Cough, dyspnea, and exercise intolerance are among the early clinical manifestations of chronic obstructive pulmonary disease (COPD).\(^1\) As the disease progresses, several extrathoracic organs are affected, such that COPD is now recognized as a multisystem disease. Altered kidney and endothelial function,\(^2\) endocrine abnormalities,\(^3\) osteoporosis,\(^4\) and peripheral muscle dysfunction\(^5\) are now commonly reported in COPD. Among these extrathoracic manifestations of COPD, the involvement of the peripheral muscles is the subject of intense research because it may influence quality of life, functional status, and survival independently of the alteration in lung function. Thus, the improvement in peripheral muscle function represents a potential and valid therapeutic target for many patients with COPD.

Our understanding of the mechanisms underlying the alteration in peripheral muscle function in COPD is in its early stages. Although promising pathophysiologic concepts are emerging from experimental models, such as cultured muscle cells and cachectic animals, the precise mechanisms of the alterations in peripheral muscle function seen in chronic diseases such as COPD have yet to be elucidated.

In this chapter, we discuss the evidence for and clinical consequences of peripheral muscle dysfunction in COPD and review potential mechanisms of muscle wasting. Finally, actual and future therapies that stop muscle proteolysis or increase muscle mass are discussed.

**EVIDENCE OF PERIPHERAL MUSCLE DYSFUNCTION**

Body weight loss and muscle wasting in COPD-affected subjects have long been recognized by clinicians,\(^6\) and many reports have confirmed the high prevalence of this phenomenon.\(^7\) Furthermore, the peripheral muscles in patients with COPD are affected not only quantitatively (wasting) but also qualitatively, as illustrated by the marked alterations in fiber-type distribution and decreased metabolic capacity. The quadriceps is the most commonly studied peripheral muscle, not only because it is readily accessible but also because it is a primary effector muscle of ambulation. Since most studies have included patients with moderate-to-severe disease, the muscle changes reported herein pertain to this patient population.

**MUSCLE MASS**

Peripheral muscle wasting is an important consequence of COPD (Figure 49-1), with an overall estimated prevalence of 30%\(^7\). The prevalence of this problem increases with the degree of airflow obstruction. A key concept is that muscle mass may be low despite the preservation of total body weight.\(^7\) The implication of this is that the prevalence of muscle wasting is likely to be underestimated if one relies only on measurements of body weight. Another implication is that in patients with COPD, there is a preferential loss of muscle tissue in comparison with other body compartments.\(^8,9\)

**MUSCLE FIBER TYPE, SIZE, AND CAPILLARIZATION**

Human skeletal muscle fibers can be grouped into separate categories on the basis of their physiologic and metabolic characteristics. Type I fibers are characterized by low contractile velocity and high oxidative capacity (which account for their relative resistance to fatigue), whereas type IIb (or IIx) fibers have a high contractile velocity and a lower oxidative capacity (and therefore are more prone to fatigue).\(^5\) Type IIa fibers are intermediate between types I and IIb.\(^5\) The fiber-type profile, an important determinant of muscle metabolic capacity, has been assessed in patients with COPD by using both classic histochemical fiber typing and analysis of myosin heavy-chain isoform expression. In patients with mild-to-moderate airflow obstruction, the
Whittom F et al. 3-hydroxyacyl-CoA dehydrogenase, fiber atrophy.

The thigh muscle cross-sectional area was considerably reduced in the COPD patients in comparison with normal subject. Reproduced with permission from Bernard S et al.8

The proportion of type I fibers is preserved.10 In patients with more advanced airflow obstruction, there is a reduction in the proportion of type I fibers (17 to 29% vs 45 to 50% in COPD and normal subjects, respectively), with a corresponding increase in the proportion of type IIb fibers, in patients with COPD in comparison with normal subjects. Values are mean ±SD. *p < .0005, ** p < .015. Reproduced with permission from Whittom F et al.11

FIGURE 49-2 Fiber-type proportions of the vastus lateralis muscle found in normal subjects and in patients with chronic obstructive pulmonary disease (COPD). As can be seen, a significant reduction in the proportion of type I fibers was found, with a corresponding increase in the proportion of type IIb fibers, in patients with COPD in comparison with normal subjects. Values are mean ±SD. *p < .0005, ** p < .015. Reproduced with permission from Whittom F et al.11

COPD. These two enzymes, which are involved in the citric acid cycle and β-oxidation of fatty acids, respectively, are good markers of muscle oxidative capacity. In contrast to the above findings, Sauleda and colleagues have reported higher activity of cytochrome c oxidase, a key enzyme of the electron transport chain (the last step of the oxidative pathway), in COPD patients than in healthy controls.14 This finding is unexpected, given that the activities of all mitochondrial enzymes usually vary in a coordinated fashion. The significance of this apparently uncoordinated expression of mitochondrial enzymes in patients with COPD needs to be further investigated.

