Any impairment in striated muscle function can interfere with the performance of daily activities, particularly for a patient already living with a respiratory disorder. However, the interaction between the respiratory and musculoskeletal systems is not always considered in the clinical management of these patients. Striated muscles are contractile elements that provide organisms with physiological functions, such as movement and generation of both air- and blood-flow. The latter two functions are essential for respiratory gas exchange. The generation of airflow requires the action of inspiratory muscles. When this muscle group contracts, the changes in intrathoracic pressure allow air to enter the lungs. When these muscles relax, the air exits from the respiratory system. If additional effort is required to exhale, the expiratory muscle group contracts, increasing the alveolar–atmosphere pressure gradient. Although the diaphragm is the main inspiratory muscle, specifically in young and healthy subjects when they are at rest, other muscles progressively participate in the effort as ventilatory demands increase. These include external intercostals, parasternal and, to a lesser degree, the scalenes, sternocleidomastoid, latissimus dorsi, serratus and pectoralis muscles. The main expiratory muscles are the internal intercostals and those constituting the abdominal wall. Skeletal muscles located in the limbs (and also called peripheral muscles), are involved in the movements of the body. Any impairment in their function can interfere with the performance of daily activities.

Muscle function becomes impaired in many different respiratory disorders, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchial asthma, obstructive sleep apnea syndrome (OSAS), kyphoscoliosis and lung cancer. Although changes in respiratory mechanics in these diseases primarily target respiratory muscles, limb muscles can also be affected. In addition, respiratory and limb muscle dysfunction can occur in patients with myopathies, neurological and neuromuscular junction disorders, chronic heart failure, sepsis and other critical illness. In the intensive care unit (ICU), the condition called ICU muscle weakness is not only a limb problem but can also hamper weaning from mechanical ventilation.

This review aims to briefly present basic concepts of skeletal muscle physiology and to describe in-depth the muscle function impairment occurring in some of the most prevalent respiratory conditions, defining the factors and mechanisms involved in the etiopathogenesis of muscle dysfunction in this setting.
**Muscle physiology**

The two main functional properties of both respiratory and limb muscles are: strength and endurance. The former can be defined as the ability to develop a brief maximal effort, whereas the latter could be described as the ability to maintain a submaximal contraction over time. Strength mainly depends on muscle mass, although other factors also contribute, such as muscle length, innervation, fiber size and the proportion of predominantly anaerobic fibers. Endurance is related to the aerobic properties of the muscle, which in turn, are conditioned by capillary density, proportion of type I fibers and enzyme activity in the oxidative pathways, among other factors. When the strength and/or endurance of skeletal muscles is reduced, this is called muscle dysfunction and can be characterized in two ways: weakness and fatigue. Muscle weakness is related to the loss of muscle strength. Therefore, it can be identified easily in clinical conditions through the assessment of muscle force (determination of pressures generated by respiratory muscles and standard dynamometry to assess limb muscles). Weakness is a constitutive and relatively stable situation, and the muscle requires long-term therapeutic measures (training and nutritional interventions). By contrast, muscle fatigue is a temporary dysfunction related to endurance, and is primarily resolved by rest. It can be identified by neurophysiological (changes in the high/low frequencies ratio or in centroid frequency) or mechanical (transient inability to perform a target task) indicators. Both conditions, weakness and fatigue, can be present simultaneously in the same patient, as a weak muscle will become fatigued much more easily.

**Respiratory muscles**

Inspiratory muscles ensure an appropriate level of ventilation to facilitate pulmonary gas exchange. Therefore, their dysfunction will result in hypoxemia and hypercapnia, and in ventilated patients can lead to difficulties in the weaning process. Malfunction of expiratory muscles will, in turn, give rise to difficulties upon exertion, coughing and attempts to expectorate secretions from the airways. Functional assessment of respiratory muscles is slightly more complicated than that of limb muscles, but can be achieved through determination of respiratory pressures. A large number of studies have demonstrated that respiratory muscle function can also be impaired in widely diverse disorders. These include COPD, cystic fibrosis, chronic asthma, scoliosis, neuromuscular diseases and also ICU muscle weakness and sepsis.

Molecular and cellular events occurring in respiratory muscles with an impaired function are identified through biopsy analysis. However, the sampling of these muscles is always very invasive, and therefore their structural and molecular properties are studied less frequently than in limb muscles. Most studies have been performed in the diaphragm, with samples obtained during thoracic or abdominal surgery owing to associated diseases [1–4]. However, data are also available regarding other inspiratory muscles, such as external intercostals, parasternals or even accessory muscles, such as latissimus dorsi [5]. Regarding expiratory muscles, data are scarce, but there are some reports on the major oblique muscle [6].

Disuse of respiratory muscles only occurs under very specific conditions, such as mechanical ventilation. Conversely, overloading occurs more frequently because many different situations result in increased breathing. On the one hand, airway resistances increase in obstructive diseases. On the other, pulmonary hyperinflation or changes in thorax geometry can deny respiratory muscles their optimal length for contraction. Although some studies support that these factors are essential for respiratory muscle dysfunction, additional elements cannot be excluded.

