AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

SKELETAL MUSCLE DYSFUNCTION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): WHAT WE KNOW AND CAN DO FOR OUR PATIENTS

*Ariel Jaitovich[1,2] and *Esther Barreiro[3,4]

[1]Division of Pulmonary and Critical Care Medicine, and [2]Department of Molecular and Cellular Physiology, Albany Medical College, Albany, New York; [3]Pulmonology Department-Muscle Wasting and Cachexia in Chronic Respiratory Diseases and Lung Cancer Research Group, IMIM-*Hospital del Mar, Parc de Salut Mar*, Health and Experimental Sciences Department (CEXS), *Universitat Pompeu Fabra* (UPF), Barcelona Biomedical Research Park (PRBB), Barcelona, Spain. [4]*Centro de Investigación en Red de Enfermedades Respiratorias* (CIBERES), *Instituto de Salud Carlos III* (ISCIII), Madrid, Spain.

* The authors have equally contributed to the work.

Correspondence and request for reprints should be addressed to Ariel Jaitovich MD, Albany Medical College, 47 New Scotland Av, Albany, NY. E-mail: jaitova@amc.edu; or Esther Barreiro MD, PhD, Pulmonology Department, IMIM-Hospital del Mar, PRBB, Dr. Aiguader, 88, E-08003 Barcelona, Spain. E-mail ebarreiro@imim.es

Authors' contributions: AJ, EB wrote and edited the paper.

Sources of funding: Part of the results reported herein have been funded by NHLBI of the National Institutes of Health under the award number K01-HL130704-01, and by the Collins Family Foundation Endowment (AJ); *Instituto de Salud Carlos-III*, contract grant numbers: CIBERES and FIS 14/00713 (FEDER), Spanish Ministry of Economy and Competitiveness, *Spanish Respiratory Society (*SEPAR*)* 2016, and Catalan Foundation of Pulmonology (FUCAP) 2016, (EB).

Word count: 4640

Running head: Muscles in COPD

Key Words: COPD, skeletal muscle dysfunction, muscle wasting, ventilatory muscles, fibers' switch

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

ABSTRACT

Skeletal muscle dysfunction occurs in COPD patients and affects both ventilatory and non-ventilatory muscle groups. It represents a very important comorbidity that associates with poor quality of life and reduced survival, and 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 etiologic contributors to this process. Muscle dysfunction worsens during COPD exacerbations, rendering patients progressively less able to perform daily-life activities and it is also associated with poor outcomes. Muscle recovery measures consisting of a combination of pulmonary rehabilitation, optimized nutrition and other strategies associate with better prognosis when administered in stable patients as well as following 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 the current review, a general overview of skeletal muscle dysfunction in COPD is offered in order to highlight its relevance and magnitude to the expert practitioners and scientists as well as to the average clinician dealing with patients with chronic respiratory diseases.

INTRODUCTION

Skeletal muscle dysfunction is a major problem in many patients with chronic obstructive pulmonary disease (COPD) that affects both ventilatory and non-ventilatory muscle groups leading to worse outcomes including increased mortality and hospitalization rates[1-3]. Although not universally present in all COPD patients, muscle wasting is more prevalent in individuals with emphysema than in airways-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 with devastating effects on their daily life. Muscle integrity mirrors general wellbeing and nutritional status, and thus indirectly associates with elements that are relevant to COPD outcomes such as susceptibility to infections, bone mineral density or exacerbations rates.

Despite representing an important comorbidity, many health-care providers have a poor understanding of this problem, in part due 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 intend to go over these fundamental aspects to facilitate the clinician's better understanding of the topic and improve the day-to-day clinical practice. We discuss the common features of ventilatory and non-ventilatory muscles, and later in the text elaborate on the specific aspects pertinent to each group. While we also introduce the readers to the major controversies in the field, due to space constrains we defer the description of its more technical elements to good clinical guidelines and statements published over the last years[8-11]. In the next section

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

we will delve into the topic's complexities and clarify definitions in order 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 a variable expression of this process making some patients with advanced COPD have a relatively preserved muscle integrity and vice versa[12]. For the same level of airways obstruction, emphysematous phenotype patients 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, yet their precise use will facilitate 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 ($_{i}Ca_{2}^{+}$) handling; **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 due to relatively better-preserved metabolic efficiency, while metabolic and electrophysiological factors may occur 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 in one single time point such as weight lifting and, in comparison 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, in comparison with muscle strength, it 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 to determine 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 dynamometer can be used to measure isolated muscle strength and endurance, although the detailed description of these determinations is beyond the scope of the present review and can be found elsewhere[9,18,19].

Metabolic muscle disruption: Muscle metabolic profile is partly influenced by the type of myosin heavy chain (MyHC) expressed by the fibers, which primarily depend on the motoneuronal innervation[20]. **Type I fibers** express MyHC type I, ***are slow-twitch***, are innervated by slow motoneurons, have a predominantly oxidative metabolism, and are more fatigue-resistant. **Type II fibers** express MyHC type II, ***are fast-twitch,*** are innervated by fast motoneurons, depend more on anaerobic metabolism and are more fatiguable[20]. Importantly, the fiber type is closely associated with its calcium sensitivity:

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

type I fibers are relatively more calcium sensitive and generate a greater fraction of their maximal force for a given amount of mobilized intracellular calcium ($_{i}Ca_{2}^{+}$)[21,22]

There are subtypes of type II fibers known as IIa, IIx and IIb[20], which are in general less oxidative, calcium sensitive and fatigue resistant than type I fibers. As discussed later in the text, fiber types' composition may change in COPD in a process known as **fibers' switch or transformation**, rendering the diaphragm metabolically more efficient and the lower extremities muscles less efficient[23]. The process of fiber switch is contributed by two distinct phenomena: 1) some fibers undergo selective atrophy, which causes an in increase in the relative abundance of the unaffected type[20,23]; 2) even in the absence of fibers atrophy, the expression of a given MyHC isoform's gene can be downregulated and a different 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 on the myofibers' metabolism are oxygen transport and utilization driven by cardiac output, capillary and mitochondrial densities, and the expression of oxidative enzymes[20,26].

Anatomical muscle disruption: Muscle anatomy refers mostly to its size and total protein content, which can be decreased because of phenotypic variability, female gender and other non-pathological factors[12,27]. Muscle anatomy can also be pathologically altered in atrophy, cachexia, or sarcopenia states, all 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, which is not associated with weight loss[29].

Atrophy, sarcopenia and cachexia are intertwined categories in COPD patients given that many of them have advanced age, heart failure, diabetes, cancer and other conditions associated with different causes of muscle dysfunction[30]. There are few studies addressing the trajectory of muscle loss in COPD[31,32] and it is uncertain whether patients evaluated on these were actively losing muscle at the time of the study and thus were cachectic, or instead they had lower muscle mass without active catabolism and thus were simply atrophic[8].

