

# Update on the Mechanisms of Muscle Dysfunction in COPD

Joaquim Gea and Esther Barreiro

Servicio de Neumología, Hospital del Mar, Unidad de Investigación en Músculo y Aparato Respiratorio (URMAR), IMIM, Departamento de Ciencias Experimentales y de la Salud (CEXS), Universidad Pompeu Fabra, CIBER en Enfermedades Respiratorias, Barcelona, Spain

Muscle function is essential for both ventilation (respiratory muscles) and interacting with the environment (peripheral muscles). One of the systemic manifestations of chronic obstructive pulmonary disease (COPD) is skeletal muscle dysfunction. While the causes of this dysfunction are poorly understood, various local and systemic factors appear to play a role. Among the systemic factors are those arising from the lung disease itself, which increases respiratory muscle activity, leads to unfavorable geometric relationships, and results in a reduction in the patient's use of the peripheral musculature. Other systemic factors include inflammation and oxidative stress, malnutrition, impaired gas exchange, comorbidity, and certain myotoxic drugs. Local factors include muscle inflammation and oxidative stress, apoptosis, injury, and impaired regenerative capacity. All of these factors interact in different ways in each muscle group, giving rise to various phenotypes and specific contractile capacities.

**Key words:** *Respiratory muscles. Peripheral muscles. Muscle dysfunction. Lung disease.*

## Introduction

Muscle contractility is a vital function in higher animals because it is essential to both movement and the ventilation-perfusion processes necessary for tissue metabolism. It is so indispensable that the proteins directly involved in contractility (actin and myosin) are found, with slight variations, in many living beings and are phylogenetically very old. In humans, the different types of muscle are usually classified into 3 categories on the basis of function and structure: smooth muscle, striated muscle, and cardiac muscle. This review deals with striated muscle, so called because of its characteristic striped or striated appearance.

Correspondence: Dr J. Gea  
Servicio de Neumología Hospital Mar  
Pg Marítim, 27  
08003 Barcelona, Spain  
E-mail: jgea@imim.es

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Actualización en los mecanismos de disfunción muscular en la EPOC

La función muscular es esencial tanto para la ventilación (músculos respiratorios) como para la vida de relación (músculos periféricos). Los pacientes con enfermedad pulmonar obstructiva crónica (EPOC), en el contexto de su afectación sistémica, presentan disfunción muscular. Las causas de ésta no están totalmente definidas, aunque parecen intervenir diferentes factores tanto sistémicos como locales. Entre los primeros figuran los derivados de la propia enfermedad pulmonar: aumento de la actividad y geometría desfavorable para los músculos respiratorios, y disminución de la actividad para los periféricos. También son factores generales la inflamación-estrés oxidativo, las alteraciones nutricionales y del intercambio de gases, la comorbilidad y los fármacos miotóxicos. En cuanto a los locales, incluyen inflamación-estrés oxidativo en los músculos, apoptosis y daño con baja capacidad regenerativa. Estos factores interaccionarían de forma diferenciada en cada grupo muscular y darían lugar a fenotipos y capacidad contráctil específicos.

**Palabras clave:** *Músculos respiratorios. Músculos periféricos. Disfunción muscular. Enfermedad pulmonar.*

The striations reflect the arrangement of the basic units of contraction, called sarcomeres, composed of myosin and actin filaments. The movement of the heads of the myosin molecule (thick filaments) along the actin molecules (thin filaments) shortens the sarcomeres causing the muscle to contract. In some cases, the purpose of this contraction is to bring together the bones to which the muscles are attached at either end, thereby making possible locomotion and the manipulation of objects. The muscles that do this are generally called the peripheral skeletal muscles. In other cases, the purpose of the contraction is to maintain structures in place despite body movements and the effect of forces such as gravity. These muscles are usually called the postural skeletal muscles or anti-gravity muscles. Finally, the purpose of the third type of contraction is to modify intrathoracic and intra-abdominal pressures, changing the volume of these compartments and causing air to move in and out of the lungs. The muscles that perform this function are called the respiratory muscles.

