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Metabolic and structural impairment of skeletal muscle in heart failure

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Abstract Physiologic endurance exercise performance is primarily limited by cardiac function. In patients with heart failure, there is dissociation between cardiac performance and exercise capacity, suggesting a distinct role of abnormal peripheral organ function, including skeletal muscle function. The impact of heart failure upon skeletal muscle and exercise performance will be discussed with a focus on molecular, structural, and functional derangements in skeletal muscle of patients with heart failure.

Keywords Skeletal muscle · Metabolism · Heart failure

Heart failure is defined as the inability of the heart to adequately perfuse peripheral tissues. The clinical syndrome of heart failure (HF) involves a complex interplay between skeletal muscle and peripheral vascular adaptations, resulting from decreased myocardial performance. The classic symptoms of HF are exertional fatigue and dyspnea. It has traditionally been hypothesized that the major limitation to exercise performance results from a reduced cardiac output response to exercise, leading to skeletal muscle hypoperfusion and lactic acidosis [1]. However, secondary changes in other organ systems such as skeletal muscle, the vascular system, and the lungs play important roles in the genesis of fatigue and dyspnea [2].

Though peak exercise capacity is clearly dependent on the cardiac output response to exercise, it is not the sole determinant of exercise performance in patients with HF since patients with similar reductions in left ventricular function have a wide range of exercise capacity. Furthermore, therapeutic interventions aimed at acutely increasing cardiac output such as inotropic drugs have limited impact on exercise capacity or peak VO_2 [3–5]. This discrepancy between enhanced cardiac output and fixed peak VO_2 can be explained on the basis of the peripheral vascular and skeletal muscle derangements in HF. Due to regional vascular or skeletal abnormalities, the augmented cardiac output cannot be utilized by the exercising muscle beds and, therefore, peak VO_2 is not altered. Evidence for a peripheral abnormality in HF was first described in the 1970s by Zelis [6, 7].

Alterations in skeletal muscle metabolism and mass also play an important role in limiting peak functional capacity in patients with HF [8–10]. Metabolic and atrophic alterations have been shown in muscles of patients with HF [11–15]. Reduced physical activity (disuse and immobilization in advanced stages) plays some part in the muscle alterations in HF but cannot explain the full extent of changes in muscle structure, function, and metabolism [16–19]. Of note, HF-related muscle abnormalities are not substantially different from those observed in other chronic conditions such as chronic pulmonary or renal disease [20]. Chronic low-level systemic inflammation characteristic of the HF state effect changes in skeletal muscle [21] and, with the progression of HF, inflammatory mediators released into the circulation further activate systemic inflammation and promote muscle atrophy. Of note, circulating levels of free fatty acids are increased in patients with HF likely due to enhanced peripheral lipolysis in adipose tissue associated with increased catecholamine levels [22]. Insulin resistance and increased glucose levels in patients with HF have been linked to increased clinical events and higher mortality [22–24] (Fig. 1).

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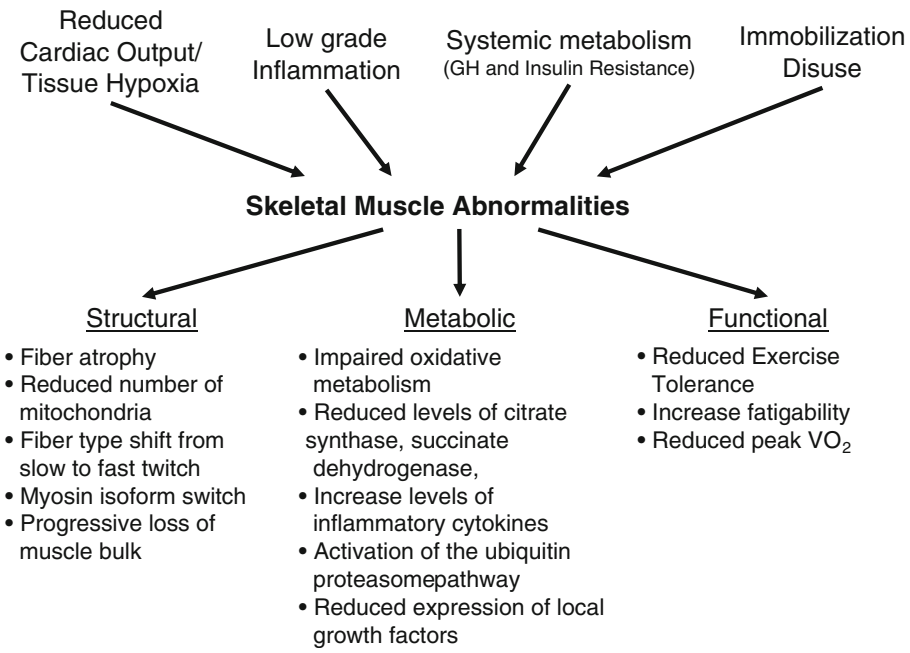

