Published in final edited form as:

Heart Fail Rev. 2013 September ; 18(5): 623–630. doi:10.1007/s10741-012-9353-8.

Metabolic and structural impairment of skeletal muscle in heart failure

Cynthia Zizola, PhD and P. Christian Schulze, MD, PhD

Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, New York, USA

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 of 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].

Address for correspondence: P. Christian Schulze, MD, PhD Assistant Professor of Medicine Columbia University Medical Center Center for Advanced Cardiac Care Department of Medicine, Division of Cardiology 622 West 168th Street, PH 10, Room 203 New York, NY 10032, USA Tel: 212-305-6916, Fax: 212-342-5355 pcs2121@mail.cumc.columbia.edu.

Disclosures Dr. Cynthia Zizola has no conflict of interest.
Dr. P. Christian Schulze has no conflict of interest.

Alterations of 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] (Figure 1).

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) as 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 was 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 VO₂ max. These findings have recently been substantiated [30]. Drexler *et al.* described decreased volume density of the mitochondria and surface density of the mitochondrial cristae, implying that oxidative transport coupling was compromised [11]. The decreased mitochondrial volume correlated with peak aerobic capacity, suggesting a major contribution of altered skeletal muscle metabolism to exercise intolerance. The concentrations of intra-mitochondrial 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, *i.e.* reduced oxidative metabolism with an earlier shift to glycolytic metabolism, has been demonstrated in patients with HF using ³¹P 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 intra-cellular 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 occurs in the absence of an associated decrease in

limb perfusion [40]. Persistent metabolic abnormalities in patients with CHF compared to normal subjects was also demonstrated during ischemic exercise, *i.e.* 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 hour urine collections of creatinine for 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 hour urinary protein measurements have 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 is 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/p70S6k 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 through 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 and IL-1 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 for 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 antihypertrophic 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 activation of several signaling pathways.

Increased skeletal muscle inflammation relates to reduced O₂ 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- κ B 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, *e.g.* through AMPK or PPAR 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 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 physiological release of IGF-1 through a mechanism that is independent from hypothalamic GH releasing hormone [81]. Ghrelin administration for three 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.

REFERENCES

1. Lunde PK, Sjaastad I, Schiotz Thorud HM, Sejersted OM. Skeletal muscle disorders in heart failure. *Acta Physiol Scand*. 2001; 171:277–294. [PubMed: 11412140]
2. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*. 1996; 28:1092–1102. [PubMed: 8890800]
3. Mancini DM, Schwartz M, Ferraro N, Seestedt R, Chance B, et al. Effect of dobutamine on skeletal muscle metabolism in patients with congestive heart failure. *Am J Cardiol*. 1990; 65:1121–1126. [PubMed: 2330898]
4. Maskin CS, Forman R, Sonnenblick EH, Frishman WH, LeJemtel TH. Failure of dobutamine to increase exercise capacity despite hemodynamic improvement in severe chronic heart failure. *Am J Cardiol*. 1983; 51:177–182. [PubMed: 6849256]
5. Wilson JR, Martin JL, Ferraro N. Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. *Am J Cardiol*. 1984; 53:1308–1315. [PubMed: 6711433]
6. Zelis R, Delea CS, Coleman HN, Mason DT. Arterial sodium content in experimental congestive heart failure. *Circulation*. 1970; 41:213–216. [PubMed: 5412982]
7. Zelis R, Mason DT, Braunwald E. A comparison of the effects of vasodilator stimuli on peripheral resistance vessels in normal subjects and in patients with congestive heart failure. *J Clin Invest*. 1968; 47:960–970. [PubMed: 5641631]
8. Jondeau G, Katz SD, Zohman L, Goldberger M, McCarthy M, et al. Active skeletal muscle mass and cardiopulmonary reserve. Failure to attain peak aerobic capacity during maximal bicycle exercise in patients with severe congestive heart failure. *Circulation*. 1992; 86:1351–1356. [PubMed: 1423946]
9. Mann DL, Reid MB. Exercise training and skeletal muscle inflammation in chronic heart failure: feeling better about fatigue. *J Am Coll Cardiol*. 2003; 42:869–872. [PubMed: 12957434]
10. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. *Br J Pharmacol*. 2008; 154:557–568. [PubMed: 18500379]
11. Drexler H, Riede U, Munzel T, König H, Funke E, et al. Alterations of skeletal muscle in chronic heart failure. *Circulation*. 1992; 85:1751–1759. [PubMed: 1315220]
12. LeJemtel TH, Maskin CS, Lucido D, Chadwick BJ. Failure to augment maximal limb blood flow in response to one-leg versus two-leg exercise in patients with severe heart failure. *Circulation*. 1986; 74:245–251. [PubMed: 3731416]
13. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation*. 1992; 86:909–918. [PubMed: 1516204]
14. Minotti JR, Christoph I, Oka R, Weiner MW, Wells L, et al. Impaired skeletal muscle function in patients with congestive heart failure. Relationship to systemic exercise performance. *J Clin Invest*. 1991; 88:2077–2082. [PubMed: 1752965]
15. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation*. 1990; 81:518–527. [PubMed: 2297859]