When, whether due to aging or a disease process, our muscles lose their ability to contract, we become fragile

and dependent and may even die. Chronic obstructive pulmonary disease (COPD) is one of the diseases associated with functionally deficient muscle contraction (dysfunction). This disease is characterized by airflow limitation that is not fully reversible, the result of structural changes in the lung parenchyma and airway caused principally by smoking.<sup>1</sup> However, in recent years there has been a growing awareness of the importance of the inflammatory processes and systemic manifestations associated with COPD.<sup>1,2</sup> It is thought that both the initial noxious stimulus and the conditions that perpetuate the COPD process may lead to the involvement of a number of different organs. Muscle dysfunction is one of the most studied systemic manifestations of COPD.<sup>3-5</sup> While the chief repercussion of this condition is a reduction in exercise capacity, the disease also affects quality of life in these patients and ultimately their survival.<sup>6</sup> Muscle dysfunction affects both respiratory and peripheral muscles, and our understanding of its causes has improved considerably in recent years. The object of this review is to provide an update on our current understanding of the mechanisms of muscle dysfunction in patients with COPD. First, however, we will describe the functions of different muscle groups and the functional properties of muscles in general.

### Peripheral Skeletal Muscles

The term peripheral muscle refers to the striated muscles located in the 2 girdles and the extremities. The muscles of the shoulder girdle and upper limbs enable us to manipulate objects and are, therefore, essential for many of the tasks involved in personal care.<sup>7,8</sup> The muscles of the pelvic girdle and lower limbs are essential for locomotion, making them crucial in the activities of daily living. Most of the research undertaken to date on peripheral muscle dysfunction and its possible causal mechanisms has focused on the quadriceps, a muscle located at the front of the thigh. Studies on muscle structure and biology, in particular, have been based on findings in the vastus lateralis, the external part of this muscle. Despite the clear advantages such a focus affords in terms of the comparability of results, there are also drawbacks. We know that certain phenotypic characteristics of the quadriceps vary considerably depending on the area of the muscle biopsied.<sup>9</sup> Moreover, the conclusions obtained in these studies have often been generalized to the muscles in other regions, an extrapolation that has been shown to be invalid.<sup>4,5,10</sup>

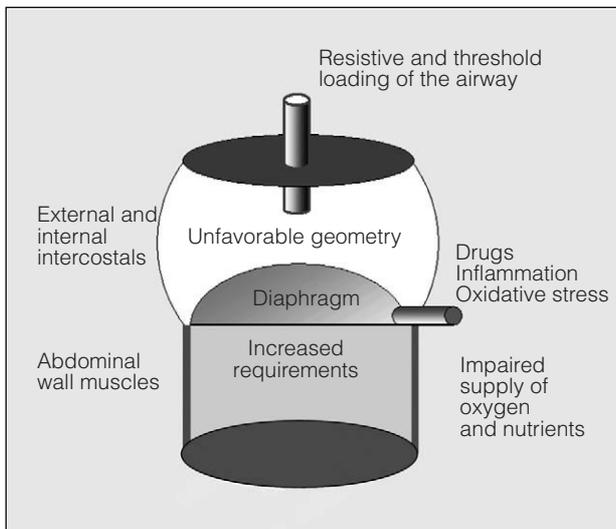
### The Respiratory Muscles

The function of the respiratory muscles is to provide the lungs with the ventilation necessary to ensure adequate gas exchange. Some muscles are specialized for inspiration, others for expiration, and a few are involved in both functions. The basic inspiratory muscles are the diaphragm (the most important muscle in this group, particularly in healthy individuals and at rest), the parasternals, and the external intercostal muscles.<sup>11-13</sup> However, when the load on the ventilatory system

increases, several other muscles gradually become involved in inspiration (the scalene, sternocleidomastoid, latissimus dorsi, serratus, and pectoral muscles).<sup>14-16</sup> All of these muscles contribute to the expansion of the thoracic cavity and this, together with the elastic recoil of the lung itself, increases intrapleural pressure. This increase is transmitted in a somewhat attenuated form to the alveoli, and the resulting difference between alveolar and atmospheric pressure causes air to flow into the lungs. The diaphragm is the most studied respiratory muscle in terms of functional contribution, structure, and biology. More recently, however, studies have been published on other muscles, including the parasternal and external intercostals, and the latissimus dorsi. Expiration, on the other hand, is an essentially passive phase in the ventilatory process under normal circumstances. When the inspiratory muscles relax, pleural pressure loses part of its negativity and alveolar pressure becomes slightly positive with respect to atmospheric pressure, causing air to move out of the lungs.<sup>17</sup> The expiratory muscle groups only come into play if an increase in the speed of exhalation is required or when the airway is obstructed. The main expiratory muscles are the abdominals (the rectus abdominis and in particular the transverse and oblique abdominals) and the internal intercostals, with the exception of the parasternal intercostals.<sup>13,18,19</sup> Certain muscles, such as the diaphragm and the external intercostals, appear to play a role throughout the entire respiratory cycle, and some authors consider them to be both inspiratory and expiratory, although they are predominantly inspiratory.