**Peripheral muscles**

The striated muscles of the upper and lower limbs constitute the peripheral muscles; the concept can also include the muscles of the shoulder and pelvic girdles. The muscles of the upper limbs are essential for manipulating objects, and for many of the tasks involved in personal care. In addition, some of them can be recruited to serve as ventilatory muscles when these are overburdened by respiratory loads [7,8]. In turn, the muscles of the lower limbs are essential for locomotion and exercise, and are crucial for many daily activities. The clinical implications of peripheral muscle dysfunction are important, as patients may be unable to work or take care of themselves, become extremely dependent on those around them and experience a reduction in their quality of life. Since tests for the functional properties of peripheral muscles are relatively simple [9], we know that many disorders can induce (or are associated with) limb muscle dysfunction, including COPD, scoliosis, chronic heart failure and cancer cachexia, among others. Peripheral muscles are very sensitive to disuse (deconditioning) and nutritional abnormalities, two factors that many authors believe are pivotal for the occurrence of muscle dysfunction. However, other factors can also be implicated.

Peripheral muscles are readily accessible for tissue sampling, facilitating analysis of the cellular and molecular changes that are associated with muscle dysfunction. In the following sections, these changes and their possible mechanisms will be reviewed. However, it is important to clarify that many of these structural and molecular studies have been performed in samples from the quadriceps muscle, particularly its external part (vastus lateralis). It is possible to speculate that not all the findings should be directly extrapolated to other peripheral muscles, whose functions are essentially different from those of the anterior thigh. Some studies performed in the upper limb muscles appear to confirm this hypothesis [10,11].

Muscle dysfunction can occur not only as a consequence of a disease or a treatment, but also in some more physiological circumstances, such as aging and extreme sedentary lifestyle. As mentioned above, it has been well described in COPD, bronchial asthma and lung cancer cachexia, among others. It is also characteristic of other disorders targeting the respiratory system, such as OSAS, neuromuscular and rib cage abnormalities [12–15]. The following sections review the causes and mechanisms of muscle dysfunction in the most common disorders that target the respiratory system and also respiratory and/or peripheral muscles (Box 1).
Respiratory disorders

Chronic obstructive pulmonary disease

COPD is a highly prevalent condition characterized by nonreversible airflow obstruction [30]. The main cause of COPD is tobacco smoking, which results in inflammatory phenomena leading to destruction of lung parenchyma and airway remodeling. In addition to airway obstruction, COPD results in pulmonary hyperinflation, increased airway resistance, changes in pulmonary compliance and gas exchange abnormalities, characterized by hypoxemia and, in some cases, hypercapnia. As a result, patients experience ventilatory limitations that impair their exercise tolerance. However, COPD is a heterogeneous disease and patients may also show extrapulmonary involvement, including malnutrition, and abnormalities in skeletal muscles, blood cells, renal and nervous systems and even bone metabolism [16–19]. Muscle dysfunction is probably the best-studied extrapulmonary manifestation occurring in COPD. It includes abnormalities in the strength and endurance of both respiratory and limb muscles [3,20], and is believed to be of multifactorial origin, with local and general factors interacting to modify the phenotype and function of any particular muscle. Muscle dysfunction is relevant because it reduces exercise capacity, which ultimately affects quality of life and influences patient survival [21].

Respiratory muscle dysfunction is frequently observed in many COPD patients [22–24], mostly in those with more advanced stages of the disease, and can involve both inspiratory and expiratory muscle groups. Regarding inspiratory muscle dysfunction, it is believed to mainly be the consequence of changes in lung function [23,25]. On the one hand, pulmonary hyperinflation, present in many patients, has a dramatic impact in the length–tension relationships of both the diaphragm and intercostal muscles (Figure 1). These muscles become shorter and larger, respectively, than their optimal length for generating force [25]. In addition, the costal and crural parts of the diaphragm lose their summatory action and become physiologically independent [26]. On the other hand, increased airway resistance and impaired gas exchange lead to an imbalance between demand and supply in the muscle [7,8]. One of the reasons to believe that hyperinflation is crucial for the development of respiratory muscle dysfunction in COPD is that although these patients develop lower respiratory pressures than healthy subjects, they can generate even greater force than the controls when both groups perform a test maneuver at similar high lung volumes [25]. This finding also suggests some muscle adaptation to pulmonary hyperinflation. However, respiratory muscles are subjected to the same deleterious general factors as other muscles, including inflammation, oxidative stress, nutritional abnormalities and the effects of tobacco and some drugs (Figure 1) [27–30]. The combination of these systemic factors and the adaptive changes that occur in the face of increased mechanical loads leads to important changes in the phenotype of respiratory muscles. On the one hand, the percentages of myosin heavy chain I, type I fibers (with a predominantly aerobic metabolism), capillary and mitochondria increase in the diaphragm, leading to a more oxidative phenotype [1–3,31,32]. On the other hand, sarcomerae appear to shorten in this muscle, partially restoring their optimal length for contraction [2]. Interestingly, these positive phenomena coexist with signs of myopathy (paracristalline inclusions), as well as oxidative stress, changes in the expression of local cytokines and protein imbalance [33–35], all of which can contribute to the loss of muscle function. Data from external intercostal, parasternal and accessory muscles are much more scarce, but also suggest a combination of adaptive and negative phenomena [3,36–39]. Regarding expiratory muscles, the information is even more scant. Although their function deteriorates in many COPD patients [24,40], some of the factors should be different from those acting in the inspiratory or peripheral muscle groups. Changes in lung volumes will only negatively affect the length–tension relationships of intercostals, not those of abdominal muscles [41]. Moreover, deconditioning is unlikely since expiratory muscles are chronically activated for both the breathing effort and coughing in COPD patients [42,43]. However, they are also subject to all of the systemic factors present in other muscles. All of these circumstances result in changes to their phenotype and metabolism [7,8]. In this regard,
Figure 1. Contributing factors to the respiratory muscle dysfunction of chronic obstructive pulmonary disease patients.

