Muscle Dysfunction in COPD

Metabolic derangements in COPD muscle dysfunction

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Submitted 3 July 2012; accepted in final form 27 December 2012

Puente-Maestu L, Lázaro A, Humanes B. Metabolic derangements in COPD muscle dysfunction. J Appl Physiol 114: 1282–1290, 2013. First published January 3, 2013; doi:10.1152/japplphysiol.00815.2012.—Mitochondrial muscle alterations are common in patients with chronic obstructive pulmonary disease (COPD) and manifest mainly as decreased oxidative capacity and excessive production of reactive oxygen species (ROS). The significant loss of oxidative capacity observed in the quadriceps of COPD patients is mainly due to reduced mitochondrial content in the fibers, a finding consistent with the characteristic loss of type I fibers observed in that muscle. Decreased oxidative capacity does not directly limit maximum performance; however, it is associated with increased lactate production at lower exercise intensity and reduced endurance. Since type I fiber atrophy does not occur in respiratory muscles, the loss of such fibers in the quadriceps could be the result of disuse. In contrast, excessive production of ROS and oxidative stress are observed in both the respiratory muscles and the quadriceps of COPD patients. The causes of increased ROS production are not clear, and a number of different mechanisms can play a role. Several mitochondrial alterations in the quadriceps of COPD patients are similar to those observed in diabetic patients, thus suggesting a role for muscle alterations in this comorbidity. Amino acid metabolism is also altered. Expression of peroxisome proliferator-activated receptor-γ coactivator-1α mRNA is low in the quadriceps of COPD patients, which could also be a consequence of type I fiber loss; nevertheless, its response to exercise is not altered. Patterns of muscle cytochrome oxidase gene activation after training differ between COPD patients and healthy subjects, and the profile is consistent with hypoxic stress, even in nonhypoxic patients.

electron transport chain; bioenergetics; mitochondria; permeability transition pore; reactive oxygen species; oxidative enzymes; magnetic resonance spectroscopy

THE MITOCHONDRION is a membrane-enclosed organelle found in most eukaryotic cells (37). It ranges in diameter from 0.5 to 1.0 μm. Mitochondria generate most of the cell’s supply of adenosine triphosphate (ATP), the source of chemical energy (62), and are involved in a range of other processes, such as signaling, cellular differentiation, apoptosis, and control of the cell cycle and cell growth (62). Mitochondrial dysfunction has been implicated in a number of human diseases, including chronic obstructive pulmonary disease (COPD) (50, 75, 84).

Skeletal muscle dysfunction (SMD), historically one of the first recognized extrapulmonary consequences of COPD, limits exercise capacity and jeopardizes health status in these patients (3). In the present paper, we review mitochondrial involvement in SMD in patients with COPD. It is important to remember, however, that, in vivo, these organelles are key parts of the cell and that, as such, alterations in mitochondria cannot be separated, and frequently are determined, by changes in the cells to which they belong.

Energy Conversion

During exercise, the aerobic metabolism of skeletal muscle increases by 20- to 50-fold of the baseline rate (3). This increase depends on a sufficient supply of oxygen and the ability of the mitochondria to resynthesize ATP at the necessary rate. The ability to oxidize various substrates to convert the energy stored in their chemical bonds into ATP is the most important and the most extensively studied function of mitochondria.

Lower limb muscles. Compared with healthy controls, blood lactate concentration starts to rise at lower absolute work rates in COPD patients (12, 58, 88). This phenomenon is accounted for by the lactate produced in the legs, but not by that produced in the respiratory muscles (19), and is regarded as a consequence of a low-energy status in the skeletal muscle fibers of...
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of COX genes is higher in the quadriceps of COPD patients compared with respirometric assay for COX activity with antimycin A (77), or differences in oxidative capacity, since it can also result from reduced oxygen supply or may be a spurious consequence of comparing different intensities of exercise relative to the maximum capacity of the tested muscles.

