The Muscle in Dire Straits: Mechanisms of Wasting in Heart Failure

**Running title:** von Haehling, Mechanisms of wasting in heart failure

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It has been established for centuries that body wasting and changes in body composition play important roles in patients with chronic diseases. This is also true for patients with heart failure (HF). For clinicians not actively involved in this area of research, however, it may be difficult to decipher the complex and sometimes confusing terminology used in this context. Cachexia, body wasting, anorexia, sarcopenia, malnutrition, or even the recent addition myopenia – do they essentially all mean the same? Is loss of fat mass commonly propagated for healthy people or patients with cardiovascular disease also beneficial once HF is present? Or is it at least preferable to muscle loss? No physician would seriously suggest to a patient with malignant cancer to start losing weight as this is generally thought of as a signum mali ominis. Just the same may be true for HF. Current guidelines for coronary artery disease, however, do not distinguish between those who do and those who do not suffer from concomitant HF, and, hence, all these patients are lumped together and provided with guidance that is everything but evidence-based.

In order to more fully understand the changes in body composition that take place over the course of HF, it is necessary to differentiate changes with versus those without weight loss. Both may be detrimental and associated with decreased exercise capacity, quality of life, or even increased mortality. Further differentiation is needed with regards to voluntary versus involuntary weight loss, and all changes in body weight that are deemed clinically relevant need to be measured in an edema-free state. According to a recent consensus definition, the term "cachexia" describes involuntary weight loss in patients with chronic disease; the key component of the diagnostic criteria is weight loss that exceeds 5% within 12 months or less. In patients with HF, such weight loss may be the result of reduction in fat or muscle mass, however, counterintuitively the muscle compartment may be predominantly affected.

The last two decades have seen extensive research into the field of muscle function and
muscle mass. Both can be affected by chronic diseases but also by the process of aging itself. The term "sarcopenia", from Greek *sarx* (flesh) and *penia* (loss), literally meaning poverty of flesh, was originally suggested in 1988 by Rosenberg to describe muscle changes that occur during “healthy aging”. Whilst aging muscle mass decreases at an annual rate of 1–2%, muscle strength declines by 1.5% per year between ages 50 and 60 and by as much as 3% thereafter. In contrast to cachexia, reaching a diagnosis of sarcopenia requires much more than a pair of scales. The reason is that sarcopenia is not usually associated with weight loss when muscle bulk is replaced by the deposition of lipids. The affair is further complicated by the fact that a heated debate exists whether or not the term “sarcopenia” should be restricted to healthy aging, whereas loss of functional muscle mass in chronic disease should be named otherwise. This somewhat academic discussion should not divert clinicians’ attention from what is truly important: to improve our patients’ capability to fulfill their activities of daily living. Even rising from a chair may become difficult once muscle mass is reduced.

It is well acknowledged that exercise training is currently one of the few interventions that can help counter sarcopenia in the elderly. For patients with clinically stable HF, such training is being advocated by European and North American guidelines. In this issue of Circulation, Gielen et al. present intriguing data on the role of endurance training and muscle pathophysiology in patients with HF from the Leipzig Exercise Intervention in Chronic HF and Aging (LEICA) study. In this randomized, controlled, open label efficacy study, 60 patients with clinical signs of HF and a left ventricular ejection fraction <40% were assigned to either a training group that exercised 4 supervised 20-minute training sessions per weekday on a bicycle ergometer or to an inactive control group on usual medical care. The effort behind this study is outstanding. A biopsy from vastus lateralis muscle was obtained before and after the
intervention. In addition, the authors investigated control groups of similar age. Patients and controls were stratified according to age strata $\leq 55$ versus $\geq 65$ years. At baseline, mRNA muscle tissue levels of muscle ring finger 1 (MuRF-1) and insulin-like growth factor 1 (IGF-1) were significantly lower in the two groups of patients with chronic HF than in the control groups. In contrast, mRNA expression in muscle and serum values of tumor necrosis factor-$\alpha$ were significantly elevated in patients with HF.

