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HIGHLIGHTED TOPIC | *Muscle Dysfunction in COPD*

Pathophysiology of muscle dysfunction in COPD

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Gea J, Agustí A, Roca J. Pathophysiology of muscle dysfunction in COPD. *J Appl Physiol* 114: 1222–1234, 2013. First published March 21, 2013; doi:10.1152/japplphysiol.00981.2012.—Muscle dysfunction often occurs in patients with chronic obstructive pulmonary disease (COPD) and may involve both respiratory and locomotor (peripheral) muscles. The loss of strength and/or endurance in the former can lead to ventilatory insufficiency, whereas in the latter it limits exercise capacity and activities of daily life. Muscle dysfunction is the consequence of complex interactions between local and systemic factors, frequently coexisting in COPD patients. Pulmonary hyperinflation along with the increase in work of breathing that occur in COPD appear as the main contributing factors to respiratory muscle dysfunction. By contrast, deconditioning seems to play a key role in peripheral muscle dysfunction. However, additional systemic factors, including tobacco smoking, systemic inflammation, exercise, exacerbations, nutritional and gas exchange abnormalities, anabolic insufficiency, comorbidities and drugs, can also influence the function of both respiratory and peripheral muscles, by inducing modifications in their local microenvironment. Under all these circumstances, protein metabolism imbalance, oxidative stress, inflammatory events, as well as muscle injury may occur, determining the final structure and modulating the function of different muscle groups. Respiratory muscles show signs of injury as well as an increase in several elements involved in aerobic metabolism (proportion of type I fibers, capillary density, and aerobic enzyme activity) whereas limb muscles exhibit a loss of the same elements, injury, and a reduction in fiber size. In the present review we examine the current state of the art of the pathophysiology of muscle dysfunction in COPD.

respiratory muscles; limb muscles; muscle dysfunction; hyperinflation; deconditioning; muscle wasting; exercise; exacerbations

MUSCLE STRUCTURE AND FUNCTION are frequently abnormal in patients with chronic obstructive pulmonary disease (COPD) (5, 66, 123). This common systemic manifestation can have direct clinical consequences among patients since respiratory muscles are needed for achieving an appropriate level of alveolar ventilation, whereas lower limb muscles are essential for daily life activities. In fact, several studies have shown that muscle dysfunction reduces both the health-related quality of life and the life expectancy of COPD patients (118, 158, 191). The present review is to a great extent an introduction to eight other minireviews of the highlighted topic on COPD muscle dysfunction. In those reviews, the most relevant biological contributors to muscle dysfunction in COPD will be extensively discussed. Therefore, in the following sections we will *1*) discuss its definition, principal physiological concepts, and factors involved in its pathogenesis; and *2*) review from a general perspective the main clinical, cellular, and molecular mechanisms that contribute to dysfunction in both respiratory and locomotor muscles.

MUSCLE DYSFUNCTION: DEFINITION AND MAIN PHYSIOLOGICAL CONCEPTS

Muscle dysfunction is defined as the loss of at least one of the two main muscle properties: strength and endurance (64). The former corresponds to the capacity to develop a short maximal contractile effort, whereas the latter is characterized by the ability to maintain a submaximal exercise load throughout a more prolonged period of time. Strength mainly depends on muscle mass (which in turn is determined by the size and density of the fibers), muscle resting length, velocity of shortening, and the recruitment pattern of motor units (87). Conversely, endurance is mainly determined by the coordination of all different elements involved in oxygen delivery and utilization by the muscle (type I fiber proportion, capillary density, and oxidative enzyme activities, among others) (5). Muscle strength can be easily assessed by means of its direct determi-

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nation using dynamometry (limb muscles) or the measurement of maximal respiratory pressures (respiratory muscles) both in clinical and experimental settings (5, 179, 208). In general maximal efforts are obtained through voluntary maneuvers but the use of either electrical or magnetic stimulation avoids relying on the subject's full collaboration (117, 120). Muscle endurance is more difficult to assess but can be evaluated using tests that involve the use of either progressive loads or a continuous submaximal load until exhaustion. It is worth noting that in this latter modality the outcome variable is time, which is most appropriate to reflect endurance. In any case, both strategies are useful to explore this functional property either in peripheral or respiratory muscles (28, 156, 157).

The concept of muscle dysfunction includes the presence of at least one of the following conditions: weakness, reduced endurance, and fatigue. Either muscle weakness, characterized by a reduction in muscle force, or reduced muscle endurance are relatively stable situations, which can be easily identified (see above). The restoration of either muscle force or endurance requires medium- or long-term therapeutic measures, including strength training and nutritional interventions, and endurance training, respectively (5). Conversely, muscle fatigue implies a temporary loss of the contractile function that can be reversed by rest. Muscle fatigue can be partial or complete, involving in this case the total inability to further maintain the effort. Moreover, muscle fatigue might also be considered as acute or chronic depending on whether its development occurs suddenly or gradually over time (53). However, the concept of chronic fatigue is controversial and has lost support in recent years. Fatigue can also be divided into central and peripheral, depending on whether its origin lies on the nervous system or muscle structures, respectively (53). Muscle fatigue can be identified through neurophysiological or mechanical indicators, both revealing the transient inability to perform a target task. These indicators revert to a physiological level under resting conditions. Importantly, weakness, reduced endurance, and fatigue can be present simultaneously in the same patient. Moreover, a weak muscle will become fatigued much more easily. Muscle dysfunction in COPD is the end result of a complex interaction between several factors, which, in turn, induce many different molecular and cellular events within the muscle (10, 11, 14, 38, 137, 171). These factors and their biological consequences are not always equivalent for respiratory and limb muscles. For this reason, in the following sections these two muscle groups will be reviewed separately.