MECHANISMS OF SKELETAL MUSCLE DYSFUNCTION IN PATIENTS WITH COPD

Although this is an expanding area of research, we summarize here the biological mechanisms of COPD-associated muscle dysfunction. A more detailed description of the mechanisms regulating this process can be found elsewhere[33-36]. There is consensus that no single biological process leading to muscle wasting exists but instead there are different phenomena converging in the COPD phenotype[37]. Indeed, different muscle groups such as diaphragm, lower extremities, abdominal and upper extremities present variable and sometimes divergent characteristics[38], which suggests the non-systemic nature of the process. On the other hand, the fact that muscle groups in different regions are exposed to variable loads make 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

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

protective effect demonstrated by a negative correlation between local inflammation and muscle weakness[42]. An issue that remains unclear refers to whether locomotor muscle dysfunction in COPD is driven by chronic immobility or 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 associated with immobility, including atrophy, loss of type I fibers, lower oxidative enzyme activity and others[43]; and that exercise can potentially restore to some extent a normal muscle phenotype[44]. Behind the myopathy theory is evidence that some aspects of muscle dysfunction are poorly correlated to the level of physical activity of COPD patients[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 while others are emerging as potential targets to interfere with this process. We define intrinsic mechanisms as the ones primarily taking place in the neuromuscular unit and leading to clinical/functional, metabolic or anatomic dysfunction; extrinsic mechanisms as the ones originated in other structures such as the chest wall; and mixed mechanisms as the ones combining the previous 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 the lysosomal pathways[51], 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 26 S proteasome[52]. This specificity is

conferred by muscle-specific E3-ubiquitin ligases like MuRF1, atrogin-1 and NEDD4, which are upregulated in muscle biopsies from COPD patients[50,53,54]. Experimental interference with this mechanism prevents muscle loss in the context of chronic hypercapnia[48]. Importantly, as the proteasome can only degrade proteins in monomeric form, the muscle sarcomere needs to be first 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 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) insulin-like growth factor pathway, which induces muscle growth and is boosted during pulmonary rehabilitation[57,58]; 2) myostatin-Smad3 pathway, that acts as a negative regulator[37,54] and is upregulated during training of COPD patients[59]. There is evidence of relative anabolic suppression of locomotor muscles compared with the diaphragm in COPD patients[60], which is consistent with the adaptation of ventilatory muscles described below. Also, there is evidence of subnormal testosterone level in some COPD patients which could contribute to depressed anabolism and thus contribute to wasting[61].

Calcium desensitization: As mentioned before, 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 efficiency[21,22]. Altered sarcoplasmic calcium reuptake compromising relaxation efficiency[62] and differential calcium sensitivity of contractile proteins[20] could also

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

contribute to worse performance, although not specifically demonstrated in COPD patients.

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 non-ventilatory muscle work in COPD.

Extrinsic mechanisms:

Chest wall remodeling: The diaphragm from COPD patients chronically adapts to the increased inspiratory loads and reduced elastic recoil forces 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 COPD patients can generate more force than the control subjects'[71]. Despite that, from the clinical/functional standpoint ventilatory dysfunction is very significant in COPD, and is mainly caused 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 a chest wall bone configuration[74], which creates a less efficient ventilatory work. Studies of patients before and after lung volume reduction surgery (LVRS) showed increased postoperative diaphragm length and strength; and improved exercise capacity and maximum voluntary ventilation[75]. These changes are also associated with chest wall remodeling due to 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 muscles dysfunctions in COPD patients is relevant in 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]. Due to *slow-to-fast twitch fiber type transformation* in peripheral muscles, COPD patients 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 contribute to COPD outcomes: First, the association of COPD patients' survival with their muscle integrity persists even after correcting for surrogates of pulmonary function[1-3]. In other words, patients with similar lung functions will be more or less likely to survive in the long-term based on the presence of muscle dysfunction[1-3]. Second, pulmonary rehabilitation, which has a beneficial effect on muscle dysfunction, associates with better outcomes without affecting the history of the pulmonary disease[79,80]. It is important to emphasize that although skeletal muscle wasting associates with lower COPD survival, pulmonary rehabilitation's beneficial

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

effects on skeletal muscle have not been demonstrated to associate with overall lower mortality[81]. The reason for that disconnect is unclear but could be due to heterogeneous response to rehabilitation among different patients[8] or other factors.

In the following two sections, we will summarize clinical evidence supporting the relevance of muscle dysfunction and recovery on the prognosis of COPD, and clarify the significance of weight changes on muscle mass and on patients' outcomes.

Effects of clinical/functional disruption and recovery on COPD outcomes: ***Peripheral muscle weakness*** defined as poor muscle strength[3] is associated with increased mortality[3]. Similarly, underperformance of 6-minute-walk distance[82] and handgrip strength test[83] also predict mortality. Recovery of muscle force in the context of pulmonary rehabilitation is associated with improved symptoms, limb muscle function, exercise capacity, quality of life and other outcomes[84-86].

Ventilatory muscle weakness has been consistently demonstrated in patients with COPD leading to reduced maximum inspiratory pressure (MIP) 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 non-invasive ventilation can prevent intubation, and reduces length of hospital stay and mortality[91,92].

Effects of metabolic disruption and recovery on COPD outcomes: ***Peripheral muscles metabolic disruption:*** In quadriceps muscles from COPD patients the relative number of type I fibers decrease compared to 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], functional performance[17,97] and mortality[98]. Indeed, pulmonary

rehabilitation associates with higher expression of the relatively more oxidative type I and IIa fibers[94,99].

Metabolic disruption in ventilatory muscles: In contrast to peripheral muscles, diaphragm muscles from COPD patients undergo *fast-to-slow fiber transformation*[33,100], which associates 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 pulmonary rehabilitation associates with 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*** was associated with worse prognosis. Indeed, CT scan-measured mid-thigh muscle cross sectional areas in stable COPD patients correlated with mortality and was a better predictor than body mass index (BMI)[1]. Also, smaller pectoralis muscle area (PMA) associates with higher disease severity as measured by GOLD stage, lower resting oxygen saturations, BODE score, quality of life scores, and exercise capacity[12]. A recent report indicates that lower erector spinae muscles (ESM) mass is associated with worse dyspnea score, BMI, emphysema, FEV1 and 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 pre exacerbation baseline, similarly to what is observed with the pulmonary function[109] and the amount of emphysema[110]. Indeed, lower quadriceps mass at the time of exacerbation predicts higher chances of needing readmission and death[111], and in-hospital rehabilitation starting on the second day of admission attenuates the muscle mass decline observed during exacerbations[112].

