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Muscular Alterations in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure at Rest and during Exercise

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Summary

Reduced skeletal muscle performance contributes to exercise intolerance in COPD and CHF patients, independent of the severity of local organ dysfunction. Striking similarities are observed in morphological and metabolic abnormalities in peripheral skeletal muscle between these two disorders, pointing towards a decreased oxidative capacity. Both diseases also share striking differences between peripheral muscles and the diaphragm, which may therefore require a different therapeutical approach. The following possible underlying factors of muscular alterations in COPD and CHF are discussed: hypoxia, oxidative stress, disuse, weight loss and altered substrate metabolism.

According to the definitions of the World Health Organization chronic diseases are not only characterized by their primary impairments, but also by the resulting disabilities or even handicaps [1]. Although the primary impairments in chronic obstructive pulmonary disease (COPD) and chronic heart faulure (CHF) clearly differ, there is a striking resemblance in the systemic consequences of these diseases and their effect on exercise capacity and health status. Skeletal muscle function in COPD and CHF has long been ignored as potential contributor by focusing on the ventilatory and cardiac limitations of exercise performance, respectively; but recent research has shown that skeletal muscle function is impaired in moderate to severe COPD and CHF and also is an important predictor of exercise limitation in both diseases [2–4]. Muscle function depends, among others, on perfusion, muscle mass, fibre composition and energy metabolism [5]. It can be inferred that alterations in one or more of these determinants play a role in reduced muscle performance. Indeed, both in COPD and in CHF such changes have been found and striking similarities between the two etiologically distinct disorders appear to be present.

In this paper we will first present an overview of clinical studies that have investigated impaired muscle function with special emphasis on muscle morphology and energy metabolism in COPD and CHF. In the second part of the paper, potential causes will be discussed including hypoxia, oxidative stress, disuse, weight loss and altered substrate metabolism.

Muscular Alterations in COPD and CHF

Muscle Performance

Muscle performance is largely characterized by strength and endurance. Strength is defined as the capacity of the muscle to develop maximal force and endurance as the capacity of the muscle to maintain a certain force in

time, thus to resist fatigue. Loss of either one of these aspects results in muscle weakness and, hence, in impaired muscle performance. Numerous studies have now convincingly demonstrated that COPD and CHF are commonly associated with muscle weakness [6–8]. Hamilton et al. [3] found significantly reduced strengths of both peripheral and respiratory muscles in patients suffering from respiratory failure, heart failure, or a combination of both as compared to healthy subjects. 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 both disorders [7, 8], compared to a much stronger correlation in healthy subjects [9]. It implies that the strength component of muscle weakness is affected differently in peripheral and respiratory muscles. In healthy subjects, as well as in patients, exercise limiting symptoms are the sense of leg effort (exertional discomfort) and/or breathlessness (exertional dyspnoea) [10, 11]. Despite correlations between peripheral muscle strength and performance in COPD and CHF [7, 10], reduced *endurance* (~ fatigue) seems to be the dominating limiting factor in peripheral muscles in these patients, since the sense of leg effort was one of the main reasons to stop exercise [3, 11–13]. Recently, it has been shown that early lactic acidosis occurs in COPD during exercise [14] and that this is largely the result of lactate release from the lower exercising limb [15]. In CHF reports lactate release is thought to be a result of decreased blood flow to the peripheral muscles. Muscle acidosis is a contributing factor to muscle fatigue [16].