RESPIRATORY MUSCLES

Inspiratory muscles expand the thoracic cage generating the negative alveolar pressure that results in inspiratory flow. Among them, the diaphragm has been classically considered as the main inspiratory muscle, at least in healthy and young subjects breathing under resting conditions. However, when the ventilatory demands increase as a result of aging, respiratory diseases, and/or exercise, other muscles progressively participate in the breathing effort, becoming even more relevant than the diaphragm (24, 42, 44). In these cases, the external and parasternal (the interchondral extension of the internal interosseus) intercostals become major players. The diaphragm is a dome-shaped muscle, which is composed by costal and crural parts, acting mainly by expanding the lower rib cage (41). Whereas the costal part appears to be more relevant for inspiration, the crural portion also plays a relevant role in the gastroesophageal function (187). Contraction of external and parasternal intercostal muscles enlarges mostly the global chest cross-sectional area, whereas scalenes expand the upper rib cage. The diaphragm, parasternal intercostals, and scalenes are considered as primary inspiratory muscles, since they are phasically recruited with each inspiration. Muscles that are inactive under normal ventilatory conditions, and are recruited only upon increased ventilatory demands, are called accessory muscles. The combined action of inspiratory muscles expanding the thorax and the elastic recoil of the lung results in a more negative pleural pressure, which is transmitted to the alveolar region and causes the entry of air into the lungs.

Although expiration is normally a passive process, secondary to the relaxation of the inspiratory muscles, air exhalation can be facilitated by the contraction of other muscle groups, including those of the abdominal wall and the internal intercostals. This action along with the air trapping that may concomitantly occur appears to be involved in the increase of dyspnea and lack of bronchodilator response shown by some COPD patients (111, 139).

The function of respiratory muscles, which is frequently impaired in COPD patients (165, 203), may contribute to hypercapnic respiratory failure and exercise limitation. Respiratory muscle dysfunction has been associated with an increased risk for repeated hospital admissions (203) and premature death (158). As already mentioned, respiratory muscle dysfunction in COPD is caused by the combination of different local and systemic factors (Fig. 1). On the one hand, muscles are facing an increase in mechanical ventilatory loads. Since COPD is mainly characterized by airflow limitation, as well as pulmonary hyperinflation and increased compliance, this will have important mechanical consequences. Different elastic (derived from changes in the thorax wall and lung parenchyma), resistive (caused by air passage through the narrowed airways) and threshold (such as that derived from the intrinsic positive end-expiratory pressure, PEEPI) loads increase in patients (53, 65, 66), thus imposing an increased work of breathing and overloading respiratory muscles (53, 166). On the other hand, static pulmonary hyperinflation modifies thorax geometry, shortening the diaphragmatic length (166, 182), a situation that can be even accentuated by dynamic pulmonary hyperinflation. In this regard, the diaphragm is displaced away from its optimal length to generate force, and its costal and crural parts probably become less coordinated (110). All these factors lead to a mismatching between mechanical requirements of the respiratory system and functional capacity of the ventilatory muscles, as well as between the metabolic demands and the energy supply to these muscles (66, 204).

Besides local influences, a number of systemic factors may also negatively affect this already adverse scenario in the respiratory muscles. These systemic factors, which can also be present in other muscle groups, include systemic inflammation, pulmonary gas exchange and nutritional abnormalities, the systemic consequences of concomitant disorders, and the direct effects of tobacco and some drugs used in the treatment of COPD patients, such as systemic steroids (13, 39, 43, 180) (see next sections). All in all, this leads to more metabolic derangements superimposed on top of the mechanical factors discussed

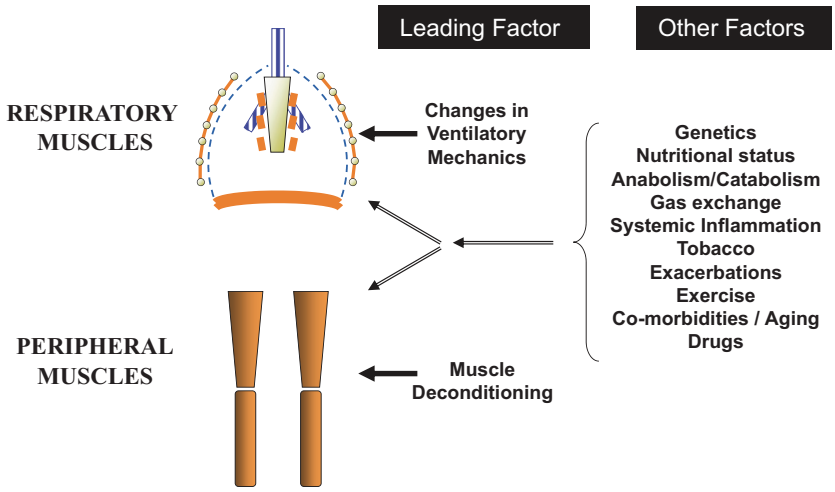

Fig. 1. Main factors thought to contribute to respiratory and/or peripheral muscle dysfunction in chronic obstructive pulmonary disease (COPD). Pulmonary hyperinflation appears as the main factor contributing to respiratory muscle dysfunction, whereas deconditioning seems to play the key role in limb muscle dysfunction. However, additional systemic factors, such as tobacco smoking, systemic inflammation, intense exercise, exacerbations, nutritional and gas exchange abnormalities, anabolic insufficiency, comorbidities, and drugs also modulate muscle function.