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

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

BODY WEIGHT ON COPD PROGNOSIS:

Lower body mass index (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]. There is agreement that underweighted COPD patients have worse outcomes[116,118], yet the effect of obesity-driven higher BMI has generated controversy[119]. Despite that an analysis of outcomes in patients that were followed up for 8 years after hospital admission for an acute exacerbation showed that overweight was a predictor of survival[120], a recent analysis based on 3,600 patients from the COPDGene study indicated that obesity was associated with worse outcomes including QOL, 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, while weight loss is most of the times associated 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 cornerstone 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 paragraphs.

Pulmonary Rehabilitation (PR)

Exercise training, which is a formal component of pulmonary rehabilitation, is the most significant currently available intervention to treat 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 non-recovery[124] to very robust improvements[44], and that variability can be due to different tolerances to exercises[8], genetic and epigenetic factors, regenerative potential and oxidative metabolism[125]. Also, some reports indicate that whole body rehabilitation is less effective than training localized specific muscle groups[99,126].

Exercise protocols in PR: The ideal rehabilitation program should 1) tailor the training protocol to the specific patients' requirements to accommodate it to comorbid conditions and avoid exercise-induced muscle injury, particularly in 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, and the latter, in the form of cycling or walking exercise, is a common modality of PR[81]. Typically, endurance and strength training of the lower and upper extremities are 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 PH can be found in

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

excellent resources[81] and a summary of exercise training principles of PH are presented in **Table 2**.

Timing of PR: Traditionally, PR was offered to patients with severe COPD, yet there is evidence that muscle dysfunction[129] and its PR-associated recovery[94] occur also in early stages. PR should be provided during or shortly after an exacerbation as it accelerates the functional recovery and decreases the chances of readmission[81]. Also, in stable patients it improves health-related quality of life, readmissions rates 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 precludes massive implementation[84]. Health-care providers should engage patients and families to facilitate recognition and adherence to PR by reviewing its benefits during the clinical encounters (**Table 3**). Another area of interest is related to the length of PR, which is typically recommended for a minimum of eight weeks[130]. While experts recommend that patients should continue to exercise beyond the PR program period, there is controversy regarding the ideal maintenance plan: some studies found no benefits of maintenance technique beyond one year[131] while others suggest that longer protocols extend the benefits of PR[132]. A recent trial involving stable COPD patients found that a more prolonged and intensive PR associates with better BODE index and 6MWD when compared with a standard strategy. These effects are significant at 2 years, yet they vanish after that[133].

Nutritional support: The central relevance of adequate nutrition in COPD has been recognized for all patients and 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 associate with the development of metabolic syndrome in these patients[136]. COPD patients demonstrate some muscle ultrastructural and molecular changes typically found in starvation, such as the upregulation of 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 non-cachectic patients undergoing the same treatment[57]. Part of the PR benefits consists of transforming the nutritional substrates provided by an optimized diet into larger muscle mass, re-gaining oxidative capacity and exercise tolerance, both in the form of strength and endurance (**Figure 2**.

Evidence around nutrition in COPD is controverted: while some reports indicate the benefits of nutritional optimization as a strategy to improve PR outcome[137-139], some other trials have found no clear benefits[140,141], or identified specific subgroups with better potential[142]. There is agreement that nutritional support with no exercise has a very limited effect: 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, while a benefit of about 2 kilograms 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 COPD patient should include branched-chain amino acids[145], polyunsaturated fatty acids[146], and suggest the potential benefit of whey supplementation on exercise tolerance and quality of life[147]. A recent trial found that optimizing nutrition with leucine, vitamin D, and omega-3 fatty acids significantly

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

improved the effects of high intensity exercise on lower limbs muscle strength and exercise performance in COPD[148].

Neuromuscular electrical stimulation (NMES): Patients with severe exercise limitation are sometimes unable to undergo pulmonary rehabilitations 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 both in stable patients[149-152] and during exacerbations[153]. In a recent double-blind, placebo-controlled trial, NMES improved functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. The effects are maximal at 6 weeks and wean over time[154]. An alternative approach that is less frequently used but could be better tolerated is quadriceps magnetic stimulation. This approach showed 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 COPD male patients[61], a trial involving its administration to severe COPD men 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, which had the limitation of lacking of a control group[158]. 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 around the recently developed nonsteroidal selective androgen receptor modulator (SARM). These drugs

have preliminarily shown improvement in lean body mass and physical function in different forms of cachexia, although not tried in COPD so far[159]. Appetite stimulant megestrol acetate led to an improvement in body weight that did not reflect 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, and also in myostatin inhibitors, although the data supporting them is very preliminary or not confirmed and thus 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 survival. It is often considered a minor aspect of this disease; yet abundant evidence supports its significance and the role of pulmonary rehabilitation 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 health-care providers improve the day-to-day clinical practice to alleviate the 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 targeting exercise tolerance and nutritional status, which should be routinely implemented to attempt reversing the pathophysiology of the process (**Figure 2**). Early-detection of muscle dysfunction and wasting; and engagement of patients and their families in strategies to deal with the problem could prevent disease progression and improve prognosis

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

regardless of the degree of pulmonary disease. The current report will represent a useful tool to the average clinician to better manage patients with major chronic respiratory conditions.

REFERENCES

1. Marquis, K.*, et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **166**, 809-813 (2002).
2. Shrikrishna, D.*, et al.* Quadriceps wasting and physical inactivity in patients with COPD. *Eur Respir J* **40**, 1115-1122 (2012).
3. Swallow, E.B.*, et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* **62**, 115-120 (2007).
4. Vanfleteren, L.E.*, et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **187**, 728-735 (2013).
5. Filley, G.F., Beckwitt, H.J., Reeves, J.T. & Mitchell, R.S. Chronic obstructive bronchopulmonary disease. II. Oxygen transport in two clinical types. *Am J Med* **44**, 26-38 (1968).
6. Gea, J.G.*, et al.* Metabolic characteristics of the deltoid muscle in patients with chronic obstructive pulmonary disease. *The European respiratory journal* **17**, 939-945 (2001).
7. Gosselink, R., Troosters, T. & Decramer, M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* **20**, 353-360 (2000).
8. Maltais, F.*, et al.* 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* **189**, e15-62 (2014).
9. American Thoracic Society/European Respiratory, S. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* **166**, 518-624 (2002).
10. Barreiro, E. & Gea, J. Molecular and biological pathways of skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Chron Respir Dis* **13**, 297-311 (2016).
11. Barreiro, E.*, et al.* Guidelines for the evaluation and treatment of muscle dysfunction in patients with chronic obstructive pulmonary disease. *Arch Bronconeumol* **51**, 384-395 (2015).
12. McDonald, M.L.*, et al.* Quantitative computed tomography measures of pectoralis muscle area and disease severity in chronic obstructive pulmonary disease. A cross-sectional study. *Ann Am Thorac Soc* **11**, 326-334 (2014).
13. Schliwa, M. & Woehlke, G. Molecular motors. *Nature* **422**, 759-765 (2003).
14. Vermeeren, M.A.*, et al.* Prevalence of nutritional depletion in a large out-patient population of patients with COPD. *Respir Med* **100**, 1349-1355 (2006).
15. Berg, H.E., Larsson, L. & Tesch, P.A. Lower limb skeletal muscle function after 6 wk of bed rest. *J Appl Physiol (1985)* **82**, 182-188 (1997).
16. Barreiro, E. & Gea, J. Respiratory and Limb Muscle Dysfunction in COPD. *COPD* **12**, 413-426 (2015).
17. Allaire, J.*, et al.* Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* **59**, 673-678 (2004).
18. Nyberg, A., Saey, D. & Maltais, F. Why and How Limb Muscle Mass and Function Should Be Measured in Patients with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* **12**, 1269-1277 (2015).
19. Abdulai, R.M.*, et al.* Deterioration of Limb Muscle Function During Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* (2017).
20. Schiaffino, S. & Reggiani, C. Fiber types in mammalian skeletal muscles. *Physiol Rev* **91**, 1447-1531 (2011).
21. Stephenson, D.G. & Williams, D.A. Calcium-activated force responses in fast- and slow-twitch skinned muscle fibres of the rat at different temperatures. *J Physiol* **317**, 281-302 (1981).