Oxidative capacity can be more directly assessed by measuring the activity of key enzymes, such as those of the tricarboxylic acid cycle (Kreb cycle) [i.e., citrate synthase (CS) and succinate dehydrogenase] and β-hydroxyacyl-CoA dehydrogenase (an enzyme involved in β-oxidation of fatty acids), the concentrations of which are typically lower in patients with COPD than in healthy controls (43, 57, 88, 103). In contrast with the activity of oxidative enzymes, cytoplasmic glycolytic enzyme activity is elevated (43, 57, 88, 103). Consistent with these results, the recovery time for PCr after exercise, measured by 31P-MRS, a marker of mitochondrial oxidative function in vivo, is significantly prolonged (i.e., reduced oxidative capacity) in patients with COPD (76, 107). Moreover, tissue oxygenation, measured using near-infrared spectroscopy, has the same time course as PCr recovery measured using 31P-MRS and is considered its surrogate (63). With near-infrared spectroscopy, the rate of the reoxygenation of the underlying muscle has been shown to correlate well with CS activity in the quadriceps of COPD patients (88).

Results for the specific activity (i.e., activity corrected by mitochondrial density) of cytochrome oxidase (COX), the terminal enzyme in the mitochondrial electron transport chain, are conflicting. While some authors have found it to be increased in COPD patients with resting hypoxemia (102) and with exercise hypoxemia (84), others found that the increase was not significant (77). The reasons for such discrepancies are not clear and may include lack of statistical power due to small sample size (77), methodology employed (i.e., activity (84, 102) compared with respirometric assay for COX activity with N,N,N’,N’-tetramethyl-p-phenylenediamine dihydrochloride plus ascorbate in the presence of antimycin A (77)), or differences in the sampled subjects’ resting or exercise arterial blood oxygen content. Interestingly, after several weeks of training, expression of COX genes is higher in the quadriceps of COPD patients without hypoxemia at rest than in healthy sedentary subjects (92). Moreover, some genes (COXII, COX15) are upregulated exclusively in the COPD patients after training (92). Since COX is an important determinant of mitochondrial oxygen affinity (25), its upregulation may indicate an adaptation to enhance the efficiency of oxygen extraction (30) in patients with hypoxia (102) and in patients who develop hypoxia during exercise (84) or to reduced oxygen supply to muscle tissue during whole body exercise (9, 92, 96) or at least during certain phases of exercise, such as the on-transient phase, which is known to be prolonged in patients with COPD (86). The mechanism for sensing hypoxia and subsequent stimulation of mitochondrial gene expression could involve the mitochondrial respiratory chain itself (34) and the hypoxia-induced transcriptional factor HIF-1 (92).

Maximal mitochondrial respiration (Fig. 1) or ATP production in state 3 (i.e., stimulated by high concentrations of ADP and substrate), measured both in isolated mitochondria and in skinned muscle fibers, provides an indication of the integrated functioning of the different enzymatic systems involved in energy metabolism and is believed to reflect the maximal oxidative function of the mitochondrion during aerobic exercise (87, 102). Furthermore, by normalizing these measurements using an index of mitochondrial density, such as mitochondrial protein concentration or CS activity, it is possible to assess the specific efficiency of the organelle itself.

Compared with control subjects, patients with mild or moderate COPD usually show reduced state 3 mitochondrial oxygen consumption and ATP production in the quadriceps femoris (70, 77, 84, 91). However, when normalized by measures of mitochondrial density, the differences in mitochondrial oxygen consumption and ATP production between COPD and healthy individuals are small (84) or nonexistent (77). ATP-to-oxygen consumption ratio is normal (with succinate as substrate) in the quadriceps of moderate COPD patients of normal body mass index (84); however, other indexes of mitochondrial coupling, such as the respiratory control ratio (also known as respiratory control index or acceptor control ratio), have been found low in COPD patients (70, 84, 91), particularly in those with low body mass index (91). This occurs despite a low concentration of uncoupling protein 3 content in the fibers (29). Possible causes of lower respiratory control index in the quadriceps muscle of COPD are fiber-type shift, since type II fibers apparently have lower respiratory control index (78), higher state 2 respiration (70) associated