above. Further, these factors (and perhaps some others that still remain unidentified) induce a series of cellular and molecular events within the muscles that can have a negative effect on their structure and function. Muscle damage (137), the presence of local oxidative stress (11, 119) and inflammatory elements (24), the activation of proteolytic pathways (193), and even some signs of a true myopathy (for instance the presence of paracrystalline inclusions) (109), have been described in respiratory muscles of COPD patients and can jeopardize their function (Table 1).

Certainly, the diaphragm of hyperinflated COPD patients develops less force than that of healthy subjects when both groups are making the effort at their own functional residual capacity (FRC). However, the situation becomes completely different if healthy volunteers are forced to increase their lung volume to similar levels than those of the patients. Then, it has been shown that the latter group can develop even greater diaphragmatic force than the former (182). This suggests that to some extent respiratory muscles undergo a beneficial adaptation in COPD that coexists with the negative scenario that has been described in previous paragraphs. It is believed that this adaptation also derives from the increase in mechanical loads that occurs in the respiratory system of COPD patients, which would emulate muscle training. The molecular and cellular changes that are believed to be induced by this "training effect" in the diaphragm of COPD patients include shorter sarcomeres (136), increases in the proportion of myosin heavy chain I (MyHC-I), type I fibers (45, 103), capillary contacts per fiber (45), and mitochondrial density (136), and enhanced mitochondrial respiratory chain capacity (163, 207).

Whereas changes in sarcomere length would partially counterbalance the negative effects induced by the displacement of the diaphragm length-tension curve on diaphragmatic force in COPD patients, the other changes would confer the muscle an enhanced aerobic capacity. Importantly, some of these modifications are not restricted to the diaphragm since they have also been found in other respiratory muscles (85, 104, 163). This is the case of the external intercostal muscle of COPD patients, which has shown an increased oxidative capacity in vitro (163), probably related to its higher capillary density and enhanced activity of different enzymes involved in the aerobic pathways (85, 163, 172). However, no significant changes have been consistently found in the proportion of type I fibers in this muscle. By contrast, in the only study published so far in which the structure of the parasternal muscles was analyzed in COPD patients, an increase in the percentage of type I fibers and MyHC-I was reported (104).

In summary, in patients with COPD many different factors can influence respiratory muscle structure and function, acting in opposite directions. A few of them exert clear deleterious effects, while others may also exert a beneficial influence that would counterbalance, at least in part, the impact of the former. Therefore, it can be assumed that respiratory muscles operate in a sort of delicate balance in COPD. Any additional deleterious event taking place in this precarious scenario (i.e., exacerbation, exercise) may easily lead to ventilatory failure.

LOCOMOTOR MUSCLES

Functional impairment of limb muscles (often referred to as peripheral muscles) is present in about one-third of COPD patients, having important clinical consequences for them, since it is associated with low exercise tolerance (72), a reduction in quality of life (132), greater use of health care resources (40) and higher mortality (191). Numerous studies have demonstrated the loss of muscle strength that occurs in the limbs of patients with COPD (16, 72, 73, 79, 156). Most of these studies have been performed in lower limb muscles, especially the quadriceps (16, 73, 79), although there are also some studies in upper limb muscles (72, 156). Interestingly, the decline in limb muscle strength, and particularly that of the quadriceps muscle, has been shown to be two to four times faster in COPD patients than in healthy individuals (79). Although limb muscle endurance has been less studied than strength, different studies have shown that this functional property is also reduced in COPD patients (28, 196, 199). It should be noted that limb muscle dysfunction may occur even in individuals exhibiting mild to moderate airway obstruction (179). Moreover, limb muscle dysfunction is absent in half of the COPD patients with severe disease (179). This interindividual heterogeneity for the same level of lung function impairment implies that the latter is not the main factor that causes muscle dysfunction in COPD patients. There are many evidences that suggest that a significant role should be attrib-

Table 1. *Main structural and functional findings described in skeletal muscles of COPD patients*