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

22. Sieck, G.C. & Prakash, Y.S. Cross-bridge kinetics in respiratory muscles. *Eur Respir J* **10**, 2147-2158 (1997).
23. Ciciliot, S., Rossi, A.C., Dyar, K.A., Blaauw, B. & Schiaffino, S. Muscle type and fiber type specificity in muscle wasting. *Int J Biochem Cell Biol* **45**, 2191-2199 (2013).
24. Schiaffino, S.*, et al.* Myosin heavy chain isoforms and velocity of shortening of type 2 skeletal muscle fibres. *Acta Physiol Scand* **134**, 575-576 (1988).
25. Klitgaard, H.*, et al.* Co-existence of myosin heavy chain I and IIa isoforms in human skeletal muscle fibres with endurance training. *Pflugers Arch* **416**, 470-472 (1990).
26. Maltais, F.*, et al.* Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax* **55**, 848-853 (2000).
27. Janssen, I., Heymsfield, S.B., Wang, Z.M. & Ross, R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol (1985)* **89**, 81-88 (2000).
28. Evans, W.J.*, et al.* Cachexia: a new definition. *Clin Nutr* **27**, 793-799 (2008).
29. Evans, W.J. What is sarcopenia? *J Gerontol A Biol Sci Med Sci* **50 Spec No**, 5-8 (1995).
30. Fabbri, L.M., Luppi, F., Beghe, B. & Rabe, K.F. Complex chronic comorbidities of COPD. *Eur Respir J* **31**, 204-212 (2008).
31. Hopkinson, N.S.*, et al.* A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* **8**, 25 (2007).
32. van den Borst, B.*, et al.* Is age-related decline in lean mass and physical function accelerated by obstructive lung disease or smoking? *Thorax* **66**, 961-969 (2011).
33. Levine, S., Kaiser, L., Leferovich, J. & Tikunov, B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med* **337**, 1799-1806 (1997).
34. Debigare, R., Cote, C.H. & Maltais, F. Ubiquitination and proteolysis in limb and respiratory muscles of patients with chronic obstructive pulmonary disease. *Proc Am Thorac Soc* **7**, 84-90 (2010).
35. Caron, M.A., Debigare, R., Dekhuijzen, P.N. & Maltais, F. Comparative assessment of the quadriceps and the diaphragm in patients with COPD. *J Appl Physiol (1985)* **107**, 952-961 (2009).
36. Sanders, K.J., Kneppers, A.E., van de Bool, C., Langen, R.C. & Schols, A.M. Cachexia in chronic obstructive pulmonary disease: new insights and therapeutic perspective. *J Cachexia Sarcopenia Muscle* **7**, 5-22 (2016).
37. Schiaffino, S., Dyar, K.A., Ciciliot, S., Blaauw, B. & Sandri, M. Mechanisms regulating skeletal muscle growth and atrophy. *FEBS J* **280**, 4294-4314 (2013).
38. Polkey, M.I. & Rabe, K.F. Chicken or egg: physical activity in COPD revisited. *Eur Respir J* **33**, 227-229 (2009).
39. Sin, D.D. & Reid, W.D. Is inflammation good, bad or irrelevant for skeletal muscles in COPD? *Thorax* **63**, 95-96 (2008).
40. Debigare, R.*, et al.* Catabolic/anabolic balance and muscle wasting in patients with COPD. *Chest* **124**, 83-89 (2003).
41. Crul, T.*, et al.* Markers of inflammation and disuse in vastus lateralis of chronic obstructive pulmonary disease patients. *Eur J Clin Invest* **37**, 897-904 (2007).
42. Barreiro, E.*, et al.* Cytokine profile in quadriceps muscles of patients with severe COPD. *Thorax* **63**, 100-107 (2008).
43. Larsson, L. & Ansved, T. Effects of long-term physical training and detraining on enzyme histochemical and functional skeletal muscle characteristic in man. *Muscle Nerve* **8**, 714-722 (1985).
44. Bronstad, E.*, et al.* High-intensity knee extensor training restores skeletal muscle function in COPD patients. *Eur Respir J* **40**, 1130-1136 (2012).