Fig. 1 Factors contributing to skeletal muscle abnormalities and specific intrinsic muscle derangements in advanced HF

Table 1 Skeletal muscle fiber distribution

	Type I	Type IIa	Type IIx
Contraction time	Slow	Moderate. Fast	Fast
Oxidative capacity	High	High	Intermediate
Mitochondrial density	High	High	Medium
Glycolytic capacity	Low	High	High
Resistance to fatigue	High	Fairly high	Intermediate
Major storage fuel	Triglycerides	PhosCr, Glycogen	PhosCr, Glycogen
Capillary density	High	Intermediate	Low

Histologic changes of skeletal muscle in HF

Histomorphologic and metabolic changes of skeletal muscle in HF include changes in the fiber composition of muscle, fiber atrophy, fatty infiltration, and decreased oxidative enzyme levels. Adult human muscle is composed of distinct types: I, IIa, and IIx. The fiber types are defined by their myosin heavy-chain isoforms and can be identified by ATPase staining or immunohistochemistry [25, 26] (Table 1).

Several investigators have reported that patients with HF develop a characteristic shift in muscle fiber distribution with an increased number of type II fibers (anaerobic, glycolytic) when compared to type I (aerobic, oxidative) [27, 28]. In muscle biopsies, an increase in glycolytic, fast-twitch type IIa/x fibers, fiber atrophy, and a reduction in lipolytic and oxidative enzymes were described [19, 29]. Although conventional wisdom suggests that fiber type is shifted in HF, this could be due to muscle disuse. Excellent work by Mettauer et al. [18], which controlled for deconditioning in the HF population, found no fiber-type shift compared to controls with similar VO_2 max. These findings have recently been substantiated [30]. Drexler et al. [11] described decreased volume density of the mitochondria and surface density of the mitochondrial cristae, implying that oxidative transport coupling was compromised. The decreased mitochondrial volume correlated with peak aerobic capacity, suggesting a major contribution of altered skeletal muscle metabolism to exercise intolerance. The concentrations of intramitochondrial citrate synthase, total cytosolic creatine kinase (CK), skeletal muscle-specific CK (MM-CK), and lactate dehydrogenase (LDH) decrease in HF patients [18]. Notably, angiotensin-converting enzyme inhibition, an established therapeutic intervention with impact on survival and exercise performance in HF, seems to prevent the fiber-type switch from type I to II in the skeletal muscle [31–33].

Abnormal skeletal muscle metabolism in HF

Muscle metabolism in various muscle groups has been studied in patients with HF. Abnormal skeletal muscle metabolism, that is, reduced oxidative metabolism with an earlier shift to glycolytic metabolism, has been demonstrated in patients with HF using ^{31}P magnetic resonance spectroscopy [17, 34–38]. These studies consistently show an

increased utilization of the high-energy molecule phosphocreatine (PCr), accumulation of inorganic phosphate (Pi, a by-product of ATP utilization), early intracellular acidification, and delayed PCr recovery after exercise. These abnormalities appear to be independent of total limb perfusion [34, 35, 39, 40], histochemical changes [15], muscle mass [41], or severe tissue hypoxia [42]. Venous plethysmography to measure limb blood flow demonstrated that metabolic changes during exercise in HF occur in the absence of an associated decrease in limb perfusion [40]. Persistent metabolic abnormalities in patients with CHF compared with normal subjects were also demonstrated during ischemic exercise, that is, exercise performed during arterial occlusion. Acutely increasing cardiac output with therapeutic agents such as dobutamine did not improve the metabolic abnormalities observed in these patients [4].

Simultaneous monitoring of cellular metabolism and oxygenation during leg exercise in HF patients by coupling ^{31}P magnetic resonance spectroscopy to near infrared spectroscopy revealed that metabolic abnormalities observed in patients with HF occurred despite what appears to be adequate muscle oxygenation [36]. This again supports an intrinsic skeletal muscle metabolic change in these patients. Overall, patients with HF experience metabolic alterations that are similar to those reported after deconditioning. To what extent muscle atrophy, fibrosis, and inflammation underlie ^{31}P-MRS metabolic alterations remains unclear.