	Fibers	Capillarity	Mitochondria	Muscle Injury	Oxidative Stress	Local Inflammation	Apoptosis	Protein Imbalance	Oxidative Capacity	Contractility Defect
Respiratory Muscles										
Diaphragm	Type-I % ↑ Size ↓/=	Density ↑ Contacts ↑	Density ↑ Inclusions present Abnormal function*	↑	↑	Cells =, Cytokines ↑	↑ (TUNEL) = (EM)	Present	↑ O/G ↑/=	Present
External intercostals	Type-I % ↓/= Size =	Density ↑	Density ↑ Abnormal function	↑	NA	Cells = Cytokines ↑	= (TUNEL) = (EM)	NA	↑ O/G ↓/=	Absent
Parasternals	Type-I % ↑ Size =	NA	NA	NA	NA	NA	NA	NA	NA	NA
External oblique	Type-I % ↓ Size =	NA	NA	NA	NA	NA	NA	NA	NA	NA
Peripheral Muscles										
Quadriceps muscle	Type-I % ↓ Size ↓/=	Contacts ↓	Density ↓ Abnormal function*	↑	↑	Cells ↑ Cytokines ↓/↑	↑ (TUNEL) = (EM)	Present	↓ O/G ↓	Not clear
Tibialis anterior	NA	Density ↓ Contacts ↓	Density ↓	Possible	NA	NA	NA	NA	= =	NA
Deltoid muscle	Type I % = Size ↑ + ↓	NA	NA	NA	NA	NA	NA	NA	O/G =	NA
Biceps brachii	Type I % ↑/= Size ↓	NA	NA	NA	NA	NA	NA	NA	O/G =	NA
Other Muscles										
Latissimus dorsi	Type I % = Size ↑	NA	Abnormal function	NA	NA	NA	NA	NA	O/G =	NA

COPD, chronic obstructive pulmonary disease; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; EM, electron microscopy (ultrastructural analysis); O/G, oxidative/glycolytic enzyme ratio; contractility defect: force generation in isolated fibers. NA, no data available; =, unchanged; /, or; +, coexistence; *, respiratory chain capacity ↓ and reactive oxygen species ↑.

uted to muscle deconditioning (or "detraining"), which would result primarily from the sedentary lifestyle that frequently follows the increased breathlessness during exercise that characterizes COPD (Fig. 1) (20, 66). Interestingly, limb muscle dysfunction can also contribute to a further reduction in physical activity, generating a vicious circle. Moreover, it has been shown that maintenance of even a moderate level of physical activity reduces hospital admissions (59), and is associated with better functional status (61) and life expectancy (59) in COPD patients, while it delays lung functional decline and even COPD risk in smokers (60). Three main arguments support the key pathogenic role attributed to muscle deconditioning in limb muscle dysfunction. First is the fact that functional and structural impairment appears to be more pronounced in lower limb than in upper limb muscles (63, 64, 76), which are believed to be less severely exposed to the consequences of a reduction in physical activity (63). Second, many of the changes and phenomena reported in peripheral muscles of COPD patients (this will be reviewed in more detail in other reviews of the present highlighted topic) are quite similar to those described in muscle disuse (17, 26, 27). This is the case, for instance, of fiber atrophy, decreased percentage of aerobic fibers, reductions in the activity of oxidative enzymes and capillary density, as well as the presence of oxidative stress and early lactate release during exercise (66, 144). Third, most of these findings can be partially reversed by muscle training (114, 135). However, some other abnormalities such as marked cachexia or increased muscle oxygen consumption at isocharge (171) still persist despite training, suggesting the presence of additional factors that are also involved in the pathogenesis of peripheral muscle dysfunction in COPD. Those factors are most probably of systemic nature and presumably include genetic background, tobacco smoking, aging and comorbidities, systemic inflammation, exacerbations, intense exercise, nutritional and gas exchange abnormalities, anabolic/catabolic hormone imbalance, and the effects of some drugs (5, 66).

SYSTEMIC FACTORS INVOLVED IN MUSCLE DYSFUNCTION

A controversial issue refers to which elements related to muscle dysfunction in COPD would be considered ethiopathogenic factors, and which others should be treated as mechanisms of such a dysfunction or merely as muscle findings. In this regard, in the present review, "factors" have been defined as those elements of systemic origin that may influence muscle function in COPD patients. However, events occurring inside the muscle tissue, which in turn, may provoke further structural or biological derangements or even directly alter muscle function, have been defined as "mechanisms." Since many of the systemic factors involved in the impairment of muscle function will be extensively discussed in the other minireviews of this Highlighted Topic, in the present review, the different mechanisms potentially involved in COPD muscle dysfunction will be discussed using a rather general approach.

Systemic inflammation. The inflammatory response may lead to the activation of different cellular pathways that can result in muscle atrophy and/or muscle dysfunction. This is the case of apoptosis, autophagy, oxidative stress, and catabolic systems such as that of the ubiquitin proteasome (62). Furthermore, certain proinflammatory cytokines can directly inhibit muscle contraction (161). Systemic inflammation may occur in pa-

tients with COPD as shown in different reports, in which increases in blood levels of white cells and different biomarkers such as C-reactive protein, fibrinogen, and several proinflammatory cytokines have been demonstrated (43, 58). Initially, it was thought that systemic inflammation found in COPD derives from that which occurs primarily in the lung, which would spread later on to the rest of the body through the bloodstream ("spillover" theory) (183). However, the absence of correlations between the level of inflammatory markers in the lung and blood or other organs including muscles, and the presence of muscle changes preceding pulmonary abnormalities strongly argue against this possibility (13, 66, 183). This suggests that extrapulmonary manifestations of COPD may start in parallel to the lung disease, being the direct consequence of the same insults. Another intriguing question is to elucidate the mechanisms involved in the perpetuation of the inflammatory response after cessation of the initial stimulus. Recent evidence seems to indicate that these mechanisms are probably related to an abnormal immunologic response (19). It should be noted, however, that not all authors have been able to find systemic inflammation in stable COPD patients (43, 90, 192). In fact, this situation is much more evident during exacerbations (90).

