

Heart and muscle, cut from the same striated cloth

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Abstract

In patients with heart failure, skeletal muscle appears to be almost as important as the myocardium in maintaining physical functioning and well-being. Skeletal muscle wasting is present in almost 20% of ambulatory patients with chronic heart failure. Its presence is associated with reduced exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed. Bicycle ergometer training is very effective at reducing the intramuscular imbalance between anabolic and catabolic mediators. It is currently not known if systemic treatments can be used effectively to reduce this imbalance at a whole-body level, but the evidence from smaller trials suggests beneficial effects of essential amino acid supplementation, recombinant human growth hormone, synthetic ghrelin, and intramuscular injection of testosterone. ■ *Heart Metab.* 2014;64:4–7

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Muscle is key to motion. Skeletal muscle mass is directly related to peak oxygen consumption in treadmill-exercise testing and thus determines not only exercise capacity, but essentially also quality of life. Many patients with chronic heart failure (HF) are limited in their capability to exercise, and common clinical belief holds that cardiac function is the only important determinant in this regard. However, skeletal muscle appears to be almost as important as the myocardium in maintaining physical functioning and well-being in these patients. Indeed, exercise capacity is directly related to left ventricular ejection fraction, mitral regurgitation, and peak cardiac index.^{1,2} On the other hand, many other factors likely influence exercise capacity in the course of heart failure: the degree of endothelial dysfunction, hemoglobin

level, iron deficiency, the presence of sleep-disordered breathing, or the presence of comorbidities, just to name a few. One factor that has been largely neglected in the past decades is the status of the skeletal muscle. Over the last several years, HF research has started to focus on skeletal muscle, whose mass and function are indeed “in dire straits” as HF progresses.³

In order to understand the importance of skeletal muscle in patients with HF, it is important to acknowledge that this tissue undergoes permanent changes. The predominant pathway of muscle degradation is represented by the proteasome, a multisubunit protease found in all eukaryotic cell types that specifically degrades proteins marked by ubiquitin. It is not entirely clear what the mechanisms are that regulate the activity of the ubiquitin-proteasome pathway, but

Abbreviations

DEXA: dual energy x-ray absorptiometry; **HF:** heart failure

proinflammatory cytokines such as tumor necrosis factor, interleukin 1 β , and interleukin 6 all stimulate its activity.^{3,4} Anabolic factors like growth hormones that regulate liver insulin-like growth factor 1 expression attenuate the activity of the ubiquitin ligases. Therefore, it is not surprising that both a downregulation of the expression of anabolic players and an upregulation of catabolic players is found in HF patients presenting with reduced muscle mass and/or function (Figure 1).

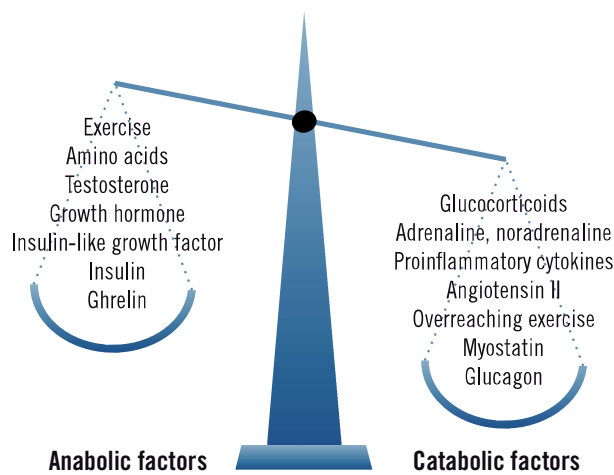


Fig. 1 Imbalance between anabolic and catabolic factors in patients with heart failure.

Muscle wasting, sarcopenia, cachexia, frailty—all the same?

Four main outcomes are clinically meaningful when skeletal muscle is lost: (i) anorexia; (ii) dehydration; (iii) sarcopenia; and (iv) cachexia.^{5,6} Cachexia is defined as an involuntary weight loss of >5% of body weight in the

presence of a chronic disease such as HF.⁷ Another possible presentation is the development of sarcopenia, which is present in “a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group.”^{8,9} Even though this definition may be useful in answering research questions, it is rather cumbersome in daily clinical practice.⁹ Thus, it is not surprising that a diagnosis of sarcopenia remains rare in daily clinical practice, and the fact that some workers have argued that the term sarcopenia should be restricted to “healthy aging” does not make matters easier.¹⁰ More recently, the term “muscle wasting disease” has been proposed¹¹ to cover all aspects of muscle wasting in patients with chronic diseases as opposed to sarcopenia that should be diagnosed in healthy elderly subjects only. Table 1 provides an overview of some of the terms that are used in this context.