PERIPHERAL MUSCLE METABOLISM AT REST AND DURING EXERCISE

In keeping with the morphologic and enzymic muscle changes, muscle energy metabolism is modified at rest and during exercise in COPD. At rest, low intracellular pH, reduced phosphocreatine (PCr) and ATP concentrations, and increased lactate and inosine monophosphate concentrations have been found in the vastus lateralis muscle.15 When nuclear magnetic resonance spectroscopy (13P-NMR) was used to study the oxidative metabolism of skeletal muscle during exercise (reviewed by Levy and colleagues16), greater declines in muscle intracellular pH and PCr/inorganic phosphate ratio were observed during exercise in patients with COPD than in normal subjects. These findings are indicative of impaired oxidative phosphorylation and ATP resynthesis, with a high reliance on anaerobic glycolysis within the contracting muscles. Although these exercise-induced peripheral muscle metabolic abnormalities are worsened by hypoxemia and can be partially reversed with oxygen supplementation, they have also been reported in patients with little or no reduction in peripheral oxygen delivery,17 suggesting that altered muscle metabolism during exercise is related, at least in part, to poor muscle oxidative capacity or abnormal metabolic regulation.

UPPER EXTREMITY AND RESPIRATORY MUSCLES VERSUS LOWER LIMB MUSCLES

Interestingly, all peripheral muscles are not affected to the same extent in patients with COPD. For instance, the strength of the upper extremity muscles is relatively preserved in comparison with that of the lower extremities,8,18 and the activity of citrate synthase in the deltoid muscle was found to be preserved in patients with severe COPD in comparison with subjects with normal respiratory function.19 The adaptation of the diaphragm in COPD is also different to that of the vastus lateralis muscle.20,21 Whereas the vastus lateralis muscle shows a low capacity for aerobic metabolism and increased susceptibility to fatigue,13 the diaphragm is characterized by an increased proportion of fatigue-resistant fibers.20,21 The observation of differential adaptation of the respiratory, upper limb, and lower limb muscles is intriguing and may lead to insights into the mechanisms responsible for peripheral muscle dysfunction in COPD (see below). For instance, differential adaptive responses of the different muscle groups do not support the presence of a generalized myopathic disorder but would be
consistent with involvement of local muscular events in the deterioration of lower limb muscle function.

**PERIPHERAL MUSCLE DYSFUNCTION AND CLINICAL STATUS**

Functional peripheral muscle tissue is necessary for activities of daily living and vital functions such as breathing and eating. Moreover, muscle tissue can serve as an important reservoir from which amino acids can be drawn to support intense protein synthesis, such as during the systemic inflammatory response to infections or injuries. The interactions between actin and myosin, which are responsible for force production and movement, require a continuous supply of energy, which is ensured by ATP production by either glycolytic or oxidative metabolism. The relative proportions of the different myosin isoforms determine the speed of contraction, whereas the magnitude of force production is proportional to the muscle cross-sectional area. It is thus evident that alterations in muscle mass, morphologic characteristics, and enzymic characteristics will have negative influences at numerous levels.

**MUSCLE WEAKNESS AND ENDURANCE**

In patients with moderate-to-severe airflow obstruction, the quadriceps muscle strength is reduced by approximately 30%. The strength of the quadriceps muscle is an important determinant of exercise capacity in COPD. This may be related to the influence of muscle strength on the perception of leg effort during exercise, the main limiting symptom in 40 to 45% of patients with COPD. The question of whether muscle weakness is merely the consequence of muscle atrophy or contractile dysfunction and/or abnormal neural recruitment may contribute to loss of strength has been recently addressed. In patients with COPD, the quadriceps muscle strength/midthigh cross-sectional area ratio is similar to that of normal subjects. To further address this question, in vitro contractile properties of the vastus lateralis muscle were studied in 16 patients with COPD and 9 control subjects. Muscle bundles from the vastus lateralis muscle obtained by open biopsy were vertically suspended in an organ bath, and their contractile properties were measured. This experimental setup is interesting because under such conditions the maximal force production is totally independent of motivational factors. The maximal isometric peak forces, both in absolute values and normalized for the muscle bundle cross-sectional area, were similar for COPD and control subjects. On the basis of the in vivo and in vitro data, it is concluded that the contractile properties of the vastus lateralis muscle are preserved in patients with COPD. Therefore, the reduction in quadriceps muscle strength in patients with COPD can be explained not on the basis of an alteration of the contractile apparatus but rather on the basis of a loss in muscle mass. However, the loss in strength may be out of proportion to the loss of muscle mass in patients exposed to systemic corticosteroids. This is in accordance with previous animal studies showing that corticosteroids may alter muscle function without causing muscle atrophy.

In line with the histochemical and enzymic changes, the resistance to fatigue of the vastus lateralis muscle, measured during isometric contractions, is reduced in patients with COPD.

**Exercise Intolerance**

Exercise intolerance is a major consequence of COPD, and this fact cannot be explained solely on the basis of limitations in ventilation and gas exchange. For instance, the degree of impairment in lung function is a poor predictor of exercise capacity. Perhaps the most striking clinical observation pointing to a peripheral component of exercise limitation in COPD is that exercise capacity remains abnormally low in most lung transplant recipients despite normalization of lung function.