16. Chati Z, Zannad F, Jeandel C, Lherbier B, Escanye JM, et al. Physical deconditioning may be a mechanism for the skeletal muscle energy phosphate metabolism abnormalities in chronic heart failure. *Am Heart J*. 1996; 131:560–566. [PubMed: 8604638]
17. Chati Z, Zannad F, Robin-Lherbier B, Escanye JM, Jeandel C, et al. Contribution of specific skeletal muscle metabolic abnormalities to limitation of exercise capacity in patients with chronic heart failure: a phosphorus 31 nuclear magnetic resonance study. *Am Heart J*. 1994; 128:781–792. [PubMed: 7942449]
18. Mettauer B, Zoll J, Sanchez H, Lampert E, Ribera F, et al. Oxidative capacity of skeletal muscle in heart failure patients versus sedentary or active control subjects. *J Am Coll Cardiol*. 2001; 38:947–954. [PubMed: 11583863]
19. Simonini A, Long CS, Dudley GA, Yue P, McElhinny J, et al. Heart failure in rats causes changes in skeletal muscle morphology and gene expression that are not explained by reduced activity. *Circ Res*. 1996; 79:128–136. [PubMed: 8925560]
20. Troosters T, Gosselink R, Decramer M. Chronic obstructive pulmonary disease and chronic heart failure: two muscle diseases? *J Cardiopulm Rehabil*. 2004; 24:137–145. [PubMed: 15235292]
21. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res*. 2002; 91:988–998. [PubMed: 12456484]
22. Opie LH, Knuuti J. The adrenergic-fatty acid load in heart failure. *J Am Coll Cardiol*. 2009; 54:1637–1646. [PubMed: 19850204]
23. Doehner W, Rauchhaus M, Ponikowski P, Godsland IF, von Haehling S, et al. Impaired insulin sensitivity as an independent risk factor for mortality in patients with stable chronic heart failure. *J Am Coll Cardiol*. 2005; 46:1019–1026. [PubMed: 16168285]
24. Doehner W, von Haehling S, Anker SD. Insulin Resistance in Chronic Heart Failure. *J Am Coll Cardiol*. 2008; 52:239. [PubMed: 18617075]
25. Gollnick PD, Armstrong RB, Saubert CW, Piehl K, Saltin B. Enzyme activity and fiber composition in skeletal muscle of untrained and trained men. *J Appl Physiol*. 1972; 33:312–319. [PubMed: 4403464]
26. Schiaffino S, Reggiani C. Molecular diversity of myofibrillar proteins: gene regulation and functional significance. *Physiol Rev*. 1996; 76:371–423. [PubMed: 8618961]
27. Schaefelberger M, Eriksson BO, Grimby G, Held P, Swedberg K. Skeletal muscle fiber composition and capillarization in patients with chronic heart failure: relation to exercise capacity and central hemodynamics. *J Card Fail*. 1995; 1:267–272. [PubMed: 9420659]
28. Szentesi P, Bekedam MA, van Beek-Harmsen BJ, van der Laarse WJ, Zaremba R, et al. Depression of force production and ATPase activity in different types of human skeletal muscle fibers from patients with chronic heart failure. *J Appl Physiol*. 2005; 99:2189–2195. [PubMed: 16051711]
29. Opasich C, Aquilani R, Dossena M, Foppa P, Catapano M, et al. Biochemical analysis of muscle biopsy in overnight fasting patients with severe chronic heart failure. *Eur Heart J*. 1996; 17:1686–1693. [PubMed: 8922917]
30. Miller MS, Vanburen P, Lewinter MM, Lecker SH, Selby DE, et al. Mechanisms underlying skeletal muscle weakness in human heart failure: alterations in single fiber myosin protein content and function. *Circ Heart Fail*. 2009; 2:700–706. [PubMed: 19919996]
31. Sabbah HN, Shimoyama H, Sharov VG, Kono T, Gupta RC, et al. Effects of ACE inhibition and beta-blockade on skeletal muscle fiber types in dogs with moderate heart failure. *Am J Physiol*. 1996; 270:H115–H120. [PubMed: 8769741]
32. Schieffer B, Wollert KC, Berchtold M, Saal K, Schieffer E, et al. Development and prevention of skeletal muscle structural alterations after experimental myocardial infarction. *Am J Physiol*. 1995; 269:H1507–H1513. [PubMed: 7503242]
33. Vescovo G, Dalla LL, Serafini F, Leprotti C, Facchin L, et al. Improved exercise tolerance after losartan and enalapril in heart failure: correlation with changes in skeletal muscle myosin heavy chain composition. *Circulation*. 1998; 98:1742–1749. [PubMed: 9788828]
34. Fregosi RF, Seals DR. Hypoxic potentiation of the ventilatory response to dynamic forearm exercise. *J Appl Physiol*. 1993; 74:2365–2372. [PubMed: 8335569]

35. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol.* 1988; 18:187–195. [PubMed: 2830194]
36. Mancini DM, Coyle E, Coggan A, Beltz J, Ferraro N, et al. Contribution of intrinsic skeletal muscle changes to ³¹P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation.* 1989; 80:1338–1346. [PubMed: 2805270]
37. McCully K, Mancini D, Levine S. Nuclear magnetic resonance spectroscopy: its role in providing valuable insight into diverse clinical problems. *Chest.* 1999; 116:1434–1441. [PubMed: 10559109]
38. Oelberg DA, Evans AB, Hrovat MI, Pappagianopoulos PP, Patz S, et al. Skeletal muscle chemoreflex and pHi in exercise ventilatory control. *J Appl Physiol.* 1998; 84:676–682. [PubMed: 9475880]
39. Massie B, Conway M, Yonge R, Frostick S, Ledingham J, et al. Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation.* 1987; 76:1009–1019. [PubMed: 3664989]
40. Wiener DH, Fink LI, Maris J, Jones RA, Chance B, et al. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation.* 1986; 73:1127–1136. [PubMed: 3698247]
41. Lang CC, Chomsky DB, Rayos G, Yeoh TK, Wilson JR. Skeletal muscle mass and exercise performance in stable ambulatory patients with heart failure. *J Appl Physiol.* 1997; 82:257–261. [PubMed: 9029224]
42. Katz SD, Maskin C, Jondeau G, Cocke T, Berkowitz R, et al. Near-maximal fractional oxygen extraction by active skeletal muscle in patients with chronic heart failure. *J Appl Physiol.* 2000; 88:2138–2142. [PubMed: 10846028]
43. Peters DG, Mitchell HL, McCune SA, Park S, Williams JH, et al. Skeletal muscle sarcoplasmic reticulum Ca(2+)-ATPase gene expression in congestive heart failure. *Circ Res.* 1997; 81:703–710. [PubMed: 9351444]
44. Bellinger AM, Mongillo M, Marks AR. Stressed out: the skeletal muscle ryanodine receptor as a target of stress. *J Clin Invest.* 2008; 118:445–453. [PubMed: 18246195]
45. Lunde PK, Dahlstedt AJ, Bruton JD, Lannergren J, Thoren P, et al. Contraction and intracellular Ca(2+) handling in isolated skeletal muscle of rats with congestive heart failure. *Circ Res.* 2001; 88:1299–1305. [PubMed: 11420307]
46. Mancini DM, Walter G, Reichel N, Lenkinski R, McCully KK, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation.* 1992; 85:1364–1373. [PubMed: 1555280]
47. Williams AD, Selig S, Hare DL, Hayes A, Krum H, et al. Reduced exercise tolerance in CHF may be related to factors other than impaired skeletal muscle oxidative capacity. *J Card Fail.* 2004; 10:141–148. [PubMed: 15101026]
48. Schrepper A, Schwarzer M, Schöpe M, Amorim PA, Doenst T. Biphasic response of skeletal muscle mitochondria to chronic cardiac pressure overload - role of respiratory chain complex activity. *J Mol Cell Cardiol.* 2012; 52:125–135. [PubMed: 22100228]
49. Mancini DM, Ferraro N, Tuchler M, Chance B, Wilson JR. Detection of abnormal calf muscle metabolism in patients with heart failure using phosphorus-31 nuclear magnetic resonance. *Am J Cardiol.* 1988; 62:1234–1240. [PubMed: 3195484]
50. Witte KK, Clark AL. Why does chronic heart failure cause breathlessness and fatigue? *Prog Cardiovasc Dis.* 2007; 49:366–384. [PubMed: 17329182]
51. Duscha BD, Schulze PC, Robbins JL, Forman DE. Implications of chronic heart failure on peripheral vasculature and skeletal muscle before and after exercise training. *Heart Fail Rev.* 2008; 13:21–37. [PubMed: 17955365]
52. Miller MS, VanBuren P, LeWinter MM, Braddock JM, Ades PA, et al. Chronic heart failure decreases cross-bridge kinetics in single skeletal muscle fibres from humans. *J Physiol.* 2010; 588:4039–4053. [PubMed: 20724360]
53. Okada Y, Toth MJ, VanBuren P. Skeletal muscle contractile protein function is preserved in human heart failure. *J Appl Physiol.* 2008; 104:952–957. [PubMed: 18202167]

54. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol.* 2007; 49:171–180. [PubMed: 17222727]
55. Song YH, Li Y, Du J, Mitch WE, Rosenthal N, et al. Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. *J Clin Invest.* 2005; 115:451–458.
56. Du J, Wang X, Miereles C, Bailey JL, Debigare R, et al. Activation of caspase-3 is an initial step triggering accelerated muscle proteolysis in catabolic conditions. *J Clin Invest.* 2004; 113:115–123. [PubMed: 14702115]
57. Schulze PC, Fang J, Kassik KA, Gannon J, Cupesi M, et al. Transgenic overexpression of locally acting insulin-like growth factor-1 inhibits ubiquitin-mediated muscle atrophy in chronic left-ventricular dysfunction. *Circ Res.* 2005; 97:418–426. [PubMed: 16051886]
58. Song YH, Li Y, Du J, Mitch WE, Rosenthal N, et al. Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. *J Clin Invest.* 2005; 115:451–458. [PubMed: 15650772]
59. Pedersen BK, Febbraio MA. Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6. *Physiol Rev.* 2008; 88:1379–1406. [PubMed: 18923185]
60. Caminiti G, Volterrani M, Iellamo F, Marazzi G, Massaro R, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol.* 2009; 54:919–927. [PubMed: 19712802]
61. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation.* 2006; 114:1829–1837. [PubMed: 17030678]
62. Sacca L. Heart failure as a multiple hormonal deficiency syndrome. *Circ Heart Fail.* 2009; 2:151–156. [PubMed: 19808331]
63. Aukrust P, Ueland T, Gullestad L, Yndestad A. Testosterone: A Novel Therapeutic Approach in Chronic Heart Failure? *J Am Coll Cardiol.* 2009; 54:928–929. [PubMed: 19712803]
64. Bhasin S, Woodhouse L, Storer TW. Proof of the effect of testosterone on skeletal muscle. *J Endocrinol.* 2001; 170:27–38. [PubMed: 11431134]
65. Heineke J, Auger-Messier M, Xu J, Sargent M, York A, et al. Genetic deletion of myostatin from the heart prevents skeletal muscle atrophy in heart failure. *Circulation.* 2010; 121:419–425. [PubMed: 20065166]
66. George I, Bish LT, Kamalakkannan G, Petrilli CM, Oz MC, et al. Myostatin activation in patients with advanced heart failure and after mechanical unloading. *Eur J Heart Fail.* 2010; 12:444–453. [PubMed: 20348550]
67. Yndestad A, Ueland T, Oie E, Florholmen G, Halvorsen B, et al. Elevated levels of activin A in heart failure: potential role in myocardial remodeling. *Circulation.* 2004; 109:1379–1385. [PubMed: 14993131]
68. Ferrari R, Bachetti T, Confortini R, Opasich C, Febo O, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation.* 1995; 92:1479–1486. [PubMed: 7664430]
69. Testa M, Yeh M, Lee P, Fanelli R, Loperfido F, et al. Circulating levels of cytokines and their endogenous modulators in patients with mild to severe congestive heart failure due to coronary artery disease or hypertension. *J Am Coll Cardiol.* 1996; 28:964–971. [PubMed: 8837575]
70. Gielen S, Adams V, Mobius-Winkler S, Linke A, Erbs S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 2003; 42:861–868. [PubMed: 12957433]
71. Mourkioti F, Rosenthal N. NF-kappaB signaling in skeletal muscle: prospects for intervention in muscle diseases. *J Mol Med.* 2008; 86:747–759. [PubMed: 18246321]
72. Janssen SP, Gayan-Ramirez G, Van den Bergh A, Herijgers P, Maes K, et al. Interleukin-6 causes myocardial failure and skeletal muscle atrophy in rats. *Circulation.* 2005; 111:996–1005. [PubMed: 15710765]