O$_2$D: Oxygen delivery; Q: Perfusion; $V_A$: Alveolar ventilation; VO$_2$: Oxygen consumption.

some reports have described fiber atrophy and minor changes in the proportions of fiber types in expiratory muscles of COPD patients [6,8]. Therefore, we can conclude that adaptation is not homogeneous for all respiratory muscles.

As discussed above, peripheral muscles constitute a heterogeneous group involved in many different tasks. The function of both lower and upper limb muscles appears to be impaired, to varying degrees, in many COPD patients [9,24,44–48], contributing to their exercise limitations [46,47,49,50]. The main cause of peripheral muscle dysfunction appears to be deconditioning due to a reduction in daily activities (Figure 2) [51,52]. This reduction would be the product of both the initial ventilatory defect and the emotional impairment frequently associated with COPD. A strong argument in favor of the key role played by muscle deconditioning in peripheral muscle dysfunction is that most of the changes described can be reversed by muscle training [51,53]. However, some of the changes are irreversible [47,51], which suggests that other factors may be implicated. Among these are the general factors described as affecting the respiratory muscles, which also affect limb muscles: systemic inflammation and oxidative stress, tobacco smoking, nutritional abnormalities, comorbidity and drugs, among others (Figure 2) [20]. The many studies of structural and molecular changes in the quadriceps of COPD patients have established that this muscle undergoes protein imbalance and atrophy (see next sections), as well as losses in different aerobic components. These include declines in myosin heavy chain I expression, percentage of type I fibers, fiber size, capillary density and myoglobin content, as well as impaired enzyme activities in the oxidative pathways [53–58]. All of these components could contribute to reduce both the strength and resistance of lower limb muscles in COPD patients. Moreover, some studies support the idea of impaired bioenergetics in the quadriceps of such patients, showing that this muscle is inefficient in its intracellular use of oxygen [47,48]. Therefore, it could require greater oxygen consumption than healthy subjects for the same amount of work. The quadriceps also show major oxidative stress that targets essential proteins in muscle structure and metabolism [59,60]. As a result, muscle damage occurs [61], and there is some evidence that this phenomenon is associated with defects in the muscle regeneration process [62]. The latter, in turn, might be related to the underexpression of some local cytokines [63], but more evidence is necessary. Other authors have reported increased levels of inflammatory cells and proinflammatory cytokines in the quadriceps muscle of COPD patients [64]. All of these phenomena could contribute to the loss in muscle mass and function in the lower limbs. By contrast, muscles located in the scapular girdle and upper limbs show fewer dramatic changes [10,31,65], contributing to the heterogeneity of muscle adaptations that characterizes COPD. This is not surprising because these muscles probably have a lower exposure to a reduction in their activity. Moreover, they can even show an increase in their activity, as they frequently support ventilation under increased loads in COPD patients. For instance, normal, hypertrophic and atrophic fibers coexist in the deltoid muscle, which preserves its fiber type proportions and oxidative enzyme activities in COPD patients [10,11]. In a similar way, brachial biceps show fiber atrophy but maintain their fiber type percentages [65].

Acute exacerbations contribute to the progression of COPD and the deterioration of muscle function [66]. The increased inflammatory load present in the lung during exacerbations may also have systemic repercussions and affect other regions, including skeletal muscles. In this regard, some authors have reported a reduction in muscle mass in various parts of the body during exacerbations [67]. This would be the result of a negative protein balance [68] and the activation of multiple pathways leading to a reduction in MyoD and IGF-1, and subsequent muscle atrophy [69–72]. In addition, the reduction in activity that frequently occurs during an exacerbation would also negatively affect limb muscles. In the case of respiratory muscles, the situation would be further aggravated by the indirect effects of the exacerbation in the mechanical loads of the ventilatory system. Conversely, muscle dysfunction has been shown to be an independent risk factor for severe exacerbations requiring hospital admission [73].

As a general conclusion, muscle dysfunction associated with COPD can involve many muscle groups. The extension and
intensity of the functional impairment is a consequence of the complex interaction of local and general factors in each muscle.

