

General principles

1. Exercise must be tailored to specific patient's needs
2. Exercise must exceed the regular loads patient is used to overcoming
3. Exercise must progress as patient improves performance

Specific strategies

1. Endurance training
   Goal: To improve general aerobic capacity and not any specific muscle group
   Mode: Cycling and walking are commonly used.
2. Interval training (99)
   Goal: To provide training for patients unable to tolerate regular endurance exercises (previous point)
   Mode: High intensity interspersed with lower intensity or rest
3. Resistance/strength training
   Goal: To target specific local muscle groups and improve their function
   Mode: Repetitive lifting of heavy weights
4. Upper limb training
   Goal: To improve activities of daily living (e.g., dressing, bathing)
   Mode: Endurance (cycle ergometer) and/or resistance (weights) exercises
5. Inspiratory muscle training
   Goal: To improve exercise capacity and dyspnea
   Mode: Use of loads ⩾30% of maximal inspiratory pressure

Timing of PR. Traditionally, PR is offered to patients with severe COPD, but there is evidence that muscle dysfunction (129) and its PR-associated recovery (94) also occur in early stages. PR should be provided during or shortly after an exacerbation because it accelerates functional recovery and decreases the chances of readmission (81). Also, in stable patients, it improves health-related quality of life, readmission rate, and other outcomes (123).

PR implementation problems and maintenance strategies. PR should be provided to patients who are maximally treated with appropriate medications, including bronchodilators and supplemental oxygen, but limited recognition of its benefits and the lack of available programs for its delivery preclude massive implementation (84). During clinical encounters, healthcare providers should engage patients and families to facilitate recognition and adherence to PR by reviewing its benefits (Table 3). Another area of interest is the duration of PR, which is typically recommended for a minimum of 8 weeks (130). Although experts recommend that patients should continue to exercise beyond the PR program period, there is controversy regarding the ideal maintenance plan. Some studies have shown no benefits of maintenance technique beyond 1 year (131), whereas others have demonstrated that longer protocols extend the benefits of PR (132). A recent trial involving stable patients with COPD revealed that more prolonged and intensive PR was associated with better BODE index and 6MWD than a standard strategy. These effects were significant at 2 years, but they vanished after that (133).

Table 3. Benefits of Pulmonary Rehabilitation

- Reduced hospitalization
- Reduced unscheduled healthcare visits
- Improved exercise capacity
- Reduced symptoms of dyspnea and leg discomfort
- Improved limb muscle strength and endurance
- Improved health-related quality of life
- Improved functional capacity (e.g., activities of daily living)
- Improved emotional function
- Enhanced self-efficacy and knowledge
- Enhanced collaborative self-management
- Potential for increased daily physical activity levels

Practitioners should dedicate time to discussing the general benefits of exercise and nutrition, and specifically pulmonary rehabilitation, with patients with chronic obstructive pulmonary disease and their families. Adapted from Reference 84.

Nutritional Support

The central relevance of adequate nutrition in COPD has been recognized for all

patients, not only for those with weight loss and muscle wasting (134). Indeed, obesity has been identified as a potential risk factor for COPD (135), and age-related sarcopenia seems to be associated with the development of metabolic syndrome in these patients (136). Patients with COPD demonstrate some muscle ultrastructural and molecular changes typically found in starvation, such as upregulation of the lysosomal–autophagy pathway and oxidative stress (51). Importantly, severe malnutrition associated with cachexia still portends significant potential for recovery, although some aspects of it are different from those exhibited by patients without cachexia undergoing the same treatment (57). Some of the PR benefits consist of transforming the nutritional substrates provided by an optimized diet into larger muscle mass as well as regaining oxidative capacity and exercise tolerance in the form of both strength and endurance (Figure 2).

Evidence centered on nutrition in COPD is controverted: Whereas some reports indicate the benefits of nutritional optimization as a strategy to improve PR outcome (137–139), others show no clear benefits (140, 141) or identify specific subgroups with better potential (142). There is agreement that nutritional support with no exercise has a very limited effect. Authors of a meta-analysis of 17 studies involving more than 600 patients found that nutritional supplementation alone led to a marginal weight gain in patients with COPD and normal nutritional status, whereas a benefit of about 2 kg was seen in those patients who were initially malnourished (143). There is evidence that low dietary fiber intake is associated with higher risk of COPD (144), and some reports indicate that the composition of the ideal diet for a malnourished patient with COPD should include branched-chain amino acids (145) and polyunsaturated fatty acids (146); and a potential benefit of whey supplementation on exercise tolerance and quality of life has been suggested (147). Researchers in a recent trial found that optimizing nutrition with leucine, vitamin D, and omega-3 fatty acids significantly improved the effects of high-intensity exercise on lower limb muscle strength and exercise performance in COPD (148).

