Mechanisms of striated muscle dysfunction during acute exacerbations of COPD

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During acute exacerbations of chronic obstructive pulmonary disease (COPD), limb and respiratory muscle dysfunction develops rapidly and functional recovery is partial and slow. The mechanisms leading to this muscle dysfunction are not yet fully established. However, recent evidence has shown that several pathways involved in muscle catabolism, apoptosis, and oxidative stress are activated in the vastus lateralis muscle of patients during acute exacerbations of COPD, while those implicated in mitochondrial function are downregulated. These pathways may be targeted in different ways by factors related to exacerbations. These factors include enhanced systemic inflammation, oxidative stress, impaired energy balance, hypoxia, hypercapnia and acidosis, corticosteroid treatment, and physical inactivity.

Data on the respiratory muscles are limited, but these muscles are undoubtedly overloaded during exacerbations. While they are also subjected to the same systemic elements as the limb muscles (except for inactivity), they also face a specific mechanical disadvantage caused by changes in lung volume during exacerbation. The latter will affect the ability to generate force by the foreshortening of the muscle (especially for the diaphragm), but also by altering rib orientation and motion (especially for the parasternal intercostals and the external intercostals).

Because acute exacerbations of COPD are associated with an increase in both prevalence and severity of generalized muscle dysfunction, and both remain present even during recovery, early interventions to minimize muscle dysfunction during exacerbation are warranted. Although rehabilitation may be promising, other therapeutic strategies such as counterbalancing the adverse effects of exacerbations on skeletal muscle pathways may also be used.
(Fig. 1) (16, 55, 74). The reduction in quadriceps force was not due to the loss of body weight only because it still remained when the analysis was limited to hospitalized patients with a normal body mass index (BMI defined as the ratio of weight/height\(^2\) (range, 18.5–24.9 kg/m\(^2\)) according to Worth Health Organization classification; Ref. 84) (74). The reduction in quadriceps force during hospitalization was significantly correlated with less improvement in walking time 1 mo after discharge (55), showing that the loss of force during hospitalization had a serious and long-term consequence on functional status. Importantly, quadriceps force partially recovered 3 mo after discharge from hospital (Fig. 1) (74), indicating that spontaneous functional recovery without any structured exercise program was slow. Obviously, any new exacerbation at that time point would further affect muscle force and compromise functional recovery.

Interestingly, upper limb muscle function, which is usually preserved in patients with COPD, is also affected during acute exacerbations. Handgrip force was, indeed, reduced compared with patients with clinically stable COPD (74). However, in contrast to quadriceps strength, handgrip force did not further decrease over time during hospitalization (74). But the deleterious effect of exacerbation is underlined by the reduction in handgrip strength occurring more frequently and to a greater extent in patients with a history of frequent exacerbation (4). Finally, handgrip force dysfunction was associated with an increased risk for hospital admission due to acute exacerbation, irrespective of body weight and BMI (81). This study in fact highlighted that the prevalence and severity of muscle dysfunction remained elevated despite clinical stability (82).

**Respiratory muscles.** During acute exacerbations, the maximal pressure that can be generated by the respiratory muscles is reduced, as is the muscle efficiency (ratio of mechanical work output to the total metabolic cost) for the inspiratory muscles, especially the diaphragm. Indeed, acute dynamic hyperinflation further shortens the inspiratory muscles, particularly the diaphragm, and causes functional muscle weakness. Therefore, the accessory muscles of breathing are maximally recruited (as shown by maximal activation with electromyographic measurement) and significant alterations in thoraco-abdominal pathway of motion are often evident. Patients are also at greater risk for the development of respiratory muscle fatigue than healthy subjects because the relative force that these muscles exert for each breath is higher compared with their maximal capacity (8).

In patients with COPD who develop acute hypercapnic respiratory failure requiring noninvasive mechanical ventilation, it has been shown that muscle strength of both inspiratory and expiratory muscles was reduced (62). Even at discharge from a respiratory intensive care unit after severe, acute exacerbation, more than one-third of these patients still presented respiratory muscle dysfunction (82) that would require further care and rehabilitation to restore functional impairment.