**Bronchial asthma**
This disorder is characterized by reversible episodes of airflow obstruction, which are the consequence of airway inflammation and edema, as well as hyperresponsiveness of bronchial smooth muscles. Limb muscle weakness can occur, but is almost exclusive to chronic patients, as it is related to steroid treatment and muscle disuse. Unfortunately, structural and metabolic analyses of these muscles are surprisingly scarce, and the potential bias of a steroid myopathy (see ‘Treatments commonly used in respiratory disease patients’ section) is not always controlled. From some of these studies we know that magnesium tends to be diminished in the quadriceps muscle of these patients. However, the precise impact of this abnormality on muscle function remains unknown. Respiratory muscles in turn appear to maintain or improve their functional properties in chronic asthma patients, even in the presence of pulmonary hyperinflation. Since these muscles are actively recruited in chronic asthma, it is possible to hypothesize a training-like phenomenon similar to that present in COPD. As for peripheral muscles, there are few studies on the structural and molecular properties of respiratory muscles in patients with asthma. Moreover, most research has been carried out on necropsy specimens. Some studies suggest that the diaphragm is hypertrophied in patients with chronic asthma, but others have reported fiber atrophy. It is possible that the relative weight of the contributing factors in different populations of chronic asthma patients may account for these conflicting results.

Acute asthma attacks represent a completely different situation. In this case, the combination of an acute increase in mechanical loads (greater airway resistance and pulmonary hyperinflation), and deteriorated oxygen delivery to the tissues act on a non-trained muscle and can result in transitory muscle dysfunction. However, if the situation progresses to a severe asthma exacerbation, rhabdomyolysis and/or muscle fatigue may occur, and it may even be fatal.

**Respiratory disorders related to sleep**
Sleep apnea syndrome and related disorders are characterized by the presence of repeated partial or total occlusions of the upper airways during sleep. The consequences include nocturnal hypoxemia, loss of sleep structure and diurnal hypersomnia. Skeletal muscle dysfunction has been described in patients with sleep disorders, and specifically in those with OSAS. These patients can show impaired strength and endurance in both inspiratory and limb muscles, although fatigability appears to only be increased in the inspiratory group. These abnormalities appear to be related to the absence of reparative rest during sleep deprivation, and mostly to the presence of hypoxia–normoxia cycles. Functional impairment is associated with cellular and molecular changes in different limb muscles (quadriceps and tibialis anterior), such as increases in the size of type II fibers, protein content and the number of blood vessels. The increase in capillarity in turn is probably the result of the overexpression of VEGF, as a consequence of the repeated bouts of hypoxia. Sleep deprivation and hypoxia would also affect respiratory muscles, but in this case another factor is present: inspiratory muscles perform progressively submaximal efforts in apneic events that could result in muscle fatigue, but might also mimic muscle training. In fact, respiratory muscle strength and endurance appear to be roughly maintained in many patients with sleep apnea. However, as previously mentioned, there is a reduction in their reserve against fatigue, mostly in those patients with severe disease. Structural and molecular studies performed in the external intercostal muscle have demonstrated an increase in the size of type II fibers coexisting with a decrease in oxidative stress and the proportion of type I fibers. Although treatment with continuous positive airway pressure (CPAP) restores sleep quality and reduces nocturnal ventilatory...
effort, it only partially improves respiratory muscle function [97,99]. The lack of complete restoration might be explained by the persistence of oxidative stress in the muscle [99] and the probable presence of pulmonary hyperinflation due to the CPAP treatment. Finally, upper airway muscles, which have an important role in the pathophysiology of OSAS, have shown mechanical, structural and metabolic changes in patients suffering from this condition. Musculus uvulae, for instance, shows an increased strength along with larger fibers, a higher protein content and better anaerobic enzyme capacity in OSAS patients than in nonapneic snorers [100,101]. Although genioglossus dysfunction has been reported in patients with OSAS, cellular findings are less impressive [102] and only a mild increase in the proportion of anaerobic fibers has been reported [103]. Interestingly, CPAP reverse these functional and structural changes, suggesting that these are the consequence, and not the cause, of the obstructive problem.

**Cystic fibrosis**

Muscle dysfunction is also frequent in cystic fibrosis. Cachexia, systemic inflammation and gas exchange abnormalities are frequently associated with advanced stages of the disease, potentially targeting all skeletal muscles [104,105]. These factors, along with deconditioning, will determine the weakness reported for limb muscles. However, respiratory muscles will face a chronic increase in ventilatory workloads, which would have effects similar to those reported in COPD patients. Therefore, although structural studies are lacking, this muscle group would exhibit phenotypes and function resulting from the complex interaction of multiple deleterious factors with a training effect [105].

**Scoliosis & other thoracic deformities**

Scoliosis is defined by a lateral curvature of the spine associated with vertebral rotation. This also results in chest deformity, back pain, ventilatory restriction, respiratory and limb muscle weakness and exercise limitation [105,106]. Although respiratory muscle dysfunction has classically been attributed to chest deformity, limb muscle dysfunction appears to be the consequence of deconditioning, probably thorough the development of local oxidative stress [106]. Therefore, especially in adolescents with scoliosis, muscle training would improve their physical performance. By contrast, chest surgery options do not appear to improve muscle function in these patients [Gea et al., unpublished data]. In individuals with advanced stages of thoracic deformity and chronic respiratory failure, noninvasive mechanical ventilation can be useful to improve ventilation and gas exchange [107,108].