![Fig. 1. Description of the modified titration protocol used to assess mitochondrial (mt) respiration and respiratory control. It starts by adding mitochondria to the measurement medium and the substrate of interest (84). A certain degree of respiration due to endogenous adenosine diphosphate (ADP), proton leakage, and reactive oxygen species (ROS) production is observed. Activation is achieved after addition of ADP (state 3). Respiration is initially high until ADP is gradually depleted by phosphorylation to adenosine triphosphate (ATP), and respiration drops in the transition to state 4, which, as with state 2 in this protocol, is an ADP-limited resting state. A second ADP titration is followed by another state 3 → state 4 transition. Finally, respiration becomes oxygen limited in the closed oxygraph chamber. [O2], oxygen concentration.](1283/fig1.png)
with enhanced rates of superoxide production observed in COPD patients or other unknown causes (77, 87), or to some amount of uncoupled state 3 respiration due to oxidative stress (81, 108).

In accordance with the overall decreased oxidative capacity and mitochondrial respiration, measured mitochondrial density has also been found lower in COPD than in age-matched, healthy controls (28, 83). The reduced mitochondrial density and oxidative capacity found in COPD patients are likely a consequence of the shift from type I fibers (slow, oxidative) to type IIx fibers (fast twitch, glycolytic) that is consistently observed in the peripheral skeletal muscle of COPD patients (31, 42, 77, 78). While such muscle atrophy and loss of oxidative capacity is the typical physiological response to muscle disuse/deconditioning (17, 40) and can be corrected with training (10, 56, 64, 88), mechanisms for SMD other than inactivity (i.e., inflammation, hypoxia, oxidative stress, nutrition) have been postulated (3) and are still under debate.

Respiratory muscles. Because of technical difficulties, \( ^{31}\)P-NMR has not been used to assess respiratory muscle bioenergetics; therefore, most data are from biopsy studies. Several authors have reported that the activity of the oxidative enzymes CS, succinate dehydrogenase, and \( \beta \)-hydroxyacyl-CoA dehydrogenase is elevated in the diaphragm of patients with severe COPD (in contrast with the leg muscles) (18, 51, 110), whereas the activity of the glycolytic enzymes hexokinase and lactic dehydrogenase is decreased (100). This enzymatic profile is consistent with a predominance of type I or IIa fibers reported in the diaphragms of COPD patients (in contrast with leg muscles) (52, 66). Interestingly, such enzymatic profiles have not been uniformly observed in patients with moderate COPD (18, 100).

Enhanced mitochondrial state 3 respiration has also been reported in the diaphragm of patients with very severe COPD, and significant correlations were found between the maximal oxidative capacity and pulmonary obstruction indexes (95). Together, these data indicate that changes in oxidative capacity and mitochondrial function in the diaphragm are in the opposite direction than in the quadriceps femoris and likely reflect a training effect of the muscles (18, 51, 100).

In other respiratory or accessory muscles, such as the external intercostal muscles (74, 95), serratus (101), and latissimus dorsi (101), oxidative capacity seems to be increased or at least remains preserved compared with the quadriceps (84). Consistent with these findings, increased, or at least preserved, proportions of type I fibers have been reported (11, 24, 41, 66).

Mitochondrial function and exercise performance in COPD.

Exercise depends on a system in which ventilation, gas exchange, blood flow, hemoglobin, muscle oxygen, carbon dioxide transport, and oxygen utilization/carbon dioxide production all function in series; therefore, exercise limitation is usually difficult to ascribe to any single structural or functional abnormality, both in healthy individuals and in COPD patients (109). Analysis of the maximal respiratory capacity of the mitochondria (104) reveals that mammals, including humans (26), use only 60–80% of their in vitro oxidative capacity when exercising at peak oxygen uptake (\( V_{O_{2peak}} \)) (26, 40). Therefore, in healthy individuals, the enzymatic capacity of the energy-transducing pathways may not limit exercise function. Maximal exercise in the knee extensor of one leg, where the muscle mass is small, increases the specific \( V_{O_{2peak}} \) to almost normal ranges in COPD patients (97), a finding that is in keeping with the estimated \( V_{O_{2peak}} \) from mitochondrial studies (70, 77, 84). Therefore, in most patients with COPD, whole body peak exercise is not directly limited by the oxidative capacity of the muscles, as is the case with healthy people as well (9, 96). Even so, low oxidative capacity may play an indirect role in exercise limitation. First, early lactic acidosis increases ventilatory demands (12, 86) and dyspneic sensation (82) at a lower absolute exercise intensity. Second, patients with COPD also have poor resistance and increased susceptibility to muscle fatigue, even in isolated leg exercises (55). Oxidative capacity is related to muscle endurance (2, 88) and can contribute to muscle fatigue to high-intensity exercise (3).