In patients with COPD, exercise termination usually occurs before a true plateau in oxygen consumption (VO₂) is reached. In many patients, psychological factors such as anxiety, fear of dyspnea, and poor motivation may contribute to exercise intolerance. As a result, the physiologic contribution of individual factors to reduced peak VO₂ is difficult to assess. The contribution of peripheral muscle abnormalities to exercise limitation in COPD has been challenged by Richardson and colleagues. These authors showed that the aerobic capacity of the lower limb muscle was not reached during cycling exercise (when a large muscle mass was involved) because of the early occurrence of central limitation to exercise. The implication of this is that the aerobic capacity of the exercising muscles of the lower limbs, even if reduced, is not overwhelmed during whole body exercise in patients with COPD. It must be remembered, however, that patients with COPD stop exercising because of exertional discomfort and not necessarily because of physiologic constraints. Leg fatigue is commonly perceived at peak exercise in patients with COPD; this could be related to the fact that peripheral muscle alterations increasing susceptibility to contractile fatigue, such as poor oxidative capacity, atrophy, and weakness, are common in this disease. In line with these observations, Mador and colleagues confirmed that contractile fatigue of the quadriceps muscle might occur during exercise in patients with COPD. We recently evaluated the impact of leg fatigue on the exercise response to acute bronchodilatation in patients with COPD in order to test the hypothesis that the improvement in airflow obstruction should not translate into greater exercise capacity in patients with higher susceptibility to leg fatigue. Patients with COPD performed two constant-work-rate cycling exercises up to exhaustion. These tests were preceded by nebulization of placebo or 500 μg of ipratropium bromide. Muscle fatigue was defined as a postexercise reduction in quadriceps muscle twitch force >15% of the resting value. Nine patients developed contractile fatigue after placebo exercise. In these patients, ipratropium bromide did not increase endurance time, despite an 11% improvement in forced expiratory volume in 1 second. In the nine patients who did not show fatigue after placebo exercise, endurance time was increased by ipratropium bromide. There was a significant correlation between the improvement in endurance time with ipratropium bromide and quadriceps
muscle twitch force at 10 minutes after placebo exercise. In summary, improved exercise response after bronchodilata-
tion may be prevented by concomitant leg fatigue, providing
direct evidence of the role of peripheral muscle dysfunction
in exercise intolerance in COPD.

Lower capacity for muscle aerobic metabolism may influ-
ence exercise tolerance in several ways. Increased lactic
acidosis for a given exercise work rate, which is a common
finding in COPD, increases ventilatory needs by
increasing nonaerobic carbon dioxide production. This
imposes an additional burden on the respiratory muscles,
which are already facing increased impedance to breathing.
In addition, the resulting acidemia may act as a breathing
stimulus through the carotid bodies. Premature muscle ac-
dosis, a contributory factor to muscle fatigue and early exercise
termination in healthy subjects, may be an important
mechanism contributing to exercise intolerance in COPD. This
may be exacerbated by a tendency to retain carbon
dioxide (respiratory acidosis) during exercise.

Our interpretation of the current literature is that
although muscle oxidative potential may not be fully used
during a maximal exercise test, the muscle atrophy and
weakness and the alterations in muscle metabolism during exercise that have been repeatedly reported in COPD are
likely to influence the capacity to perform exercise by
increasing the perception of leg effort and the ventilatory
requirements and by contributing to the development of
contractile fatigue of the peripheral muscles.

Other Consequences of Muscle Dysfunction

Other likely consequences of muscle wasting and poor peripheral muscle function in COPD include reduction in
quality of life, greater utilization of health care resources, and poor survival.

Etiology of Peripheral Muscle Dysfunction in COPD

Several factors have been suggested to explain the occurrence of muscle dysfunction in COPD, and their relative
importance is likely to vary among patients. Peripheral muscle
dysfunction is probably multifactorial in origin and is
unlikely to be explained by one mechanism in all patients.
Chronically using corticosteroid use, nutritional imbalance, systemic corti-
costeroid use, hypoxemia, systemic inflammation with
increased circulating levels of proinflammatory cytokines, electrolyte disturbances, and low anabolic hormone
levels have all been suggested as potential contributors
to the development of poor peripheral muscle function in
COPD. However, a causal link between these abnormal
states and the deterioration in muscle function has not been established.

It is often supposed that muscle wasting in COPD is due
to an imbalance between caloric intake and energy expendi-
ture, leading to a reduction in protein synthesis. However, attempts to increase nutritional intake have resulted in only modest and inconsistent improvements in
body weight and muscle mass and strength (reviewed by
Ferreira and colleagues). As in many chronic disorders, increased muscle proteolysis is likely to be present in
COPD and could explain the lack of efficacy of nutritional
interventions in ameliorating muscle dysfunction in
COPD.