In order to appreciate these results, it is important to understand the roles of several key mediators of muscle protein turnover. The adenosine triphosphate-dependent ubiquitin-proteasome pathway is the most important player in this regard$^{12}$. The proteasome is a multisubunit protease found in all eukaryotic cell types that specifically degrades proteins marked by ubiquitin. The process of ubiquitin-labelling – ubiquitinylation – requires activity of three different enzymes, termed E1, E2, and E3. Two E3 ubiquitin ligases, the above mentioned MuRF-1 and muscle atrophy F-box (MAFbx) were among the primary focus of the study by Gielen et al. The mechanisms that regulate the activity of this pathway are not entirely understood, but pro-inflammatory cytokines like tumor necrosis factor $\alpha$, interleukin 1 and interleukin 6 all stimulate its activity. One of the anabolic mediators that attenuate the activity of the ubiquitin ligases is growth hormone that regulates liver IGF-1 expression with downstream anabolic effects in skeletal muscle.

The LEICA study provides interesting insight into the mechanisms of muscle protein turnover in HF; MuRF-1 and local IGF-1 play significant roles in this regard. On the other hand it is questionable that permanent over-activity of the ubiquitin-proteasome system is present, and future studies need to elucidate whether episodic increases in the activity of the system take place, for example during clinical deterioration. Another important finding of the LEICA is that
only 4 weeks of endurance exercise can help to improve the imbalance between anabolic and catabolic mechanisms. Unfortunately, this effect failed to translate into an increase in the cross-sectional area as measured by computed tomography or into increases in the maximal isometric force of the quadriceps muscle. A significantly longer follow-up would be required to raise realistic hopes for improvements in these parameters. Still, exercise capacity as assessed by spiroergometry was improved in all HF patients randomized to exercise training, and it appears that these findings can partly be explained by increases in left ventricular ejection fraction.

One of the reasons for the impressive results of the LEICA study is most probably the rather short duration of the therapeutic intervention – only 4 weeks. Unfortunately, clinical experience shows that patients’ therapeutic enthusiasm usually declines with the duration of therapy, particularly when much more than taking a daily tablet is involved. Although the authors enrolled a “real-world” cohort of patients with HF – about 30% of patients undergoing biopsies were even receiving oral anticoagulants – we do not know whether patients with muscle loss that meets the criteria of sarcopenia are more likely than those without to benefit from an exercise intervention. The authors acknowledge that they did not aim to recruit a representative sample of all patients with HF. This may partly explain why no patient with HF and no elderly control subject met the criteria of sarcopenia. Another explanation might be that the group of young control subjects was still too old for reaching the correct diagnosis – the mean age of the two control groups was 46 and 47 years, respectively. This consideration is important, because a sarcopenia consensus conference recently suggested to diagnose this perturbation in a person whose “lean appendicular mass corrected for height squared is 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group”13. In addition, computed tomography scans provide only a small window to a patient’s muscle
mass, and techniques such as dual energy X-ray absorptiometry (DEXA) or bioimpedance may provide a more thorough view of a patient’s overall muscle mass.

The authors of the LEICA study state that their data do not support their initial hypothesis of a “sarcopenia-cachexia overlap” being present in HF. “Sarcopenia” implies the loss of functioning muscle fibres, “cachexia” implies that weight loss is present. Preliminary data obtained using DEXA scanning from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF)\textsuperscript{14} have recently shown that approximately 18\% of patients with chronic HF show muscle loss that fulfils the criteria of sarcopenia\textsuperscript{15}. These data need to be confirmed in larger cohorts, and it also needs to be clearly demonstrated whether these patients are likely to benefit from exercise interventions. One the other hand, the results from the LEICA study also raise hopes that MuRF-1 may be a therapeutic target in the future. As always: more – and larger – studies are needed. What the English author Samuel Johnson said as early as 1709 is very true for muscle research today: “Great works are performed not by strength, but by perseverance”\textsuperscript{16}.

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