### ALTERATIONS WITHIN THE MUSCLE DURING EXACERBATION

Alterations in local gene expression have been addressed only in the vastus lateralis muscle (Fig. 2). In a first study, Crul et al. (16) showed that on day 4 of hospitalization, the protein levels of MyoD, the master regulatory gene for skeletal myogenesis, were reduced in hospitalized patients with COPD compared with healthy elderly, and they were unchanged in patients with stable COPD. In addition, the anabolic marker insulin-like growth factor I (IGF-I) mRNA levels were reduced in COPD but to a similar extent in stable and hospitalized patients (16). In addition, the MyoD protein levels were positively correlated with quadriceps force, suggesting a functional role for MyoD in the observed muscle weakness (16). Similar alterations in MyoD and IGF-I have been observed in disuse models (6, 49), supporting the idea that disuse plays a role in increased muscle weakness during exacerbation. Interestingly, local inflammation determined by measuring interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α) mRNA revealed very low levels of IL-6 and IL-8 in the vastus lateralis of these patients (16). TNF-α mRNA was not detectable (16). These data suggest that local inflammation is likely not playing a role in muscle weakness during exacerbation.

In a subsequent study, Crul et al. (17) established the gene expression profile in the vastus lateralis muscle using microarray analysis. This study showed that compared with patients with stable COPD, several pathways leading to muscle atrophy and mitochondrial dysfunction were activated in the muscles of patients during an acute exacerbation of COPD. In particular, the ubiquitin-dependent protein catabolism, the Akt/FoxO pathway, and apoptotic signaling were upregulated, whereas oxidoreductase activity acting on NADP-NADPH, oxidative phosphorylation, and the mitochondrial respiratory chain were downregulated (17). Importantly, most of these pathways were already impaired in

Fig. 2. Factors related to exacerbation that may affect limb (A) and respiratory (B) muscle function in COPD during acute exacerbations.
patients with stable COPD and were further affected during exacerbation. As in the previous study (16), the gene profiling study did not find evidence of local inflammation in the muscle of patients with COPD during an acute exacerbation (17). But this study clearly highlighted the importance of proteolysis, apoptosis, and mitochondrial dysfunction.

There are no data on alterations within other limb muscles during an acute exacerbation. For the respiratory muscles, analysis of postmortem diaphragm specimens from patients with severe COPD revealed that acute-on-chronic ventilatory loading induced extensive diaphragmatic injury and collagen accumulation (70).

**POTENTIAL MECHANISMS LEADING TO MUSCLE WEAKNESS DURING EXACERBATION**

The causes of muscle weakness during exacerbation (Fig. 2) are probably multifactorial and may vary from patient to patient. While most causes may affect both limb muscles and respiratory muscles, some of them specifically target either the respiratory muscles or the limb muscles. In fact, during exacerbations, additional systemic inflammation (15, 23, 74, 83), oxidative stress (64, 65), impaired energy balance (15, 77), alterations in the biochemical environment (hypercapnia, acidoxia, hypoxia, depletion of metabolic substrates) (18, 32), corticosteroid administration (20, 21), inactivity (55), and bed rest may affect peripheral and respiratory muscles. But respiratory muscles are also subjected to the alterations occurring in chest wall configuration caused by changes in lung volumes during exacerbation (Fig. 3).

**Enhanced systemic inflammation.** Acute exacerbations are associated with an additional increase in systemic inflammation with higher blood levels of C-reactive protein (CRP), cytokines (IL-6, IL-8, TNF-α), leptin, endothelin-1, and fibrinogen (15, 23, 83). This acute systemic inflammation state during exacerbations may potentially contribute to deterioration of muscle function and probably affects both limb and respiratory muscles. In fact, systemic levels of IL-8 and IL-6 were shown to be inversely related to isometric quadriceps strength (74). In that study, IL-8 was the only systemic inflammatory marker to independently contribute to the variance in quadriceps strength in hospitalized patients with acute exacerbation of COPD (74). Systemic IL-8 was moreover inversely correlated with handgrip force in these patients. This relationship was specific to patients with acute exacerbation, as it was not observed in patients with stable COPD (74). Finally, the presence of inflammatory markers within the muscle was not evident (16).