73. Adamopoulos S, Coats AJ, Brunotte F, Arnolda L, Meyer T, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J Am Coll Cardiol.* 1993; 21:1101–1106. [PubMed: 8459063]
74. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 1997; 29:1067–1073. [PubMed: 9120161]
75. Hambrecht R, Schulze PC, Gielen S, Linke A, Mobius-Winkler S, et al. Effects of exercise training on insulin-like growth factor-I expression in the skeletal muscle of non-cachectic patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil.* 2005; 12:401–406. [PubMed: 16079650]
76. Williams AD, Carey MF, Selig S, Hayes A, Krum H, et al. Circuit resistance training in chronic heart failure improves skeletal muscle mitochondrial ATP production rate--a randomized controlled trial. *J Card Fail.* 2007; 13:79–85. [PubMed: 17395046]
77. Shahzad K, Chokshi A, Schulze PC. Supplementation of glutamine and omega-3 polyunsaturated fatty acids as a novel therapeutic intervention targeting metabolic dysfunction and exercise intolerance in patients with heart failure. *Curr Clin Pharmacol.* 2011; 6:288–294. [PubMed: 22082326]
78. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, et al. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol.* 2011; 57:870–879. [PubMed: 21215550]
79. Gissi HFI, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008; 372:1223–1230. [PubMed: 18757090]
80. Schulze PC, Fang J, Kassik KA, Gannon J, Cupesi M, et al. Transgenic overexpression of locally acting insulin-like growth factor-I inhibits ubiquitin-mediated muscle atrophy in chronic left-ventricular dysfunction. *Circ Res.* 2005; 97:418–426. [PubMed: 16051886]
81. Nagaya N, Moriya J, Yasumura Y, Uematsu M, Ono F, et al. Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. *Circulation.* 2004; 110:3674–3679. [PubMed: 15569841]
82. Nagaya N, Itoh T, Murakami S, Oya H, Uematsu M, et al. Treatment of cachexia with ghrelin in patients with COPD. *Chest.* 2005; 128:1187–1193. [PubMed: 16162705]
83. Adamopoulos S, Parissis J, Kroupis C, Georgiadis M, Karatzas D, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. *Eur Heart J.* 2001; 22:791–797. [PubMed: 11350112]
84. Hambrecht R, Fiehn E, Niebauer J, Dieterle T, Offner B, et al. Effects of physical exercise on oxidative enzyme activity and fiber type distribution in skeletal muscle of patients with chronic failure. *J Am Coll Cardiol.* 1995; 29:1067–1073. [PubMed: 9120161]
85. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation.* 1998; 98:2709–2715. [PubMed: 9851957]
86. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. A randomised trial. *JAMA.* 2000; 283:3095–3101. [PubMed: 10865304]

Figure 1.

Table 1

Skeletal muscle fiber distribution

	Type I	Type IIa	Type IIx
Contraction Time	Slow	Mod. Fast	Fast
Oxidative Capacity	High	High	Intermediate
Mitochondrial Density	High	High	Medium
Glycolytic Capacity	High	Low	High
Resistance to Fatigue	Fairly High	High	Intermediate
Major storage fuel	Triglycerides	PhosCr, Glycogen	PhosCr, Glycogen
Capillary Density	High	Intermediate	Low