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SKELETAL MUSCLE PROTEIN METABOLISM IN HUMAN HEART FAILURE

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Abstract

Purpose of review—This review considers evidence that the clinical condition of heart failure (HF) alters skeletal muscle protein synthesis and/or breakdown to promote skeletal muscle wasting and functional decrements that ultimately contribute to the symptomology of the disease.

Recent findings—Advanced heart failure is frequently accompanied by muscle atrophy and a cachectic phenotype. Protein metabolic derangements that promote this phenotype are understudied and poorly understood. Instead, most investigations have evaluated regulatory hormones/signaling pathways thought to be reflective of protein synthesis and breakdown. Several of these recent studies have provided exciting data suggesting that the dysfunctional myocardium releases catabolic agents that could promote the skeletal muscle myopathic phenotype either directly or through modulation of other regulatory systems (eg, energy balance).

Summary—While our understanding of skeletal muscle atrophy and dysfunction in heart failure is limited, recent studies have provided clues about the nature and timing of protein metabolic dysfunction. More specifically, skeletal muscle protein metabolic derangements likely evolve during periods of disease-related stress (ie, acute disease exacerbation and hospitalization) and potentially derive in part, from signals promoted in the damaged/dysfunctional myocardium. Despite these compelling studies, there is a surprising lack of data regarding the nature or timing of specific protein metabolic defects in HF.

Keywords

Cachexia; Disuse; Myostatin; Proteolysis; Inflammation

Introduction

Heart failure (HF) is the final common pathway for a range of cardiac diseases. Although cardiac dysfunction is at the root of the disease, the resulting syndrome of HF is characterized by changes in numerous physiological systems that ultimately contribute to its symptomology and progression (1). Exercise intolerance, manifesting as breathlessness and muscle fatigue, is the cardinal symptom of HF. Reduced work capacity, in turn, impairs the ability to perform simple activities of daily living and contributes to a poor quality of life.

Cardiac insufficiency plays a role in these symptoms, but adaptations in the peripheral musculature, such as loss of muscle quantity and functionality, also contribute. Over the last two decades, research examining the skeletal muscle myopathy of HF has focused on potential disease-related “effectors” of these maladaptations (eg, inflammation, muscle disuse, etc). What these studies have overlooked, however, is the fact that adaptations in skeletal muscle size and/or function must result from modifications in skeletal muscle protein metabolism. Thus, any attempt to decipher the inciting factor for HF-induced adaptations in the peripheral musculature should be informed by underlying changes in protein turnover. To this end, our review describes changes in skeletal muscle protein metabolism in HF that may contribute to altered protein content and function, with consideration of classes of proteins important for maintaining the size and functional integrity of skeletal muscle.

Skeletal muscle atrophy and protein metabolism in HF

Conventional wisdom holds that HF patients are frequently characterized by muscle atrophy, although data to support this notion is surprisingly limited. To our knowledge, no longitudinal assessments of skeletal muscle size have been conducted in HF patients, leaving only cross-sectional studies as the basis for this claim. Cross-sectional estimates are biased, however, by the fact that weight loss frequently accompanies the disease (2). As expected, patients experiencing weight loss have significantly reduced muscle mass (3); whereas, in weight-stable HF patients, no difference in muscle mass are found compared to non-diseased controls (3). If substantiated in larger cohorts, this result would suggest that a substantial portion of the muscle atrophy in HF patients occurs secondary to weight loss, rather than to a specific protein metabolic defect. In this scenario, improved nutritional intervention and prevention of weight loss would be the most effective therapy to prevent muscle atrophy. This is not to suggest that other factors do not contribute, but improved nutritional management may be the most effective, and practically feasible, clinical course to stem muscle atrophy.

Few studies have performed direct assessments of skeletal muscle protein metabolism in HF patients. Early studies using arteriovenous (AV) balance techniques showed profound increases in fasting skeletal muscle protein breakdown (myofibrillar protein in particular) in HF patients tested following inpatient clinical management (4). Whether increased proteolysis is due to the disease process per se, or other factors associated with hospitalization (eg, malnutrition, bedrest, etc), is uncertain. In contrast, similar studies in clinically-stable patients (ie, chronic HF) utilizing stable isotopes in combination with AV balance or muscle biopsies have shown no effect of the disease on fasting muscle protein synthesis or breakdown (5–7). Recent work assessing AV differences of amino acids in HF patients referred for transplantation showed increased proteolysis in those with BMIs below 25 kg/m²; whereas, proteolysis was lessened in more overweight/obese patients (8). The authors argue that these results are explained by a protective effect of adiposity on protein metabolism, although this conclusion is complicated by differences in disease severity between groups. Indeed, the same authors have failed to show enhanced fasting proteolysis in non-obese HF patients with less severe disease, although they showed enhanced proteolysis during exercise (9). Our laboratory did not find enhanced proteolysis in stable

HF patients following a brief fast (~30 hrs), but we observed an impairment in insulin-induced suppression of skeletal muscle proteolysis under euglycemic-hyperinsulinemic-hyperaminoacidemic conditions (6). One final study found impaired muscle protein synthesis response to oral feeding (10), although our studies have not identified any impairment in protein synthesis under fasting (7) or simulated feeding conditions (6).