### The Functional Properties of Muscles and Muscle Dysfunction

All striated muscles have 2 basic functional properties, strength and endurance. Strength is the mechanical expression of the maximum contractile force of the muscle. Endurance, on the other hand, is the ability to sustain a submaximal force over time. Strength and endurance depend on different structural and biological elements. While strength is, above all, a function of muscle mass, endurance depends on the aerobic capacity of the muscle (since aerobic metabolism is more efficient and sustainable than anaerobic metabolism). In other words, endurance depends on the proportion of type I fibers in the muscle, capillary density, mitochondrial density, and enzyme activity in metabolic pathways, such as the Krebs cycle and oxidative phosphorylation. Muscle power is defined as the amount of work carried out or of force expended per unit of time, and muscle fatigue is the process that renders a muscle temporarily incapable of functioning. Since this incapacity may be either partial or total, many physiologists consider muscle fatigue to be a continuous process rather than a specific threshold. Muscle fatigue is generally caused by an imbalance between load and capacity, and rest restores the working capacity of the affected muscle. Muscle weakness, by contrast, is defined as a permanent inability of the muscle to contract with sufficient force. Constitutional circumstances are usually responsible for such weakness,



**Figure 1.** Schematic representation of the factors that influence respiratory muscle function in patients with chronic obstructive pulmonary disease (see text for details).

and rest does not restore working capacity. Consequently, other types of interventions must be considered in the treatment of muscle weakness. However, fatigue and weakness are obviously not altogether independent of one another since a weak muscle will become fatigued much more easily.

People whose limb muscles stop functioning properly are unable to work or take care of themselves. Moreover, the inevitable reduction in mobility makes them extremely dependent on those around them and has a negative impact on their quality of life. Failure on the part of the inspiratory muscles to do their job results in hypoventilation and difficulty in sustaining effort, accompanied by disruption of gas homeostasis and the acid-base balance. Malfunction of the expiratory muscles gives rise to difficulties on exertion, coughing, and expectoration of secretions from the airways.

## The Effect of COPD on the Different Muscle Groups

### Mechanical Factors

Besides fixed airway limitation,<sup>1</sup> COPD also gives rise to increased lung volumes, a phenomenon called hyperinflation. Pulmonary hyperinflation has a direct impact on inspiratory muscle function because it changes the length of both the diaphragm (which becomes flatter and shorter) and the external intercostal muscles (which are lengthened), displacing them from the optimal configuration for contraction.<sup>4,17,20</sup> This effect is compounded by increased resistive and threshold loads within the system (greater airway resistance, intrinsic positive end-expiratory pressure, and impaired supply of nutrients and oxygen) (Figure 1).<sup>4,5,10</sup> If to this picture we add the possible presence of inflammatory phenomena, oxidative stress, comorbidity, age, or drugs that affect muscle negatively, a deterioration in muscle function

would appear to be inevitable. It is not surprising, therefore, that the muscles of inspiration in patients with COPD have less strength and endurance than those of healthy individuals of the same age.<sup>21-23</sup> However, the observation that the inspiratory force of COPD patients is maintained relative to the lung volume at which they are obliged to breathe<sup>22</sup> suggests that the most important factor is hyperinflation, although other factors may play a secondary role.<sup>4,5,17</sup> The hypothesis that other factors contribute to muscle dysfunction is supported by evidence that the contractile capacity of fibers taken from the diaphragms of COPD patients continues to deteriorate in vitro.<sup>24</sup>