Summary. The results of studies on mitochondrial function suggest that, despite the possibility of a certain degree of specific mitochondrial dysfunction/inefficiency, the main determinant of the decreased oxidative capacity seen in the quadriceps femoris of patients with COPD is a decrease in the mitochondrial content of muscle fiber.

While the capacity of the mitochondria for energy conversion does not appear to be a limiting factor for whole body exercise, it might play an indirect role by producing early lactic acidosis and reducing muscle endurance.

In normoxic, normocapnic patients, energy conversion remains intact or is even enhanced in the respiratory muscles, a finding that is consistent with the preserved or increased proportion of type I fibers also observed.

Differences in energy metabolism between both groups of muscles may be due to the different pattern of use.

Role of Reactive Species

SMD in patients with COPD is also characterized by excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (7, 14, 67, 83, 98). At least two sources of increased ROS production during exercise have been identified in these patients: xanthine oxidase (38) and the electron transport chain of the mitochondria (Fig. 2) (44, 87). The mitochondria from COPD patients produce about three times more ROS than mitochondria from controls (84, 87). To date, the origin of the excessive RNS in the skeletal muscle of COPD patients is not well defined, but the mitochondria is one likely source (7, 67, 98).

Susceptibility to ROS/RNS depends largely on tissue antioxidant status (Fig. 2) (45). Concentrations of superoxide dismutase, a major mitochondrial enzyme that is responsible for dismutation of the superoxide anion, has been reported to be higher in the resting quadriceps femoris of COPD patients than in that of healthy controls (7, 27, 84), whereas catalase (7) and glutathione peroxidase (14) activity is similar between COPD patients and healthy controls. Since the activity of antioxidant enzymes is typically significantly lower in type IIx fibers than in type I fibers (78), these results reflect a mechanism of adaptation that predominates over the histological changes in favor of type IIx fiber in the muscle of the COPD patients compared with healthy controls (31). In contrast to antioxidant enzymes, dietary antioxidants, such as vitamin E, are low in the quadriceps of COPD patients (27).

Damage of lipids, proteins, and mitochondrial DNA caused by ROS/RNS has been observed in the skeletal muscle of COPD patients (Fig. 3) (7, 14, 67, 83, 98). This damage could,
ROS produced by complex I, thus leaving complex III as the mitochondrial matrix antioxidant system seems to fully offset the where type I fiber atrophy does not occur (60, 84). While both to be elevated in the respiratory muscles of COPD patients could be accounted for by the reported change in the proportion (78), but it is not clear whether the measured output (84, 87) increase in proton-motive force (47, 106). These increases in proton-motive force may well play a role in COPD, since the activity of the electron transport chain enzymes seems to be increased (84, 102) with no corresponding significant additional change in the efficiency of mitochondrial oxidative energy transfer, as measured by the ATP-to-oxygen consumption ratio (84). Paradoxically, hypoxia has been shown to enhance ROS production at complex III (34) and could be a contributing factor in patients developing tissue hypoxia during exercise.

Although ROS production increases in the diaphragm and external intercostalis muscles of COPD patients (60, 84), the antioxidant systems do not seem to be increased in parallel (5, 20, 84), despite the increased oxidative stress reported, at least in the diaphragm of severe COPD patients (60). Nitrosative stress has not been observed in the diaphragm of COPD patients, as it has in the quadriceps femoris (60).

