Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives

Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives[1–3]

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ABSTRACT Low exercise tolerance has a large influence on health status in chronic obstructive pulmonary disease and chronic heart failure. In addition to primary organ dysfunction, impaired skeletal muscle performance is a strong predictor of low exercise capacity. There are striking similarities between both disorders with respect to the muscular alterations underlying the impairment. However, different alterations occur in different muscle types. Histologic and metabolic data show that peripheral muscles undergo a shift from oxidative to glycolytic energy metabolism, whereas the opposite is observed in the diaphragm. These findings are in line with the notion that peripheral and diaphragm muscle are limited mainly by endurance and strength capacity, respectively. In both diseases, muscular impairment is multifactorially determined; hypoxia, oxidative stress, disuse, medication, nutritional depletion, and systemic inflammation may contribute to the observed muscle abnormalities and each factor has its own potential for innovative treatment approaches. *Am J Clin Nutr* 2000;71:1033–47.

KEY WORDS Chronic obstructive pulmonary disease, COPD, chronic heart failure, CHF, skeletal muscle, peripheral muscle, respiratory muscle, exercise intolerance, muscle performance, muscle morphology, muscle metabolism, hypoxia, oxidative stress, medication, disuse, nutritional depletion, systemic inflammation, oxygen therapy, antioxidant status, training, nutritional support, anabolic steroids, review

INTRODUCTION

According to the definitions of the World Health Organization, chronic diseases are characterized not only by the primary impairments they cause, but also by the disabilities or even handicaps that result from them (1). Although the primary impairments in chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) clearly differ, there is a striking resemblance in the systemic consequences of these diseases and their effects on exercise capacity and health status (**Figure 1**). Impaired skeletal muscle function in COPD and CHF has long been ignored by focusing on the respective ventilatory and cardiac limitations on exercise performance. Research has shown that impaired skeletal muscle function is also an important predictor of exercise limitation in both diseases (2–6). Progression of the primary impairments in these disorders can be slowed down with medication (7, 8). Reversion can be only partially achieved through surgical interventions such as lung volume reduction surgery and lung transplantation (9, 10) and coronary bypass surgery and heart transplantation (11). However, there are limits on the age of most eligible patients and the availability of donor organs for these interventions. In addition, such interventions do not always confer a survival benefit; no improvement was found after lung transplantation in patients with end-stage emphysema (12). Also, irrespective of the reversibility of the organ impairment, exercise intolerance in both COPD and CHF remains after surgical intervention (13, 14), indicating that more detailed insight into the systemic consequences is required for effective treatment of these diseases.

Muscle function depends, though not completely, on perfusion, muscle mass, fiber composition, and energy metabolism (15). It can be inferred that alterations in one or more of these determinants play a role in reduced muscle performance. Indeed, such changes have been found in both COPD and CHF and there are striking similarities between the 2 etiologically distinct disorders.

In this review, we first present an overview of the clinical studies that have investigated impaired muscle function, with special emphasis on muscle morphology and energy metabolism in COPD and CHF. The advantage of discussing both diseases simultaneously is that the evidence about each complements that of the other and therefore provides more insight into the possible underlying causes of the muscle alterations. In the second part of the article, potential causes will be discussed, including hypoxia, oxidative stress, disuse, medication, nutritional depletion, and systemic inflammation. The third part deals with therapeutic perspectives.

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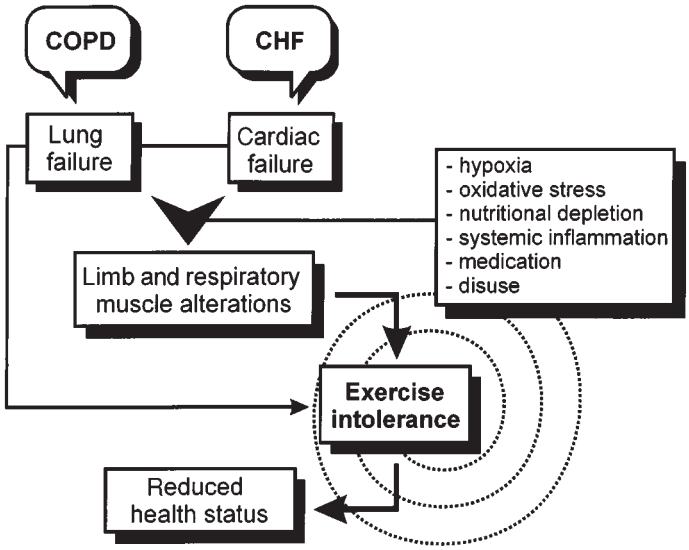

FIGURE 1. Contributors to exercise intolerance in chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF).

MUSCLE ALTERATIONS IN COPD AND CHF

Muscle performance

Muscle performance is characterized largely by strength and endurance. Strength is defined as the capacity of the muscle to develop maximal force, and endurance is defined as the capacity of the muscle to maintain a certain force over time, thus, to resist fatigue. Loss of either one of these aspects results in muscle weakness and impaired muscle performance. Numerous studies have now convincingly shown that COPD and CHF are commonly associated with muscle weakness (6, 16–21). Probably the most extensive study on the influence of muscle weakness on exercise capacity in cardiorespiratory disorders was done by Hamilton et al (4). Compared with healthy subjects, patients with respiratory failure, heart failure, or a combination of both had significantly less strength in both peripheral and respiratory muscles. However, strength and endurance seem not to be affected in the same way in respiratory and peripheral muscles. This is illustrated by the poor correlation between the strengths of both muscle groups in the 2 disorders (18, 20, 21) compared with the much stronger correlation in healthy subjects (22). This implies that the strength component of muscle weakness is affected differently in peripheral and respiratory muscles. In healthy subjects as well as in patients with COPD or CHF, exercise-limiting symptoms are the sense of leg effort (exertional discomfort) or breathlessness (exertional dyspnea) (23, 24). Thus, despite correlations between peripheral muscle strength and performance in COPD and CHF (18, 23, 25), reduced endurance (ie, fatigue) seems to be the dominant limiting factor in peripheral muscles in these patients because the sense of leg effort was one of the main reasons to stop exercising (4, 24, 26–29). It was shown that early lactic acidosis occurs in COPD during exercise (30, 31) and that this is largely the result of lactate release from the lower exercising limbs (32). Muscle acidosis is a contributing factor to muscle fatigue (33).