45. Bossenbroek, L., de Greef, M.H., Wempe, J.B., Krijnen, W.P. & Ten Hacken, N.H. Daily physical activity in patients with chronic obstructive pulmonary disease: a systematic review. *COPD* **8**, 306-319 (2011).
46. Couillard, A. & Prefaut, C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J* **26**, 703-719 (2005).
47. Barreiro, E., Sznajder, J.I., Nader, G.A. & Budinger, G.R. Muscle dysfunction in patients with lung diseases: a growing epidemic. *Am J Respir Crit Care Med* **191**, 616-619 (2015).
48. Jaitovich, A.*, et al.* High CO2 levels cause skeletal muscle atrophy via AMP-activated kinase (AMPK), FoxO3a protein, and muscle-specific Ring finger protein 1 (MuRF1). *J Biol Chem* **290**, 9183-9194 (2015).
49. Degens, H., Gayan-Ramirez, G. & van Hees, H.W. Smoking-induced skeletal muscle dysfunction: from evidence to mechanisms. *Am J Respir Crit Care Med* **191**, 620-625 (2015).
50. Doucet, M.*, et al.* Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **176**, 261-269 (2007).
51. Guo, Y.*, et al.* Autophagy in locomotor muscles of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **188**, 1313-1320 (2013).
52. Glickman, M.H. & Ciechanover, A. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. *Physiological reviews* **82**, 373-428 (2002).
53. Crul, T.*, et al.* Gene expression profiling in vastus lateralis muscle during an acute exacerbation of COPD. *Cell Physiol Biochem* **25**, 491-500 (2010).
54. Plant, P.J.*, et al.* Cellular markers of muscle atrophy in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* **42**, 461-471 (2010).
55. Goll, D.E., Thompson, V.F., Taylor, R.G. & Christiansen, J.A. Role of the calpain system in muscle growth. *Biochimie* **74**, 225-237 (1992).
56. Puig-Vilanova, E.*, et al.* Oxidative stress, redox signaling pathways, and autophagy in cachectic muscles of male patients with advanced COPD and lung cancer. *Free Radic Biol Med* **79**, 91-108 (2015).
57. Vogiatzis, I.*, et al.* Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. *Eur Respir J* **36**, 301-310 (2010).
58. Vogiatzis, I.*, et al.* Effects of rehabilitative exercise on peripheral muscle TNFalpha, IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax* **62**, 950-956 (2007).
59. Lewis, M.I.*, et al.* Skeletal muscle adaptations to testosterone and resistance training in men with COPD. *J Appl Physiol (1985)* **103**, 1299-1310 (2007).
60. Doucet, M.*, et al.* Atrophy and hypertrophy signalling of the quadriceps and diaphragm in COPD. *Thorax* **65**, 963-970 (2010).
61. Kamischke, A.*, et al.* Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. *Eur Respir J* **11**, 41-45 (1998).
62. Ferguson, D.G. & Franzini-Armstrong, C. The Ca2+ ATPase content of slow and fast twitch fibers of guinea pig. *Muscle Nerve* **11**, 561-570 (1988).
63. Martinez-Llorens, J.*, et al.* [Activation of satellite cells in the intercostal muscles of patients with chronic obstructive pulmonary disease]. *Arch Bronconeumol* **44**, 239-244 (2008).
64. Patel, T.J., Cuizon, D., Mathieu-Costello, O., Friden, J. & Lieber, R.L. Increased oxidative capacity does not protect skeletal muscle fibers from eccentric contraction-induced injury. *Am J Physiol* **274**, R1300-1308 (1998).
65. Polkey, M.I., Griffiths, M.J. & Kemp, P.R. Muscle Regeneration after Critical Illness: Are Satellite Cells the Answer? *Am J Respir Crit Care Med* **194**, 780-782 (2016).
66. Pomies, P.*, et al.* Reduced myotube diameter, atrophic signalling and elevated oxidative stress in cultured satellite cells from COPD patients. *J Cell Mol Med* **19**, 175-186 (2015).

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

67. Theriault, M.E., Pare, M.E., Maltais, F. & Debigare, R. Satellite cells senescence in limb muscle of severe patients with COPD. *PLoS One* **7**, e39124 (2012).
68. Ottenheijm, C.A.*, et al.* Titin and diaphragm dysfunction in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **173**, 527-534 (2006).
69. Barreiro, E.*, et al.* Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **171**, 1116-1124 (2005).
70. Ottenheijm, C.A., Heunks, L.M. & Dekhuijzen, P.N. Diaphragm muscle fiber dysfunction in chronic obstructive pulmonary disease: toward a pathophysiological concept. *American journal of respiratory and critical care medicine* **175**, 1233-1240 (2007).
71. Similowski, T., Yan, S., Gauthier, A.P., Macklem, P.T. & Bellemare, F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* **325**, 917-923 (1991).
72. Rochester, D.F. & Braun, N.M. Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. *The American review of respiratory disease* **132**, 42-47 (1985).
73. Rochester, D.F., Braun, N.M. & Arora, N.S. Respiratory muscle strength in chronic obstructive pulmonary disease. *The American review of respiratory disease* **119**, 151-154 (1979).
74. Lando, Y.*, et al.* Effect of lung volume reduction surgery on bony thorax configuration in severe COPD. *Chest* **116**, 30-39 (1999).
75. Lando, Y.*, et al.* Effect of lung volume reduction surgery on diaphragm length in severe chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **159**, 796-805 (1999).
76. Casaburi, R.*, et al.* Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* **143**, 9-18 (1991).
77. Maltais, F.*, et al.* Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med* **153**, 288-293 (1996).
78. Saey, D.*, et al.* Contractile fatigue, muscle morphometry, and blood lactate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **171**, 1109-1115 (2005).
79. Franssen, F.M., Broekhuizen, R., Janssen, P.P., Wouters, E.F. & Schols, A.M. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. *Chest* **125**, 2021-2028 (2004).
80. Spruit, M.A., Gosselink, R., Troosters, T., De Paepe, K. & Decramer, M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* **19**, 1072-1078 (2002).
81. Spruit, M.A.*, et al.* An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* **188**, e13-64 (2013).
82. Dajczman, E.*, et al.* Six minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. *Can Respir J* **22**, 225-229 (2015).
83. Burtin, C.*, et al.* Handgrip weakness and mortality risk in COPD: a multicentre analysis. *Thorax* **71**, 86-87 (2016).
84. Rochester, C.L.*, et al.* An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am J Respir Crit Care Med* **192**, 1373-1386 (2015).
85. Puhan, M.A.*, et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews*, CD005305 (2011).
86. Puhan, M.A. & Lareau, S.C. Evidence-based outcomes from pulmonary rehabilitation in the chronic obstructive pulmonary disease patient. *Clinics in chest medicine* **35**, 295-301 (2014).