The expiratory muscles of patients with COPD have also been shown to have reduced strength and endurance.<sup>23,25</sup> However, in this case, the mechanical changes in the respiratory system should not cause muscle dysfunction, particularly in the case of the abdominal wall muscles, since any shortening of these muscles should bring them even closer to the optimal contractile position.<sup>4,17,26</sup> Although the expiratory muscles have to work against increased loads, it is thought that the underlying cause of their dysfunction in COPD must be either systemic factors or factors intrinsic to the muscle.<sup>4,5</sup>

Mechanical ventilation is a special case because it involves the partial reduction or total cessation of respiratory muscle activity, a situation that gives rise to atrophy and other harmful phenomena that contribute to dysfunction.<sup>27</sup> The consequences of this have important implications in both the process of weaning the patient off the ventilator and in the subsequent clinical course. In critically ill patients, ventilatory muscle dysfunction is further aggravated by additional factors, such as sepsis, nutritional abnormalities, and certain types of medication.<sup>4,28,29</sup>

Patients with COPD clearly lose muscle function in the extremities, and this loss is characterized by reductions in strength,<sup>23</sup> endurance,<sup>30,31</sup> and efficiency (greater expenditure of energy for a given load, with earlier production of lactic acid).<sup>32,33</sup> There is a qualitative difference between the peripheral muscle dysfunction of the upper and the lower limbs in that the leg muscles are very probably the group most affected in COPD while upper-limb muscle function is relatively better preserved.<sup>23,34</sup> It is important to note that peripheral muscle dysfunction is not just a local problem, but rather one that has a significant impact on the patients' exercise tolerance.<sup>32,35,36</sup> The mechanical factor that affects the limb muscles is the reduction in activity brought about by the ventilatory limitation and other symptoms associated with the lung disease, although the generally sedentary lifestyle of the population in developed countries also appears to play an important role.<sup>4</sup> This reduced level of activity gives rise to a series of local changes (deconditioning) that in turn lead to a further decline in functional capacity.<sup>37</sup> The relative preservation of muscle function in the arms may be explained by the fact that these limbs are less affected by the deconditioning cycle described above. The hypothesis that deconditioning plays a significant role in peripheral muscle dysfunction in

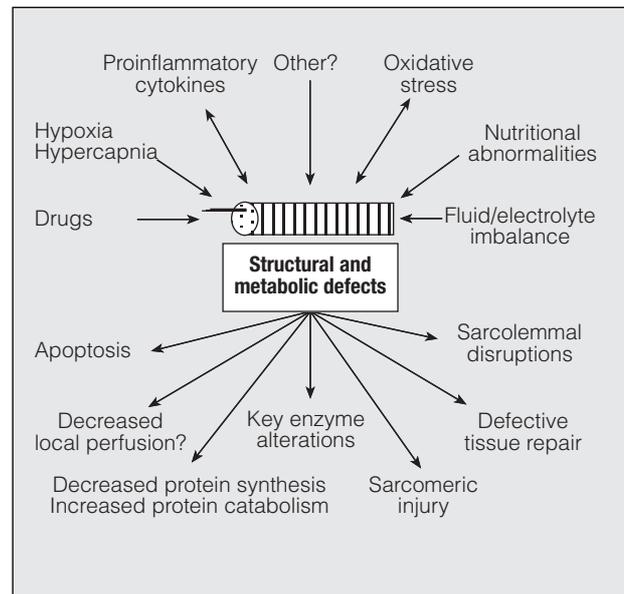
COPD is supported by evidence of a strong similarity between findings in the muscles of COPD patients and the results of studies in models or diseases involving immobilization or a significant reduction in physical activity.<sup>38</sup> Moreover, many of the functional and structural changes identified can be reversed by muscle training.<sup>39</sup> Some of these changes are irreversible,<sup>32,39</sup> however, and some of the same alterations are also found in the arm muscles<sup>23,40</sup> (which are much less subject to the reduction in activity). This leads us to conclude that—as in the case of the inspiratory and expiratory muscles—a number of additional factors favoring peripheral muscle dysfunction come into play and interact with the mechanical factors (Figure 2).<sup>3-5,10</sup>