Impaired skeletal muscle excitation contraction coupling in HF

Excitation contraction coupling of the skeletal muscle sarcomere is abnormal in HF, which is in part related to abnormalities in intracellular calcium handling that lead to an intracellular calcium-overload state. Skeletal muscles from animals with HF exhibit increased Ca^{2+} spark frequency, decreased Ca^{2+} spark amplitude, and increased Ca^{2+} spark duration consistent with leaky sarcoplasmic reticulum Ca^{2+} release and with decreased sarcoplasmic reticulum Ca^{2+} content [43]. Comparable to the failing myocardium, the muscle-specific type 1 ryanodine receptor (RyR1) becomes leaky in HF as chronic adrenergic stimulation results in hyperphosphorylation of the channel. This change dissociates calstabin-1, the stabilizing protein that keeps the RyR1 channel in a closed state [44]. Data regarding sarcoplasmic reticulum Ca^{2+} pumping in HF differ in fast- and slow-twitch muscles and with level of fatigue [45]. SR Ca^{2+} pumping appears to be most impaired in slow-twitch muscles in HF. Data regarding skeletal muscle protein and mRNA expression of SERCA 1a, the skeletal muscle-specific isoform of SERCA, are divergent in HF [1, 43]. Predominant muscle fiber composition, degree of functional impairment, and nature of the HF model may in part account for the disparate findings that have been occasionally correlated with early muscle fatigue.

Skeletal muscle mitochondrial dysfunction in HF

A central pathophysiologic role has been suggested for abnormal mitochondrial function and structure as well as reduced oxidative metabolism in skeletal muscle of patients with HF [11, 35, 36, 39, 46–48]. Structural abnormalities include reduced cristae, decreased size, and reduced total number of mitochondria per muscle fiber [13, 46, 49]. Several studies have shown reduced expression levels and decreased activity of key metabolic enzymes of mitochondrial oxidative metabolism including the Krebs cycle enzymes citrate synthase and succinate dehydrogenase [13]. These changes have been linked to reduced flux through the Krebs cycle and a reduction in ATP levels suggestive of energy depletion of skeletal muscle in HF. Further, muscle fiber switching with reduced oxidative type I fibers and increased glycolytic type II fibers is directly linked to changes in oxidative metabolism [11, 18, 39]. Myosin isoform expression also follows this distinct metabolic pattern [30].

Muscle fiber atrophy and changes in total muscle mass

In relation to fiber atrophy noted on muscle biopsy, HF patients develop generalized muscle atrophy [46]. Analysis of skinfold fat thickness, arm circumference, and 24-h urine collections of creatinine for the estimation of total muscle mass showed that patients with HF have adequate fat stores but frequently develop muscle loss. In another study, calf muscle volume assessed by magnetic resonance imaging (MRI) revealed reduced muscle volume in patients with HF and significant water and/or fat infiltration was also noted in the muscle sections of these patients. Calf muscle mass was reported to be lower in patients with severe HF as evidenced by a peak VO_2 of 13 ml/min/kg when compared to age- and gender-matched controls [49]. However, other studies reported normal muscle mass in patients with HF [41]. Further, controversy exists regarding the extent of muscle atrophy in experimental models of HF, and some authors have suggested that muscle atrophy develops only secondary to inactivity in patients with advanced HF [1, 30, 50].

The assessment of muscle function in patients with HF consistently showed decreased muscle strength and increased fatigability when normalized to fiber cross-sectional area in patients with HF [51]. Slowing of relaxation and steady decline in strength has been reported during low-frequency stimulation of slow-twitch muscles in rats with congestive HF [45]. Reduced isometric force and

calcium-activated actomyosin ATPase activity in patients with HF may be due to a decline in density of contractile proteins and the specific rate of cross-bridge attachment or in both [28, 30, 52]. A reduction in contractile protein content appears to be the most likely explanation of reduced muscle strength since single-fiber muscle contractile protein function has been reported to unaltered in patients with HF [53].

The impact of muscle mass on peak VO_2 has been investigated by several groups, and a weak but significant correlation with total skeletal muscle mass derived from equations using 24-h urinary protein measurements has been reported [43, 46]. LeJemtel contrasted peak oxygen consumption during combined upper arm and maximal leg exercise [54]. In normal subjects, the addition of more muscle mass via arm exercise did not increase peak exercise performance and VO_2 remained unchanged, suggesting that under normal conditions, cardiac output response to exercise, rather than the amount of exercising muscle, determines peak VO_2. However, in patients with severe HF, the addition of upper arm exercise significantly increases peak VO_2, suggesting the importance of skeletal muscle mass in determining peak VO_2 in patients with HF. An alternative hypothesis is that the peripheral vasodilatory abnormalities in these patients resulted in a physiologic shunt to the upper arm musculature resulting in higher peak VO_2 with combined arm and leg exercise.