Fatigue is probably not the main limiting factor in respiratory muscle function. Morrison et al (34) found that COPD patients have low respiratory muscle strength and endurance. Fatigue of the respiratory muscles may indeed occur during exercise, but it is not certain whether this is an independent determinant of exercise capacity (27, 35–38). In addition, it is unlikely that the respiratory muscles of exercising COPD patients contribute to the lactate response mentioned earlier (39). It should also be emphasized that the respiratory muscles must operate against the mechanical airway impedances in this specific disorder (40), for which the force component of respiratory muscle function is most likely of great importance. For CHF it was found that respiratory muscle strength and not respiratory muscle fatigability correlated with the degree of dyspnea (41). Thus, it seems that strength is the limiting aspect of muscle performance in the respiratory muscles, whereas endurance is limiting in peripheral muscles. However, more detailed studies are required to clarify the individual roles of strength and endurance limitation in peripheral and respiratory muscles in COPD and CHF.

Muscle morphology

In both CHF (23, 42–44) and COPD (3, 45–50), marked loss of muscle mass or decline in cross-sectional muscle area is observed. This muscle wasting plays an important role in the loss of exercise tolerance in these patients. However, morphologic alterations may also be related to impairment of muscle function, although direct relations with exercise performance have not yet been shown. Some histologic information is available on abnormalities in skeletal muscle in CHF but there is hardly any on COPD. Gertz et al (51) found no signs of increased fibrosis or other alterations in intercostal muscles of patients with respiratory failure, whereas endomysial fibrosis has been found in skeletal muscle of a limited number of CHF patients (52). Increased activity of acid phosphatase, a lysosomal enzyme contributing to protein degradation, has been found in the quadriceps of some patients with CHF (25) or respiratory failure (50). Increased lipid deposits have been found in the quadriceps, biceps, and deltoids of some patients with CHF (25, 52). Contradictory results have been obtained with respect to capillary density in peripheral skeletal muscle in CHF. A normal capillary density has been found (25), which agrees with results of 2 other

studies in which both reduced capillary-fiber ratios and atrophy resulted in unchanged capillary densities (53, 54). An unaltered capillary-fiber ratio has also been reported, however, with greater capillary density due to fiber atrophy (55). In contrast, reduced capillary density in combination with a reduced capillary-fiber ratio has been shown in CHF patients (56) and even in heart transplant recipients (57). Thus, overall, there is a tendency toward a reduced capillary-fiber ratio, but depending on the degree of atrophy, the capillary density may even be elevated. This tendency was recently confirmed in COPD (46).

In a few studies, morphometry of mitochondria with use of electron microscopy showed that mitochondrial volume densities in skeletal muscle were lower in CHF patients than in control subjects (56, 58), and this was still the case 10 mo after heart transplantation (57). Histochemical alterations reflecting mitochondrial abnormalities have also been reported in biceps muscle biopsies of COPD patients (50). These results suggest that the oxidative capacity of peripheral skeletal muscles may be altered in both diseases.

Muscle fiber type distribution

Probably the most remarkable muscle alteration in COPD and CHF is a relative shift in fiber composition that seems to occur in opposite directions in peripheral and respiratory muscles. Fiber typing is mainly performed histochemically, and is based on differences between fibers in myosin ATPase activities or immunocytochemistry (59). Adult mammalian skeletal muscle contains 4 myosin heavy chain (MyHC) isoforms, namely, types I, IIa, IIb, and IIx (60). In most older studies, fiber typing was limited to determining fiber types I, IIa, and IIb. Furthermore, human fibers formerly identified as being IIb with myosin ATPase staining are probably IIx fibers (61). Therefore, the notation IIb/x is used in the subsequent text. Fiber type I has a slow twitch and develops a relatively small tension, but because it depends mainly on aerobic metabolism, it is fatigue resistant. In contrast, fiber type IIb/x has a fast twitch and develops large tensions, but it is susceptible to fatigue because its energy conversion is based on anaerobic, glycolytic metabolism. Fiber type IIa has intermediate properties in that it also has a fast twitch, develops a moderate tension, is relatively resistant to fatigue, and is apt to work under both aerobic and anaerobic conditions (15, 59, 62).

A lower percentage of type I fibers and a corresponding higher percentage of type II (mainly type IIb/x) fibers, compared with those of normal subjects, has been reported in limb muscles of COPD (46, 63–66) and CHF (25, 53–56, 67) patients. In addition, in one of these studies an increase in intermediate fiber types (I + II) was also observed in CHF patients (55). These fibers may represent transformation intermediates in the I→IIb/x shift. In contrast with that in peripheral muscles, a shift from type IIb/x to type I fibers has been reported in the diaphragms of both COPD and CHF patients. In healthy subjects, the diaphragm has ≈50% type I, 25% type IIa, and 25% IIb/x fibers (68), whereas the diaphragms of CHF patients contain 60% type I, 35% type IIa, and only 10% type IIb/x fibers (69). A IIb/x→I shift was also observed when the distribution of MyHC isoforms was analyzed in diaphragms of patients with CHF (70) or COPD (71). Furthermore, a larger population of type I fibers in the diaphragm (corrected for the percentage of type I fibers in the quadriceps femoris) was found in both COPD and CHF patients (26, 72) compared with sedentary control subjects (68, 73). The proportion of type I fibers in both the internal and external intercostal muscles was ≈62% in both COPD patients and control subjects in some studies (68, 74), but in other studies COPD patients had lower proportions of type I fibers (46–48%) in these muscles (73, 75). Also, elevated expression of fast MyHC has been reported in the external intercostal muscles of COPD patients (76). These results suggest that the accessory respiratory muscles do not show the II→I fiber shift that occurs in the diaphragm. No such data have been published for CHF patients.