#### Other Factors Involved in Muscle Dysfunction

**Inflammation.** It has recently been suggested that the systemic manifestations of COPD may be associated with an attenuated form of systemic inflammatory response syndrome.<sup>41</sup> The concept of a systemic inflammatory response syndrome has, until now, generally been used in the context of multiorgan failure associated with sepsis.<sup>28</sup> However, various authors have proposed that other entities, including COPD,<sup>4,41</sup> are also characterized by systemic inflammation (albeit of low intensity) and multiorgan involvement, including muscle dysfunction.<sup>4</sup> There is overwhelming evidence to support the hypothesis that a certain level of systemic inflammation is present in COPD. It has been shown that serum levels of certain markers (C-reactive protein, fibrinogen, and several cytokines) are elevated in these patients<sup>42,43</sup> and higher white blood cell counts have also been found.<sup>43,44</sup>

Inflammation of skeletal muscle can be both a systemic and a local factor. The damaging effect of inflammatory mediators synthesized in other tissues on muscle structure and function has systemic repercussions. It is known that these substances can directly affect the contractile capacity of muscle fibers and may induce increased protein degradation through the activation of catabolic pathways.<sup>5,45</sup> In addition, the presence of inflammatory events in the muscle tissue has also been reported. Some authors have observed an increase in inflammatory cells and cytokines in the limb muscles themselves,<sup>46</sup> although others have been unable to confirm these findings and have even reported a reduction in the expression of inflammatory cytokines in the quadriceps of COPD patients.<sup>47</sup> The respiratory muscles, on the other hand, consistently show increased expression of proinflammatory cytokines, although this phenomenon is not accompanied by the presence of inflammatory cells.<sup>48</sup>

Nevertheless, it remains unclear whether the initial stimulus that affects the muscle is a direct result of the aggressive action of smoking itself<sup>49</sup> or a consequence of the inflammation in the lung parenchyma and airway caused by smoking. In any case, inflammation comes to affect systemic circulation, reaches various organs (including the muscles), and appears to contribute to their dysfunction.<sup>43,50</sup> An intriguing question is what causes the inflammatory response to persist after the initial noxious



**Figure 2.** General factors with local influence on the structure and function of muscle throughout the organism in patients with chronic obstructive pulmonary disease.

stimulus has disappeared. Current thinking on this question is based on the hypothesis that the mechanisms that perpetuate inflammation may be immunological.<sup>51</sup>

What effect exacerbations of COPD may have on muscle mass and function is also an interesting question. If we accept that the inflammatory load of the lungs, whether infectious or not, plays a role in COPD exacerbation,<sup>52</sup> it is then possible to hypothesize that this inflammation may also have systemic repercussions and affect other regions, including skeletal muscle. The situation would be further aggravated by the indirect effect of the exacerbation itself, which increases the mechanical and metabolic load on the respiratory muscles and reduces muscle activity in the limbs. Although research is still needed to clarify this matter, a number of authors have reported a reduction in muscle strength and mass in various parts of the body during exacerbations.<sup>53</sup> It also appears that the physical activity level (a determinant of muscle phenotype) is a prognostic factor for exacerbation in patients with COPD.<sup>54</sup>

**Oxidative and nitrosative stress.** Oxidative-nitrosative stress and inflammation are closely related because the inflammatory mediators—in conjunction with blood perfusion, hypoxia, and muscle activity (whether excessive or insufficient)—regulate the presence of such stress.<sup>5,55,56</sup> Inversely, stress may act as a signal for the expression of proinflammatory molecules.<sup>56</sup>

Reactive oxygen species (ROS) are a product of aerobic metabolism derived from the mitochondrial respiratory chain and certain microsomal enzymes. The presence of a certain proportion of ROS is not harmful and is actually essential for proper muscle contraction.<sup>57</sup> Nitric oxide (NO) is also found in normal muscle and plays an essential role in carbohydrate metabolism, the regulation of blood flow to muscle fiber, and neuromechanical transduction.<sup>58</sup>