Mechanisms of skeletal muscle atrophy

The mechanisms that mediate skeletal muscle wasting and atrophy have only recently been studied in patients with HF and animal models of cardiac dysfunction. Muscle atrophy, in general, may result from decreased protein synthesis, increased protein degradation, or both. There is controversy on the impact of clinical status and disease exacerbations on muscle atrophy in HF. The majority of studies have shown no defects in either muscle protein synthesis or breakdown in clinically stable HF patients. It is possible that muscle atrophy initiation and progression are directly linked to episodes of disease exacerbation. Unfortunately, no studies have tested patients during acute disease exacerbation to determine what metabolic defects account for muscle atrophy. Several key signaling pathways that involved in protein degradation and synthesis will be discussed below [55].

Enhanced protein degradation

Experimental data in a murine model of HF indicate that the ubiquitin-proteasome pathway plays an important role in HF-induced skeletal muscle atrophy [56]. Through this central pathway of protein degradation, proteins are marked by ubiquitin for rapid degradation through the 26S proteasome in an ATP-dependent pathway that yields peptides and intact ubiquitin. Skeletal muscle from mice with left ventricular dysfunction revealed activation of the ubiquitin-proteasome pathway with increased protein ubiquitination, FOXO transcription factor activation, increased expression of muscle-specific atrogenes, and overall muscle atrophy [57]. Further experimental data regarding the critical inhibitory role of IGF-1 in the development of skeletal muscle atrophy have been provided in a model of skeletal muscle wasting induced by chronic administration of angiotensin II (Ang II) [58]. Chronic administration of Ang II suppresses IGF-1 signaling via the Akt/mTOR/p70S6 k pathway that is critical for caspase-3 activation, actin cleavage, ubiquitination, and apoptosis. Caspase-3 activation is another important mechanism for muscle protein degradation [56], and muscle-specific expression of IGF-1 blocks the Ang II-induced muscle atrophy [58]. Whether the beneficial effects of ACE inhibition on skeletal muscle in HF patients are mediated though the IGF-1 pathway or result from direct effects on skeletal muscle vasculature via improvement of vascular endothelial function remains to be determined. In addition to Ang II, elevated cytokines such as TNF-α and IL-1β can directly activate the ubiquitin-proteasome pathway and thereby result in skeletal muscle protein degradation [59].

Impaired growth factor signaling and protein synthesis

HF is a catabolic state with deficiencies in several anabolic hormones [60–62]. In male HF patients, deficiencies in circulating total testosterone, dehydroepiandrosterone (DHEA), and IGF-1 are common and correlate with a poor prognosis [63]. Testosterone produces skeletal muscle hypertrophy by increasing fractional muscle protein synthesis [64]. Testosterone appears to stimulate IGF-1 expression, but the exact molecular pathways are incompletely understood. At supra-physiologic doses, testosterone appears to act through androgen receptor-independent mechanisms. In HF patients, serum levels of free testosterone and DHEA are decreased, and this decrease correlates with HF severity [63].

Several authors have suggested a role of myostatin in muscle atrophy in patients with advanced HF [65]. Myostatin is a local and circulating factor secreted from skeletal muscle with anti-anabolic and anti-hypertrophic actions. In fact, such a mechanism may be operable in patients since circulating levels of myostatin [66] and other TGF receptor ligands, such as activin [67], are increased in HF patients.

Skeletal muscle inflammation

HF induces a chronic low-level inflammatory state as evidenced by modest elevation of circulating IL-1, IL-6, and TNF-α [68, 69]. The initiating factors of skeletal muscle inflammation are incompletely understood. Disuse-induced atrophy promotes skeletal muscle inflammation through the activation of several signaling pathways.

Increased skeletal muscle inflammation relates to reduced O_2 delivery and local IGF-1 concentration as well as increasing oxidative stress. In turn, muscle inflammation induces cytokines, especially IL-6 and TNF-α and expression of inducible nitric oxide synthase (iNOS) [70]. Elevated IL-6 and TNF-α concentrations activate the NF-κB signaling pathway that modulates immune and inflammatory skeletal muscle responses, thereby exacerbating muscle wasting [71]. Increased IL-6 has been associated with skeletal muscle and diaphragmatic atrophy in rats and the Janus-activated kinase (JAK), signal transducer and activator of transcription (STAT), and cAMP-activated protein kinase (AMPK) signaling pathways [72]. As previously mentioned, increased FOXO activity precipitates muscle protein degradation and muscle atrophy through the ubiquitin-proteasome pathway in HF. In summary, skeletal muscle inflammation exacerbates skeletal muscle atrophy through stimulation of multiple cytokine-activated signaling pathways.