**Idiopathic pulmonary hypertension**

This condition is characterized by an increase in the blood pressure in pulmonary vessels. One of the most frequent symptoms in idiopathic pulmonary hypertension is exercise intolerance. Although this is believed to be caused mainly by vascular factors, some authors have suggested a role for muscle dysfunction [109,110]. This would affect both respiratory and peripheral muscles, suggesting the involvement of systemic factors. Moreover, the impairment in functional outcomes has been shown to be associated with structural and molecular changes, including muscle atrophy and a reduction in the proportion of aerobic fibers in the quadriceps muscle [111].

**Other circumstances related to respiratory system targeting of skeletal muscles**

**ICU muscle weakness**

Many different factors, such as systemic inflammation, sepsis, multiorgan failure, malnutrition, malposition, drugs, dys electrolytemia and mechanical ventilation [112–115], can contribute to muscle weakness in critically ill patients. These and other still unknown factors can result in axonal and demyelinating neuropathies, defects in the neuromuscular junction and acute myopathies. The latter have specific characteristics, including fiber atrophy, the loss of myosin and the presence of mitochondria with paracrystalline inclusions [116,117]. The consequences of muscle dysfunction in ICU patients are very relevant because the weaning process will be more difficult as a result [118,119], and intense rehabilitation is required to ensure reintegration into everyday activities.

The different modalities of mechanical ventilation (MV) assist or substitute for respiratory muscles in their function of providing ventilation to maintain pulmonary gas exchange. Classical MV with anesthesia-paralysis results in early respiratory and peripheral muscle dysfunction. This appears to mainly be the consequence of inactivity, a very harmful factor that can induce diaphragm atrophy at only 48 h of MV [113]. By contrast, noninvasive MV and those forms of classical MV involving the periodic use of respiratory muscles do not appear to induce severe dysfunction because contractile activity is preserved. On the contrary, in most cases they provide rest to fatigued muscles and reduce the work of weakened muscles.

**Lung cancer cachexia**

Cachexia is a complex metabolic syndrome characterized by the loss of muscle mass, which is common in advanced malignant diseases, including lung cancer. Anorexia is frequently associated with cachexia [120,121], which targets muscle by inducing protein imbalance and atrophy [122], both resulting in muscle weakness. On the one hand, gluconeogenesis degrades structural and functional muscle proteins as a source of energy. On the other, protein synthesis also becomes affected [123–125]. Moreover, some cytokines, such as TNF-α, IL-1β, IL-6 and IFN-γ [126,127], oxidative stress derived from metabolic changes and the use of antineoplastic drugs appear to be directly involved in this protein imbalance [128,129]. Peripheral muscle weakness occurring in cachectic patients causes their quality of life to deteriorate through progressive limitation of their daily activities. In addition, ventilatory failure may occur when respiratory muscles become affected. In fact, a third of deaths in cancer patients have been attributed to muscle dysfunction.

Skeletal muscle wasting is a prominent feature in patients with lung cancer [130], even in those with normal bodyweight [131]. In addition, this has been shown to be not only a risk factor for prognosis, but a predictor of cancer treatment toxicity [131]. In the
same regard, proteolysis has been shown to be negatively related to survival in non-small-cell lung cancer [132].

**General factors involved in muscle dysfunction in respiratory disorders**

Although some general factors, such as tobacco smoking, are more specific to COPD, others (systemic inflammation, sedentarism, comorbidity, aging, drug effects and so on) are common to various respiratory diseases. Below, we review the most relevant general factors believed to influence muscle function in respiratory patients:

**Tobacco smoking**

Different reports appear to indicate that tobacco smoking per se can induce muscle dysfunction by different mechanisms, including oxidative stress and a decrease in protein synthesis [30,133–135]. Therefore, a point that still remains unclear is whether the initial stimulus that affects the muscle is just the direct result of the aggressive action of smoking itself or is secondary to the inflammation caused by smoking in lung parenchyma, pulmonary blood vessels and the airways [136]. In either case, and indeed they probably coexist, inflammation will affect systemic circulation reaching various organs (including muscles) and contributing to their dysfunction [137,138]. An intriguing question is what causes the inflammatory response to persist after the initial noxious stimulus has disappeared. Current thinking on the answer to this question is based on the hypothesis that these mechanisms may be immunological [139].