A similar conclusion was reached with regard to several other illnesses, leading to the development of the concept of cachexia. Cachexia (Greek: bad condition), in con-
trast to starvation, is characterized by preferential loss in the
muscle tissue compartment associated with systemic inflam-
mation and lack of response to nutritional supplementa-
tion. The preferential loss of muscle tissue, the lack of
response to nutritional supplementation, and the presence
of low-grade systemic inflammation with increased blood
levels of proinflammatory cytokines strongly suggest that
the loss in body weight and muscle mass in patients with
COPD can be considered to constitute a state of cachexia.

Regulation of Muscle Protein Synthesis

and Degradation

The muscle tissue is a primary reservoir of amino acids in
the body. In response to disease or fasting, amino acids
released from muscle tissue are mobilized to sustain liver
protein synthesis (acute-phase protein synthesis) or immune cell replication, as well as for energy production
(glucocorticogenesis). The amount of muscle tissue (ie, its
protein content) in a given individual is the result of a tight
balance between protein synthesis and breakdown. Increased protein degradation is a hallmark of many dis-
cases, such as cancer, sepsis, and chronic renal failure.
For COPD, there have been only two studies in which pro-
tein metabolism was assessed, and their conclusions con-
flict. In comparison with healthy subjects, one study
found decreased protein synthesis in COPD patients, whereas the other found simultaneous increases in protein
synthesis and degradation, reflecting increased whole body
protein turnover. Lack of agreement between these studies
may be explained by the use of different techniques to measure
protein metabolism, in addition to the disparity in the
subjects studied. Further studies of protein metabolism will
be needed to clarify this issue.

Muscle Proteolysis

There are different pathways for degrading proteins. Lysosomes contain proteases that have optimal activity at an
acidic pH (eg, cathepsins) and degrade membrane or endo-
cyted proteins. Traditionally, degradation by this pathway
has been thought to be nonspecific, but there is growing
evidence that some intracellular proteins can be specifically
targeted by the lysosome for degradation. A second pro-
teolytic pathway involves Ca2+-dependent proteases (eg, calpains). These proteases are believed to play a role in
 cytoskeletal reorganization. A third intracellular prote-
olytic system is even more obscure and involves proteolysis
that does not require energy. The specific enzymes involved
and the mechanisms that regulate their activities are
poorly understood, but this category may include metallo-
proteases and proteases involved in apoptosis. Finally,
there are energy-requiring proteolytic systems. The fourth
and best-described system for muscle proteolysis is the
ubiquitin–proteasome pathway, which requires ATP and degrades the bulk of cellular and some membrane proteins.\(^{55}\)

Activation of the ubiquitin–proteasome system has been well established in a wide range of animal models\(^ {47}\) and to a lesser extent in human muscle tissues in association with diverse illnesses such as cancer,\(^ {56}\) sepsis,\(^ {57}\) head trauma,\(^ {58}\) and AIDS.\(^ {59}\) However, the role of the ubiquitin–proteasome system in the wasting process in patients with COPD has not been established. In most animal models of cachexia, the genes encoding for different components of the ubiquitin–proteasome system are up-regulated two- to fourfold during muscle atrophic processes.\(^ {47}\) This system is complex and consists of a highly organized cascade of enzymic reactions, which select, mark, and degrade proteins (Figure 49-3).\(^ {35}\) Proteins destined for degradation by this system are first modified by the attachment of a small protein, ubiquitin. Ubiquitin is abundantly expressed in all higher eukaryotic cells and is one of the most evolutionarily conserved proteins known. In most cases, ubiquitin is linked to the substrate protein through an isopeptide bond between the ε-amino groups of lysines in the target protein and the C-terminal glycine of ubiquitin. Cycles of these reactions link additional ubiquitins to lysines with ubiquitins added previously.\(^ {55}\)

The conjugation of ubiquitin and protein substrates involves a series of complex steps. Initially, an ubiquitin-activating E1 enzyme uses ATP to form an E1–ubiquitin thioester adduct with the C-terminal glycine of ubiquitin. A single E1 enzyme is responsible for ubiquitin activation in all mammalian cells. After ubiquitin activation, members of the E2 ubiquitin-carrier family (also called ubiquitin-conjugating enzymes) participate in the transfer of the activated ubiquitin to protein substrates. In the vast majority of cases, a member of the E3 ubiquitin–protein ligase family also participates in the conjugation process. The purpose of the various E3 ubiquitin ligases is to provide selectivity to the ubiquitination process by serving as docking proteins that bring the substrate protein and the E2 carrier protein with activated ubiquitin together. In some instances, accessory proteins required for ubiquitin conjugation interact with E3 ubiquitin ligases. The E3 ubiquitin ligases are grouped into three major families, on the basis of structural similarities and the functional classes of substrates that they recognize. These three groups are the HECT domain ubiquitin ligases, and the two groups comprising the RING finger ubiquitin ligases, the single-unit and multisubunit enzymes.\(^ {55}\) Recently, two groups have identified new ubiquitin ligases that are expressed specifically and robustly in wasting muscles of animals in catabolic states. MuRF1 (muscle RING finger-1) is a single-subunit RING finger E3 ligase.\(^ {60}\) Atrogin-1 (atrophy gene-1),\(^ {61}\) also known as MAFbx (muscle atrophy F-box),\(^ {59}\) is an F-box–containing protein that is a member of the family of the multisubunit E3 ubiquitin ligases.