Fatigue probably is *not* the main limiting factor in respiratory muscle function. Morrison et al. [17] found that COPD subjects have decreased respiratory muscle strength and endurance. Fatigue of the respiratory muscle may indeed occur during exercise, but it is not certain whether this is an independent determinant of exercise capacity [12, 18, 19]. In addition, it is unlikely that the respiratory muscles from exercising COPD patients contribute to the lactate response mentioned earlier [20]. It also should be emphasized that the respiratory muscles must operate against the mechanical airway impedances in this specific disorder [21], 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 dyspnoea [22]. It thus seems that strength is the limiting aspect of muscle performance in the respiratory muscle, whereas endurance limitation dominates 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 [10, 23] and COPD [2, 24–27] marked loss of muscle mass or decline in cross-sectional area is observed. This muscle wasting plays an important role in the loss of exercise tolerance in these patients. Morphological alterations may also be related to muscle function impairment, although direct relationship with exercise performance have not (yet) been shown. Some histological information is available on abnormalities in skeletal muscle in CHF but hardly any on COPD. Recently, reduced fibre cross-sectional area has been demonstrated in the vastus lateralis of COPD [28] and CHF [29]. Gertz et al. [30] found no sings of increased fibrosis or other alterations in intercostal muscles from patients with respiratory failure, whereas endomyosal fibrosis has been found in skeletal muscle of a limited number of CHF patients [31]. Increased acid phosphatase activity, a lysosomal enzyme contributing to protein degradation, has been found in the quadriceps of some patients with CHF [32] or respiratory failure [27]. Increased lipid deposits have been found in the quadriceps, biceps and deltoids of some patients with CHF [27, 32]. Very contradicting results have been obtained with respect to capillary density in peripheral skeletal muscle in CHF. A normal capillary density has been found [27], which is in confirmation with other studies where both a reduced capillary/fibre ratio and atrophy resulted in an unchanged capillary density [32]. An unaltered capillary/fibre ratio has also been reported; however, capillary density increased due to fibre atrophy [34]. In contrast, reduced capillary density in combination with a reduced capillary/fibre ratio has been shown in CHF patients [35] and even in heart transplantation recipients [36]. Thus, there is an overall tendency for a reduced capillary/fibre ratio, but depending on the degree of atrophy the capillary density may even be increased. This has recently been confirmed for COPD [25]. In a few studies morphometry of mitochondria has been performed using electron microscopy, showing that mitochondrial volume densities in skeletal muscle are lower in CHF patients compared to control subjects [35, 37], which was still the case 10 months after heart transplantation [36]. Histochemical alterations reflecting mitochondrial abnormalities have also been reported in biceps muscle biopsies of COPD patients [27]. These results suggest that oxidative capacity in peripheral skeletal muscles may be altered.

Muscle Fibre Type Distribution

The most remarkable muscle alteration in COPD and CHF is a relative shift in fibre composition which seems to occur in opposite direction in peripheral and respiratory muscle. Fibre typing is mainly performed histochemically, based on the differences in myosin ATPase activities, or immunocytochemically [38]. Adult mammalian skeletal muscle contains four myosin heavy chain (MyHC) isoforms, namely type I, IIa, IIb and IIx [39]. In most older studies fibre typing is limited to determining fibre types I, IIa and IIb. Furthermore, human fibres formerly identified as being IIb with myosin ATPase staining are probably IIx fibres [40]. Therefore the notation IIb/x will be used in the subsequent text. Fibre type I has a slow-twitch and develops a relative small tension, but since it depends mainly on aerobic metabolism it is fatigue resistant. In contrast, fibre type IIb/x has a fast-twitch and develops large tensions, but it is susceptible for fatigue, since in type IIb/x fibres energy conversion is based on anaerobic, glycolytic metabolism. Fibre type II 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 [5, 38]. A decrease of the percentage of type I fibres and a corresponding increase in type II (mainly type IIb/x) fibres compared to normal subjects has been reported for COPD [25, 41, 42] and for CHF [32–35, 43] in limb muscles. In addition, recently we demonstrated increased proportions of I/IIa and IIa/IIx hybrid fibres in COPD [44]. These fibres may represent transformation intermediates in the I→IIx shift. In contrast to peripheral muscles, a shift from type IIb/x to type I fibres has been reported in the diaphragm in both COPD and CHF patients. Despite some variation in the results obtained till now, there is most likely a I→IIb/x shift in peripheral muscles and a IIb/x→I shift in the respiratory muscle. It is feasible that these shifts have functional consequences in the affected muscles, since the distinct fibre 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, since peripheral muscle fatigue is the main limiting factor in these patients. This is confirmed by a study in which a faster twitch response in combination with less resistance to fatigue was observed in leg muscles of CHF patients [45]. Accordingly, a IIb/x→I shift towards more oxidative metabolism in the respiratory muscle implies a shift towards a more fatique-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 Energy Metabolism