Systemic oxidative stress. Reactive oxygen species (ROS) are a product of the aerobic metabolism and are normally present in different tissues including muscles. However, when there is an imbalance between the production of ROS and the antioxidant systems, oxidative stress occurs leading to deleterious changes in different key molecules and tissue damage (66). Oxidative stress and inflammation are mutually interrelated. Whereas the former can act as a signal for the expression of inflammatory mediators (65), the latter (along with other factors such as a reduced blood flow, hypoxia and contractile activity) can modulate the level of ROS production and therefore of oxidative stress (65, 190) (Fig. 2). Oxidative stress has been found not only in the lungs but also in the blood and muscles of stable COPD patients (10, 11, 155, 167). Moreover, both exacerbations and exercise can increase plasma and/or muscle levels of oxidative stress markers (12, 77, 90). Although the relationships between systemic oxidative stress and muscle dysfunction are not yet clearly elucidated, a direct relationship has been found between the level of oxidative stress within the muscle tissue and muscle function impairment (11).

Gas exchange abnormalities. Both hypoxia and hypercapnia may have deleterious effects on muscle function in COPD patients (2, 94). Muscle hypoxia can be present in such patients due to the reduction in oxygen delivery to the tissues (141) derived from their hypoxemia and the frequent coexistence of anemia (212). Hypoxia may induce systemic inflammation, oxidative stress, protein imbalance, apoptosis and impaired muscle regeneration (22, 67, 99, 214), generating a reduction in muscle mass and targeting different elements involved in the oxidative capacity of muscles (80, 141). Therefore, it is not surprising that hypoxia can lead to impaired muscle strength and endurance in COPD patients (66). Hypercapnia, in turn, may act in skeletal muscles directly or through inducing a decrease in extracellular and cellular pH. Whereas hypercapnia has been shown to induce muscle dysfunction both in normal subjects and in COPD patients (2, 154), acidosis may induce impaired muscle proteostasis (balance between protein synthesis and breakdown) (52).

Inefficiency of anabolic hormones. Growth hormone is an anabolic agent that induces an increase in the production of the insulin-like growth factor 1 (IGF-1), subsequently promoting an increment in protein synthesis and inhibition of protein degradation (54). Therefore, it results in muscle growth and increases in muscle mass (106). The levels of the growth hormone can be reduced, normal, or even increased in COPD patients (112, 176), but its interaction with IGF-I seems to be altered (33), potentially leading to reductions in muscle mass. Although exogenous growth hormone increases body weight and muscle mass in undernourished COPD patients, no clear effects have been demonstrated in muscle function (23).

Testosterone is a steroid hormone secreted by the gonads and to a lesser extent by the adrenals that has relevant anabolic effects. Its levels are much higher in men than in women, participating in the differential development of their muscle mass. Testosterone increases the synthesis of muscle structural proteins, an action that can lead to muscle hypertrophy (21). Different authors have shown that testosterone levels can be low in COPD patients, potentially leading to a reduced muscle mass (91, 100). However, the implications of this hypogonadism on muscle dysfunction are not clear, since either muscle strength and endurance or exercise capacity appears to remain unaltered (100). The mechanisms of testosterone deficiency in COPD remain unclear although aging, hypoxia, smoking, and steroid therapy might be involved (5, 33).

Comorbidities and aging. With the increase in life expectancy in developed societies, the number of elderly COPD patients is becoming very high. One of the main causes of muscle functional impairment in aged populations is sarcopenia, characterized by the loss of skeletal muscle mass and changes in muscle characteristics (fiber atrophy and loss,

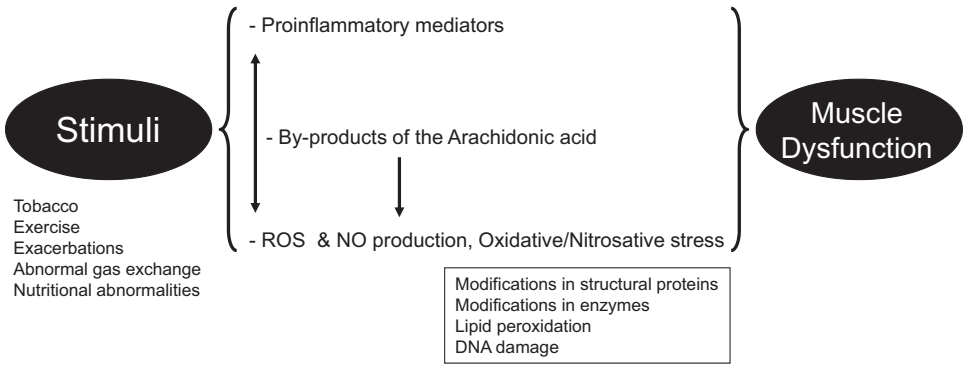

Fig. 2. Role and relationships of inflammation and oxidative stress in skeletal muscle dysfunction of COPD patients. Factors involved. ROS, reactive oxygen species.

fibrosis, degeneration of the neuromuscular junction) (129), both leading to muscle dysfunction (66). Moreover, changes in muscle mass and muscle dysfunction are also frequent in highly prevalent comorbidities of COPD such as chronic cardiac failure, diabetes, and cancer (35, 160, 188).