**Summary.** Production of ROS is elevated in the skeletal muscles of patients with COPD. The mitochondrial respiratory chain is an important source of these radicals. Damage of lipids, proteins, and mitochondrial DNA by ROS has been observed in the skeletal muscle of both the quadriceps femoris and the diaphragm of COPD patients, despite the increased capacity of the main antioxidant systems (in the quadriceps only). Nitrosative stress has been observed in the quadriceps of COPD patients, but not in the diaphragm.

Oxidative and nitrosative stress likely affect oxidative capacity of the mitochondrion and could contribute to muscle damage, impair mitochondrial oxidative function by jeopardizing the integrity of the electron transport chain and uncoupling oxidative phosphorylation by decreasing transmembrane potential (15, 81, 108). Markers of oxidative stress (i.e., increases in muscle lipid peroxidation and oxidized proteins after exercise) have been found to be inversely correlated with the endurance capacity of the quadriceps in COPD patients, thus supporting a deleterious effect of ROS on the oxidative capacity of the mitochondria (14). Protein oxidation and nitrosation may modify their structure or chemical properties (16, 72). These alterations may cause a decline in protein function or even complete protein unfolding in muscle cells (44, 72, 81). Some of the proteins affected are myofibrillar muscle proteins, which may become more susceptible to proteases (69). Thus muscle atrophy can be enhanced by ROS/RNS-induced protein damage.

The mechanisms underlying this substantial increase in release ROS by the mitochondrial are not fully understood. Increased ROS production is characteristic of type II fibers (78), but it is not clear whether the measured output (84, 87) could be accounted for by the reported change in the proportion of type II fibers (31, 78); in addition, ROS production appears to be elevated in the respiratory muscles of COPD patients where type I fiber atrophy does not occur (60, 84). While both complexes I and III appear to produce more ROS, the mitochondrial matrix antioxidant system seems to fully offset the ROS produced by complex I, thus leaving complex III as the main source of the ROS that enter the cytoplasm (87). Studies in isolated mitochondria indicate that membrane potential is a key determinant of ROS production. Its production increases exponentially, even in response to small increases in proton-motive force (47, 106). These increases in proton-motive force may well play a role in COPD, since the activity of the electron transport chain enzymes seems to be increased (84, 102) with no corresponding significant additional change in the efficiency of mitochondrial oxidative energy transfer, as measured by the ATP-to-oxygen consumption ratio (84). Paradoxically, hypoxia has been shown to enhance ROS production at complex III (34) and could be a contributing factor in patients developing tissue hypoxia during exercise.

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atrophy by denaturing key proteins. Although the mechanisms underlying this increase in release of ROS in skeletal muscle of COPD patients are not known, the predominance of type IIX fibers appears to play a role, as may also the increased activity of respiratory chain enzymes.

Changes in Muscle Metabolism in COPD

The relative shift from oxidation to glycolysis in the quadriceps muscle is consistent with the decreased proportion of type I fibers and a relative increase in the proportion of type II fibers (see above) (31). Nonetheless, data on cerebral bioenergetics in patients with stable COPD have shown an increased dependence on glycolysis for energy production within brain cells (61), suggesting that other factors may play a role.

Intrinsic alterations have also been observed in the metabolism of amino acids such as leucine, which is altered in patients with COPD (23). Other studies have also reported altered glutamate metabolism associated with reduced muscle glutathione concentration in biopsy specimens of patients with emphysema (21, 23). Alterations in glutamate concentration and reduced glutathione metabolism are muscle specific, affecting the quadriceps but not the diaphragm (20), and may be responsible for the reduced capacity of COPD patients to synthesize glutathione in response to training of the quadriceps (89, 90, 98). In COPD a significant reduction can be observed in the concentration of most amino acids in the quadriceps after exercise; in plasma, however, amino acid levels increase (22), suggesting enhanced amino acid release and enhanced nitrogen efflux from the muscle during exercise (22, 48). This augmented amino acid turnover may be the consequence of exercise-induced inflammation (49, 92), which may impact on muscle protein metabolism in two ways: first, by increasing demand for amino acids to synthesize acute phase proteins in the liver, and second, by the direct effects of circulating proinflammatory cytokines on muscle protein synthesis and degradation (92). This inflammatory mechanism is supported by the distinctive mitogen-activated protein kinase 9 gene (MAPK-9) gene activation in the quadriceps of COPD patients after training (92), which is usually mediated by proinflammatory cytokines (92).