**Inflammation**

There is overwhelming evidence to support the hypothesis that a certain level of systemic inflammation is present in COPD [52]. It has been shown that serum levels of certain inflammatory biomarkers (C-reactive protein, fibrinogen and several cytokines) are elevated in these patients [27,137], and higher white blood cell counts have also been found [137,140]. Moreover, it has recently been suggested that the systemic manifestations of COPD may be an expression of an attenuated form of the systemic inflammatory response syndrome [141]. This syndrome has traditionally been conceptualized in the context of the multiorgan failure associated with sepsis [112], but could also be present in a minor form in other chronic conditions, such as COPD [141,142], cystic fibrosis [105] or asthma. Systemic inflammation can have important effects on muscles: various cytokines can induce an increase in local protein degradation through oxidative stress or the activation of proteolytic pathways [143,144], both found in COPD muscles [29,59,145,146]. Furthermore, certain proinflammatory cytokines can inhibit muscle contraction [147], although they appear to be necessary for muscle repair [148].

**Oxidative stress**

This is closely related to inflammatory mediators, which in conjunction with other factors also present in chronic diseases, such as COPD, lead to oxidative and nitrosative stress [8,149,150]. Inversely, the stress can act as a signal for increased expression of proinflammatory cytokines [150]. Oxidative stress is the result of an imbalance between reactive oxygen species, a product of aerobic metabolism, and antioxidant mechanisms present in cells and tissues. When the action of oxidants overcomes that of antioxidants, certain molecules become modified and their function is impaired as a result. Oxidative stress has been found in various organs of COPD patients, including the lungs, blood and muscles [4,34,59,151]. Although both respiratory and peripheral muscles exhibit oxidative stress, it appears to be greater in the limbs of both these patients and animal models of COPD [4,60,152].

**Nutritional abnormalities**

Although relatively frequent in COPD, cystic fibrosis, scoliosis and lung cancer [104,105,130,153,154], nutritional impairment is relatively rare in other conditions, such as bronchial asthma. In the particular case of COPD there is wide geographical diversity in the prevalence of nutritional abnormalities. The range is from approximately 5% in Mediterranean countries to 25% or more in Northern Europe and North America [155]. Nutritional abnormalities have been attributed to factors such as lifestyle, a reduction in food intake [156], an increase in metabolic costs [53] and, more recently, the presence of systemic inflammation [27,157] and changes in the metabolism of certain substances, such as leptin [156]. Nutritional status is a good predictor of mortality in COPD and lung cancer patients [131,158] and can influence their muscles. Specifically, malnutrition results in decreased muscle mass, changes in fiber type percentages and muscle dysfunction [159,160].

**Comorbidity & aging**

The increased life expectancy in developed societies has resulted in a high percentage of elderly patients [161]. In addition, as a consequence of the etiopathogenic factors shared by respiratory conditions and other disorders, comorbidity is frequently observed. In these circumstances, muscle dysfunction has been attributed to sarcopenia, characteristic of elderly subjects, and to abnormalities in muscle function also present in highly prevalent diseases, such as chronic heart failure, diabetes and rheumatological diseases [46,162,163].

**Extreme sedentarism**

This is very common in developed countries and leads to cardiovascular and muscle deconditioning. In fact, the level of physical activity, which is the determinant for an appropriate muscle phenotype, is a prognostic factor for exacerbations and even for life expectancy in patients with COPD [164–166]. However, this factor seems to be especially important in peripheral muscles because the activity of respiratory muscles would even be increased in sedentary individuals with respiratory disorders.

**Gas-exchange abnormalities**

Hypoxemia and hypercapnia are frequently observed in many respiratory diseases and can result in a decrease in muscle strength or endurance [167–169]. Hypoxemia can reduce oxygen delivery to the muscle. This reduction will be even higher in the presence of anemia, a circumstance also very prevalent in chronic diseases,
such as COPD. If tissue hypoxia develops it can result in a reduction in stored energy and protein synthesis, impairing muscle contraction [170–172]. In a similar way the presence of hypercapnia will affect muscle contractility, both directly and indirectly, through the development of muscle acidosis [167,173].

Treatments commonly used in respiratory disease patients

Corticosteroids can induce both acute and chronic myopathies, mostly when used systemically [174]. Although the use of systemic corticosteroids has declined considerably, these agents are still necessary in the management of certain seriously ill patients. 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 myopathy can develop following administration of high doses of corticosteroids [175] and is characterized by marked weakness that can affect various muscle groups [176]. The structural bases of this functional impairment are the loss of myosin filaments and rhabdomyolysis [177,178]. Chronic myopathy in turn is the consequence of long-term administration of steroids, even at relatively low doses [179]. It is mainly characterized by muscle weakness in proximal muscle groups (girdles and trunk) [179]. Cellular and biochemical abnormalities underlying chronic myopathy include type II fiber abnormalities in carbohydrate metabolism [179,180].

Anticholinergics are used in respiratory patients as bronchodilators to block muscarinic receptors of acetylcholine, and thus relax airway smooth muscles. Although their effects on skeletal muscles are irrelevant at standard doses, higher levels can impair diaphragm contraction [181] and reduce muscle reaction time [182].

β-blockers are competitive antagonists of β-adrenergic receptors and are widely used in cardiovascular disorders, such as hypertension and ischemic heart disease. Since many patients with respiratory diseases also present these comorbidities, they frequently receive systemic β-blockers. This occurs even in subjects also receiving inhaled β-agonists. β-blockers decrease myocardial contractility [183,184] and have also been shown to facilitate skeletal muscle fatigue [185], although they do not appear to reduce skeletal muscle strength [186].