These findings appear equivocal, but some trends emerge. Enhanced proteolysis is the most consistent finding, whereas there is limited evidence for reduced protein synthesis. Importantly, increased proteolysis in HF only presents during periods of metabolic/disease-related stress (eg, hospitalization (4), end-stage disease (8), exercise (9), malnutritional (6)). Accordingly, the timing of protein metabolism measurements relative to disease stage (eg, acute disease exacerbation (acute HF) or stable, chronic HF) and metabolic stressors is essential to uncovering defects in protein metabolism that could predispose to muscle atrophy.

Skeletal muscle dysfunction and protein metabolism in HF

In addition to gross muscle atrophy, alterations in anatomical or functional domains of muscle occur with HF. Changes in the quantity or functional integrity (eg, oxidative modification; (11)) of specific proteins, or groups of proteins, could develop or be favored because of modifications in their synthesis or breakdown rates. In turn, these changes could lead to reduced muscle contractile function (12) or endurance (13) that contribute to exercise intolerance, the cardinal symptom of the disease.

The two protein classes most relevant to muscle function are the myofilament and mitochondrial proteins. Both classes have been shown to undergo quantitative and functional changes with HF. Regarding myofilament proteins, animal and clinical studies suggest the loss of the most abundant contractile protein myosin (7, 14, 15), which contributes to diminished muscle function (7, 14, 15). Regarding mitochondrial proteins, studies have shown reduced mitochondrial content (16) and function (17) in HF patients, either of which could increase susceptibility to fatigue (13). Of note, recent studies have suggested that reduced mitochondrial density (18) and dysfunction (19) in HF may be related to muscle disuse that accompanies the disease, rather than a unique feature of the disease process (for review see (20)).

Little is known about how HF affects the metabolism of specific proteins or classes of proteins to bring about these phenotypes. Our laboratory has found no reduction in the fractional synthesis rate of myosin heavy chain in HF patients (MHC; (7)) and no evidence for increased myosin proteolysis (14). In contrast, rat models of HF have shown that myosin loss is prevented by pharmacological inhibition of muscle proteolysis (21). Because HF in animal models is untreated and more severe than the well-managed, clinically-stable patients in our studies, differences in findings may relate to the severity of disease/timing of measurements. That is, increased myosin proteolysis may occur in human patients during acute periods of disease exacerbation, where the severity of disease is more comparable to pre-clinical models. Taken together with our observations above, these findings further

reinforce that the timing of measurements (ie, during/close to periods of disease exacerbation) is essential to identifying the skeletal muscle protein metabolic derangements.

“Effectors” of protein metabolic changes in HF

In contrast to the paucity of studies directly measuring protein metabolism, the majority of work in this field has evaluated “effectors” of changes in protein metabolism and have implicitly or explicitly assumed that they are proxies of protein synthesis or breakdown. However, caution is urged when drawing conclusions from alterations in such proxy measures of protein metabolism, as they do not always correspond with assumed protein metabolic alterations (23–27). Nonetheless, these studies are valuable in further refining our search for the nature and temporal context of skeletal muscle protein metabolic alterations in HF (22).

The bulk of work in this field has been directed towards the role of cytokines and has led to the widely-held notion that increased circulating or locally-produced cytokines contribute to skeletal muscle atrophy and dysfunction (eg, (28)). Although this conclusion is supported by cross-sectional studies and pre-clinical models (29), strong evidence of a link between inflammatory pathways and altered protein metabolism in HF is lacking. In fact, recent studies in healthy humans have found minimal skeletal muscle protein catabolic effects of key cytokines (30, 31). Cytokines may contribute indirectly to the skeletal muscle myopathy by inducing anabolic resistance (eg, to growth hormone (32) and/or insulin (6)), however, the notion that cytokines directly promote protein metabolic defects that cause skeletal muscle protein loss/dysfunction remains to be unambiguously demonstrated (for review, see van Hall, 2012 (33)).

In addition to increased inflammation, heightened neurohormonal activation in HF, manifested as increased circulating norepinephrine and epinephrine and angiotensin II (AII), may alter protein metabolism. In animal models, AII promotes muscle atrophy through increased proteolysis and decreased circulating and skeletal muscle insulin like growth factor 1 (IGF-1) (34). In addition, AII has been implicated in malnutrition through its central anorexigenic effects (35). In this context, AII may be an effector of weight loss-induced skeletal muscle atrophy described above. A role for AII in well-managed patients seems unlikely, however, since its effects are likely blocked via angiotensin converting enzyme (ACE) inhibitors/receptor blockers, the cornerstone therapy for HF.

