



Conference on ‘Nutrition and age-related muscle loss, sarcopenia and cachexia’ Symposium 2: Mechanisms for loss of muscle mass, strength and clinical measurement of malnutrition and cachexia

The wasting continuum in heart failure: from sarcopenia to cachexia

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Sarcopenia (muscle wasting) and cachexia share some pathophysiological aspects. Sarcopenia affects approximately 20 %, cachexia <10 % of ambulatory patients with heart failure (HF). Whilst sarcopenia means loss of skeletal muscle mass and strength that predominantly affects postural rather than non-postural muscles, cachexia means loss of muscle and fat tissue that leads to weight loss. The wasting continuum in HF implies that skeletal muscle is lost earlier than fat tissue and may lead from sarcopenia to cachexia. Both tissues require conservation, and therapies that stop the wasting process have tremendous therapeutic appeal. The present paper reviews the pathophysiology of muscle and fat wasting in HF and discusses potential treatments, including exercise training, appetite stimulants, essential amino acids, growth hormone, testosterone, electrical muscle stimulation, ghrelin and its analogues, ghrelin receptor agonists and myostatin antibodies.

Sarcopenia: Cachexia: Muscle: Fat tissue: Heart failure: Wasting

A large number of answers are possible for a patient who complains about difficulty in rising from a chair⁽¹⁾. Indeed, a decrease in skeletal muscle mass starts after age 40 years, and this decrease is usually more pronounced in the lower than the upper limbs⁽²⁾. The differential diagnosis therefore depends largely on the patient's age, because with advancing age, the likelihood of sarcopenia increases progressively⁽³⁾. The term sarcopenia, literally meaning ‘poverty of flesh’, was coined in 1989⁽⁴⁾. Since then, interest in the field was predominantly spearheaded by geriatricians whose patients are by far most frequently affected. Cardiologists became interested in the field of tissue wasting with the publication of the original prognostic paper on cardiac cachexia, which was published in 1997 by Anker *et al.*⁽⁵⁾, even though the term had appeared in the literature for much longer⁽⁶⁾. It is important to understand that sarcopenia and cachexia are, although overlapping, still different clinical entities. Whilst sarcopenia affects only skeletal muscle and, by definition, appears only without chronic disease

being present as a phenomenon of ‘healthy ageing’^(7,8), cachexia can, by definition, only become apparent in the context of chronic illness (Table 1). Sarcopenia means loss of functioning skeletal muscle through denervation, replacement by adipose tissue or other mechanisms; the original definition implied ‘involuntary loss of skeletal muscle mass and consequently of strength’⁽⁹⁾, which is logical, because sarcopenia predominantly affects postural rather than non-postural muscles⁽¹⁰⁾. It has been argued that the assessment of muscle strength may be more suitable in men using hand grip strength assessment, whilst in women knee extension strength could be more appropriate⁽¹¹⁾. In comparison, cachexia means loss of any tissue that leads to involuntary weight loss. To phrase it very simply: cachexia can easily be diagnosed using only weighing scales; a diagnosis of sarcopenia requires more sophisticated technology⁽¹⁴⁾. This is particularly true even though a number of screening tools have been developed^(12,13); however these have not become routine clinical practice yet.

Abbreviation: HF, heart failure.

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Table 1. Definitions and prevalence of sarcopenia and cachexia in heart failure

| | Estimated prevalence among ambulatory heart failure patients (%) | Definition | Reference |
|---------------------------|--|--|-----------|
| Sarcopenia/muscle wasting | 20 | Lean appendicular mass corrected for height squared of 2 sd or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group AND reduced walking speed ≤ 1 m/s or walking distance < 400 m on the 6-min walk test | 122 |
| Cachexia | 10 | Weight loss of at least 5 % of body weight in 12 months or less in the presence of chronic illness and in the presence of three of five of the following criteria: (i) decreased muscle strength, (ii) fatigue, (iii) anorexia, (iv) low fat-free mass index and (v) abnormal biochemistry | 123 |

Sarcopenia is a phenomenon associated with the ageing process but chronic disease may still exacerbate this process⁽¹⁵⁾. The ageing process *per se* is associated with loss of skeletal muscle of approximately 1–2 % per year^(16,17). Sarcopenia affects 5–13 % of the subjects aged 60–70 years and up to 50 % of all octogenarians^(3,7,18). To avoid misinterpretation, I prefer the term muscle wasting over sarcopenia, when chronic disease is present, even though this point is a matter of on-going debate^(15,19). Recent data from the studies investigating co-morbidities aggravating heart failure have shown that 19.5 % of all ambulatory patients with heart failure (HF) are affected by muscle wasting⁽²⁰⁾. The prevalence of cachexia is lower, and usually patients lose muscle first, adipose tissue only later, and this is when weight loss becomes apparent^(21,22). In patients with HF, muscle wasting remains an independent predictor of reduced exercise capacity as assessed using spiroergometry, even after adjusting for a large number of clinically relevant parameters⁽²⁰⁾.