87. Polkey, M.I*., et al.* Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **154**, 1310-1317 (1996).
88. Levine, S., Bashir, M.H., Clanton, T.L., Powers, S.K. & Singhal, S. COPD elicits remodeling of the diaphragm and vastus lateralis muscles in humans. *J Appl Physiol (1985)* **114**, 1235-1245 (2013).
89. Vilaro, J*., et al.* Global muscle dysfunction as a risk factor of readmission to hospital due to COPD exacerbations. *Respiratory medicine* **104**, 1896-1902 (2010).
90. Antenora, F*., et al.* Prevalence and outcomes of diaphragmatic dysfunction assessed by ultrasound technology during acute exacerbation of COPD: A pilot study. *Respirology* **22**, 338-344 (2017).
91. Brochard, L*., et al.* Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *The New England journal of medicine* **323**, 1523-1530 (1990).
92. Brochard, L*., et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *The New England journal of medicine* **333**, 817-822 (1995).
93. Whittom, F*., et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* **30**, 1467-1474 (1998).
94. Vogiatzis, I*., et al.* Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* **140**, 744-752 (2011).
95. Gosker, H.R., Zeegers, M.P., Wouters, E.F. & Schols, A.M. Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax* **62**, 944-949 (2007).
96. Natanek, S.A*., et al.* Heterogeneity of quadriceps muscle phenotype in chronic obstructive pulmonary disease (Copd); implications for stratified medicine? *Muscle Nerve* **48**, 488-497 (2013).
97. Patel, M.S*., et al.* Phenotypic characteristics associated with reduced short physical performance battery score in COPD. *Chest* **145**, 1016-1024 (2014).
98. Patel, M.S*., et al.* Vastus lateralis fiber shift is an independent predictor of mortality in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **190**, 350-352 (2014).
99. Vogiatzis, I*., et al.* Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest* **128**, 3838-3845 (2005).
100. Levine, S*., et al.* Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med* **168**, 706-713 (2003).
101. Wijnhoven, J.H., Janssen, A.J., van Kuppevelt, T.H., Rodenburg, R.J. & Dekhuijzen, P.N. Metabolic capacity of the diaphragm in patients with COPD. *Respiratory medicine* **100**, 1064-1071 (2006).
102. Sanchez, J., Bastien, C., Medrano, G., Riquet, M. & Derenne, J.P. Metabolic enzymatic activities in the diaphragm of normal men and patients with moderate chronic obstructive pulmonary disease. *Bull Eur Physiopathol Respir* **20**, 535-540 (1984).
103. Geiger, P.C., Cody, M.J., Macken, R.L. & Sieck, G.C. Maximum specific force depends on myosin heavy chain content in rat diaphragm muscle fibers. *J Appl Physiol (1985)* **89**, 695-703 (2000).
104. Ramirez-Sarmiento, A*., et al.* Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *Am J Respir Crit Care Med* **166**, 1491-1497 (2002).
105. Tanimura, K*., et al.* Quantitative Assessment of Erector Spinae Muscles in Patients with Chronic Obstructive Pulmonary Disease. Novel Chest Computed Tomography-derived Index for Prognosis. *Annals of the American Thoracic Society* **13**, 334-341 (2016).

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

106. Spruit, M.A*., et al.* Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* **58**, 752-756 (2003).
107. Pitta, F*., et al.* Physical activity and hospitalization for exacerbation of COPD. *Chest* **129**, 536-544 (2006).
108. Donaldson, G.C., Wilkinson, T.M., Hurst, J.R., Perera, W.R. & Wedzicha, J.A. Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **171**, 446-452 (2005).
109. Donaldson, G.C., Seemungal, T.A., Bhowmik, A. & Wedzicha, J.A. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* **57**, 847-852 (2002).
110. Tanabe, N*., et al.* Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **183**, 1653-1659 (2011).
111. Greening, N.J*., et al.* Bedside Assessment of Quadriceps Muscle by Ultrasound after Admission for Acute Exacerbations of Chronic Respiratory Disease. *American journal of respiratory and critical care medicine* **192**, 810-816 (2015).
112. Troosters, T*., et al.* Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* **181**, 1072-1077 (2010).
113. Arora, N.S. & Rochester, D.F. COPD and human diaphragm muscle dimensions. *Chest* **91**, 719-724 (1987).
114. Baria, M.R*., et al.* B-mode ultrasound assessment of diaphragm structure and function in patients with COPD. *Chest* **146**, 680-685 (2014).
115. Guerri, R*., et al.* Mass of intercostal muscles associates with risk of multiple exacerbations in COPD. *Respiratory medicine* **104**, 378-388 (2010).
116. Celli, B.R*., et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *The New England journal of medicine* **350**, 1005-1012 (2004).
117. Schols, A.M., Broekhuizen, R., Weling-Scheepers, C.A. & Wouters, E.F. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* **82**, 53-59 (2005).
118. Hallin, R*., et al.* Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respiratory medicine* **101**, 1954-1960 (2007).
119. Galesanu, R.G*., et al.* Obesity in chronic obstructive pulmonary disease: is fatter really better? *Can Respir J* **21**, 297-301 (2014).
120. Stoll, P., Foerster, S., Virchow, J.C. & Lommatzsch, M. Overweight is a predictor of long-term survival in hospitalised patients with exacerbations of COPD. *Respir Med* **116**, 59-62 (2016).
121. Lambert, A.A*., et al.* Obesity Is Associated With Increased Morbidity in Moderate to Severe COPD. *Chest* **151**, 68-77 (2017).
122. He, J., Watkins, S. & Kelley, D.E. Skeletal muscle lipid content and oxidative enzyme activity in relation to muscle fiber type in type 2 diabetes and obesity. *Diabetes* **50**, 817-823 (2001).
123. Ries, A.L*., et al.* Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* **131**, 4S-42S (2007).
124. Troosters, T., Gosselink, R. & Decramer, M. Exercise training in COPD: how to distinguish responders from nonresponders. *J Cardiopulm Rehabil* **21**, 10-17 (2001).
125. Bouchard, C*., et al.* Genomic predictors of the maximal O(2) uptake response to standardized exercise training programs. *J Appl Physiol (1985)* **110**, 1160-1170 (2011).
126. Dolmage, T.E. & Goldstein, R.S. Effects of one-legged exercise training of patients with COPD. *Chest* **133**, 370-376 (2008).

127. Larson, J.L., Kim, M.J., Sharp, J.T. & Larson, D.A. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* **138**, 689-696 (1988).
128. Mota, S.*, et al.* Clinical outcomes of expiratory muscle training in severe COPD patients. *Respir Med* **101**, 516-524 (2007).
129. Spruit, M.A.*, et al.* Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade. *Respir Med* **101**, 2454-2463 (2007).
130. Troosters, T., Casaburi, R., Gosselink, R. & Decramer, M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **172**, 19-38 (2005).
131. Ries, A.L., Kaplan, R.M., Myers, R. & Prewitt, L.M. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med* **167**, 880-888 (2003).
132. Guell, R.*, et al.* Long-term effects of outpatient rehabilitation of COPD: A randomized trial. *Chest* **117**, 976-983 (2000).
133. Guell, M.R.*, et al.* Benefits of Long-Term Pulmonary Rehabilitation Maintenance Program in Patients with Severe Chronic Obstructive Pulmonary Disease. Three-Year Follow-up. *Am J Respir Crit Care Med* **195**, 622-629 (2017).
134. Schols, A.M. Nutritional advances in patients with respiratory diseases. *Eur Respir Rev* **24**, 17-22 (2015).
135. Behrens, G., Matthews, C.E., Moore, S.C., Hollenbeck, A.R. & Leitzmann, M.F. Body size and physical activity in relation to incidence of chronic obstructive pulmonary disease. *CMAJ* **186**, E457-469 (2014).
136. Chung, J.H.*, et al.* Association between sarcopenia and metabolic syndrome in chronic obstructive pulmonary disease: the Korea National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2011. *COPD* **12**, 82-89 (2015).
137. Pison, C.M.*, et al.* Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. *Thorax* **66**, 953-960 (2011).
138. van Wetering, C.R.*, et al.* Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. *J Am Med Dir Assoc* **11**, 179-187 (2010).
139. Creutzberg, E.C., Wouters, E.F., Mostert, R., Pluymers, R.J. & Schols, A.M. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* **124**, 1733-1742 (2003).
140. Constantin, D.*, et al.* Skeletal muscle molecular responses to resistance training and dietary supplementation in COPD. *Thorax* **68**, 625-633 (2013).
141. Deacon, S.J.*, et al.* Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **178**, 233-239 (2008).
142. Steiner, M.C., Barton, R.L., Singh, S.J. & Morgan, M.D. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* **58**, 745-751 (2003).
143. Ferreira, I.M., Brooks, D., White, J. & Goldstein, R. Nutritional supplementation for stable chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* **12**, CD000998 (2012).
144. Fonseca Wald, E.L.A., van den Borst, B., Gosker, H.R. & Schols, A. Dietary fibre and fatty acids in chronic obstructive pulmonary disease risk and progression: a systematic review. *Respirology* **19**, 176-184 (2014).