Whether increased cytokines may cause muscle weakness is difficult to determine in human situations. However, animal studies have shown that administration of IL-6 to rats for 7 days resulted in respiratory and peripheral skeletal muscle atrophy (39). Importantly, these data were obtained at IL-6 serum levels within the range attainable in patients (39). This treatment was moreover associated with blood flow redistribution resulting from myocardial failure induced by IL-6 admin-

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Fig. 3. Representative pressure-volume plots in stable COPD (A) and COPD exacerbation (B). During exacerbation, worsening of expiratory flow limitation results in dynamic hyperinflation with increased end expiratory lung volume (EELV) and residual volume (RV) with a corresponding reduction in inspiratory capacity (IC) and inspiratory reserve volume (IRV), although total lung capacity (TLC) is unchanged. As a consequence, tidal breathing is shifted rightward on the pressure-volume curve, closer to TLC. Therefore, increased pressures (ΔP) must be generated to maintain tidal volume (VT). During exacerbation, intrapulmonary pressures do not return to zero at EELV. This results in the development of an intrinsic positive end expiratory pressure (PEEPi), which acts as an inspiratory threshold load (ITL) that the respiratory muscles must first overcome to generate inspiratory flow. Reproduced from (52) COPD exacerbations. 3: Pathophysiology, O’Donnell DE, Parker CM, Thorax 61: 354–361, 2006 with permission from BMJ Publishing Group Ltd.
istration (39). By contrast, IL-8 administration to rats failed to induce any effect on respiratory and peripheral muscles even at high doses (100 and 250 μg·kg-day) (38). The effects of TNF-α on skeletal muscle are divergent and have generated doubt as to whether or not this cytokine has a role in muscle dysfunction and wasting (5).

There are no data on relationship between systemic inflammation and respiratory muscle dysfunction during exacerbation.

**Oxidative stress.** During acute exacerbation, oxidative stress is further increased in the vastus lateralis muscle of hospitalized patients with COPD (17). Microarray analysis revealed upregulation of the transcripts of the response to oxygen species; more specifically, the superoxide dismutase 2 and glutathione peroxidase 3 (17). Excessive reactive oxygen species production within the muscle is known to target mainly mitochondria and myofilaments. This would lead to apoptosis, mitochondrial respiration chain dysfunction, alteration in myofilament contractile properties, or a combination of these [reviewed in (14)]. In fact, gene profiling in vastus lateralis muscle of hospitalized patients with COPD showed that during acute exacerbation apoptosis is upregulated, whereas several genes involved in the mitochondrial respiration chain process (e.g., cytochrome-c oxidase, a marker of mitochondrial respiration) are downregulated (17).

Apoptosis normally leads to cell death but it can also cause cell atrophy, especially in multinucleated cells (2) such as skeletal muscle cells. In patients with heart failure, the magnitude of apoptosis in the vastus lateralis muscle was shown to be associated with the degree of muscle atrophy (79), suggesting that apoptosis might play a role in determining muscle bulk loss (79). As a result, enhanced apoptosis during exacerbation may contribute to muscle wasting and may thus affect muscle force. In addition, this may eventually postpone muscle recovery in these patients. Of note is that apoptosis during exacerbation of COPD may have been stimulated by excess reactive oxygen species but also by reduced serum and muscle IGF-I (16, 74). IGF-I is, indeed, known to exert antiapoptotic effects (43). Therefore, its decrease during an acute exacerbation may have contributed to enhanced apoptosis.

Downregulation of mitochondrial respiration chain processes during acute exacerbation would add to the mitochondrial dysfunction already present in the muscle of patients with COPD under stable situations (49, 60, 63). This will probably contribute to further impair exercise capacity and may also slow down functional recovery while decreasing fatigue resistance.

Whether oxidative stress is further enhanced in the respiratory muscles during exacerbation has not yet been determined.

**Impaired energy balance.** Impaired energy balance during exacerbation may also play a role in muscle dysfunction. In fact, dietary intake is reduced in patients with COPD during the first day of acute exacerbation because symptoms such as dyspnea and fatigue make it difficult to eat more (77). Also, leptin, an appetite-suppressing hormone and inflammatory cytokine, is increased during exacerbation (15) and, as such, it may further contribute to reduced appetite. In addition, resting energy expenditure is acutely increased during the first days of hospitalization (77). The low ratio between dietary intake and resting energy expenditure was shown to be inversely related to elevated levels of systemic inflammatory markers such as TNF-α receptor 55 (15). Importantly, prevalence of malnutrition is elevated in these patients, and nutritional parameters (fat free mass, muscle mass, body mass index, serum albumin) have been shown to be related to hospitalization length and readmission (33).