The synthesis of NO depends on both constitutive endothelial enzymes and the muscle fibers themselves, although there is also an inducible enzyme form that increases the production of NO in the muscle under certain circumstances.<sup>58</sup> NO can bind to the superoxide anion ( $O_2^-$ ) giving rise to peroxynitrite ( $ONOO^-$ ), one of the most potent ROS.<sup>56</sup> When ROS production increases or the scavenging systems are unable to cope with them, oxidative stress occurs. If NO is involved in the genesis of such stress, it is termed nitrosative. Oxidative stress has significant repercussions on muscle in that it damages enzymes, structural proteins, and cellular lipids, and alters DNA<sup>56</sup> thereby exercising a significant effect on the physiology and very survival of the muscle fiber. In COPD patients, oxidative stress has been found in various systems and organs, including the lower limb and respiratory muscles.<sup>59-61</sup> Moreover, the degree of oxidative stress in the respiratory muscles appears to depend on the mechanical load they have to support<sup>59,62</sup> and is directly proportional to the degree of muscle dysfunction.<sup>59</sup> However, the leg muscles show even greater stress than the respiratory muscles,<sup>56</sup> and this gives rise to significant functional repercussions probably caused by damaged molecular structures.<sup>63</sup>

**Nutritional abnormalities.** Nutritional abnormalities are common in patients with COPD and result in loss of body weight and mass as well as negative alterations in the composition of the organism.<sup>64,65</sup> However, it is thought that phenotype varies considerably depending on the geographical area where the patient lives.<sup>66</sup> It is still not known whether the factors are predominantly genetic or related to lifestyle, although there is some support for the theory that lifestyle is the determining factor.<sup>66</sup> The tools traditionally used to identify nutritional abnormalities in COPD patients are body weight (absolute, variation, or deviation from ideal weight) and the body mass index. Although this is a good system and it is, in fact, predictive of mortality in these patients,<sup>67</sup> it has recently been criticized because of the possibility that it may underestimate nutritional abnormality, particularly in patients with COPD. This concern has given rise to proposals for a new parameter based on body composition: the fat-free mass index.<sup>68</sup> The recommendation to use one method or the other would depend on the proportion of women in the population of patients under study and the assessment methods available.

The effects of nutritional abnormalities on striated muscle include decreases in muscle mass and variations in the proportions of the different types of muscle fibers.<sup>69</sup> Logically, these changes have functional repercussions.<sup>70</sup> The reasons for these phenotypic changes are poorly understood and, in addition to the classical explanations based on increased energy consumption and decreased dietary intake related to the ventilatory problem, it has recently been suggested that changes in the metabolism of certain substances, such as leptin,<sup>71</sup> or the effects of systemic inflammation may also play a part in this process.<sup>72</sup>

**Hypoxia and hypercapnia.** Abnormalities in pulmonary gas exchange in COPD patients are the result of the

ventilation-perfusion mismatches caused by the disease, and ventilatory muscle dysfunction can also contribute by causing a relative degree of hypoventilation. In any case, once hypoxemia and hypercapnia occur they can have a negative effect on contractility. Hypoxemia gives rise to tissue hypoxia and a reduction in both stored energy and protein synthesis,<sup>73</sup> with significant repercussions on muscle strength and endurance as well as exercise capacity.<sup>74,75</sup> Hypercapnia affects muscle contractility both directly and indirectly (the latter by way of tissue acidosis). This has been demonstrated both in vitro and in patients with COPD.<sup>76,77</sup>

**Certain drugs.** Systemic corticosteroids, the drugs most known to contribute to muscle dysfunction, can trigger a specific chronic or acute myopathy that may even have a negative effect on patient survival.<sup>78</sup> Although the use of systemic corticosteroids has declined considerably, these agents are still necessary in the management of certain seriously ill patients and individuals who have frequent exacerbations. Corticosteroids also appear to be used more liberally in certain European countries and in North America, perhaps owing to the particular characteristics of the health systems in those countries. Acute corticosteroid myopathy appears a few days after start of treatment and affects different muscle groups in a largely random manner.<sup>5</sup> However, chronic myopathy, which can develop even with very low doses administered over a long period, is characterized by a predominantly proximal muscle weakness (both girdles).<sup>5,78</sup>

**Miscellaneous.** Many other general factors of great importance should also be taken into account in the consideration of muscle dysfunction in COPD. The most notable of these are comorbidity, aging, electrolyte imbalance, and continued tobacco use. Recent evidence indicates that many of the alterations found in the muscles of patients with COPD are superimposed on changes caused by smoking itself.