Tobacco. Despite the difficulties to separate the effects of tobacco smoking from those of COPD, it is known that nonsymptomatic smokers often complain of whole body fatigability (29), showing less muscle resistance (131). Moreover, evidence emerging from animal and human studies supports the fact that tobacco smoking may induce muscle dysfunction through different mechanisms (13, 210). These include oxidative stress, inflammation, imbalance between protein synthesis and degradation within the muscle, neuromuscular transmission failure, tampering in the oxidative capacity of the muscle and CO toxicity (13, 140, 210, 215).

Exercise and training. The understanding of muscle adaptations to exercise and training is essential for the analysis of the factors leading to muscle dysfunction in COPD. Exercise is necessary to maintain an appropriate performance in skeletal muscles. However, intense exercise can induce metabolic changes (lipolysis, dysregulation of carbohydrate use, altered amino acid kinetics) (56, 57), systemic inflammation, systemic and local (muscle) oxidative stress (30, 31), hampered expression of key muscle genes regulated by the nuclear transcription factor kappa B (NF-κB) (such as those encoding inflammatory cytokines, antioxidants, heat-shock proteins, and antiapoptotic factors) (126), muscle damage (137), and muscle function impairment (98) in COPD patients. Interestingly, some of these findings are more evident in those individuals with low body weight (56, 57, 198).

Compared with healthy subjects, some COPD patients exhibit an abnormally high muscle oxygen uptake and ATP consumption at a given submaximal mechanical load during exercise (101, 102, 164, 171). While the mechanism underlying this phenomenon, known as mechanical-energetic inefficiency, is unclear in COPD, in chronic cardiac failure nitroso-redox imbalance seems to be a main contributing factor (12, 74, 75, 167, 184). Interestingly, recent studies using systems biology approaches have analyzed differences between COPD patients and healthy sedentary subjects regarding skeletal muscle transcriptomes (195) and proteomes (12) together with altered blood metabolomes (168). These studies have shown that patients exhibit a lack of correlation between the expression of genes involved in bioenergetics and tissue remodeling pathways, as well as an abnormal expression of enzymes involved in chromatin modification (195). Moreover, some of these abnormalities as well as an abnormal amino acidic profile observed in blood (168) seem to be more evident in patients exhibiting muscle wasting. These findings may suggest the presence of altered myogenesis and the activation of epigenetic mechanisms in skeletal muscles of COPD patients. Besides, the failure to activate relevant skeletal muscle pathways in a coordinated fashion would eventually lead to the development of structural changes. Finally, the significant association found between a number of histone modifiers and peak oxygen uptake during exercise in COPD patients supports the hypothesis that cell hypoxia also plays a role in muscle dysfunction (195). Taken together, it is possible to speculate that in peripheral muscles of COPD patients an abnormal interplay between sedentarism and the systemic factors would result in altered muscle structure and biology (including impaired regeneration and remodeling capacity) leading to the occurrence of muscle dysfunction.

It is widely accepted that standard training programs are clinically beneficial at any stage of the disease (171). However, the effects of training on muscles of COPD patients are much more complex. In contrast with healthy subjects, who show a marked enhancement in their muscle antioxidant potential after training, COPD patients exhibit only a minor increase or even a decrease (152, 153). Again, this phenomenon is especially important in those patients with muscle wasting (153), in whom high-intensity endurance training may induce oxidative stress at muscle level over the first weeks (12). Interestingly, these effects seem to be transient, not being evident at the end of training programs of standard duration (8 wk) (167). It is of note that training-induced adaptations of COPD patients, reflected in muscle transcriptomic and blood metabolomic profiles (168, 195), show abnormalities consistent with the alterations alluded to above, such as abnormal amino acid metabolism and altered tissue remodeling. Additionally, training does not modify the abnormal relationships observed between cell bioenergetics and tissue remodeling (195).

Exacerbations. COPD patients exhibiting respiratory or peripheral muscle weakness have an increased risk of hospital admissions due to exacerbations of their disease (6, 203). Moreover, exacerbations appear to further contribute to muscle wasting and dysfunction (142, 185, 203), probably as a result of the increased systemic inflammation and oxidative stress (1, 34, 185), infection, marked physical inactivity (142), and negative energy imbalance (32, 82, 200) that characterize these episodes, as well as some of the drugs used in their treatment (39). Moreover, multiple pathways involved in muscle dysfunction (ubiquitin-dependent protein catabolism, apoptosis, oxidative stress, among others) seem to concomitantly occur under these circumstances (34). Therefore, it is not surprising that muscle functional impairment develops quickly during exacerbations, lasting for a relatively long time (185). Inactivity again appears to play a leading role in the loss of muscle mass and function taking place during the course of exacerbations, as training was shown to prevent, at least in part, this impairment (170) through upregulating anabolic pathways in muscles (194).