The overall outcome of the studies done until now (despite some variation in the results) has been that there is a I→IIb/x shift in peripheral muscles and a IIb/x→I shift in the diaphragm in COPD and CHF. It is possible that these shifts have functional consequences in the affected muscles because the distinct fiber types have different contractile properties with respect to twitch and fatigue resistance. Therefore, in COPD and CHF, a I→IIb/x shift accompanied by more glycolytic and less oxidative capacity in peripheral muscles implies loss of fatigue resistance. This change might contribute to the observed loss of exercise tolerance because peripheral muscle fatigue is the main exercise-limiting factor in these patients. This was confirmed by a study in which a faster twitch response in combination with less resistance to fatigue was observed in the leg muscles of CHF patients (77). Accordingly, a IIb/x→I shift toward more oxidative metabolism in the diaphragm implies a shift toward a more fatigue-resistant but less strength-adapted muscle. This too is in line with our notion that strength and not fatigue seems to be the main limiting factor for respiratory muscle function.

Muscle metabolism

Much data are available on skeletal muscle metabolism in CHF and COPD, partly because of the applicability of ^{31}P-nuclear magnetic resonance (^{31}P-NMR), which has enabled a direct and noninvasive assessment of tissue concentrations of high-energy phosphates and pH. High concentrations of ATP, creatine phosphate (CrP), and nicotinamide adenine dinucleotide in the reduced form (NADH) reflect a high-energy state, whereas elevated concentrations of ADP, AMP, inorganic phosphate (P_i), and oxidized nicotinamide adenine dinucleotide (NAD^+) commonly reflect a low-energy state. Lactate and glycogen concentrations are often measured in muscle metabolism, but note that low concentrations may reflect either increased clearance or reduced formation, and vice versa for high concentrations. Although activities of enzymes involved in muscle energy metabolism measured in vitro do not reflect the physiologic situation because maximal activities are obtained under optimal, artificial circumstances, they do provide an indication of adaptations in the expression of proteins involved in metabolic pathways. Typical oxidative enzymes are citrate synthase, succinate dehydrogenase, and β-hydroxyacyl-CoA dehydrogenase (HAD). Typical glycolytic enzymes are hexokinase, phosphofructokinase, and lactate dehydrogenase—the latter of which catalyzes the last step of anaerobic glycolysis.

Measurements of substrate and cofactor concentrations in peripheral skeletal muscle of COPD and CHF patients indicate impaired energy metabolism (**Table 1**). Most striking are the observed reduced concentrations of high-energy phosphates at rest. Pouw et al (81) observed the higher P_i-CrP and ADP-ATP ratios were associated with slightly but statistically significantly elevated inosine monophosphate (IMP) concentrations. The latter may be due to increased degradation of accumulating AMP by deamination, which probably reflects reduced aerobic capacity

TABLE 1
Muscle metabolite concentrations in chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF)[1]

Metabolite and muscle	Direction relative to reference values	References
Creative phosphate		
QF (COPD)	▼	51, 64, 73, 78[2]
QF (CHF)	▼	79, 80[2]
IIC and EIC (COPD)	▼	51, 75
ATP		
QF (COPD)	▼	51, 64, 73, 78[2]
QF (CHF)	▼	79, 80[2]
IIC and EIC (COPD)	▼	51, 75
IMP		
TA (COPD)	▲	81
Glycogen		
QF (CHF)	▼	53, 79, 80
QF (COPD)	▼	64, 73[2]
Glucose		
IIC and EIC (COPD)	▲	51
QF (CHF)	▼	82
Lactate		
QF (COPD)	▲	51, 78
QF (CHF)	▲	82
IIC and EIC (COPD)	▲	51
Pyruvate		
QF (CHF)	▲	53

[1] CrP, creatine phosphate; IMP, inosine monophosphate; QF, quadriceps femoris; IIC, internal intercostal; EIC, external intercostal; TA, tibialis anterior.
[2] Nearly significantly different from reference values.

(83). The situation becomes even worse during exercise: a greater increase in the P_i-CrP ratio and a faster drop in pH were found in the calf muscle of COPD (47, 84, 85) and CHF (55, 86, 87) patients performing exercise than in healthy persons. Similar results were obtained for the forearm muscle (14, 87–89). In addition, a slower recovery of CrP concentrations was observed after exercise in COPD and CHF patients than in healthy persons (14, 47, 55, 85–89). These results suggest that rephosphorylation of high-energy phosphates is less efficient in these patients, both during and after muscular exercise. In addition, glycogen contents in COPD and CHF patients tend to be lower, whereas lactate concentrations are higher than in healthy persons (Table 1). Thus, it seems that anaerobic energy metabolism is enhanced in these diseases, and because this process yields far less ATP than does complete oxidative degradation of glucose, this could explain the reduced high-energy phosphate concentrations.

Analysis of enzyme activities also suggests an overall increase in glycolytic and an overall decrease in oxidative activities in peripheral muscles of both COPD and CHF patients (**Table 2**). Because these enzyme activities depend largely on the fiber type (95), it is likely that this shift in activities is related to the shift in fiber distribution mentioned above. Whether enzyme activities adapt to the fiber type redistribution or the fiber type redistribution adapts to enzyme activities remains unclear. In addition to these chronic alterations of enzyme activities, which are measured in vitro, there is probably also an acute effect on the activities of these enzymes. As a consequence of impaired electron transport, regeneration of NAD^+ from NADH is reduced and citrate synthase and HAD are inhibited by a high NADH-NAD^+ ratio (96). In addition, elevated AMP concentrations, resulting from the inefficient rephosphorylation of ATP, stimulate glycolysis (96). However, note that this acute effect is invisible in the in vitro activity measurements. In 2 studies, an additional inverse relation of oxidative enzyme activities with arterial lactate concentrations was found during exercise, emphasizing the assumed shift from oxidative toward glycolytic energy generation (30, 91). This loss of oxidative capacity probably accounts for the above-mentioned lipid deposits (97) because fatty acid consumption may be reduced while the supply of blood fatty acids continues. Recently, activities of 2 other oxidative enzymes, cytochrome-*c* oxidase (COX) and NADH dehydrogenase, were found to be elevated in COPD and CHF patients (Table 2). On first notice, this seems to be paradoxical in light of the observed reductions in the oxidative enzymes mentioned earlier. However, the oxidative enzymes mentioned earlier are involved in either the citric acid cycle or fatty acid oxidation, whereas COX and NADH dehydrogenase are enzymes of the respiratory chain. COX interacts with oxygen and therefore is the main determinant of mitochondrial oxygen affinity (98). Because a correlation between COX activity and hypoxemia was found (93), it may be that an increased number of COX molecules is a mechanism that enhances the efficiency of residual oxygen extraction and utilization and, thus, respiratory chain function. In this study, COX-I (a mitochondrial encoded subunit of COX) messenger RNA concentrations were not elevated but mitochondrial 12S ribosomal RNA concentrations were. Because this particular ribosomal RNA is a component of mitochondrial ribosomes, which are involved in translation, mitochondrial protein synthesis may be enhanced. The mechanism of hypoxia sensing and subsequent stimulation of mitochondrial gene expression remains, however, unclear (93).