Considerable amounts of 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 non-invasive assessment of tissue levels of high-energy phosphates and pH. High levels of adenosine triphosphate (ATP), creatine phosphate (CrP) and nicotinamide adenine dinucleotide in the reduced form (NADH) reflect a high energy state, whereas elevated levels of adenosine diphosphate (ADP), adenosine monophosphate (AMP), inorganic phosphate (Pi) and oxidized nicotinamide adenine dinucleotide (NAD^+) commonly reflect a low energy state. Lactate and glycogen levels are often measured, but it must be noted that low levels may reflect either increased clearance or reduced formation and vice versa for high levels. Although activities of enzymes involved in muscle energy metabolism do not reflect the physiological situation since only maximal activities are obtained under the optimal circumstances of in vitro measurements, they do provide an indication for adaptations in expressions of proteins involved in metabolic pathways. Typical oxidative enzymes are citrate synthase (CS), succinate dehydrogenase (SDH) and β-hydroxyacyl-CoA dehydrogenase (HAD). Typical glycolytic enzymes are hexokinase (HK), phosphofructokinase (PFK) and lactate dehydrogenase (LDH), the latter catalysing the last step of anaerobic glycolysis. Measurements of substrate and cofactor levels in peripheral skeletal muscle of COPD and CHF patients indicate impaired energy metabolism (see table 3). Most striking are the observed reduced levels of the high-energy phosphates in rest. Pouw et al. [46] observed higher Pi/Crp and ADP/ATP ratios associated with slightly, but statistically significantly elevated inosine monophosphate (IMP) levels. The latter may be due to increased degradation of accumulating AMP by deamination, which probably reflects reduced aerobic capacity [47]. The situation becomes even worse during exercise: greater increase of the Pi/CrP ratio and a faster drop in pH were found in the calf muscle of COPD patients [48, 49] and of CHF patients [34, 50, 51] performing exercise. Similar results have been obtained for the forearm muscle [51, 52] (table 1). In addition, a slower recovery of CrP was observed

Table 1. Changes in muscle energy metabolism during exercise

Disorder	Ref.	Muscle	Variables of NMR spectroscopy					
			PCr	Pi/PCr	PCr/(PCr+Pi)	ATP	relATP	pH
COPD	54	calf	↓					↓
	53	calf		↑		=		↓
	55	calf		↑			↓	↓
	56	quadriceps		=				=
	57	forearm			↓ NS			=
	58	forearm		↑	↓		↑	↓
CHF	60	calf*	=	=	=	=	=	=
	60	calf**		↑		=	↑	↓
	59	calf			=			↓
	34	calf						↓
	61	calf						↓
	57	forearm		↓ NS				=

Pi = Inorganic phosphate; PCr = phosphocreatine; ATP = adenosime triphosphate; relATP = ATP corrected for Pi/PCr; ↑ significantly increased compared to controls; ↓ significantly decreased compared to controls; = means in patients not significantly different from controls; * compared to sedentary controls; ** compared to trained controls.

Table 2. Muscle energy metabolism in the recovery phase after exercise

Disorder	Ref.	Muscle	Variables of NMR spectroscopy					
			$PCr/RT^1/_2$	$PCr/(PCr+Pi)/RT^1/_2$	Pi/PCr	$RT^1/_2$	pH	$pH/RT^1/_2$
COPD	53	calf	↑					
	54	calf	=					
	55	calf	↑					
	58	forearm		↑				↑
	57	forearm			↑		↓	↑
CHF	60	calf*				=		
	60	calf**				=		
	61	calf	↑					
	57	forearm	↑		↓	↑	↓ NS	

Pi = Inorganic phosphate; PCr = phosphocreatine; $RT^1/_2$ = recovery halftime; ↑ significantly increased compared to controls; ↓ significantly decreased compared to controls; = means in patients not significantly different from controls; * compared to sedentary controls; ** compared to trained controls.