Clearly, activation of the ubiquitin–proteasome system is necessary for muscle wasting. However, muscle proteolysis does not directly depend on activation of this system. For instance, actomyosin complexes and myofibrils are resistant to degradation by this system.\(^ {62}\) In order to undergo ubiquitination and eventually degradation by the proteasome, contractile proteins must be released from the myofibril and cleaved. One appealing hypothesis is that activation of proapoptotic proteases that could cleave actomyosin complexes and actin into fragments is necessary to trigger their degradation by the ubiquitin–proteasome system.\(^ {63}\) Other investigators have suggested that the role played by the Ca\(^ {2+}\)-dependent proteolytic enzyme calpain is a key step in the release of actin and myosin from the sarcomere.\(^ {64}\) It has also been suggested that the oxidation of contractile proteins as a consequence of muscle oxidative stress could be one mechanism triggering the ubiquitination and degradation of myofibril proteins (see below).

Although muscle proteolysis and activation of the ubiquitin–proteasome system are thought to be of the utmost importance in the development of cachexia in various conditions, the signals that trigger this process seem to differ from one pathologic state to another. For instance,
Inflammation and Oxidative Stress

A common finding in different wasting conditions is the elevated blood levels of proinflammatory cytokines. The role of these cytokines in the wasting process is based on the following observations: (1) cultured myoblasts exposed to TNF-α or other cytokines do not undergo normal differentiation and (2) muscle cachexia can be induced in small animals by systemic injection of proinflammatory cytokines, and this can be prevented by inhibiting the activity of these cytokines or their receptors. Although proinflammatory cytokines such as TNF-α and interleukin-6 (IL-6) can activate the ubiquitin–proteasome pathway, they do not reduce lean body mass directly. In this regard, the activation of nuclear factor kappa B (NFkB) seems to be a key intermediate step. NFkB is a ubiquitous transcription factor, present in the cytosol in an inactive form when coupled to its natural inhibitor, IκB. Inflammatory cytokines can activate NFkB by initiating the degradation of IκB by the proteasome. Free of its inhibitor, NFkB can then translocate into the nucleus, bind to target DNA elements, and regulate the transcription of several genes coding for inflammatory and growth molecules. In muscle, NFkB can inhibit the expression of MyoD, which is a transcription factor that is essential and specific for skeletal muscle differentiation and repair. Direct inhibition of NFkB prevents muscle wasting in animal models. The negative action of NFkB on muscle growth and repair is subject to tight counterregulatory mechanisms. For instance, NFkB can also suppress the transcription of the proteasome C3 subunit in muscle cells, thus blocking muscle protein degradation. Interestingly, glucocorticoids exert their catabolic effect by opposing the NFkB proteasome suppression.

Inflammation may also induce an oxidant–antioxidant imbalance in patients with chronic disorders by providing a continuous source of oxidative stress, which may contribute to poor muscle performance and impaired muscle regeneration because oxidative stress also inhibits myogenic differentiation. It was recently shown that mild oxidative stress increases protein degradation in skeletal muscle by causing increased expression of the major components of the ubiquitin–proteasome pathway. In addition, skeletal muscle proteins modified by reactive oxygen species (ROS) can be easily degraded by the proteasome. Interestingly, antioxidants may prevent muscle wasting in a murine model of cachexia induced by TNF-α. Thus, inflammation and ROS may have interrelated actions and act synergistically in inducing muscle proteolysis.

COPD is characterized by low-grade systemic inflammation (reviewed by Debigaré and colleagues), which is often accompanied by low blood levels of anabolic hormones. Elevated blood levels of IL-6, IL-8, TNF-α, and C-reactive protein in COPD patients have been associated with low muscle mass, increased resting energy expenditure, and unresponsiveness to nutritional interventions, giving support to the concept that these cytokines play a role in COPD-associated cachexia. In addition, levels of adhesion molecules are increased in bronchoalveolar fluids and plasma of COPD patients in comparison with healthy subjects. The presence of adhesion molecules in the blood is necessary for the initiation of bronchial inflammatory cell infiltration. In theory, these adhesion molecules could also induce inflammatory cell infiltration in other tissues, such as skeletal muscle, but this has yet to be verified. Accordingly, it is conceivable that a low-grade and chronic systemic inflammatory process may participate in the development of peripheral muscle wasting and dysfunction in COPD (reviewed by Debigaré and colleagues).