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

145. Engelen, M.P.*, et al.* Supplementation of soy protein with branched-chain amino acids alters protein metabolism in healthy elderly and even more in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr* **85**, 431-439 (2007).
146. Broekhuizen, R., Wouters, E.F., Creutzberg, E.C., Weling-Scheepers, C.A. & Schols, A.M. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. *Thorax* **60**, 376-382 (2005).
147. Laviolette, L.*, et al.* Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. *J Med Food* **13**, 589-598 (2010).
148. van de Bool, C.*, et al.* A randomized clinical trial investigating the efficacy of targeted nutrition as adjunct to exercise training in COPD. *J Cachexia Sarcopenia Muscle* **8**, 748-758 (2017).
149. Neder, J.A.*, et al.* Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* **57**, 333-337 (2002).
150. Bourjeily-Habr, G., Rochester, C.L., Palermo, F., Snyder, P. & Mohsenin, V. Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. *Thorax* **57**, 1045-1049 (2002).
151. Sillen, M.J.*, et al.* Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest* **136**, 44-61 (2009).
152. Jones, S.*, et al.* Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. *The Cochrane database of systematic reviews* **10**, CD009419 (2016).
153. Abdellaoui, A.*, et al.* Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *The European respiratory journal* **38**, 781-788 (2011).
154. Maddocks, M.*, et al.* Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. *Lancet Respir Med* **4**, 27-36 (2016).
155. Bustamante, V.*, et al.* Redox balance following magnetic stimulation training in the quadriceps of patients with severe COPD. *Free Radic Res* **42**, 939-948 (2008).
156. Bustamante, V., Lopez de Santa Maria, E., Gorostiza, A., Jimenez, U. & Galdiz, J.B. Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients. *Respiratory medicine* **104**, 237-245 (2010).
157. Casaburi, R.*, et al.* Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **170**, 870-878 (2004).
158. Yeh, S.S., DeGuzman, B., Kramer, T. & Group, M.S. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest* **122**, 421-428 (2002).
159. Dalton, J.T.*, et al.* The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. *J Cachexia Sarcopenia Muscle* **2**, 153-161 (2011).
160. Weisberg, J.*, et al.* Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest* **121**, 1070-1078 (2002).
161. Travaline, J.M.*, et al.* Effect of N-acetylcysteine on human diaphragm strength and fatigability. *Am J Respir Crit Care Med* **156**, 1567-1571 (1997).
162. Doorduin, J.*, et al.* The calcium sensitizer levosimendan improves human diaphragm function. *Am J Respir Crit Care Med* **185**, 90-95 (2012).
163. Nagaya, N.*, et al.* Treatment of cachexia with ghrelin in patients with COPD. *Chest* **128**, 1187-1193 (2005).

LEGENDS

Table 1: General mechanisms participating in COPD-associated muscle dysfunction

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.

Table 2: Basic aspects of exercising in pulmonary rehabilitation

General principles and specific strategies, with goals and modes of implementation are summarized.

Table 3: Benefits of pulmonary rehabilitation

Practitioner should dedicate time to discuss the general benefits of exercise and nutrition, and specifically pulmonary rehabilitation with COPD patients and their families.

Figure 1: Pathophysiology of COPD-associated muscle dysfunction

Cigarette smoking and other factors, and exacerbations are the main causes of COPD progression, which associates 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 causes peripheral muscle dysfunction and deconditioning.

Figure 2: Holistic approach to prevent and reverse COPD-associated muscle dysfunction

Combination of optimized diet with resistance and endurance exercise training programs associate with improved muscle mass and oxidative capacity in locomotor muscles, with in turn decreases fatigue upon exercise. Bronchodilators, cigarette smoking cessation and, occasionally lung volume reduction surgery, decrease hyperinflation and lead to better dyspnea

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

control. All these measures contribute to reconditioning, eventually, regaining functional capacity in the patients.

TABLE 1: Mechanisms contributing to skeletal muscle dysfunction in COPD
Signals and stimuli that initiate the muscle loss -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 patway 2) Lysosomal/autophagy pathways 3) Anabolic suppresion 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) Bonny thoracic remodeling (diaphragm) 3) Lactate hyperproduction and lower exercise tolerance