An interesting detail that should be borne in mind is that none of the systemic factors mentioned above are specific to COPD. In fact, to a greater or lesser degree, they are all found in a number of chronic conditions, such as heart failure, rheumatic disease, physiological aging, and certain chronic infections. Muscle dysfunction is also found in all of those circumstances, and in such cases its pathogenesis probably has much in common with that of similar dysfunction in COPD.

### Muscle Remodeling

Muscle remodeling is an interesting process that is closely related to both dysfunction and adaptation of muscle in COPD. Different stimuli can cause muscle lesions, and the subsequent repair may be complete (*restitutio ad integrum*) or may produce tissue with new characteristics (remodeling) (Figure 3). Sometimes remodeling occurs in the absence of any apparent lesion, with the activation of certain genes being sufficient stimulus to provoke changes in the characteristics of the tissue. In the respiratory muscles, it appears that the process can be activated by a chronic increase in ventilatory

loads,<sup>79</sup> a phenomenon associated, in the diaphragm at least, with the appearance of sarcolemmal and sarcomeric lesions.<sup>80,81</sup> The repair of these lesions results in a new phenotype characterized by a higher proportion of fatigue-resistant fibers, mitochondria, and blood vessels.<sup>82-84</sup> These findings are accompanied by occasional signs of myopathy.<sup>85</sup> The situation is somewhat different in the case of the other respiratory muscles, such as the external and parasternal intercostals.<sup>10,86-89</sup> While phenotypic changes in these muscles are found in COPD patients, the level of damage appears to be much lower. An increase in the proportion of anaerobic fibers in the external intercostals was reported in one study,<sup>86</sup> while in another the parasternal muscles seemed to move towards an aerobic phenotype more similar to that of the diaphragm.<sup>89</sup> This difference is probably related to the stimuli and to the particular actions of each muscle, the existence of which provides the system with the set of functional properties most appropriate to its task. In contrast to the relative abundance of data concerning the muscles of inspiration, very little has been published concerning phenotypic changes in the expiratory muscles. It would appear that minor changes in the proportions of the different types of muscle fiber are found in the expiratory muscles of COPD patients, although the metabolic properties of the fibers do not change.<sup>5,10</sup>

A number of studies have investigated the structural changes that occur in the limb muscles of these patients, especially in those of the legs and in particular the quadriceps. These studies have found a reduction in both fiber size and the elements that favor aerobic metabolism. Reductions have been observed in the proportion of type I fibers, capillary density, myoglobin levels, and the activity of enzymes belonging to the oxidative pathways.<sup>90-94</sup> However, enzyme activity in the glycolytic pathway appears to be preserved.<sup>92</sup> The results of a smaller number of studies concerning the upper limb muscles are suggestive of a mixed phenotype. This phenotype is probably influenced by the same factors that affect the lower limb muscles, although the reduction in activity is less pronounced and activity may even increase in the groups involved in ventilatory work. For example, oxidative enzyme activity and the size and proportions of muscle fibers are preserved in the deltoid muscles,<sup>95</sup> although there is a wide variability in fiber size and subpopulations of atrophic and hypertrophic fibers are found together with fibers of normal size.<sup>96</sup> The proportions of fibers in the brachial biceps are preserved in COPD, although cell size is somewhat smaller than in healthy individuals.<sup>97</sup>

In summary, the phenotypic changes found in the muscles of COPD patients are particular to each muscle or muscle group, and are probably the result of a number of different factors that interact in a particular way in each case.<sup>4,10</sup>

### New Therapeutic Approaches

Although this review deals mainly with new perspectives on muscle dysfunction in COPD, the ultimate goal of this research is obviously the treatment of these

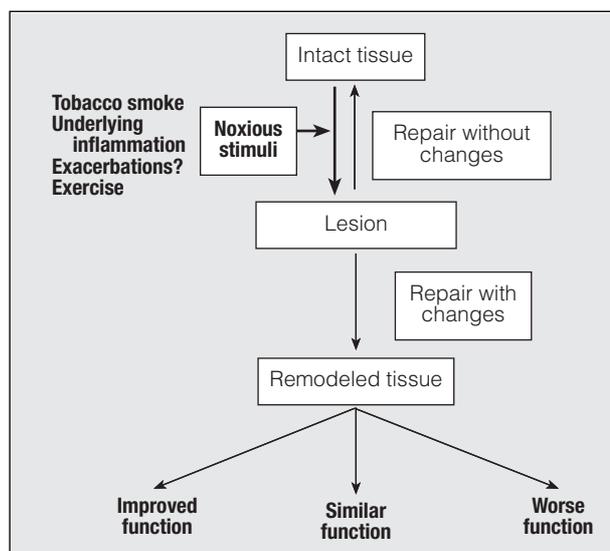


Figure 3. Simplified representation of the muscle remodeling process.