after exercise [34, 49–52]. COPD patients also show a prolonged half-time ($RT^1/_2$) for pH [53–55, 57, 58] (table 2). These results suggest that rephosphorylation of high-energy phosphates is less efficient in these patients both during and after muscular exercise. In CHF patients, Chati et al. [60] compared NMR spectra of calf muscles during exercise with sedentary and trained controls. They found no difference between patients and sedentary controls and concluded deconditioning being an important factor for the abnormalities. In addition, glycogen contents in patients tend to be lower, whereas lactate levels are higher (table 3). It thus seems that anaerobic energy metabolism is enhanced and since this process yields far less ATP compared to complete oxidative degradation of

Table 3. Muscle metabolite concentrations in COPD and CHF

Metabolite	Muscle	Disorder	Direction	References
CrP	QF	COPD	↓	30, 124, 125, 126*
	QF	CHF	↓	127, 128*
ATP	QF	COPD	↓	30, 124, 125, 126*
	QF	CHF	↓	127, 128*
IMP	TA	COPD	↑	46
Glycogen	QF	CHF	↓	32, 127, 128
	QF	COPD	↓	124, 125*
Lactate	QF	COPD	↑	30, 126
	QF	CHF	↑	129
Pyruvate	QF	CHF	↑	32
	QF	COPD	↑	14

ATP = Adenosine triphosphate; CrP = creatine phosphate; IMP = inosine monophosphate; QF = quadriceps femoris; TA = tibialis anterior; * nearly reached significance.

Table 4. Muscle enzyme activities

Enzyme	Muscle	Disorder	Direction	References
CS	QF	COPD	↓	130, 131
	QF	CHF	↓	32, 34, 129, 132
	DIA	CHF	↑	133
HAD	QF	COPD	↓	130, 131
	QF	CHF	↓	32, 34, 129, 132
	DIA	CHF	↑	133
SDH	QF	COPD	↓	131
	QF	CHF	↓	32, 132
LDH	QF	COPD	↑	131
	QF	CHF	↑	129*
	DIA	CHF	↓	133
	DIA	COPD	↓	134
HK	QF	CHF	↓	132
	DIA	COPD	↓	134
PFK	QF	COPD	↑	131

CS = Citrate synthase; HAD = β-hydroxyacyl-CoA dehydrogenase; SDH = succinate dehydrogenase; HK = hexokinase; PFK = phosphofructokinase; LDH = lactate dehydrogenase; QF = quadriceps femoris; DIA = diaphragm.

glucose this could explain the reduced high-energy phosphate levels.

Analysis of enzyme activities too suggest an overall increase of glycolytic and an overall decrease of oxidative activities in peripheral muscles of both COPD and CHF patients (table 4). Since these enzyme activities depend largely on the fibre type [62], it is likely that this shift in activities is related to the shift in fibre distribution mentioned above. Whether enzyme activities adapt to the fibre type redistribution or the other way around remains unclear. Due to technical difficulties with ^{31}P-NMR and muscle biopsies of the diaphragm and accessory respiratory muscles, very little is known about energy metabolism in these muscles. However, the observed alterations for enzyme activities (table 4) are in confirmation with the morphological data, in that oxidative enzyme activities are reduced and glycolytic enzyme activities are increased. As in peripheral muscles, this shift probably results from the shift in fibre type distribution.

Possible Underlying Factors

Hypoxia

In COPD and CHF oxygen delivery to peripheral and respiratory muscles may be insufficient, caused by either hypoxemia and/or reduced blood supply. In both cases muscle tissue may become hypoxic and this could lead to the adaptive changes in skeletal muscle as those described above. In this respect relevant information is now available from mountaineering expeditions (lasting at least 6 weeks above 5,000 m), since oxygen is limited at this altitude. Under these conditions reductions in mitochondrial volume densities, in oxidative enzyme activities and in cross sectional areas of muscle fibers were found in the quadriceps [63, 64]. But 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 towards more oxidative metabolism [65].