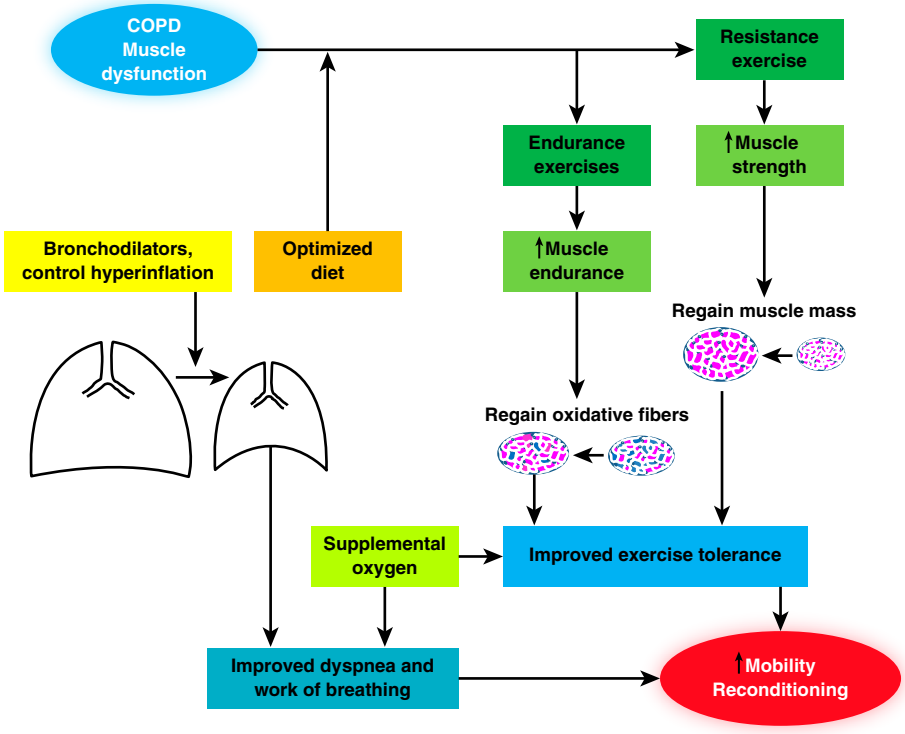

Figure 2. Holistic approach to prevent and reverse chronic obstructive pulmonary disease (COPD)-associated muscle dysfunction. Combination of optimized diet with resistance and endurance exercise training programs is associated with improved muscle mass and oxidative capacity in locomotor muscles, which in turn decrease fatigue upon exercise. Bronchodilators, cigarette smoking cessation, and occasionally lung volume reduction surgery decrease hyperinflation and lead to better dyspnea control. All these measures contribute to reconditioning and eventually to regaining functional capacity in these patients.

Neuromuscular Electrical Stimulation

Patients with severe exercise limitation are sometimes unable to undergo PR and can be good candidates for an alternative mode of muscle stimulation via transcutaneous electrical probes (81). Dyspnea, functional capacity, and muscle strength improved using this approach in stable patients (149–152) and during exacerbations (153). In a recent double-blind, placebo-controlled trial, neuromuscular electrical stimulation improved functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. The effects are maximal at 6 weeks and wane over time (154). An alternative approach that is less frequently used but could be better tolerated is quadriceps magnetic stimulation. This approach was shown to improve strength, exercise capacity, and metabolic profile as reflected by an increase in type I fiber size (155, 156).

Anabolic Steroids

Based on observations that low testosterone is present in many male patients with COPD (61), a trial involving its administration to men with severe COPD with low basal levels led to improved lean body mass and strength, which was amplified by concomitant resistant training (157). Oxandrolone increased lean body mass in an open-label, prospective, multicenter trial of a stable outpatient COPD population with cachexia; however, the trial had the limitation of lacking a control group (158). Researchers in another trial evaluated the potential benefit of nandrolone during respiratory rehabilitation and found no significant differences in outcomes between groups as measured by muscle function, exercise capacity, and health status (139). The main concern regarding anabolic steroids is related to their side effects in the long term, which created interest in the recently developed nonsteroidal selective androgen

receptor modulators. These drugs have preliminarily been shown to lead to improvement in lean body mass and physical function in different forms of cachexia, although they have not been tried in COPD so far (159). The appetite stimulant megestrol acetate led to an improvement in body weight that was not reflected in improved respiratory muscle function or exercise tolerance (160).

Other Potential Therapeutic Strategies

There is also some evidence supporting the possible benefit of *N*-acetylcysteine (161) and the calcium sensitizer levosimendan (162) on diaphragmatic function. Also, there is interest in the muscle anabolic effects of growth hormone secretagogues such as ghrelin, as well as in myostatin inhibitors, although the data supporting them is very preliminary or not confirmed, and thus they are beyond the scope of the present review (19, 163).

Conclusions

Skeletal muscle dysfunction is a relevant comorbidity in COPD that is associated with worse outcomes, including greater hospitalizations rates, worse quality of life, and lower survival. It is often considered a minor aspect of this disease; yet, abundant evidence supports its significance and the role of PR and other measures in dealing with the problem. Although it still represents an expanding territory in COPD research, enough information is already available to help healthcare providers improve their day-to-day clinical practice to alleviate their patients' symptoms and make them less vulnerable to worse outcomes. Muscle dysfunction in COPD should be regarded as a systemic phenomenon that demands a holistic approach aimed at exercise tolerance and nutritional status, which should be routinely implemented to attempt to reverse the pathophysiology of the process (Figure 2). Early detection of muscle dysfunction and wasting, as well as engagement of patients and their families in strategies to deal with the problem, could prevent disease progression and improve prognosis, regardless of the degree of pulmonary disease. The present review represents a useful tool for the average clinician to improve management of patients with major chronic respiratory conditions. ■

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