Muscle wasting. Patients with COPD often show nutritional abnormalities, while a subgroup is clearly cachectic (9, 178, 201, 209). Moreover, malnourishment often associates with muscle weakness (5, 201) and poor prognosis (202, 211), which is believed to be the result of the interaction between different factors, including reduced energy intake, systemic inflammation, enhanced lipolysis and, of particular interest, a mismatching between muscle protein synthesis and degradation (50, 51, 78, 96, 130, 146, 177, 213). Skeletal muscles are major protein stores, and some of the amino acids that compose these proteins are potential sources of energy. Therefore, it is not surprising that, under conditions involving an increase in energy expenditure (8, 177), muscle proteolysis becomes increased. In COPD, this occurs mostly through activation of the ubiquitin-proteasome system (34, 46, 55, 143). The proteasome is a cellular structure that degrades proteins (mostly those previously tagged with ubiquitins through different ligases) and peptides (especially those which have been modified by oxidative stress) (18, 133, 162, 173, 186, 197) (Fig. 3). In

contrast, other biological pathways such as mitogen-activated protein kinases (MAPK), myogenin, myostatin, and oxidants (which will act as second messengers), do not seem to play a major role in the activation of proteolysis in these patients. A key point to better understand the relationships between muscle wasting and muscle dysfunction in COPD is to clearly identify the differences present in the quadriceps muscle of patients with normal and low body weight. In this regard, the latter show *1*) more abnormal transcriptomic and proteomic profiles (12, 195); *2*) more reduced protein synthesis (48, 130); *3*) increased levels of protein ubiquitination (55); *4*) higher levels of nitrosative stress and activation of NF-κB (4, 55); *5*) a lower exercise-induced increase (or even a decrease) in antioxidants (152, 153); and *6*) a significant loss of structural proteins and content of key enzymes (55, 128), as well as smaller fibers (55), when compared with patients with normal body weight.

Drugs. Different drugs used in COPD patients for the treatment of the disease or its comorbidities can induce changes in skeletal muscles. Corticosteroids, especially when used systemically, can induce both acute and chronic myopathies. Although the systemic use of these drugs has decreased considerably, they are still useful in exacerbations and in those patients with a very advanced disease. The acute form of the steroid-induced myopathy is characterized by rhabdomyolysis and the loss of thick myosin filaments both resulting in marked weakness that may affect different muscle groups (159, 205). This myopathy can be observed mostly following the administration of high doses of corticosteroids (89). The chronic myopathy induced by these drugs, in turn, is usually the result of a long-term administration of even moderate doses (39), being characterized by the atrophy of type II fibers, abnormalities in carbohydrate metabolism and a negative balance in protein metabolism (39, 107). All these changes result in muscle weakness, characterized in this case by targeting proximal muscle groups (39).

Anticholinergic drugs are widely used in patients with COPD because of its relaxing effect of the bronchial smooth muscle, which favors bronchodilation. They do not have relevant effects on skeletal muscles at standard doses, but at higher levels can lead to a reduction in the contractile reaction time and to muscle dysfunction (92, 151). Other drugs used frequently in patients with COPD are inhibitors of phosphodiesterase 4 and 5 (PDE_4 and PDE_5, respectively), which act by relaxing smooth muscles. Whereas PDE_4 is used to reduce airway inflammation and bronchoconstriction, PDE_5 is being employed to treat primary and secondary pulmonary hypertension (25, 97). An interesting effect of PDE_5 is its potential in reducing muscle damage in some myopathies (7). However, some of the phosphodiesterase inhibitors have also been shown to reduce the effects of insulin on skeletal muscles and might result in an impairment in their function (113). Finally, there is a wide variety of drugs used in cardiovascular comorbidities of COPD that may also have harmful effects on skeletal muscles. This is the case of β-blockers that can facilitate muscle fatigue (88), calcium channel blockers that can reduce contraction and attenuate muscle regeneration (145), statins that can induce a specific myopathy (97), and some diuretics that can induce dyselectrolytemia, potentially tampering muscle function (124).

SKELETAL MUSCLE FINDINGS AND LOCAL MECHANISMS

A significant number of studies have investigated the metabolic and structural changes that occur in skeletal muscles. Most of these studies were conducted in limb muscles, given the difficulties to have access to samples of respiratory muscles. Since the findings reported in the latter have already been mentioned in a previous section this part will focus on peripheral muscles. The changes that have been described in this muscle group vary (Table 1) but can be classified according with their potential effects. In this regard, different authors have shown *1*) reduced muscle mass (122, 169) and fiber size (55, 68, 206), likely to be related, at least in part, to the concomitant imbalance between protein synthesis (reduced) and breakdown (enhanced) (36, 37, 38); *2*) reductions in the expression of the MyHC-I isoform, percentage of type-I fibers, mitochondrial density, capillary density and capillary-fiber ratio, myoglobin content, and activities of different key oxidative enzymes (69, 70, 83, 84, 86, 115, 174, 181, 206); *3*) mitochondrial abnormalities including an increase in the local production of ROS (147, 148, 149, 150), uncoupling in oxidative pathways (83, 115, 134, 175), abnormal transition pore kinetics and cytochrome *c* release, and changes in mitochondrial DNA (12, 134, 147); and *4*) oxidative stress (targeting