Because of technical difficulties with ^{31}P-NMR and muscle biopsies of the diaphragm and accessory respiratory muscles, little is known about energy metabolism in these muscles. However, the observed alterations in enzyme activities (Table 2) confirm the morphologic data, in that oxidative enzyme activities are reduced and glycolytic enzyme activities are elevated in COPD and CHF compared with the healthy state. As in peripheral muscles, this shift probably results from the shift in fiber type distribution.

POSSIBLE UNDERLYING FACTORS

Hypoxia

In COPD and CHF, oxygen delivery to peripheral and respiratory muscles may be insufficient as a result of hypoxemia, reduced blood supply, or both. In both cases, muscle tissue may become hypoxic and this could lead to the adaptive changes in skeletal muscle described above. In this respect, relevant information is now available from mountaineering expeditions (lasting ≥6 wk above 5000 m), because oxygen is limited at this altitude. Under these conditions, reductions in mitochondrial volume densities, oxidative enzyme activities, and cross-sectional areas of muscle fibers were found in the quadriceps (99–101). Note, however, that such expeditions are accompanied by strenuous physical activity, which also causes muscular adaptations other than those caused by hypoxia. In fact, the effect of training in combination with hypoxia may even cause a shift toward more oxidative metabolism (102). More information about the effect of hypoxia on muscle has been obtained from animal studies.

TABLE 2
Muscle enzyme activities in chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF)[1]

Enzyme and muscle	Direction relative to reference values	References
CS		
QF (COPD)	▼	30, 90
QF (CHF)	▼	53, 55, 82, 91
DIA (CHF)	▲	70
IIC and EIC (COPD)	▲	92
HAD		
QF (COPD)	▼	30, 90
QF (CHF)	▼	53, 55, 82, 91
DIA (CHF)	▲	70
IIC and EIC (COPD)	▲	92
SDH		
QF (COPD)	▼	90
QF (CHF)	▼	53, 91
COX		
QF (COPD)	▲	93
CCRT		
QF (CHF)	▲	80
HK		
QF (CHF)	▼	91
DIA (COPD)	▼	94
IIC and EIC (COPD)	▲	92
PFK		
QF (COPD)	▲	90
LDH		
QF (COPD)	▲	90[2]
QF (CHF)	▲	82[2]
DIA (CHF)	▼	70
DIA (COPD)	▼	94
IIC and EIC (COPD)	▼	92

[1] CS, citrate synthase; HAD, β-hydroxyacyl-CoA dehydrogenase; SDH, succinate dehydrogenase; COX, cytochrome *c* oxidase; CCRT, NADH cytochrome *c* reductase; HK, hexokinase; PFK, phosphofructokinase; LDH, lactate dehydrogenase; QF, quadriceps femoris; DIA, diaphragm; IIC, internal intercostal; EIC, external intercostal.

[2] Nearly significantly different from reference values.

Several animal studies have shown that hypoxia can indeed lead to the muscular alterations described for the limb muscles of COPD and CHF patients. For example, reduced fiber diameters in combination with unaffected numbers of capillaries, resulting in increased capillary densities, have been reported in rats exposed to hypoxia (103–105). It is suggested that the availability of oxygen to remaining muscle mitochondria is enhanced by this increased capillary density in combination with the loss of oxidative capacity (99). Furthermore, animal studies showed that hypoxia depresses protein synthesis (106–109), even in muscle tissue (106, 107). Whether hypoxia itself can contribute to the shift in muscle fiber distribution observed in COPD and CHF patients remains uncertain. There is evidence that chronic hypoxia inhibits the normal conversion of type IIa to type I fibers in growing rats, with the final outcome that these rats have a predominating proportion of type IIa fibers, unlike in control rats (110–112). However, no differences in fiber types were found when full-grown, adult rats were exposed to chronic hypoxia (110, 111, 113). Thus, it seems that hypoxia does not directly cause a type I→II fiber shift and it is more likely that the abnormal fiber type distribution results from alterations in muscular development. A similar mechanism may underlie the abnormal fiber type distribution in the regeneration of damaged muscle or the adaption of muscles to consequences of the disease in COPD and CHF.

In addition, there is evidence that hypoxia causes a shift toward glycolytic metabolism. In studies in which rats were exposed to intermittent hypoxia, it was found that citric acid cycle activity was reduced whereas glycolytic metabolism was enhanced, resulting in an increased ratio of lactate to pyruvate (114, 115). Malate dehydrogenase, a citric acid cycle enzyme, was also found to be reduced by hypoxia (116). Furthermore, hypoxia causes stimulation of glucose transport (117) and increased concentrations of membrane-associated glucose transporters (GLUT1 and GLUT4) in rat muscle (118). In muscle cell cultures, this up-regulation of GLUT1 can be mediated by either hypoxia or inhibition of the respiratory chain (119), suggesting that hypoxia affects glucose transport (and probably also metabolism) via impairment of oxidative phosphorylation.

However, in COPD and CHF this reduction in oxidative capacity does not occur in the diaphragm. Hypoxia may cause an endurance training effect in the diaphragm because of increased ventilation, which overrides its direct effect, ultimately resulting in a shift toward more aerobic metabolism.