In view of the possible interaction between proinflammatory cytokines and ROS, it is interesting that there is increased generation of ROS, originating from the contrac
tile muscles, after low-intensity exercise and after local exercise of the quadriceps muscle in patients with COPD. As a result, local muscle exercise induces an imbalance between oxidant and antioxidant defenses in patients with COPD. Indeed, muscle oxidative stress causes noticeable damage to myocyte organelles, DNA, proteins, and lipids and results in excessive rises in intracellular free Ca²⁺ level, mitochondrial dysfunction, and bioenergetic enzyme down-regulation.

Decreased Anabolism

Although increased catabolism is a hallmark of muscle wasting, there is also support for the hypothesis that anabolic factors are equally important for muscle mass homeostasis. A mechanistic link between anabolic factors and the maintenance of muscle mass is emerging. For instance, it was recently demonstrated that insulin and insulin-like growth factors (IGFs) stimulate myofibril synthesis. Conversely, insulin and IGFs can decrease protein degradation by reducing the activity of the ubiquitin–proteasome pathway. Interestingly, proinflammatory cytokines can exert a suppressive action on IGF-1 by up-regulating the expression of its circulating inhibitor, insulin-like growth factor binding protein-1. This indicates that there is a close relationship between the catabolic and anabolic pathways. Other factors regulating muscle growth, such as myostatin and myogenin, have been recently identified, and their role in wasting disorders is currently being investigated.

Concurrently with the low-grade systemic inflammation, patients with COPD also show a higher prevalence of low...
plasma levels of testosterone$^{44,76}$ and IGF-1$^{43}$ than healthy subjects of a similar age. The clinical relevance of this finding remains to be elucidated as correlations between body weight or muscle mass and plasma levels of these hormones, taken individually, are weak$^{44,76}$ and supplementation with anabolic steroids$^{59}$ or growth hormone$^{86}$ had only a modest effect on lean mass and functional status. However, a significant relationship has been described between IL-6/DHEAS (dehydroepiandrosterone, DHEAS sulfate) ratio and midtigh muscle cross-sectional area in patients with COPD, supporting the concept that the balance between catabolic and anabolic factors is more relevant to muscle wasting than either category of factors taken individually.$^{76}$ This finding also suggests that there is an intimate relationship between the catabolic and anabolic pathways in regulating muscle mass.

**Nutritional Imbalance**

Increased total daily and resting energy expenditure is common in patients with COPD and could contribute to body weight and muscle mass loss.$^{87,88}$ In many patients, the greater energy expenditure is compensated for by increases in caloric intake, so that body weight is maintained. However, this adaptation is progressively lost in patients with severe COPD, as indicated by Schols and colleagues, who reported a decrease in caloric intake with increasing severity of airflow obstruction.$^{88}$ Although nutritional imbalance may play a role in muscle wasting in some patients, the absent or modest improvement in peripheral muscle function associated with nutritional supplementation suggests that a negative energetic balance is not the primary mechanism of muscle wasting in most cases.$^{46}$

**Hypoxemia**

In healthy subjects, chronic hypoxia decreases muscle mass, lowers the oxidative capacity of skeletal muscle, and reduces the cross-sectional area of type I fibers.$^{89}$ In keeping with this, a positive correlation between the arterial partial pressure of oxygen ($P_aO_2$) and percentage of type I fibers in the vastus lateralis muscle has been reported in patients with COPD.$^{40}$ Although such a relationship should be interpreted with caution, since hypoxemia only occurs in patients with advanced disease and severe functional impairment, it raises the possibility that chronic hypoxemia may play a role in patients with low resting $P_aO_2$ or in those with repeated oxygen desaturation occurring during sleep and/or exercise.$^{90}$ Hypoxemia may also contribute to wasting in COPD by decreasing anabolic hormone levels$^{91}$ and increasing proinflammatory cytokine levels.$^{92}$ The presence of hypoxemia is also associated with the generation of ROS, which contribute to oxidative stress.$^{78}$ Overall, hypoxemia may contribute to wasting by shifting the balance between anabolic and catabolic factors in favor of the latter.

**Chronic Inactivity and Deconditioning**

Chronic inactivity leading to muscle deconditioning is the most often quoted cause of peripheral muscle dysfunction in COPD. It is a common observation that patients with COPD often reduce their level of activity to avoid the dyspnea that ambulation engenders. Furthermore, the similarity between the histochemical and enzymic muscle changes associated with chronic inactivity in healthy humans and those reported in patients with COPD$^5$ is another indication that muscle deconditioning is likely in COPD. The different degrees of activation of the lower limb muscles and upper limb and diaphragmatic muscles may be responsible for the different levels of abnormalities in these three muscle groups.$^{8,20}$ In comparison with lower limb muscles, those of the upper limb probably remain more active in daily living, explaining why their function is relatively maintained.$^{8,19}$ Furthermore, in COPD, the pectoralis major and latissimus dorsi muscles may also act as accessory inspiratory muscles, another potential source of stimulation.$^{93}$ The level of activation of the diaphragm is greater than that of the lower limb muscles in COPD, and the chronic increase in work of breathing faced by the diaphragm is, in fact, a continuous training stimulus. The increased proportion of type I fibers in the emphysematous diaphragm is likely to represent an adaptation to training, reinforcing the role of deconditioning in peripheral muscle dysfunction in these individuals.$^{20}$ Finally, the improvement in skeletal muscle oxidative capacity observed after training also supports a role for deconditioning.$^{78}$