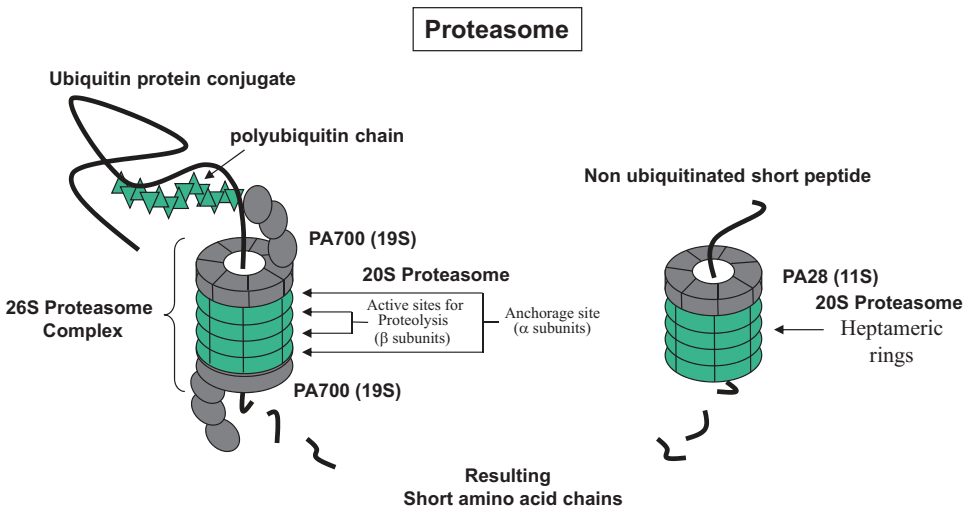

Fig. 3. Proteolytic pathways: 26S (*left*) and 20S-PA28(11S) (*right*) proteasome complexes. The 26S proteasome is composed of two regulator structures (PA700) and a catalytic core (20S proteasome), which in turn consists of two inner and two outer heptameric rings forming a cylinder. Proteolysis occurs in the inner rings (β subunits) whereas each one of the outer rings (α subunits) acts as an anchor point for a PA700 (19S). Ubiquitinated proteins enter to this structure and become degradated. The 20S unit can also be attached to other structure, named PA28 (11S), which is able to degradated short peptides that have been previously modified by reactive oxygen species and are nonubiquitinated.

DNA and essential structural proteins and enzymes) (10, 11, 55, 150), local inflammation (14, 125, 127), enhanced apoptosis (3, 14), sarcolemmal and sarcomera damage (138), and a reduction in the expression of key-molecules involved in muscle growth and regeneration (i.e., myogenin and m-cadherin) (55; Martínez-Llorens JM, unpublished observations). Significantly, although some authors have suggested the involvement of autophagy in muscle dysfunction (81), its presence has not been demonstrated to date (143). Some of the abnormalities mentioned here such as those included in *point 1* will have a main impact on muscle strength (66), whereas others such as those referred to mostly in *point 2* would impair the aerobic components of the muscle predominantly targeting muscle endurance (196), or may contribute to impaired muscle bioenergetics such as those included in *point 3* (49, 171), or would tamper directly the contractile properties of the muscle resulting in muscle dysfunction in general as for those mentioned in *point 4*. It should be noted that some of the changes found in the quadriceps and tibialis anterior muscles such as the decrease in the proportion of type I fibers are more pronounced in patients with more severe COPD (71), while others can be seen even in mild-to-moderate stages of the disease (10). It is also important to highlight that most of the studies mentioned here were performed using quadriceps muscle samples (most often obtained from its vastus lateralis portion). Therefore, some findings may not be directly extrapolated to other peripheral muscles, and especially to those located in the upper limbs. This is the case, for instance, for the reported reduced activity of oxidative enzymes or fiber atrophy described in the quadriceps and/or the tibialis anterior that appear to be absent or less marked in the deltoid muscle (63, 76).

Taken together, the abovementioned hallmarks would characterize an impaired limb muscle phenotype that becomes inadequate to correctly perform its functional tasks, thus contributing to the patients' exercise limitation. In fact, this limb muscle phenotype can be considered as less balanced than that of respiratory muscles, where negative and positive changes coexist in COPD patients.

FUTURE PERSPECTIVES

Current evidence emerging from a great deal of investigations conducted in the last two decades has clearly demonstrated the contribution of different local and systemic factors and several molecular and cellular mechanisms to muscle dysfunction in COPD. However, although these biological insights have certainly enhanced our knowledge on this clinical problem, a complete and comprehensive view of its etiology is still lacking. The incorporation of new technical and conceptual advances in basic sciences as well as new perspectives such as those coming from the bioinformatics and bioengineering fields might help investigators working on this specific arena to address questions from complementary points of view. In this regard, epigenetic studies and recent multilevel analyses using systems biology-medicine approaches are already generating novel and fascinating hypotheses (15, 105, 189, 195), which will eventually provide new biological insights accounting for the skeletal muscle dysfunction of COPD patients, in hopes that a more comprehensive understanding of the problem will be achieved in the near future. This should lead to new therapeutic and even prophylactic approaches for the management of COPD muscle dysfunction.

CONCLUSIONS

Muscle dysfunction is a common manifestation among COPD patients. Both local and systemic factors play a relevant role in its pathogenesis. Among the former, mechanical imbalance due to increased preloads and hyperinflation constitute the main factor that contributes to respiratory muscle dysfunction, whereas deconditioning due to reduced physical activity is the main driver of peripheral muscle dysfunction. As to the effects of the systemic contributors, tobacco, nutritional and gas exchange abnormalities, exercise, exacerbations, systemic inflammation, and drugs are believed to also contribute to muscle dysfunction in patients with COPD. All these factors are able to modify the local microenvironment of the muscle, resulting in protein imbalance, injury, local inflammation, and oxidative stress, among other phenomena, subsequently determining muscle structure and function.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: J.G. analyzed data; J.G. prepared figures; J.G., A.A., and J.R. drafted manuscript; J.G., A.A., and J.R. edited and revised manuscript; J.G., A.A., and J.R. approved final version of manuscript.

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