Oxidative stress

Oxidative stress may be another factor contributing to muscle damage via reactive oxygen species. Increased plasma concentrations of lipid peroxidation products have been found in both COPD and CHF patients (120, 121). The main source of these oxygen free radicals is mitochondria because 2–5% of the oxygen consumed is not fully reduced in the electron transport chain and may leak away as superoxide radicals (122, 123). An alternative source of free radicals is immune cells activated during inflammation (124). Monocytes and macrophages produce the cytokine tumor necrosis factor α (TNF-α), which may in turn induce oxidative stress in myocytes (125). Indeed, elevated TNF-α blood concentrations have been found in both COPD (126–128) and CHF (129–133) patients, particularly in those patients with weight loss or muscle wasting. A third generator of free radicals is xanthine oxidase, which is involved in the deamination of AMP to IMP under conditions of very high AMP concentrations, such as a low-energy state (123). The above-mentioned elevated IMP concentrations in COPD (81) suggest enhanced AMP breakdown.

Susceptibility to these free radicals depends largely on the antioxidant status of tissues (123). The main antioxidant scavengers and enzymes are, among others, reduced glutathione, vitamin E (in cell membranes), superoxide dismutase, glutathione peroxidase, and catalase (123, 134, 135). Repeated exposure to oxidative stress, during long-term physical training for example, stimulates the defense system against oxygen free radicals in that concentrations of scavengers and activities of antioxidant enzymes increase (122, 123, 134–136). Oxygen flux to muscles and the resulting oxidative stress can increase tremendously during exercise (123, 137) and the disuse of muscles thus may take away this antioxidant-stimulating trigger and result in low antioxidant status. Chronic hypoxia probably acts in the same way because less oxygen is available to form reactive oxygen species. Limitations of oxygen supply are indeed found to be associated with reductions in superoxide dismutase activity in mammalian tissues like brain, lungs, and heart, although this change was not

found in skeletal muscle tissue (138, 139). In addition, in myocytes obtained from chronically hypoxic human myocardium cultured at low oxygen tension, antioxidant enzyme activities were lower than in myocytes cultured at a higher oxygen tension, illustrating the direct modulatory effect of oxygen (140). In vivo and in vitro hypoxia-reoxygenation studies showed that oxygen oversupply after a period of oxygen shortage may give rise to free radical formation in myocytes (138, 141, 142). Accordingly, in COPD and CHF patients, chronic hypoxia may result in reduced antioxidant status and occasional bouts of exercise may cause a burst of free radicals that exceeds the capacity of the defense system (122). It is also possible that the patients' reduced oxidative capacity itself leads to enhanced oxidative stress because the sudden oversupply of oxygen during exercise is inefficiently metabolized.

Reactive oxygen species are capable of damaging lipids and proteins (122, 123, 134, 143). Radicals that react with fatty acyl moieties in membrane phospholipids cause a chain reaction of peroxidations that increase the membrane permeability (143). Maintenance of membrane integrity is crucial for adequate functioning of the respiratory chain because the driving force for oxidative ATP synthesis is the electrochemical proton gradient over the inner membrane of the mitochondrion, which is generated during the electron transfer from NADH to oxygen (96). Leakage of ions through a more permeable mitochondrial inner membrane may thus impair mitochondrial function by uncoupling oxidative phosphorylation. Indeed, rats with an inherited overproduction of oxygen free radicals showed a higher degree of lipid peroxidation and protein damage in combination with impaired respiratory chain function in liver mitochondria than did control rats (144). Furthermore, a marked decrease in ATP concentrations was observed in cultured endothelial cells exposed to reactive oxygen species (145). In addition, there is evidence that an intracellular calcium overload, probably caused by a damaged sarcoplasmic reticulum membrane in combination with impaired activity of calcium ATPases, accompanies oxidative stress in animal myocytes (122, 138, 141, 142, 146–148), which may further uncouple respiration from ATP production through extensive depolarization of the inner membrane (149).

Protein oxidation by oxygen free radicals leads to formation of carbonyl groups on amino acid residues, which may modify the structure or chemical properties of the proteins affected (150). These alterations may cause a decline in protein function or even complete protein unfolding. The latter gives rise to enhanced susceptibility to proteinases. These modified proteins may also be recognized as foreign substances and, hence, be attacked by the immune system. Whether radical-induced protein damage plays a role in the abnormalities in muscles of COPD and CHF patients is unclear. It was shown in animal studies that oxidative stress induced in vivo caused myofibrillar muscle protein modification and that these proteins were rapidly degraded by proteases (151). Thus, theoretically, muscle atrophy can be enhanced by radical-induced protein damage. Indeed, it was shown that a calcium overload is involved in muscle atrophy (152) and that vitamin E deficiency facilitates muscle wasting and necrosis (153), both probably mediated by oxidative damage to proteins. Also, in human skeletal muscle it was shown that mitochondria and mitochondrial proteins were more susceptible to oxidative damage than were other subcellular components (154), which suggests that protein damage may cause impaired oxidative metabolism.

As opposed to necrosis, which is the result of exogenous damage as described above, apoptosis of muscle cells is an active process of cell death, which has also been associated with oxidative stress (155). In this study, the exposure of rat myoblasts to nitric oxide or hydrogen peroxide led to apoptotic cell death. Because these chemical stimuli are also released by immune cells, we cannot exclude the possibility that apoptosis underlies muscle wasting during inflammation.

Disuse

Disuse of skeletal muscle from a low level of physical activity is also a factor that most likely contributes to the observed muscle alterations in COPD and CHF. Hampered by their disease, these patients perform less physical activity, which may have a detraining effect on their peripheral muscles. First, detraining causes muscle weakness because of reduced motor neuron activity and muscle wasting (59, 156). Second, disuse may cause a relative reduction in the percentage of type I fibers and an increase in the percentage of type IIb/x fibers (59, 157). Third, detraining causes a decline in the activity of enzymes involved in oxidative energy conversion. This occurs in both type I and type II fibers (157, 158), suggesting that loss of oxidative capacity can occur even without any change in fiber composition. As mentioned earlier, muscular disuse has a negative effect on antioxidant status and, hence, enhances the risk of oxidative damage. Reduced physical activity thus contributes to the loss of muscle mass and probably also to the I→II fiber shift and the reduced oxidative capacity observed in limb muscles in COPD and CHF patients. As mentioned above, the diaphragm is probably not disused in these diseases and a kind of endurance training effect may even occur. This may be true not only for COPD but for CHF as well because in severe CHF, dyspnea and elevated ventilation occurs even at rest (28, 159).