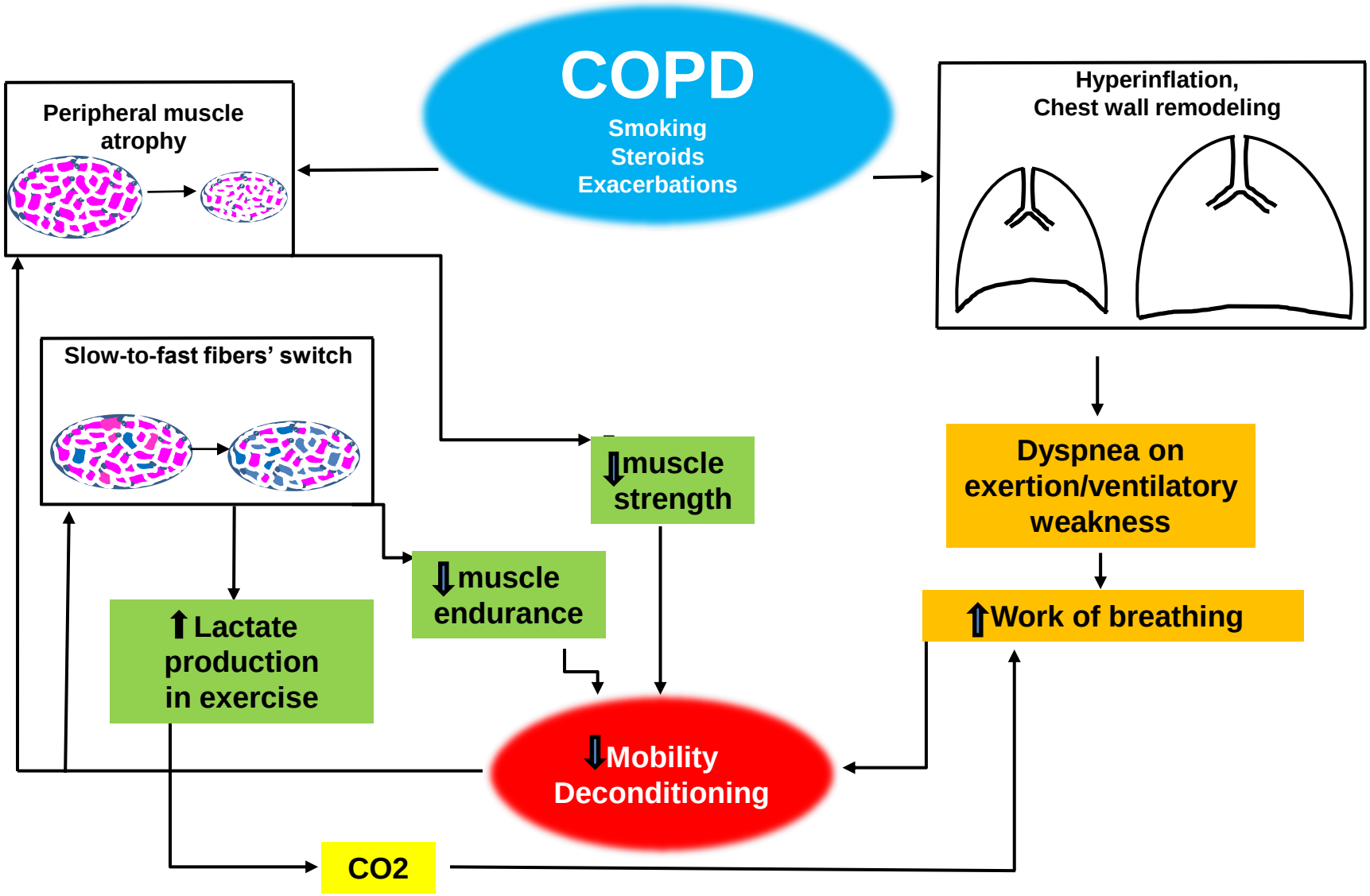
AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

TABLE 2: Basic aspects of exercising in PH
General Principles:
1) Exercise **must be tailored** to specific patients needs, *and* 2) Exercise **must exceed** the regular loads patient is used to overcoming, *and* 3) Exercise **must progress** as patient improves performance.
Specific strategies:
1) Endurance training: Goal: To improve general aerobic capacity and *notany specific* muscle group: **Mode:** Cycling and walking are commonly used **2) Interval Training: 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 limbs training: Goal:** To improve activities of daily living (dressing, bathing, etc). **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

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

AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

Figure 1



AJRCCM Articles in Press. Published on 19-March-2018 as 10.1164/rccm.201710-2140CI

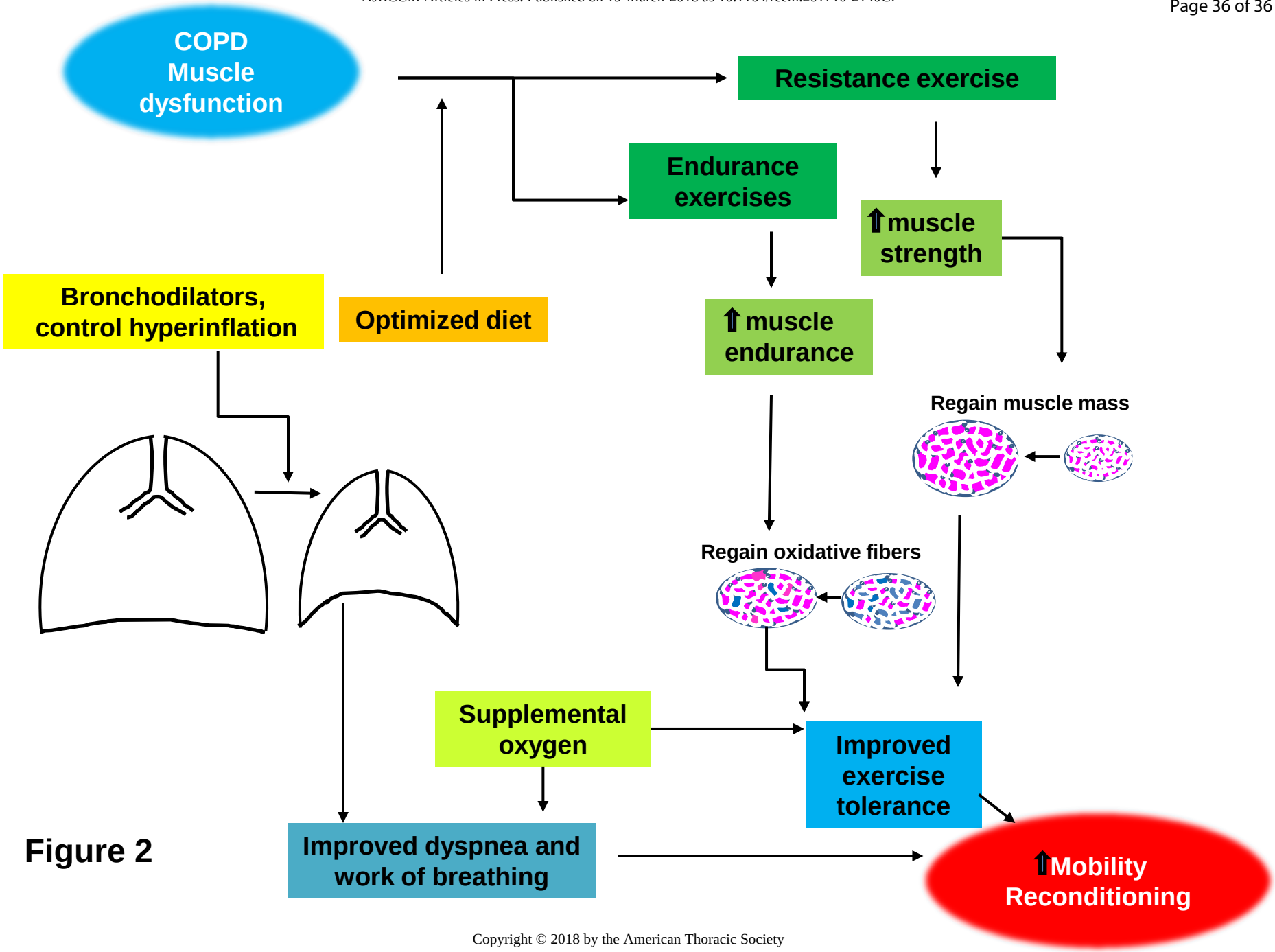


Figure 2