**Systemic versus Local Factors in Peripheral Muscle Dysfunction**

The finding that diaphragmatic function is preserved or even better than expected in COPD$^{20,21,94}$ is inconsistent with the possibility that muscle wasting is entirely due to systemic factors. Therefore, local factors must be involved in the development of peripheral muscle cachexia in COPD. The most obvious candidate is decreased level of activity. Inactivity may increase the activity of the ubiquitin–proteasome pathway$^{95}$ and reduce the production of IGF-1, one of the main muscle growth factors.$^{96}$ More recently, IGF-2, but not IGF-1, was shown to be down-regulated in muscle atrophy induced by weightlessness in rats.$^{97}$ Peripheral muscles and the liver are major sources of IGF.$^{76}$ Because of differences in the level of muscle activation, we therefore speculate that IGF-1 and IGF-2 are down-regulated in the vastus lateralis muscle but not in the diaphragm in patients with COPD. In contrast to inactivity, exercise training should improve the balance between catabolism and anabolism by increasing the levels of muscle growth factors.

Other local factors, yet to be identified, are likely to be involved in muscle wasting, as indicated by the marked modifications in the myosin heavy-chain profile of the vastus lateralis muscle in patients with COPD in comparison with healthy subjects, despite modest differences in physical fitness.$^{98}$ Perhaps the most provocative observation in this regard is the decreased hindlimb muscle oxidative capacity found in the emphysematous hamster despite there being no reduction in the level of activity in comparison with control animals.$^{99}$ We can only speculate about the factors that could also contribute at the local level to the induction of muscle wasting. The results of some animal studies suggest that muscle acidosis may be involved in protein degradation.$^{47}$ This may be relevant to patients with COPD, in whom mild exercise, such as that performed in daily
living, induces early and exaggerated muscle acidosis in comparison with healthy subjects. As indicated above, ROS may act locally to trigger muscle wasting. The exciting hypothesis that muscle wasting could occur without a decrease in muscle activation will be extremely difficult to show in humans, in whom the level of physical activity cannot be adequately controlled.

APOPTOSIS

The results of recent studies on apoptosis suggest that an increased frequency and/or intensity of this phenomenon could be responsible for the segmental loss of muscle mass in many different conditions, such as inactivity, aging, and congestive heart failure (reviewed by Sandri100). Although similar findings have also been obtained in COPD,101 it is not clear how apoptosis is triggered in skeletal muscle. Death signals originate in some foci and are translated into apoptotic events through the cell by mitochondria-related pathways. It has been suggested that apoptosis occurs in only part of the multinucleated muscle fiber as a segmental process in order to maintain the right cytoplasm/nucleus ratio.100 Perhaps, in atrophying muscle, apoptosis acts as a regulatory mechanism, maintaining a vital degree of function in the affected muscle group.

A reasonable integrative hypothesis is that cachexia in COPD is the result of an interplay of systemic factors (eg, cytokines, growth factors) that, although not remarkably elevated, may synergize with local factors (eg, inactivity, ROS, acidosis), leading to a disequilibrium between anabolism and catabolism.50 A simplified but useful schematic representation of the cellular mechanisms of muscle wasting in COPD is given in Figure 49-4. Further studies are warranted to determine the relative importance of all the potential factors involved in this complex process.

CORTICOSTEROIDS

Muscle wasting and weakness characterize steroid-induced myopathy and preferentially affect type IIb fibers.102 The potential role of corticosteroids in the development of muscle weakness should not be overlooked in some individuals submitted to chronic or even intermittent systemic corticosteroid treatment.25,102 In patients with COPD, subtle muscle weakness may appear with low doses of corticosteroids (<10 mg/day), perhaps because of greater susceptibility to the development of corticosteroid-induced myopathy.25

TREATMENT OF PERIPHERAL MUSCLE DYSFUNCTION IN COPD

The treatment of peripheral muscle dysfunction is likely to remain suboptimal as long as our understanding of this problem is incomplete. Because the etiology of peripheral muscle dysfunction in COPD appears to be multifactorial, one isolated therapeutic strategy is unlikely to completely resolve the problem. A global approach, with correction of all possible contributing factors, should have a better chance of success.

Although no cure is available for muscle wasting in COPD patients, it is important to recognize the potential therapeutic consequences of peripheral muscle wasting. Gains in muscle mass and strength have been associated with...
Peripheral Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

**Better Exercise Tolerance and Survival.** Thus, improving peripheral muscle function is an important therapeutic target in patients with COPD.