Large population studies show that there is an increased prevalence of diabetes among COPD patients (relative risk 1.5–1.8), even in patients with mild disease (59, 105). The reasons for this association are not yet understood. It is unlikely to be explained by high doses of inhaled corticosteroids, as patients who are steroid naive with mild disease also have an increased risk of diabetes (4). While inactivity is undoubtedly part of the problem (36), other factors, including mitochondrial alterations, could be involved (75).

The relationship between mitochondrial function and diabetes is beyond the scope of this review, however, several of the metabolic and mitochondrial alterations seen in COPD (46, 75) parallel those seen in diabetes, i.e., reduced pyruvate and fatty acid oxidative capacity (43, 57, 58, 88, 103), reduced muscle mitochondrial density and peroxisome proliferator-activated receptor (PPAR-γ) coactivator-1α (PGC-1α) (28, 83), increased mitochondrial DNA oxidative damage (83), and excessive ROS production (8, 13, 79, 83). Furthermore, type IIX fibers, which are predominant in leg muscles of COPD patients (31), are phenotypically less sensitive to insulin (54). A 28% decrease in the glucose transporters GLUT-1, GLUT-4 was recently reported in the quadriceps of COPD patients (33). This decrease could, in turn, lead to increase in resistance to insulin in the affected muscles.

Summary. Apart from the increased dependence of the skeletal muscles of the lower limb of COPD patients on glycolysis as an energy source, several alterations in amino acid metabolism have been described. Altered glutamate metabolism might have deleterious effects on the antioxidant system. Interestingly, mitochondrial alterations known to occur in diabetes are also present in COPD, and impaired glucose transport has been reported in the quadriceps of COPD patients.

Regulation of the Mitochondrial Permeability Transition Pore

The mitochondrial permeability transition pore (MPTP) is a nonspecific multiconductance channel that spans the inner and outer mitochondrial membranes (15). An increasing number of studies indicate that transient opening of the MPTP in low-conductance mode serves physiological regulatory purposes, such as fine-tuning of transmembrane potential, calcium homeostasis, and cell signaling (15).

In contrast to the normal physiological behavior, a very different response is observed when the changes in cytosolic calcium concentration ([Ca2+]i) are very pronounced or protracted, such as those occurring with ischemia and oxidative stress (15). When intramitochondrial [Ca2+]i levels reach a certain threshold, a pathological state develops (i.e., mitochondrial permeability transition). This state results from the opening of the MPTP in a high-conductance mode, which collapses the proton-motive force, produces mitochondrial swelling, and, depending on the energy status of the cell, can initiate apoptotic and necrotic cell death (15).

Direct evidence for MPTP functioning in the skeletal muscle of COPD patients is scarce. MPTP seems to be less sensitive to [Ca2+]i (77), in accordance with the predominant type II phenotype of the leg muscles (78), but, when opened, it produces faster and more pronounced mitochondrial swelling, which might indicate that, once opened, apoptosis becomes more likely (15, 85). In addition, in patients with COPD, the MPTP seems to be more susceptible to ROS (85)

Interestingly, increased apoptosis has been reported in both the respiratory and the peripheral skeletal muscle of patients with COPD (1, 6, 17, 111), and the MPTP might play a role in this phenomenon (15, 39, 78), since one or several factors known to produce or potentiate MPTP opening (15), low-energy status (80, 99), increased oxidative and nitrosative stress (7, 14, 67, 83, 98), low cell pH (99), or hypoxia (73), can be observed during exercise. Furthermore, impaired activity of the sarcoplasmic calcium pump sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA2) due to oxidative stress has been described in skeletal muscle of COPD, which may limit its ability to uptake calcium from the cytoplasm after its release during the contraction of the fibers (32, 68, 71) and increasing their susceptibility to [Ca2+]i overload. In addition, the expression of MAPK-9 gene, which is thought to be associated with the cytochrome c-mediated cell death pathway, is distinctly elevated in COPD patients after training (92).
Summary. Evidence on the functioning of MPTP in the skeletal muscle of COPD patients is limited; however, mechanisms that potentiate the opening of MPTP in the high-conductance mode and thus lead to mitochondrial permeability transition are enhanced, particularly during exercise. Further investigation is warranted to determine whether opening of the MPTP underlies the increased apoptosis seen both in the quadriceps femoris and the respiratory muscles.