**Hypoxia, hypercapnia, acidosis.** Acute exacerbations are characterized by deterioration in pulmonary gas exchange resulting in severe hypoxemia with or without hypercapnia (18). Worsening of gas exchange is primarily due to increased ventilation/perfusion mismatching and increased tissue oxygen consumption (7). This acute hypoxemia status during exacerbation will add to muscle weakness and will affect the skeletal muscles in several ways. Hypoxia alone can inhibit muscle protein synthesis and may activate muscle proteolysis by stimulating the calcium-dependent proteases (37). Proteolysis via the ubiquitin-proteasome pathway may be further activated through additional acidosis that often accompanies hypoxemia during severe exacerbations (37). Interestingly, acute exposure to hypoxia in humans revealed that the protein levels of hypoxia inducible factor-1α, the master regulator of the cellular response to hypoxia, are only marginally altered in skeletal muscles compared with other tissues (44), but the high pre-existing level of hypoxia inducible factor-1α in skeletal muscle may preclude any further important increase when environmental oxygenation is decreased during hypoxia (44). When the hypoxia-inducible factor-1 pathway is activated it may target several genes in muscles involved in glucose metabolism, angiogenesis, cell survival and apoptosis, oxidative metabolism, and even myosin heavy chain expression (44). Further, hypoxia may help generate low-grade systemic inflammation (42) that may alter skeletal muscle as discussed earlier. Hypoxia also increased resting muscle oxidative DNA damage in humans (45), which may also be deleterious for skeletal muscles. Finally, acute hypoxia has been shown to accelerate time to exhaustion of the adductor pollicis during voluntary contraction (30). Hypoxia may also alter skeletal muscle by indirect mechanisms that include loss of appetite, elevated circulating levels of leptin, and reduced physical activity, all being present in patients with COPD during exacerbation.

During severe exacerbations, respiratory pump failure due to airflow obstruction and respiratory muscle weakness or fatigue may lead to hypercapnic respiratory failure. Acute hypercapnic acidosis can induce a negative influence on respiratory and limb muscles. In humans, acute hypercapnic acidosis can produce rapid and significant impairment of contractility of the quadriceps and adductor pollicis muscles, in addition to increasing muscle fatigability (80). Also, diaphragm endurance time was shown to be reduced in humans during hypercapnia (40), but whether its contractility is altered remains controversial (40, 47). Quadriceps and intercostal muscles in patients with COPD and acute respiratory failure showed lower intracellular muscle pH (29, 32, 40). Moreover, there was a close relationship between arterial PCO₂ and intracellular pH in these patients just before intubation for mechanical ventilation (29, 40). Finally, in patients with COPD and acute respiratory failure, the concentrations of ATP and creatine phosphate measured on admission to an intensive care unit were low in the intercostal muscles and particularly in the quadriceps muscle (32). These data indicate that the muscles were unlikely to perform adequately, especially in view of the augmented work of breathing. Dysfunction of the respiratory muscles to sustain their task in the presence of low ATP and low creatine phosphate may represent an important component of acute respiratory failure in these patients.
Corticosteroid administration. Systemic corticosteroids are part of the hospital management of COPD exacerbations. It is well accepted that corticosteroids may affect respiratory and peripheral muscle force (20–22), and decline in fat free mass is independently associated with the use of a maintenance dose of oral corticosteroids (35). The mechanisms by which corticosteroids may affect muscle function are related to their ability to compromise the production of contractile proteins through inhibition of protein synthesis while downregulating the IGF-1 pathway and through activation of the ubiquitin proteasome and lysosomal systems while notably upregulating myostatin expression (a catabolic growth factor) (69).

During acute exacerbation, no relationship between the dose of oral corticosteroids and the changes in quadriceps muscle force between hospitalization day 3 and day 8 has been found (74). By contrast, a negative correlation between corticosteroid intake and changes in handgrip strength was reported during exacerbation but this observation might have been confounded by disease severity (68). There are no data on the effect of corticosteroids on respiratory muscles during acute exacerbation.

Nonetheless, corticosteroids may have affected skeletal muscle in several ways during acute exacerbation. Indeed, corticosteroids are known to activate muscle proteolysis (24) and to indirectly reduce protein synthesis through downregulation of IGF-I (24, 31). In fact, during exacerbation, proteolysis is enhanced in the vastus lateralis muscle of hospitalized patients with COPD, while IGF-1 expression is repressed (16, 17). Corticosteroids are also able to activate the mitochondrial-mediated apoptotic signaling pathway in skeletal muscle (24), and this pathway is activated during acute exacerbation. Further, corticosteroids exert an adverse effect on nitrogen balance and, in patients with acute exacerbation of COPD, there is a negative correlation between corticosteroid intake and nitrogen balance (68). Obviously, corticosteroids may take part in the development of skeletal muscle weakness during an acute exacerbation of COPD.