Myostatin, a critical regulator of skeletal muscle size (36), is increased in the circulation in animal models and human HF (37–39). Recent studies using mouse genetic models suggest a role for cardiac-derived myostatin in skeletal muscle atrophy in HF (37), pointing to the dysfunctional heart as a source of catabolic stimuli to the skeletal muscle. Importantly, cardiac expression of myostatin has been verified in human patients (38) and further evidence shows that aerobic exercise training, which promotes a host of positive structural and functional adaptations in skeletal muscle, reduces cardiac and/or skeletal myostatin expression in animal models of HF (40) and humans (41). Taken together, these findings suggest myocardial- and/or skeletal muscle-derived myostatin as an exciting new candidate for promoting muscle atrophy and dysfunction in HF. Of note, although many details of its

effect on protein signaling have been identified (42–44), the exact protein metabolic alteration responsible for muscle loss in response to myostatin remains unclear (45).

Intriguing new data indicate a role for myocardial-derived micro RNA miR-208a in body mass regulation in animal models of HF. miR-208a is encoded within an intron of the α cardiac myosin gene and has been shown to cause pathological myocardial hypertrophy when over-expressed in mice (46, 47). More recent studies suggest that miR-208a also regulates systemic energy metabolism, with elevated expression being linked to diet-induced obesity and insulin resistance (48). Despite a relatively lesser expression of α cardiac myosin in humans, miR-208a has been detected in the plasma within hours of myocardial infarction, but was undetectable in controls with no history of myocardial infarction (49). miR-208a's dual role in maladaptive myocardial hypertrophy and systemic metabolic dysfunction mirrors the aforementioned myostatin, by which the diseased myocardium could affect peripheral metabolism generally, and skeletal muscle protein metabolism specifically (eg, via insulin resistance; (6)).

Model for skeletal muscle protein metabolic changes in HF

Figure 1 outlines a hypothetical model to explain the protein metabolic adaptations to HF and the resulting muscle atrophy/dysfunction. In stable, well-managed, chronic HF patients, changes in muscle size and function over time are comparable to those observed in non-diseased controls attributable to normal aging (ie, slow, steady decline). These declines become accelerated dramatically, however, during periods of acute disease exacerbation and hospitalization. The basis for this assertion is that protein metabolic defects are primarily observed during periods of acute disease or metabolic stress, with the most pronounced defects being reported immediately following hospitalization (4). Accelerated protein catabolism during acute HF, owing to increased proteolysis and/or reduced protein synthesis (inset figure in grey), would be promoted by the more protein catabolic hormonal milieu present with greater disease severity (eg, increased neurohumoral activation (50), inflammation (51), release of myocardial catabolic factors (39)). Muscle disuse (ie, bedrest) and malnutrition associated with hospitalization (52) would further compound these protein catabolic stimuli (51, 53). Following remediation of acute HF, protein balance would be regained with the return of circulatory and metabolic homeostasis. Data outlined above, showing reduced muscle size and function in HF patients when compared with age-matched controls, suggests anabolic pathways are likely insufficient to return muscle size and function to pre-hospitalization levels, but the extent of correction of this phenotype is unclear (two trajectories shown with open squares). If this model is proven correct, future research should focus on point-of-care interventions to stem the decline in skeletal muscle mass and function during acute disease exacerbation.

Conclusion

Much remains to be discovered about protein metabolism and the atrophic phenotype that characterizes acute and chronic human HF. Longitudinal studies of patients undergoing lean tissue loss are understandably difficult to perform, but are necessary to answer lingering questions about the nature and extent of protein metabolic dysregulation in HF. Available

evidence implicates elevated proteolysis as a mediator of changes in muscle size and functionality and that this disturbance presents primarily during periods of environmental and/or disease-related stress (eg, acute disease exacerbation and hospitalization), although it should be acknowledged that measurements of protein synthesis are sparse. A range of effectors likely contribute to these alterations in protein metabolism, including neurohumoral factors, malnutrition and physical inactivity, with recent studies highlighting a new class of cardiac-derived catabolic stimuli that may be relevant. However, until studies define the exact protein metabolic defect and its timing (eg, acute vs. chronic), identification of the proximal effectors, and therapeutic interventions to counteract their effects, will be hampered.

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Key Points

- Longitudinal studies demonstrating altered protein metabolism explaining HF related cachexia have not been performed.
- Several interesting studies provide data suggesting the diseased myocardium might centrally mediate peripheral atrophy through myostatin and/or microRNA expression in HF.
- Available data suggest an excess muscle protein catabolism in HF patients, although diminished protein homeostasis may contribute to skeletal muscle protein metabolic dysfunction.

Figure 1.

Model for loss of skeletal muscle mass with heart failure. Our theoretical framework suggests a progressive loss in lean tissue mass in stable heart failure patients that is consistent with aging. However, this loss of skeletal muscle is greatly exaggerated during periods of disease exacerbation (grey rectangles) and results from a combination of increases in proteolysis and decreased synthesis. Current evidence suggests proteolytic process have the greatest impacts in these periods of disease progression. The time course of presumed resumption of age-appropriate atrophy processes, or partial recovery following acute decompensation is currently unknown, as indicated by “?”.