**Exercise Training**

Probably the best available therapeutic modality for increasing and/or preserving muscle mass is exercise training, which has been shown to increase muscle mass, strength, and aerobic capacity. Several studies have indicated that patients with severe COPD can sustain the necessary training intensity and duration for skeletal muscle adaptation to training to occur. After 12 weeks of leg-cycling exercise, increases were found in the activity of two mitochondrial enzymes (Figure 49-5), type I fiber size of the vastus lateralis muscle, and capillary density. As a consequence of the improvement in muscle oxidative capacity with training, changes in muscle metabolism also occur, leading to a reduction in lactic acid efflux during exercise. Other investigators have reported increased quadriceps muscle endurance during voluntary contractions after 3 weeks of endurance training. Strength training also appears to be worthwhile in patients with COPD as this type of training has more potential to improve muscle mass and strength than does aerobic training. In addition, strength training causes less dyspnea during the exercise period, making this strategy easier to tolerate by patients with severe COPD than aerobic training.

**Nutritional Intervention**

Nutritional support has been used with the hope that restoring nutritional balance will increase body weight, muscle mass and, ultimately, functional status. Comparison between studies is difficult because of the variety of nutritional interventions (reviewed by Ferreira and colleagues). Weight gain can be achieved with oral or enteral nutritional supplementation for 2 to 12 weeks, although the results are often modest and inconsistent. Patients in whom body weight increases following a nutritional intervention show a somewhat better prognosis than those in whom this intervention does not modify body weight. However, it is unclear whether the survival advantage in the responders is related to the gain in body weight per se or simply reflects the presence of more favorable patient characteristics.

Typically, the increase in body weight resulting from nutritional supplementation is due to an increase in fat, with there being little or no increase in muscle mass. It is therefore not surprising that the magnitude of improvement in muscle strength and functional status following nutritional supplementation is often disappointing. There are also important limitations to aggressive nutritional intervention in patients with severe COPD. Gastrointestinal symptoms, such as bloating, early satiety, meal-related oxygen desaturation, and postprandial dyspnea, are common side effects. Despite the lack of strong evidence for beneficial effects of nutritional intervention on muscle function, it is nevertheless advisable to restore a positive energetic balance for patients with low body weight. The first step in achieving this goal is dietetic counseling.

**Anabolic Hormone Supplementation**

The results of anabolic steroid and growth hormone supplementation have been disappointing so far. However, the doses used were probably subtherapeutic, and further studies are needed to determine optimal dosages for these anabolic hormones. The use of these drugs should also be studied in conjunction with exercise training as synergy may be observed.

**Oxygen Therapy**

Although short-term oxygen therapy enhances exercise tolerance and muscle aerobic metabolism in hypoxemic patients with COPD, little is known of the effects of long-term oxygen therapy on muscle function. Six to nine months of home oxygen therapy has been shown to facilitate the formation of muscle ATP but does not appear to improve skeletal muscle enzyme activity. It seems possible that long-term oxygen supplementation might allow an increased level of activity and therefore improved muscle function. This possibility deserves to be investigated.

**Novel Therapeutic Strategies**

Based on our current knowledge of muscle homeostasis, several novel therapeutic avenues can be proposed to reverse the wasting. One way to intervene is to increase protein synthesis with the use of growth factors such as IGF-1, which can suppress ubiquitin–proteasome activities and induce hypertrophy. Novel forms of nutritional intervention, involving branched amino acid supplementation (leucine, isoleucine, and valine), are of interest as they may inhibit proteolysis in skeletal muscle by acting as a negative feedback regulator of the lysosomal proteolytic system and by decreasing ubiquitin–proteasome system gene expression. In rats, clenbuterol, a β2-adrenergic agonist, normalizes protein breakdown and prevents skeletal muscle wasting.

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**Figure 49-5** Individuals' values for the activity of citrate synthase (CS) and 3-hydroxyacyl-CoA-dehydrogenase (HADH) in 11 patients with COPD before and after 12 weeks of exercise training. These values increased significantly after training. *p < .05, †p < .01. Reproduced with permission from Maltais F et al.
However, equivocal results have been obtained with this drug in humans.\textsuperscript{114} The efficacies of new antiinflammatory drugs, such as cytokine inhibitors or muscle-specific protease inhibitors, alone or together, in blocking muscle proteolysis and increasing muscle mass are likely to be evaluated in the near future.\textsuperscript{115} Finally, antioxidants could also represent another promising therapeutic target. Clearly, research on muscle wasting in patients with COPD and other chronic diseases will help identify new therapeutic strategies for this important problem that can reverse its adverse clinical effects.

**CONCLUSION**

Modern medicine faces the challenge of improving the care of patients with chronic diseases such as COPD. Despite all the efforts of preventive medicine, the burden of COPD is expected to increase in the coming decades. Unless a cure for the disease is found, physicians will have to deal with the systemic consequences of COPD. It will therefore be important to better address the problem of peripheral muscle dysfunction as an appropriate treatment for this condition should result in a better life for our patients in terms of both quality and duration.

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