Activation of the renin–angiotensin system results in vasoconstriction and elevated skeletal muscle concentration of Ang II, which increases local oxidative stress and lowers skeletal muscle concentration of IGF-1. These mechanisms may accelerate protein degradation while decreasing protein synthesis. Loss of skeletal muscle mass, reduction in muscle perfusion, and changes in blood flow distribution and fiber-type composition contribute to muscle reflex alterations in HF [10]. In normal subjects, muscle reflex activation helps raise blood pressure and thereby maintain muscle perfusion during muscle acidosis. In HF, muscle reflex activation occurs at the onset of exercise resulting in vasoconstriction and limited skeletal muscle perfusion.

Therapeutic interventions

Therapies targeting oxidative metabolism and mitochondrial function

Limited data are available on interventions targeting mitochondrial function and oxidative metabolism in skeletal muscle in HF. Exercise training, through so far unidentified mechanisms, increases mitochondrial density and oxidative function and corrects skeletal muscle fiber type in patients with HF [11, 70, 73–76]. Pharmacologic interventions modulating oxidative metabolism, for example, through AMPK or PPARδ agonists, have not been systematically tested in HF. Specific metabolic interventions counteracting insulin resistance, elevated circulating levels of free fatty acids, impaired flux through the Krebs cycle through anaplerotic supplementation of its substrates, or anti-inflammatory therapies using high-dose omega-3 supplements have been postulated as potential therapeutic interventions, but results are not yet available [77–79].

Growth factor therapies

In a placebo-controlled trial of 70 elderly patients with moderately severe HF, testosterone application improved exercise capacity, muscle strength, glucose metabolism, and baroreflex sensitivity [60]. Despite the beneficial effects on insulin resistance, testosterone had no apparent effects on myocardial performance and left ventricular function. Long-acting therapy seems to be well tolerated by elderly patients with moderately severe HF.

Growth hormone (GH) resistance and reduction in skeletal muscle IGF-1 concentration contribute to skeletal muscle atrophy in HF by directly reducing protein synthesis and by decreasing muscle satellite cell recruitment and differentiation [55]. Exercise training has been shown to increase local expression of IGF-1 in normal subjects and patients with HF [75]. Transgenic overexpression of a local isoform of IGF-1 prevents proteasome activation, breakdown of skeletal muscle structural proteins, and atrophy [80]. Ghrelin, a GH-releasing peptide, stimulates physiologic release of IGF-1 through a mechanism that is independent from hypothalamic GH-releasing hormone [81]. Ghrelin administration for 3 weeks improves functional capacity and alleviates skeletal muscle atrophy in patients with chronic HF and chronic obstructive pulmonary disease [82].

Exercise training

Adamopoulos [73] showed that physical conditioning substantially corrects the muscle metabolic alterations in patients with HF but did not normalize them. After 8 weeks of home-based bicycle exercise training in a randomized crossover trial, patients with HF exhibited less PCr depletion and faster PCr recovery as well as lower exercise-induced ADP formation. However, exercise-induced acidification was unaffected by physical conditioning [73, 83]. Other studies have shown improved mitochondrial function, enhanced oxidative metabolism, and reduced levels of the iNOS in skeletal muscle of patients with HF undergoing exercise training [70, 74, 76, 84–86]. Further, increased local IGF-1 levels following exercise training associated

with reduced muscle atrophy and higher endurance function have been reported following exercise training in patients with HF [75].

Concluding remarks

Chronic disease states including chronic HF are associated with reduced physical activity, resulting in disuse and low-level systemic inflammation. Both disuse and systemic inflammation promote loss of muscle mass and ultimately atrophy. Continuous loss of skeletal muscle mass activates multiple signaling pathways that mediate muscle inflammation. In turn, local inflammation activates signaling pathways that promote further loss of muscle mass and exacerbates local inflammation. The negative interaction between atrophy and inflammation within the skeletal muscle appears to progress independently from the initial event and may be related to the presence of comorbidities including hormonal deficiencies, diabetes mellitus, obesity, and sleep-disordered breathing. An important goal of therapy in HF patients is to reverse or optimally prevent the development of skeletal muscle alterations in order to restore a normal functional capacity.

Conflict of interest Dr. Cynthia Zizola and Dr. P. Christian Schulze have no conflict of interest.

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