More information about the effect of hypoxia on muscle has been obtained from animal studies. Several of these studies have shown that hypoxia can indeed lead to the muscular alterations as described for limb muscles in COPD and CHF: (1) Reduced fibre diameters in combination with unaffected numbers of capillaries, resulting in increased capillary densities, have been reported in rats exposed to hypoxia [66, 67]. (2) Some studies revealed that hypoxia depresses protein synthesis [68, 69], includ-

ing in muscle tissue [68]. Chronic hypoxia inhibits the normal conversion of type IIa to type I fibres in growing rats, resulting in a predominating proportion of type IIa fibres compared to control rats [70]. So hypoxia does not directly cause a type I $\rightarrow$ II fibre shift, but causes an abnormal fibre type distribution from alterations in muscular development. It is feasible that in COPD and CHF a similar mechanism underlies the abnormal fibre type distribution in the regeneration of damaged muscle or the adaptation of muscles to consequences of the disease. (3) There is evidence that hypoxia causes a shift towards glycolytic metabolism, resulting in an increased lactate-to-pyruvate ratio [71, 72] and reduced malate dehydrogenase, a citric acid enzyme [73]. (4) Hypoxia causes stimulation of glucose transport [74] and increased levels of membrane-associated glucose transporters (GLUT1 and GLUT4) in rat muscle [75].

It should be noted, however, that in COPD and CHF this reduction of oxidative capacity does not occur in the diaphragm. It is feasible that hypoxia causes an endurance training effect in the diaphragm due to increased ventilation, which overrides its direct effect ultimately resulting in a shift towards more aerobic metabolism.

Oxidative Stress

Oxidative stress may be another factor contributing via reactive oxygen species to muscle damage. In both COPD and CHF increased plasma levels of lipid peroxidation products have been found [76, 77]. Sources of free oxygen radicals are: (1) Mitochondria, since 2–5% of the total oxygen consumed is not fully reduced in the electron transport chain and may leak away as superoxide radicals [78, 79]. (2) Immune cells activated during inflammation [80]. Monocytes and macrophages produce cytokine tumor necrosis factor-α (TNFα) which may in turn induce oxidative stress in myocytes [81]. Elevated TNFα blood levels have indeed been found in both COPD [82, 83] and CHF [84, 85], in particular in those patients characterized by weight loss and/or muscle wasting. (3) Xanthine oxidase, in case of a low energy state, is involved in the degradation of AMP [79]. The above-mentioned elevated IMP levels in COPD [46] indeed suggest enhanced AMP breakdown. Susceptibility to these free radicals largely depends on the antioxidant status of tissue [79]. The main antioxidant scavengers and enzymes are, amongst others, reduced glutathione, vitamin E (in cell membranes), superoxide dismutase (SOD), glutathione peroxidase and catalase [79, 86]. Long-term training stimulates the defense system against oxygen free radicals [78, 79, 86] and the disuse of muscles thus may lack this antioxidant stimulating trigger resulting in a reduced antioxidant status. Chronic hypoxia probably acts in the same way, since limitations of oxygen supply are indeed found to be associated with reductions in SOD activity in mammalian tissues like brain, lungs and heart, although this change was not found in skeletal muscle tissue [87, 88]. In addition, in myocytes (obtained from chronic 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 [89]. In vivo and in vitro hypoxia-reoxygenation studies revealed that oxygen oversupply following a period of oxygen shortage may give rise to free radical formation in myocytes [87, 90]. Accordingly, in COPD and CHF chronic hypoxia may result in a reduced antioxidant status and occasional bouts of exercise may cause a boost of free radicals exceeding the capacity of the defence system [78]. It is also feasible that the reduced oxidative capacity in the patients itself leads to enhanced oxidative stress, since the sudden oversupply of oxygen during exercise is inefficiently metabolised.

Reactive oxygen species are well capable of damaging lipids and proteins [78, 79, 86, 91]. Radicals that react with fatty acyl moieties in membrane phospholipids cause a chain reaction of peroxidations increasing the membrane permeability [91]. Maintenance of membrane integrity is crucial for: (1) Adequate functioning of the respiratory chain, since 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 [92]. (2) To prevent intracellular calcium overload, caused by damaged sarcoplasmatic reticulum membrane, in combination with impaired activity of calcium ATPases, which accompanies oxidative stress in animal myocytes [78, 87, 90, 93], and may further uncouple respiration from ATP production through extensive depolarisation of the inner membrane [94].