Just like with sarcopenia and/or muscle wasting disease, a diagnosis of cachexia remains rare in daily clinical practice. Apart from the difficulties in reaching a correct diagnosis, another important reason to be considered is the lack of effective treatments that are able to directly counter losing weight. Even more important is the fact that in contrast to cachexia, where the diagnosis requires not much more than a pair of scales, the correct diagnosis of muscle wasting can only be reached using sophisticated technology because patients with muscle wasting do not necessarily lose weight. Indeed, skeletal muscle can be replaced by adipose tissue or other nonfunctional tissue, and a pronounced denervation of type II fibers with the recruitment of type I fibers into surviving motor units also occurs.¹² Therefore, the diagnostic gold standard is computed tomography or magnetic

Term	Description	Reference
Cachexia	Weight loss of at least 5% of body weight within 12 months or less in the presence of chronic illness	Evans et al, ⁷ 2008
Frailty	Increased vulnerability for developing increased dependency and death due to diminished strength, endurance, and reduced physiologic function	Morley et al, ⁸ 2011
Muscle wasting disease	Muscle wasting that fulfills the criteria of sarcopenia, associated with or without frailty and/or cachexia	Anker et al, ¹¹ 2014
Sarcopenia	Appendicular muscle mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons	Morley et al, ⁸ 2011

Table 1 Useful terms.

resonance imaging, as only these techniques are able to directly assess skeletal muscle mass. Researchers have largely relied on the less costly dual energy x-ray absorptiometry (DEXA) scanning that assesses fat-free mass as a proxy of skeletal muscle mass.¹³

Sarcopenia and muscle wasting in heart failure

The loss of skeletal muscle mass appears almost automatically during the normal aging process. On average, it is estimated that 5% to 13% of elderly people between the ages of 60 and 70 are affected by sarcopenia. These numbers appear independent of any chronic disease, and they increase to between 11% and 50% for those aged 80 years or over.^{2,14} Other sources have estimated that 8% to 40% of elderly people above the age of 60 years are sarcopenic.¹⁵ Sarcopenia may lead to frailty, but not all patients with sarcopenia are frail.¹⁶

An imbalance between anabolic and catabolic mediators in HF has already been reported 20 years ago. Since the term sarcopenia should only be restricted to healthy elderly subjects, we prefer the descriptive term of muscle wasting. Muscle wasting that fulfills the criteria of sarcopenia as described above has been reported in 19.5% of ambulatory patients with chronic HF.¹⁷ This number is considerably higher than expected for healthy subjects of the same age group whose mean age was 67 years. HF patients with muscle wasting had significantly lower values for handgrip and quadricep strength as well as lower total peak oxygen consumption ($P<0.001$), lower exercise time ($P<0.001$), and lower left ventricular ejection fraction ($P<0.05$) than patients without muscle wasting. The distance walked during a 6-minute corridor-walk test and the gait speed during the 4-minute walk were lower in patients with muscle wasting (both $P<0.05$).⁸ Interleukin 6 was significantly elevated in the serum of patients with HF and muscle wasting. Among those factors predicting lower peak oxygen consumption during a treadmill exercise test, muscle wasting remained independently predictive after adjusting for age, sex, New York Heart Association class, hemoglobin, left ventricular ejection fraction, distance walked in 6 minutes, and the number of comorbidities (odds ratio, 6.53; $P<0.01$).⁸ Thus, muscle wasting can be viewed as a new comorbidity of HF that may be worth tackling in order to maintain exercise capacity and quality of life.

How to maintain muscle mass in heart failure?

Maintenance of skeletal muscle mass appears to be an interesting target in order to maintain HF patients' exercise capacity. From a pathophysiological standpoint, several anabolic or anticatabolic mechanisms have been suggested. Apart from that, skeletal muscle protein metabolism is modified by food intake.¹⁸ Smaller clinical trials in HF have seen the beneficial use of nutritional supplementation with essential amino acids,¹⁹ recombinant human growth hormone,²⁰ administration of synthetic ghrelin,²¹ or intramuscular application of testosterone in both men and women.²² Indeed, testosterone deficiency is directly related to reduced peak oxygen consumption during treadmill exercise testing in patients with HF.²³ Even electrical muscle stimulation has been used effectively to improve HF patients' exercise capacity.²⁴ Anticatabolic therapies have been less effective. However, the main problem with these trials is their small enrollment numbers, and therefore, the lack of reliable safety data.

The only current clinically effective treatment for muscle wasting in patients with HF is exercise training.²⁵ Smaller randomized trials have shown the effectiveness of progressive resistance exercise training or bicycle ergometer training, and both European²⁶ and North American²⁷ guidelines advocate exercise training in this regard. In ambulatory patients with HF, bicycle ergometer training has been shown to reduce the imbalance of intramuscular expression of anabolic and catabolic players, particularly of those that stimulate the ubiquitin-proteasome system. These effects were already observed after 4 weeks of training, even though this did not yet translate into an increase in the cross-sectional area of the quadricep muscle measured using computed tomography or into an increase in the maximal isometric force.