patients. In this respect, recent conceptual advances have opened the way to new possibilities for the management of this disease. These include the rational use of mechanical ventilation in patients with stable COPD and the administration of drugs with anabolic, anti-inflammatory, or antioxidant properties. Specifically, nutritional supplements and anabolic agents appear to have a beneficial effect on muscle mass, quality of life, and survival in these patients.<sup>65,98</sup> However, to date the use of nutritional support has only been clearly shown to be beneficial in patients who have lost weight or lean body mass, and the use of drugs with myotrophic properties remains a subject of debate. One novel prospect is the imminent use of growth factors similar to those produced by healthy muscle during training.<sup>99</sup> Caution must be exercised with respect to the use of drugs with anti-inflammatory properties, such as antimetabolites and antibodies against tumor necrosis factor. The different cytokines may certainly cause damage in various types of tissue, but they also have beneficial effects and play a role in the repair and remodeling of damaged muscle.<sup>100,101</sup> Consequently, cytokine inhibition could have both favorable and unfavorable effects on muscle. The muscle problems caused by the use of systemic corticosteroids have been discussed above. Inhaled corticosteroids at standard doses do not appear to have any significant effect on muscle tissue. However, it is possible that their use may attenuate the systemic inflammatory signal from lung. The use of classic nonsteroidal anti-inflammatory agents to modulate muscle dysfunction is still an unexplored area, although it is being actively researched with new drugs.<sup>102</sup> Finally, a great deal of evidence has recently emerged concerning the potentially beneficial effects of substances that have an antioxidant effect on muscle (for example, N-acetylcysteine, vitamin E, and alpha tocopherol).<sup>62,103</sup>

Traditional treatment options should not be forgotten, but their use can be approached from a new standpoint.

This is the case of drugs—such as  $\beta$ -agonists, anticholinergic agents, and inhaled corticosteroids—that reduce the load on the ventilatory muscles and facilitate renewed peripheral muscle activity through direct action on bronchial obstruction and hyperinflation. Certain surgical procedures, such as bullectomy and lung volume reduction surgery, can have a beneficial effect on muscle activity but are only useful in highly selected cases.<sup>104</sup> This is also the case for rehabilitation—particularly when it involves both specific muscle and general exercise training—and its effects on muscle structure and capacity, exercise tolerance, quality of life, and survival have been clearly demonstrated.<sup>37,39,105-109</sup> Current practice guidelines on the management of COPD now recommend this modality for patients at all levels of severity.<sup>1,110</sup> It should also be remembered that muscle training improves lean body mass by increasing protein synthesis and reducing muscle inflammation and breakdown.<sup>111,112</sup> Finally, noninvasive mechanical ventilation, a technique that is already well consolidated in the management of COPD exacerbation,<sup>113</sup> could also prove useful in selected patients with stable disease. However, the usefulness of such therapy depends on identifying the most appropriate candidates, patients who are hypercapnic or are at risk for developing this condition owing to poor respiratory muscle function.<sup>4,114</sup> In such patients, ventilatory support allows the muscles the rest they need to ensure their optimal functioning once the noninvasive mechanical ventilation is withdrawn.

In summary, muscle dysfunction is a common manifestation of COPD that affects both peripheral and respiratory muscles and has significant clinical impact. It affects the different muscle groups in a heterogeneous manner and appears to be the result of a complex interaction of various factors that modify phenotype and function in each muscle region (level of activity, inflammation, oxidative stress, nutritional abnormalities, gas exchange, and drugs). While current clinical practice advocates the use of traditional treatment options, such as bronchodilators, rehabilitation, and nutritional support, recent advances in our understanding of the mechanisms that give rise to dysfunction have opened the door to the use of more specific treatments in the near future.

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