Calcium channel blockers inhibit channels that mediate the entry of extracellular Ca²⁺ into muscle cells. Calcium channel blockers are extensively used in respiratory patients with cardiovascular comorbidities (systemic hypertension, angina pectoris and so on) and have negative inotropic effects on myocardium. However, this effect has not been described for skeletal muscles. Nevertheless, there is some evidence about the action of calcium channel blockers on attenuation of contraction-induced muscle damage [187] and the differentiation of muscle myoblasts/satellite cells [188]. This could have some negative influence in the remodeling process undergone by respiratory muscles in obstructive diseases, but might also attenuate the progression of some myopathies.

Statins are widely used for dyslipidemia because they inhibit an enzyme that catalyzes an early step in cholesterol biosynthesis. Their major adverse effect is a myopathy, mainly characterized by rhabdomyolysis and intense muscle pain, that initiates in the arms and thighs [183,184]. Note that drugs, such as macrolides, frequently used in exacerbations of COPD, interact with statins and can augment their effects [183].

Diuretic drugs can lead to electrolytic imbalance, which in turn can deteriorate muscle function. In this regard, abnormalities in the plasma levels of Na⁺, K⁺, Cl⁻ and other ions can result in impaired contraction and easier fatigability.

Phosphodiesterase 5 inhibitors augment cyclic GMPc by inhibiting a key enzyme, which results in smooth muscle relaxation and vasodilation. Therefore, they are being used for pulmonary hypertension and erectile dysfunction [183,184]. Some of these drugs have also been shown to inhibit the muscle effects of insulin (capillary recruitment and glucose uptake) [189], which might result in early muscle fatigue. However, there is also some evidence in animal models that phosphodiesterase 5 inhibitors might ameliorate muscle damage in muscle dystrophy [190].

Expert commentary

Respiratory disorders (e.g., COPD, bronchial asthma and thoracic deformities) and their treatments (drugs and mechanical ventilation) are frequently associated with respiratory and/or limb muscle dysfunction. Whereas respiratory muscle dysfunction results in ventilatory problems, limb muscle dysfunction leads to a reduction in exercise tolerance and limitation of many everyday tasks. Muscle dysfunction is attributed to the complex interaction of general and local factors, including inflammation, oxidative stress, comorbidities, drugs, increases and decreases in muscle activity and changes in thorax geometry. Greater knowledge about the causes and consequences of the muscle dysfunction that occurs in respiratory disorders would open new therapeutic strategies, including a more rational use of current drugs and muscle training, and perhaps, to the adoption of new antioxidants, NSAIDs, anabolic agents and calcium sensitizers as they become available.

Five-year view

There are good reasons to believe that the next few years will bring not only increased knowledge about the mechanisms of muscle dysfunction in respiratory diseases but also new therapeutic approaches to the management and treatment of muscle dysfunction. In this respect, recent conceptual advances have opened the way to optimizing classical instruments. These include the expanded use of rehabilitation programs. Although rehabilitation is indicated in many COPD guidelines [191,301], the actual use of this integral therapy is still relatively limited. However, particularly when it involves muscle and general exercise training, rehabilitation has a considerable effect, not only on muscle function, but also on reduction of exacerbations and improved exercise tolerance, quality of life and even patient survival [51,192–194]. This can be applied, not only to COPD, but also to many other respiratory conditions, such as cystic fibrosis and scoliosis. It is important to note, however, that not all COPD patients will respond to muscle training. In the more advanced stages of the disease, when nutritional abnormalities become very relevant and/or exacerbations are extremely frequent,
these subjects would need additional measures in order to restore even minimal performance. Noninvasive MV, a technique that is already well accepted in the management of COPD exacerbations and restrictive disorders, could also prove to be useful in selected stable patients with obstructive diseases. However, this will depend on better identification of the most appropriate candidates [141,195]: those in whom ventilatory support allows the muscles the rest they need. In addition, it should be taken into account that mechanical ventilation can also have deleterious effects on muscle function in specific groups of patients. The administration of drugs with anabolic, anti-inflammatory or antioxidant properties can be expected to increase dramatically in the coming years [152,196]. Specifically, nutritional supplements, testosterone and other anabolic agents appear to have a beneficial effect on muscle mass, muscle strength, quality of life and survival in particular groups of patients [154,197,198]. For example, the use of nutritional support has been shown to be beneficial in subjects who have lost weight. One novel prospect is the potential use of ghrelin (a growth hormone secretagogue) and growth factors similar to those produced by healthy muscle during training (mechano growth factor) [199] or substances inhibiting myostatin [200]. By contrast, drugs with anti-inflammatory properties should be used with more caution, since some of the proinflammatory cytokines have dual effects on the muscles. On the one hand, they can cause damage and impair contraction, but on the other they appear to be necessary for muscle growth and regeneration [201,202]. Since one of the factors implicated in muscle dysfunction is oxidative stress, it is not surprising that there is increased evidence on the potentially beneficial effects on muscles of antioxidants, such as N-acetylcysteine, vitamin E and α-tocopherol [152,203]. Another active research field studies the use of nonsteroidal anti-inflammatory agents to modulate muscle structure and function [204]. Other drugs widely used in patients with cardiovascular disorders, such as angiotensin-converting enzyme inhibitors, have been shown to prevent cachexia and improve muscle strength [205,206]. More recently, calcium sensitizers, widely used in chronic heart failure, have demonstrated their ability to improve contractility of diaphragmatic fibers from COPD patients, as well as respiratory muscle function of healthy individuals [207]. This finding opens new perspectives for drug management of muscle dysfunction in the near future. In addition, surgical and endoscopic procedures can result in reductions of lung volume that reshape the diaphragm in COPD, thus restoring its mechanical properties [208,209]. Although these procedures are still only used in very specific patients, it is to be expected that new techniques will extend their use.