Medication

Of the wide range of drugs used to treat COPD and CHF, only corticosteroids have been associated with skeletal muscle alterations. Especially in COPD, but less frequently in CHF, corticosteroids are used in low doses as maintenance medication or in higher doses during acute disease exacerbations (160, 161). Depending on the type of steroid, the dose, and the duration of treatment, the drug-induced defects range from alterations in energy metabolism to muscle weakness with underlying muscle wasting and histologic abnormalities (160, 161). From the results of both clinical and animal studies it became clear that steroid-induced muscle wasting is often associated with an overall negative nitrogen balance, reduced protein synthesis, increased protein catabolism in muscle tissues, and increased plasma concentrations of amino acids (162). These findings suggest that corticosteroids probably stimulate the mobilization of amino acids from muscle proteins (161), supplying the liver with gluconeogenic precursors, which corresponds with a shift toward glycolytic metabolism. No such data are available for CHF, but a few reports showed that COPD patients who chronically receive corticosteroids indeed may show more muscle weakness alone or with an accompanying loss of muscle mass than do nontreated COPD patients (17, 163–165). However, because COPD patients receive corticosteroids to treat inflammation, it is difficult to distinguish between the effect of steroid administration and the effects of the disease exacerbations. Also, decreased testosterone concentrations have been reported for male COPD patients receiving glucocorticoids (166).

Assuming that corticosteroids are involved in muscular alterations, the question arises as to whether this effect is generalized or is muscle-type specific. Experimental studies indicate that the glycolytic fibers seem especially susceptible to steroid-induced muscle wasting (161, 162, 167), suggesting that vulnerability depends on muscle fiber composition. The diaphragms of affected patients have a relatively high proportion of type I fibers, and so could therefore be less affected by steroid usage; limb muscles, consisting of more type II fibers, would be more vulnerable. On the other hand, the diaphragm already has a lower type II fiber content and selective wasting of type II fibers could further reduce diaphragm strength. Because strength is the main limiting factor in diaphragm muscle performance, it may be more vulnerable to corticosteroids than are limb muscles. Furthermore, it is difficult to isolate the effect of corticosteroids on diaphragm function from the complex of other unfavorable influences on lung function in COPD (165). Therefore, Wang et al (168) studied the effect of prednisone on the respiratory muscle function of normal subjects (who had no disturbing influences on function) and found no differences from a control group. This does not exclude the possibility that other steroids might have an effect because a recent animal study showed different effects of fluorinated and nonfluorinated steroids at equipotent doses (169). The results of other animal studies confirm the hypothesized shift toward glycolytic metabolism in peripheral muscle and the shift toward oxidative metabolism in the diaphragm: in corticosteroid-treated rats it was found that diaphragm force generation and the proportion of type IIb fibers was reduced in combination with decreased activity of the glycogenolytic enzyme phosphorylase and increased activities of HAD and citrate synthase (170). Increased phosphofructokinase and glycogen synthase activities have been reported for limb muscle of corticosteroid-treated rats (169). Expressed per gram of muscle, limb twitch tension may even increase in steroid-treated animals, which indicates an increase in type II fiber content (169, 171). The fact that corticosteroids selectively affect type II fibers but are also associated with a shift toward glycolytic metabolism in peripheral muscle seems contradictory and needs further investigation.

Note that in both CHF and COPD, muscle performance is not fully recovered 5–38 mo after heart or lung transplantation; intrinsic skeletal muscle alterations remain (57, 172). Corticosteroids and cyclosporin are often used as immunosuppressive agents after transplantations and it is therefore possible that these drugs might be involved in impaired muscle function (13, 57, 172).

Nutritional depletion and systemic inflammation

Nutritional depletion commonly occurs in COPD (173, 174) and CHF (42, 175). In both disorders, nutritional depletion is an important determinant of exercise capacity (3, 44, 45, 176). Body weight (usually corrected for height) is often used to determine the nutritional status of patients, but this method neglects the differences in body composition between individuals (3). Determination of body composition with respect to nutritional depletion is important because different patterns of weight loss can be distinguished: predominant loss of fat mass, predominant loss of fat-free mass, or a combination of both.

Predominant loss of fat mass involves an impaired balance between energy requirements and energy intakes. Dietary intake can be low in COPD because of symptoms such as dyspnea, fatigue, and early satiety (177). Recently, systemic inflammation was suggested to affect appetite and dietary intake, mediated by the appetite-regulating hormone leptin (178). However, patients with COPD may lose weight despite a normal or above-normal dietary intake (179). In COPD and CHF, resting energy expenditure (REE) is often elevated (180–183). In addition, total daily energy expenditure that is elevated independently of REE has been found in COPD patients (184). Increased oxygen cost of breathing probably contributes to the increased total daily energy expenditure due to increased hyperinflation during exercise (185, 186), but because hyperinflation is not increased at rest, it is unlikely that an elevated oxygen cost of breathing accounts for the elevated REE (180). Suggested contributors to the elevated REE are the thermogenic effects of bronchodilating agents (180) and systemic inflammation (127). Furthermore, the observed loss of efficient aerobic energy metabolism might play a role in the increased REE and total daily energy expenditure. In this situation of semistarvation, loss of both fat mass and fat-free mass occurs, but the fat-free mass is relatively preserved. Therefore, intrinsic muscle abnormalities besides muscle mass probably account for impaired muscle performance.

Studies of muscle function and histology in anorexia nervosa patients have provided strong data on the effect of undernutrition in muscles. Muscle performance is markedly impaired in these patients (187–189) and is associated with weight loss, loss of muscle mass, and fiber atrophy (particularly of type II fibers) (190, 191). Data from animal studies confirm these effects of undernutrition. Loss of muscle mass associated with fiber atrophy was observed in limb muscles during nutritional deprivation (171, 192). Activities of the oxidative enzymes succinate dehydrogenase and HAD were found to be reduced (192, 193). The activity of the glycolytic enzyme phosphofructokinase was also found to be reduced (193), but this was not confirmed by Koerts-de Lang et al (169). In addition, high ADP and low CrP concentrations were observed in food-deprived animals (193, 194), suggesting that muscle energy metabolism is indeed impaired after deprivation. However, it remains unclear whether nutritional deprivation results in a general loss of activities of enzymes involved in energy metabolism or predominantly affects either oxidative or glycolytic energy metabolism. The contribution of nutritional depletion to a shift from oxidative to glycolytic metabolism in COPD and CHF patients needs further investigation.