Physical inactivity. During exacerbation, patients with COPD limit their physical activity because of excessive dyspnea, weakness, and tiredness. Quantitative measurement of physical activity revealed that during acute exacerbation, patients with COPD are very inactive (55). They spent less than 10 min per day walking even when they are close to discharge (55). They also remained inactive even 1 mo after discharge compared with patients with stable COPD with similar disease severity (55). This shows that physical inactivity is not simply the result of bed rest during hospitalization. Moreover, patients with frequent exacerbations of COPD recover their physical activity level to a lesser extent than patients without frequent exacerbations (55). In fact, patients who did not improve their walking distance within 1 mo after exacerbation are more prone to be readmitted to hospital (55). Exacerbations are, in addition, associated with a decline in outdoor activity for up to 5 wk after the onset of symptoms (26). Lower limb muscles are particularly affected by physical inactivity, whereas respiratory muscles are not. Indeed, the increased work of breathing imposed by COPD and exacerbation dictates that respiratory muscles overwork rather than decondition, like limb muscles do (51). Importantly, reduced contractile activity is associated with increased protein breakdown through activation of the ubiquitin proteasome system (66) and decreased protein synthesis through inhibition of the Akt/TSC2/mTOR pathway (27). Animal models also showed that emphysema-induced atrophy primarily affected lower limb muscles (48), and this was not related to reduced physical activity because the latter did not change in this model (46, 48). Taken together, these data suggest that the limb muscles may be the preferential target of emphysema and physical inactivity.

Physical inactivity negatively affects skeletal muscles. In humans, the primary factor driving inactivity-induced locomotor muscle wasting is depressed protein synthesis (54), whereas the effect of inactivity on proteolysis is less consistent (28, 34, 75). In fact, skeletal muscle inactivity is associated with oxidative stress that may directly stimulate proteolysis, depress protein synthesis, and induce apoptosis [reviewed in (57)]. All these processes are activated during exacerbations (17) and are compatible with the presence of physical inactivity reported under these circumstances. In addition, skeletal muscle inactivity leads to significant changes in mitochondrial morphology and biochemical properties including decreased expression of mitochondrial proteins, mitochondrial respiratory dysfunction, and increased mitochondrial reactive oxygen species production [reviewed in (58)]. Worthwhile alterations in genes involved in mitochondrial function have been found in the vastus lateralis muscle during exacerbation (17). These data are particularly important knowing that mitochondrial damage/dysfunction may contribute to inactivity-induced muscle wasting [reviewed in (58)]. Physical inactivity has also been associated with decreased IGF-I levels and alterations in the MyoD/myogenin ratio (6, 49), which may further promote muscle wasting, and both are reduced in the vastus lateralis muscle of patients with COPD during acute exacerbation (16). Collectively, these data strongly support a role for physical inactivity in impaired muscle function during exacerbation.

Mechanical disadvantage. Mechanical disadvantage concerns the respiratory muscles only. During acute exacerbation, airway resistance is abruptly increased, and this worsens expiratory flow limitation. In addition, patients tend to adopt a rapid, shallow-breathing pattern that further limits the time available for lung emptying but promotes greater dynamic hyperinflation. Worsening of expiratory flow limitation and exaggeration of dynamic hyperinflation during exacerbation may contribute to functional muscle weakness at least for the inspiratory muscles (52). Acute dynamic hyperinflation further shortens the inspiratory muscles; especially the diaphragm. Because the muscle is shorter during contraction, it generates less force and, for the diaphragm, its ability to generate pressure, in particular negative pleural pressure, is impaired [reviewed in (19)]. Acute hyperinflation also affects the parasternal intercostal and the external intercostal muscles, but this effect is more related to rib orientation and motion than to the ability of these muscles to generate pressure [reviewed in (19)]. Further, as a consequence of expiratory flow limitation, intrapulmonary pressures are positive at the end of expiration, representing intrinsic or autopositive end expiratory pressure (PEEPi) (52) (Fig. 3). PEEPi acts as an inspiratory threshold load that the respiratory muscles must overcome (52) (Fig. 3). This acute inspiratory loading may intensify muscle injury and may take part in decreased muscle strength, at least for the diaphragm (53, 70).