Finally, we should not forget that tobacco smoking is known to negatively influence muscle function in respiratory diseases. Health policies that have been implemented in many countries to eradicate smoking, along with measures devoted to increasing the level of physical activity, are expected to definitively decrease muscle dysfunction as a complication for our respiratory patients.

Acknowledgement
The authors would like to acknowledge Elaine Lilly, PhD, for editing help.

Financial & competing interests disclosure
Funded, in part, by CIBERES ISC III, Plan Nacional SAF2007-62719 and FUCAP. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Muscle dysfunction is frequent in many disorders targeting the respiratory system. These include chronic obstructive pulmonary disease, chronic asthma, obstructive sleep apnea syndrome, cystic fibrosis, lung cancer, thoracic deformities and neuromuscular disorders.
- Respiratory muscle dysfunction results in hypoco2lation and can lead to death. It can also hamper the weaning process in mechanically ventilated patients. Peripheral muscle dysfunction results in exercise limitation and restrictions in many daily activities.
- Muscle dysfunction associated with chronic obstructive pulmonary disease is probably the result of the complex interaction between local and systemic factors. While pulmonary hyperinflation appears to be the main factor contributing to respiratory muscle dysfunction, deconditioning is believed to play a determinant role in peripheral muscle dysfunction.
- Drugs typically used in respiratory disorders, including corticosteroids, β-blockers and diuretics, can impair muscle function.
- A wider and better use of both rehabilitation programs and noninvasive mechanical ventilation, as well as appropriate nutritional support and pharmacological strategies (antioxidants, nonsteroidal anti-inflammatory agents, growth factors and calcium sensitizers), will open new possibilities in the treatment of muscle dysfunction.

References
Papers of special note have been highlighted as:
• of interest
** of considerable interest

**Review**

Gea, Casadevall, Pascual, Orozco-Levi & Barreiro


• A chapter devoted to muscle dysfunction in respiratory and nonrespiratory disorders. Causes and consequences are discussed in depth.


• Recent paper describing the extension and intensity of muscle dysfunction in scoliosis, suggesting a key role for deconditioning and/or primary muscle involvement in the pathogenesis of the disease.


• Although published 12 years ago, this is an excellent review of the causes and consequences of muscle dysfunction associated with chronic obstructive pulmonary disease (COPD).


• Clinical study showing that limb muscle dysfunction in COPD is an independent factor for prognosis.


• Key paper in the understanding of the role played by tobacco smoking in the development of muscle dysfunction in COPD.


• Nice review on the nature of changes occurring in respiratory muscles of COPD patients, showing that adaptations in the human diaphragm can represent either a form of dysfunction, secondary to the systemic disease, or an adaptive process occurring in a working environment.

35 Campbell JA, Hughes RL, Shagav V, Frederiksen J, Shields TW. Alterations in intercostal muscle morphology and


•• Broad study on the prevalence of quadriiceps weakness in COPD. The study demonstrates that approximately a third of COPD patients, even those with mild-to-moderate disease, have limb muscle dysfunction.


• Classic paper on the morphological characteristics of limb muscles in COPD patients. It demonstrated that the vastus lateralis muscle is characterized by fiber atrophy and a marked decrease in the percentage of aerobic fibers.


89 Recent paper on respiratory and limb muscle dysfunction associated with the sleep apnea syndrome. Causes might include repetitive inspiratory efforts against an occluded airway, intermittent hypoxia and impaired sleep quality.


Population-based study of cachexia in patients with lung cancer, demonstrating that muscle wasting is a prominent feature despite normal or heavy bodyweight in such patients.


• Relatively recent review on the potential role played by cytokines and oxidants in muscle dysfunction associated with COPD.


146 Interesting paper showing the benefits of an antioxidant therapy in respiratory muscle dysfunction occurring in an animal model of inspiratory loading.


166 Caquelard F, Burnet H, Tagliarini F, Cauchi E, Richalet JP, Jammes Y. Effects of prolonged hypobaric hypoxia on human


Waclawik AJ, Sufit RL, Beinlich BR, Schutta HS. Acute myopathy with selective muscle weakness, as well as abnormal muscle enzymes levels in blood.


Gea, Casadevall, Pascual, Orozco-Levi & Barreiro

Websites