Conclusions

Irrespective of whether it is named sarcopenia, muscle wasting, or muscle wasting disorder, skeletal muscle wasting is present in almost 20% of outpatients with chronic HF. Its presence is associated with reduced exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed. The prevalence of this perturbation is higher than expected for this age group, and it appears that the treatment or the prophylaxis of muscle

wasting is important to maintain the physical well-being of HF patients. Bicycle ergometer training is very effective at reducing the intramuscular imbalance between anabolic and catabolic mediators. It is currently not known if systemic treatments can be used effectively to reduce this imbalance at a whole-body level, but the evidence from smaller trials suggests beneficial effects of essential amino acids, recombinant human growth hormone, synthetic ghrelin, and intramuscular injection of testosterone. Currently, reaching a correct diagnosis of muscle wasting remains difficult because sophisticated technologies such as computed tomography, magnetic resonance imaging, or DEXA are required, but it is expected that blood biomarkers will become available that may help to identify those patients who require further testing. For the time being, physicians need to stay alert and watch out for signs in their HF patients that suggest reduced muscle mass and muscle strength. These include limitations in exercise capacity such as climbing stairs or even rising from a chair. Exercise training may be effective in these patients. ■

REFERENCES

- Trivi M, Thierer J, Kuschnir P, et al. Echocardiographic predictors of exercise capacity in patients with heart failure and systolic dysfunction: role of mitral regurgitation. *Rev Esp Cardiol*. 2011;64:1096-1099.
- Hummel YM, Bugatti S, Damman K, et al. Functional and hemodynamic cardiac determinants of exercise capacity in patients with systolic heart failure. *Am J Cardiol*. 2012;110:1336-1341.
- von Haehling S. The muscle in dire straits: mechanisms of wasting in heart failure. *Circulation*. 2012;125:2686-2688.
- von Haehling S, Genth-Zotz S, Anker SD, Volk HD. Cachexia: a therapeutic approach beyond cytokine antagonism. *Int J Cardiol*. 2002;85:173-183.
- Morley JE. Sarcopenia: diagnosis and treatment. *J Nutr Health Aging*. 2008;12:452-456.
- von Haehling S, Morley JE, Anker SD. From muscle wasting to sarcopenia and myopenia: update 2012. *J Cachexia Sarcopenia Muscle*. 2012;3:213-217.
- Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr*. 2008;27:793-799.
- Morley JE, Abbatecola AM, Argiles JM, et al; Society on Sarcopenia, Cachexia and Wasting Disorders Trialist Workshop. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc*. 2011;12:403-409.
- von Haehling S, Steinbeck L, Doehner W, Springer J, Anker SD. Muscle wasting in heart failure: An overview. *Int J Biochem Cell Biol*. 2013;45:2257-2265.
- Fearon K, Evans WJ, Anker SD. Myopenia—a new universal term for muscle wasting. *J Cachexia Sarcopenia Muscle*. 2011;2:1-3.
- Anker SD, Coats AJ, Morley JE, et al. Muscle wasting disease: a proposal for a new disease classification. *J Cachexia Sarcopenia Muscle*. 2014;5:1-3.
- Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. *Osteoporos Int*. 2010;21:543-559.
- Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. *Am J Clin Nutr*. 1990;51:1106-1112.
- Morley JE, Kim MJ, Haren MT, Kevorkian R, Banks WA. Frailty and the aging male. *Aging Male*. 2005;8:135-140.
- Abellan van Kan G. Epidemiology and consequences of sarcopenia. *J Nutr Health Aging*. 2009;13:708-712.
- Morley JE, von Haehling S, Anker SD, Vellas B. From sarcopenia to frailty: a road less traveled. *J Cachexia Sarcopenia Muscle*. 2014;5:5-8.
- Fülster S, Tacke M, Sandek A, et al. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J*. 2013;34:512-519.
- Dardevet D, Rémond D, Peyron MA, Papet I, Savary-Auzeloux I, Mosoni L. Muscle wasting and resistance of muscle anabolism: the 'anabolic threshold concept' for adapted nutritional strategies during sarcopenia. *The Scientific Medical Journal*. 2012;2012:269531.
- Aquilani R, Opasich C, Gualco A, et al. Adequate energy-protein intake is not enough to improve nutritional and metabolic status in muscle-depleted patients with chronic heart failure. *Eur J Heart Fail*. 2008;10:1127-1135.
- Osterziel KJ, Strohm O, Schuler J, et al. Randomised, double-blind, placebo controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy. *Lancet*. 1998;351:1233-1237.
- Nagaya N, Moriya J, Yasumura Y, 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.
- Iellamo F, Volterrani M, Caminiti G, et al. Testosterone therapy in women with chronic heart failure: a pilot double-blind, randomized, placebo-controlled study. *J Am Coll Cardiol*. 2010;56:1310-1316.
- Jankowska EA, Filippatos G, Ponikowska B, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. *J Card Fail*. 2009;15:442-450.
- Banerjee P, Caulfield B, Crowe L, Clark AL. Prolonged electrical muscle stimulation exercise improves strength, peak VO₂, and exercise capacity in patients with stable chronic heart failure. *J Card Fail*. 2009;15:319-326.
- Lenk K, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle*. 2010;1:9-21.
- Dickstein K, Cohen-Solal A, Filippatos G, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388-2442.
- Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:e154-e235.