Predominant loss of fat-free mass involves an impaired balance between protein anabolism and catabolism that results in the loss of fat-free mass. In emphysema, reduced muscle protein synthesis was found (49), but protein degradation was probably not increased (195, 196). Also, nitrogen intake was not low in these patients but nitrogen excretion was elevated (196). Amino acids may be required in processes other than muscular protein synthesis, such as gluconeogenesis. Because weight loss and loss of fat-free mass have often been associated with systemic inflammation in both COPD and CHF (126, 127, 133), it is also possible that amino acids are required for increased synthesis of inflammatory proteins in the liver. Disturbed plasma and muscle amino acid concentrations have been observed in COPD, suggesting that amino acids are indeed redirected from muscle (197). Animal and in vitro studies confirm this notion (198): exposure of myocytes to TNF-α resulted in a decrease in protein synthesis, which occurred even during anabolic stimulation with insulin-like growth factor I (IGF-I). Furthermore, chronic administration of TNF-α led to increased muscle protein catabolism and liver protein anabolism in rats. In addition, the above-mentioned involvement of TNF-α in oxidative stress may contribute to mus-

cle wasting (125). Protein depletion itself may impair skeletal muscle performance as reflected by reduced maximum voluntary handgrip strength, reduced respiratory muscle strength, and increased fatigability of in vivo electrically stimulated adductor pollicis muscle (199).

THERAPEUTIC PERSPECTIVES

Training

It is obvious that exercise training improves muscular performance because, depending on the training program, strength, endurance, or both improve (59). Because disuse has been suggested to be an important factor responsible for the alterations in muscle metabolism in COPD and CHF, it is possible that training the affected muscles could reverse these abnormalities. Indeed, exercise training improves exercise capacity in both COPD (200, 201) and CHF (6, 43, 202) patients. Furthermore, increased cross-sectional areas of oxidative fibers and elevated oxidative enzyme activities in the quadriceps muscle in combination with less arterial lactate accumulation during exercise have been found in trained COPD patients (46, 203). Training-induced increases in oxidative capacity and muscle mass of the quadriceps muscle have also been reported for CHF patients (58, 87). The above-mentioned exercise-induced increase in the P_i-CrP ratio and drop in pH in muscle is less after training (202). Thus, in peripheral muscles, training induces a partial improvement of the oxidative capacity in combination with increased exercise performance. In general, prolonged endurance training leads to increased percentages of type I and IIa fibers accompanied with greater oxidative capacity, resulting in higher fatigue resistance (59). Therefore, considering that fatigue is the main limiting factor in peripheral muscle performance, an endurance training protocol may be most suitable for improving the exercise capacity of limb muscles in COPD patients. This is also illustrated by the fact that in COPD patients, quadriceps endurance shows a larger improvement with training than does strength (200, 201).

No data on improvement of oxidative capacity with training are available for respiratory muscles. However, the differences between respiratory and peripheral muscles in COPD and CHF suggest that different training approaches are required to effectively improve their performances. Whereas respiratory muscle training in CHF remains an unexplored field, a variety of studies have been performed for COPD (204). Although training of respiratory muscle may improve its performance, there is little evidence of real clinical benefit. The best results are probably obtained with so-called resistance training (204), in which the inspiratory muscles are subjected to an increased pressure load. The fact that this is a kind of power training affecting respiratory muscle strength especially suggests that training of the diaphragm should be more focused on strength than on endurance (205, 206).

Another possible positive effect of exercise training is the increase in antioxidant status. As discussed above, disuse (or "disuse hypoxia") has a negative effect on antioxidant status and may therefore promote oxidative damage during occasional exercise because of the temporarily enhanced oxygen supply to the exercising muscles. However, regular physical exercise involves a regular increase in exposure of muscle tissue to oxygen and training thus probably reduces the risk of oxidative stress (135).

Nutritional support, anabolic steroids, and antiinflammatory therapy

The effects of nutritional support strategies on muscle mass and muscle function have been investigated in COPD, but it is a relatively unexplored area in CHF. Several studies in nutritionally depleted patients with COPD have shown that nutritional supplementation can improve both respiratory and peripheral muscle function (174, 207, 208). It is unclear, however, to what extent this improvement in muscle function is related to the increase in muscle mass per se (209). Muscle performance may reach normal values with nutritional support while muscle mass is still lower than that of control subjects, as shown for example in anorexia nervosa patients (189), which suggests that repletion of intrinsic muscle abnormalities is important in the improvement of muscle function. An early and a late response to nutritional supplementation has been proposed (199). After the first few days of repletion, muscle function improves 10–20% without any demonstrable gain in tissue protein. This early response probably results from improved electrolyte content (210) and improved concentrations of energy-rich compounds (51, 199). Only during prolonged treatment do physiologic functions further improve, accompanied by an increase in tissue protein and muscle mass (211).

However, a substantial subgroup of COPD patients did not gain weight in response to high-energy nutritional therapy (212). This subgroup was characterized by an elevated systemic inflammatory response, as evidenced by high concentrations of acute phase proteins and soluble TNF receptors. As mentioned earlier, systemic inflammation is associated with protein catabolism and probably plays a role in the loss of muscle mass. This suggests that antiinflammatory therapy might be beneficial in this particular subgroup. Many COPD patients receive inhaled or oral corticosteroids to treat local inflammation and acute infections. Systemic inflammation, however, is not reversed during this treatment (213). In addition, oral steroids may have a negative effect on skeletal muscle as mentioned above. A possible way to modulate systemic inflammation is through ingestion of polyunsaturated fatty acids (PUFAs). PUFAs are incorporated into the phospholipids of the cell membrane and play an important role in the regulation of inflammatory processes. Indeed, fish-oil supplementation reduced inflammatory mediators and had an anticachectic effect in pancreatic cancer patients (214). No studies are yet available regarding PUFA supplementation in COPD or CHF.