Protein oxidation by oxygen free radicals leads to formation of carbonyl groups on amino acid residues, which may modify the structure and/or chemical properties of the proteins affected [95]. These alterations may cause decline in 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 has been shown in animal studies that in vivo induced oxidative stress caused myofibrillar

muscle protein modification and that these proteins were rapidly degraded by proteases [96]. Thus theoretically, muscle atrophy can be enhanced by radical induced protein damage. Indeed, it has been shown that a calcium overload is involved in muscle atrophy [97] and that vitamin E deficiency facilitates muscle wasting and necrosis [98], both probably mediated by oxidative damage to proteins. Also, in human skeletal muscle it has been shown that mitochondria and mitochondrial proteins were more susceptible to oxidative damage compared to other subcellular components [99], 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 recently also has been associated with oxidative stress [100]. In this study the exposure of rat myoblasts to nitric oxide or hydrogen peroxidase led to apoptotic cell death. Since these chemical stimuli are also released by immune cells, it cannot be excluded that apoptosis underlies muscle wasting during inflammation.

Disuse

Disuse (low level of physical exercise because of their disease) of skeletal muscle is also a factor that most likely contributes to the observed muscle alterations in COPD and CHF. This results in: (1) Muscle weakness, due to reduced motor neuron activity and muscle wasting [38, 101]. (2) Relative reduction in the percentage of type I fibres and an increase in the percentage of type IIb/x fibres [38, 102]. (3) A decline in activity of enzymes involved in oxidative energy conversion, which occurs both in type I and type II fibres [102], suggesting that it can occur even without any change in fibre composition. (4) A negative effect on the antioxidant status enhances the risk of oxidative damage. As mentioned above, the diaphragm is probably not disused and a kind of endurance training effect may even occur. This may not only be true for COPD, but for CHF as well, since especially in severe CHF dyspnoea and elevated ventilation occur already at rest [13, 103].

Weight Loss and Altered Substrate Metabolism

Weight loss commonly occurs in COPD [104, 105] and in CHF [23, 106] and is an independent determinant of mortality [107, 108]. In both disorders in particular loss of FFM is an important determinant for exercise capacity [2, 24, 109]. Determination of body composition, and not only weight, with respect to nutritional depletion is very important since at least in COPD 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 requirement and energy intake. Although limited information is available in CHF patients, a negative energy balance commonly occurs in COPD as a result of either a decreased dietary intake, elevated energy requirements or a combination of both. Total daily energy metabolism (TDE) can be divided in 3 components: resting energy expenditure (REE), measured under fasting conditions in the early morning, diet induced thermogenesis (DIT) and physical activity induced (PAI) thermogenesis. REE comprises the major part of TDE, DIT on average only 10–15% and PAI can be highly variable. While in many chronic wasting diseases, REE is increased, probably related to an enhanced systemic inflammation, TDE is not different from healthy control subjects due to a compensatory decrease in daily activities. In contrast, TDE in COPD was found to be increased as a result of an increased PAI [110]. It is yet unclear to what extent an increased PAI is related to a decreased mechanical or a decreased metabolic efficiency and what the contributing role is of peripheral skeletal muscles versus the diaphragm.

In a situation of semistarvation, either primarily due to increased energy requirements or due to decreased dietary intake, loss of both fat mass and fat-free mass occurs, but the loss of fat-free mass is relatively preserved. Therefore, intrinsic muscle abnormalities besides loss of muscle mass must account for impaired muscle performance. Studies on muscle function and histology in anorexia nervosa patients provide strong data on the effect of undernutrition per se on muscles. Muscle performance is markedly impaired in these patients [111–113] and is associated with weight loss, loss of muscle mass and fibre atrophy (particularly of type II fibres) [114, 115]. We recently demonstrated selective fibre type IIx atrophy in COPD patients associated with a reduced fat-free mass, suggesting a role for undernutrition in this disease too [44]. Data from animal studies confirm these effects of undernutrition. Decreased activities of enzymes involved in glycolytic and mitochondrial pathways have been reported from muscle biopsies of patients with anorexia nervosa [99, 111], with glycolytic capacity being affected the most [111]. The contribution of nutritional depletion to a shift from oxidative to glycolytic metabolism in COPD and CHF patients needs further investigation.