Mitogenesis

Few data have been reported on the biogenesis of mitochondria (mitogenesis) in skeletal muscle of COPD patients. PPAR content is reduced in the quadriceps muscle in COPD patients at rest (94), as is expression of PGC-1α mRNA (83, 94), and PGC-1α is involved in mitogenesis in the regulation of the antioxidant system and the differentiation to type I fibers (53). Since more PGC-1α is present in oxidative fibers (type I and type IIA) than in glycolytic fibers (type IIx), this finding may merely be a consequence of the loss of type I fibers (53).

The acute response of PGC-1α to exercise is normal or even enhanced, as is the response of superoxide dismutase and synthesis of mitochondrial DNA (83), indicating that the short-term mitochondrial biogenetic response to exercise is appropriate. However, it has been reported that several weeks of muscle training do not have a discernible effect on the antioxidant system and the differentiation to type I fibers (53). Since more PGC-1α is present in oxidative fibers (type I and type IIA) than in glycolytic fibers (type IIx), this finding may merely be a consequence of the loss of type I fibers (53).

Activation of some gene related to mitochondria function resulting from endurance training differs between COPD patients and healthy subjects (92). This distinct adaptive response in trained COPD patients consists of a higher expression of COX genes, together with an overexpression of HIF-1αRTP801, and may reflect that training exposes patients to muscle hypoxia (92).

Patients with COPD who exhibit elevated concentration of tumor necrosis factor-α in muscle may present impaired mitogenesis and low muscle mass (93).

Summary. Quadriceps muscle of COPD patients has a reduced concentration of PPAR and expression of PGC-1α mRNA, which might be also a consequence of the predominance of type IIx fibers. The acute upregulation of PGC-1α and short-term response of superoxide dismutase and mitochondrial biogenesis, as measured by mitochondrial DNA density, is not impaired; however, the already elevated antioxidant enzymes at baseline in the quadriceps muscle of COPD patients do not respond further to several weeks of exercise training, while mitochondrial density increases.

Conclusions

The mitochondrial function of leg muscles of COPD patients presents several alterations, including a relative shift from oxidative to glycolytic metabolism, decreased oxidative capacity (largely determined by the decrease in mitochondrial density), and increased production of ROS. While other factors may contribute, many of these changes seem to be due to type I fiber atrophy; since they can be explained, by a large extent, by the shift from type I oxidative fibers to type IIx glycolytic fibers (Fig. 4). In addition, the alterations affect mainly or exclusively the locomotor muscles, leaving the respiratory muscles generally spared. However, some alterations (i.e., a slight degree of uncoupling and excessive ROS production, particularly by the respiratory muscles, in which a shift in the type of fiber is not observed) cannot be fully explained by atrophy.

Increased ROS production, combined with nitrosative stress in the quadriceps, can play a key role in cell damage, since it can deteriorate mitochondrial DNA, alter the function of several proteins, and, through its effect on the mitochondrial membrane and calcium pumps of the sarcoplasmic reticulum, increase the susceptibility of the muscle to necrotic or apoptotic cell death by means of pathological opening of the MPTP.

In addition to energetic metabolism, the skeletal muscle of COPD patients is also subject to alteration of amino acid metabolism that might impair antioxidant defenses by limiting the ability to synthetize glutathione.

The parallelism observed between the mitochondrial alterations seen in the skeletal muscle of patients with diabetes and patients with COPD should be further investigated to clarify whether they form the basis for increased susceptibility to diabetes in COPD. Alterations leading to a reduced transport of glucose into the muscle have also been reported.

ACKNOWLEDGMENTS

The authors thank Alberto Tejedor for advice.

GRANTS

The authors thank the Fund for Health Research (Grant PI 09/2391) for its support in making this paper.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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