Consequences of exacerbations. Exacerbations have been associated with reduced exercise capacity (13), further impairment of quality of life (71), and increased likelihood of becoming housebound (26). Mortality...
increases with the frequency of exacerbations, especially if hospital admission is required (73). In fact, patients with COPD and recurrent hospitalization and high medical consumption are characterized by skeletal muscle weakness rather than impaired pulmonary function (21). Further, acute exacerbation of COPD is associated with an increase in both prevalence and severity of generalized muscle dysfunction measured by handgrip strength, and maximal inspiratory and expiratory pressure (81). Importantly, both prevalence and severity remain elevated even while recovering clinical stability (81). Of note, skeletal muscle force recovery after acute exacerbation is slow and partial (74). Thus any new exacerbation before complete force recovery may particularly be detrimental for patients with COPD and frequent exacerbations.

INTERVENTIONS

Knowing the impact of exacerbation on skeletal muscle, several interventions based on rehabilitation have been used early or late after exacerbation to minimize the consequences of exacerbation on muscle. A Cochrane Collaboration meta-analysis showed that pulmonary rehabilitation immediately after an exacerbation significantly improved exercise capacity and reduced hospital admissions and mortality (61). Pulmonary rehabilitation after exacerbation was also associated with an improvement in quadriceps strength (50, 72). A significant improvement in quadriceps force and 6-min walking distance were reported after a 6-wk neuromuscular electrostimulation program initiated during admission to an intensive care unit for acute COPD exacerbation (1). This was also associated with a decrease in muscle oxidative stress, improvement in myosin heavy chain content, and increased type I fiber proportion (1). Interestingly, in bed-bound patients with COPD receiving mechanical ventilation, neuromuscular electrostimulation may show improved muscle function and decreased number of days needed to transfer from bed to chair (85).

So far, very few interventions have taken place during the hospitalization period. Resistance training started from the second day of hospitalization was able to increase quadriceps force by 10% and resulted in an improvement of the 6-min walking distance at discharge (Fig. 4) (76). In addition, anabolic markers in the muscle were increased (76), whereas 1 mo after discharge, the functional status and muscle force remained better in the group that followed training during the exacerbation (Fig. 4) (76), suggesting that this modality may facilitate functional recovery after an acute exacerbation. On the other hand, nutritional intervention during hospitalization with protein intake exceeding 1.5 g/kg body wt was shown to result in protein and total energy intake improvement, but this did not translate into improvement in muscle strength (68, 78). The strong correlation between the degree of muscle wasting and the dose of corticosteroids in these nutritionally depleted patients with COPD suggests that prevention of muscle wasting is likely to be more difficult in patients treated with a corticosteroid (68).

STRATEGIES TO BE EXPLORED

There are still strategies to be explored that may eventually be combined with the interventions discussed above. First, the beneficial effect of neuromuscular electrostimulation may be sustained by implementing its home use. After a couple of supervisory sessions, a patient may be able to apply it independently (11) and the benefit may be ensured with regular feedback to the hospital and training modalities adapted in consequence. In addition, pharmacological support with an antioxidant or antiprotease may help maintain muscle bulk, and this might eventually be combined with muscle training. Otherwise, supplementation with essential amino acids to increase fat free mass or with polyunsaturated fatty acids, which have been shown to improve exercise tolerance, should be considered. Also, simple but proven to improve functional exercise capacity, the use of wheeled walking aids such as the rollator, may help and motivate a patient to be physically active (59).

CONCLUSION

In conclusion, it is now well recognized that acute exacerbations in addition to causing deterioration of lung function are particularly deleterious for skeletal muscles. Exacerbations rapidly induce loss of muscle force and activate different pathways leading to muscle wasting and dysfunction. Because functional recovery after an exacerbation is long and partial, the adverse effects of exacerbations may accumulate especially in patients with frequent exacerbations of COPD. Therefore, a need exists for action plans, and available data indicate that it is possible to limit the impact of exacerbations on skeletal muscles. Resistance training or neuromuscular electrostimulation either applied during hospitalization or immediately after exacerbation represent encouraging options because they can improve muscle strength, facilitate functional recovery, or both. Neuromuscular electrostimulation is even applicable and beneficial for patients who need mechanical ventilation. Importantly, pulmonary rehabilitation consisting of exercise training was proven to reduce hospital admissions and mortality, and this effect should not be neglected.
Obviously, it is actively to slowly impact the low drive of exacerbations on skeletal muscle. Several treatment options were shown to be effective, and their systemic use in COPD exacerbations should be promoted.

REFERENCES