Disproportionate loss of fat-free mass often referred as cachexia, involves an impaired balance between protein anabolism and catabolism. Protein depletion itself may

impair skeletal muscle performance as reflected by reduced maximum voluntary handgrip strength, reduced respiratory muscle strength and an increased fatigability of in vivo electrically stimulated adductor pollicis muscle [116]. Predominant loss of fat-free mass with relative preservation of fat mass also points towards alterations in substrate metabolism. Partly independent of pulmonary or cardiac cachexia, other disease characteristics like hypoxia or hypercapnia may alter substrate metabolism. Insulin has a central role in substrate metabolism. Hyperinsulinemia has been described in COPD and insulin resistance commonly occurs in CHF. While nearly no data are available regarding carbohydrate and fat metabolism in fasting, fed or stressed states, protein metabolism has been subject of recent investigations in COPD. In nondepleted COPD patients, an increased whole-body protein turnover was observed at rest and specifically in emphysema a suppressed whole body protein turnover was observed during and immediately after exercise [118, 119]. Whole-body protein turnover, however, does not necessarily reflect muscle protein turnover. A study in underweight patients with emphysema reported a reduced muscle protein synthesis [117], while protein degradation was not increased [119, 120]. It is feasible that amino acids are required in other processes than muscular protein synthesis, such as gluconeogenesis. Besides, recent data also showed intrinsic alterations in the amino acid profile of peripheral skeletal muscles. Most consistent results were found with respect to the amino acid glutamate (GLU). Intracellular GLU has various important functions, as it plays an important role in preserving high-energy phosphates in muscle through different metabolic mechanisms. GLU concentration is high in the free amino acid pool of human skeletal muscle. Intracellular GLU is known as an important precursor for the antioxidant glutathione (GSH) and glutamine synthesis in the muscle. Muscle GLU is indeed highly associated with muscle GSH, and patients with emphysema suffer from decreased muscular GLU and GSH levels [122]. Studies have shown that in healthy human muscle, the GLU pool functions to generate tricarboxylic acid (TCA) intermediates during the first minutes of exercise, which is achieved via the alanine aminotransferase reaction (pyruvate + GLU $\rightarrow$ alanine + α-ketoglutarate) at the cost of GLU. Moreover, this reaction can shunt the pyruvate accumulated during exercise towards alanine instead of lactate, suggesting a possible role of the intracellular GLU level in the lactate response to exercise. In line with this hypothesis early lactic acidosis during exercise in patients with COPD was indeed associated with a reduction in muscle GLU [14]. Not only at rest, but also during 20 min of submaximal constant cycle exercise a different response in amino acid status was found in skeletal muscle and plasma of COPD patients as compared with healthy age-matched controls [123]. A significant reduction of most muscle amino acids was present postexercise, whereas several plasma amino acids were increased, suggesting an enhanced amino acid release from muscle in COPD during exercise. The increase in plasma alanine and glutamine was even higher postexercise, suggesting enhanced nitrogen efflux. Although investigation of substrate metabolism in COPD and CHF is still in its infancy, the available studies clearly point towards therapeutic perspective, not only in cachectic patients, but also as anabolic stimulus to enhance muscle and exercise performance. In frail elderly it has indeed been observed that oral amino acid intake stimulates the transport of amino acids into muscle, and that there is a direct link between amino acid transport and protein synthesis when ingested before exercise or some time after exercise.

Conclusions

This review underscores that reduced skeletal muscle performance markedly contributes to exercise intolerance in COPD and CHF patients. Morphologic and metabolic abnormalities occur in the skeletal muscles of these patients which, in both disorders, probably are determined by the same set of contributing factors. Both diseases also share striking differences between peripheral muscles and the diaphragm which, therefore, may require a different therapeutical approach.

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