Administration of anabolic steroids may be an additional mode of intervention to counteract protein catabolism either by the androgen receptor–mediated promotion of protein anabolism or by neutralizing the effects of glucocorticosteroids through binding competition for the receptor mediating catabolism (215). Anabolic steroids could thus be useful in patients with muscle wasting, especially in those who are treated with corticosteroids. Anabolic steroid treatment in addition to nutritional support as an integrated part of a pulmonary rehabilitation program produced significantly enhanced fat-free mass despite a similar weight gain with nutritional support only. This increased fat-free mass was reflected in improved respiratory muscle function (209, 216). No difference in response was noted for patients receiving maintenance oral corticosteroid treatment (209). Currently, the effects of this combined treatment approach on peripheral skeletal muscle function, exercise performance, and health status is being studied. Besides effects on muscle performance, anabolic steroids resulted in an improvement in negative acute phase proteins such as albumin

and transthyretin (215) in depleted COPD patients. This may indicate an antiinflammatory effect.

Others have investigated the effects of adjuvant treatment with recombinant human growth hormone (rhGH). Administration of this hormone induces lipolysis, protein anabolism, and muscle growth, either directly or through IGF-I. Two uncontrolled studies showed the effects of rhGH in nutritionally depleted patients with COPD. Administration of rhGH for 8 d (0.03 $mg \cdot kg^{-1} \cdot d^{-1}$ subcutaneous for 4 d, plus 0.06 $mg \cdot kg^{-1} \cdot d^{-1}$ for another 4 d) did not increase respiratory and peripheral skeletal muscle strength in COPD (217). In contrast, an increase in inspiratory muscle strength was reported after 3 wk of treatment (0.05 $mg \cdot kg^{-1} \cdot d^{-1}$ subcutaneous) (218). With use of a similar treatment regimen, but in a placebo-controlled fashion, the effects of administration of rhGH on body composition, resting metabolic rate, and functional capacity in underweight COPD patients in a stable clinical state were studied (219). Although fat-free mass increased significantly during the 3-wk treatment period, no improvement was seen in muscle function and exercise capacity even decreased in the treatment group. Furthermore, a significant increase in resting metabolic rate was observed.

In the previous sections of this article, we stated that COPD and CHF patients may have increased oxidative stress, in either muscle or lung tissue. Furthermore, vitamin E deficiency is associated with the pathogenesis of the wasting and weakness in thalassemia major (220). Therefore, another mode of nutritional intervention might be supplementation with antioxidants such as vitamins, glutathione, and *N*-acetylcysteine. Several studies indeed showed a beneficial effect on wasting of antioxidant supplementation (221). For example, vitamin E protects human skeletal muscle from damage during surgical ischemia-reperfusion (222) and vitamin C supplementation reduces exercise-induced oxidative stress (223). Similar results have been obtained in animal studies (153, 224, 225). Although antioxidant supplementation does reduce physical exercise–induced oxidative stress, it remains unclear whether exercise performance is enhanced (134, 221). Most of these data were obtained from athletes, who already have a high exercise capacity, whereas vitamin supplementation may have more effect in COPD and CHF patients, who have a very low exercise capacity. In addition, there are some indications that vitamin supplementation may improve lung function (226, 227). Antioxidant administration in CHF and COPD therefore deserves further investigation.

Oxygen therapy

Long-term oxygen therapy (LTOT) improves survival and quality of life of COPD patients (228, 229), but no such data are available for CHF. It is clear that acute oxygen administration is beneficial for exercise capacity in COPD (230–232). However, very little is known about the ability of LTOT to reverse the alterations found in skeletal muscles of COPD patients. In fact, improved exercise capacity during oxygen administration, including LTOT, could very well be an acute effect with no reversal of these abnormalities. First, by supplying oxygen, hypoxemia is partly reversed and with that dyspnea may be improved (230). The latter is an important determinant of exercise tolerance in COPD. Therefore, relief of breathlessness may account for a great deal of improvement in exercise capacity (231). Second, the acute supply of oxygen to muscle tissue probably improves oxidative energy metabolism only during the oxygen administration period itself, because the indexes of oxidative energy metabolism (P_i-CrP, pH, and CrP recovery) showed some improvement in a group of COPD patients only during oxygen administration (85). After exercise while breathing room air, COPD patients receiving LTOT still had a low P_i-CrP ratio and low pH in combination with slow CrP recovery compared with control subjects. Also, supplementation of oxygen does not add to the improving effects of training (232). Only in one study was there a reported improvement of the CrP-(CrP + Cr) ratio in resting muscle of COPD patients while breathing room air after 6–9 mo of LTOT (233). However, because the partial pressure of oxygen in blood also improved, this increase was probably caused by an increased oxygen supply and was not due to any reversal of muscle abnormalities. In addition, the low glycogen concentrations failed to improve, which further suggests that the muscle abnormalities were not reversed.

Little attention has been paid to lung damage from oxidative stress with respect to oxygen administration. It is clear that free radicals play an important role in the development of COPD, because 90% of all patients are exsmokers and cigarette smoke is a rich source of oxidants that cause all sorts of lung damage (234). The concentrations of oxygen administered to COPD patients are potentially toxic and may also result in lung injury caused by oxidative stress (235, 236). More research needs to be done to establish whether oxygen administration is beneficial or may contribute to lung or even peripheral tissue damage. In the meantime, if oxygen supplementation is necessary, it is recommended that the lowest effective concentration of oxygen be used (236).

CONCLUSIONS

This review underscores the fact that reduced skeletal muscle performance contributes markedly to exercise intolerance in COPD and CHF patients. Morphologic and metabolic abnormalities occur in the skeletal muscles of these patients which, in both disorders, are probably determined by the same set of contributing factors, including hypoxia, oxidative stress, disuse, medication, nutritional depletion, and systemic inflammation. Both diseases also share striking differences between peripheral muscles and the diaphragm, which may therefore require different therapeutic approaches. Future investigations of the mechanisms and relative contributions of each of the factors leading to these intrinsic muscular alterations are required.

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