No therapy has been approved or is being advocated for the treatment of muscle wasting other than exercise training⁽²³⁾. This is not only true for HF, but also for advanced cancer. Similarly, no treatment is available for cachexia, even though a large number of drugs have been tested in clinical trials and the presence of cachexia has tremendous impact on patients' everyday lives^(24,25). Most studies, however, were undertaken in patients with cancer, in whom cachexia is most prominent⁽²⁶⁾. Only few studies were done in patients with HF even though exercise capacity has been improved by several means. A thorough understanding of molecular pathways involved in the process of muscle wasting is crucial to identify targets for therapeutic interventions^(27,28). Cachexia therapies, on the other hand, are aimed primarily at increasing body weight and thus at increasing muscle and fat tissue. Since any β -blocker can increase fat mass, this target appears easier to be reached than an increase in muscle mass, but this is true only at first sight. One of the reasons for the difficulties in increasing fat mass is, for example, the lack of appetite, i.e. anorexia that usually accompanies cachexia in many patients. Anorexia hampers the provision of the necessary energy required to increase or at least stabilise body weight. To make it again very simple: muscle means motion and therefore quality of life, fat is used

only later for energy maintenance and this also means that loss of fat is associated with reduced survival. The distinction 'muscle equals motion and fat equals survival' has a lot of appeal for being catchy; however, it may be oversimplified. Indeed, it more describes a progressive process of tissue wasting in the course of chronic disease, and both tissues require conservation. It is therefore worthwhile to start all treatments as soon as muscle loss develops; or even before that. The aim of the present paper is to describe wasting as a continuing process of HF and to provide a brief overview of mechanisms and possible treatment approaches to tissue wasting in affected patients.

Mechanisms of wasting: skeletal muscle

Muscle loss during the ageing process

Narici and Maffulli calculated that total lean mass, which approximately equals the total skeletal muscle mass but is easier to measure, declines by about 18 % in men and by 27 % in women from the second to the eighth decade of life⁽¹⁰⁾. The development of sarcopenia has been implicated in several detrimental effects that are commonly encountered in the elderly⁽²⁹⁾: (i) increased incidence of falls that can lead to injury; (ii) impaired immune function and capability to fight off infection as a consequence of reduced protein storage in skeletal muscle; and (iii) development of disability, frailty and ultimately death^(25,30). In fact, it has been estimated that the annual healthcare cost in the USA due to sarcopenia-related morbidity reaches 18.5 billion US dollar^(31,32). A fundamental difference, however, exists between disuse atrophy and ageing-associated sarcopenia, because only sarcopenia is associated with a decrease in muscle fibre size and number. Atrophy, on the other hand, is only associated with a decrease in muscle fibre size, but not number. Many different mechanisms are involved in these processes. To understand them, knowledge of the basics of skeletal muscle structure is pivotal. Indeed, muscle consists of slow twitch type I and fast twitch type II muscle fibres. Whilst type I fibres are more efficient at using oxygen for continuous, extended muscle contractions, type II fibres possess less mitochondria and preferably use anaerobic metabolism to create energy^(14,33).

The first description of different muscle fibre types dates back to 1873, when Louis Ranvier described red and white muscles in rabbits and rays as either tonic-slow or tetanic-fast, respectively⁽³⁴⁾. Red muscles, now known to be primarily composed of type I fibres, possess high oxidative capacity due to high mitochondrial density, high myoglobin content and a high number of capillaries⁽³⁵⁾. Their metabolic profile is adjusted to their long twitch contraction time and their low force production, which also makes them resistant to fatigue. In addition, type I fibres show low activity of ATPase, creatine kinase and glycolytic enzymes. Their activating motor neurons are small⁽³⁵⁾. In this context, it is important to acknowledge that mitochondria produce about 90 % of ATP required for cellular functioning during oxidative phosphorylation⁽²⁹⁾. Type II fibres are different in many ways. Not only are they activated by larger motoneurons, which means that the level of excitation will determine the pool of neurons and thus the fibre type that will contract, but they also possess high ATPase, creatine kinase and anaerobic glycolysis activity. Further, type II fibres are differentiated into type IIA and IIB fibres, which have different oxidative capacities⁽³⁵⁾. The fibre composition of any muscle can be subject to change in response to appropriate stimuli; for example, reduced muscular activity will yield slow-to-fast fibre transformation⁽³⁶⁾. The opposite transformation appears during exercise training. During the ageing process, fast type II are more prone to atrophy than type I fibres, and indeed, cross sectional area of type II fibres has been shown to be reduced by 26 % in subjects aged 80 years compared with subjects who were aged 20 years⁽³⁷⁾. No such reduction was reported for slow type I fibres. One of the reasons for this change is the preferential denervation and loss of fast motor units⁽³⁸⁾. The number of motor units remains fairly constant up to age 60 years, but declines thereafter at a rate of 3 % annually⁽³⁹⁾, amounting to 60 % loss at age 80 years⁽¹⁰⁾. Altogether it appears that up to the late seventies, type II fibres are predominantly affected, but from approximately age 80 years onwards, both types of fibres are lost⁽¹⁰⁾.

Several other factors play roles in declining muscle mass and strength (Fig. 1). The infiltration of skeletal muscle by fat and connective tissue is another major contributor⁽⁴⁰⁾. Overend *et al.*⁽⁴¹⁾ described more than 20 years ago that, even though total thigh cross-sectional area is not different between young and elderly men, older men have 13 % lower total muscle plus bone area, 26 % lower quadriceps and 18 % lower hamstring area. Using computed tomography imaging, Taaffe *et al.*⁽⁴²⁾ recently described that cessation of resistance exercise in trained older persons increases the fatty infiltration of muscle, while resumption of exercise decreases it. This effect adds to the development of mitochondrial dysfunction that is evident in the elderly and possibly a consequence of oxidative damage by reactive oxygen species^(29,43); reduced energy production may also play a role in the development of myocyte apoptosis discussed later⁽⁴⁴⁾. In fact, animal models have shown that the ATP content in aged muscle may be 50 % lower than that of young counterparts⁽⁴⁵⁾.

An anabolic/catabolic imbalance is another important player in the development of sarcopenia. From this perspective, muscle loss may be a consequence of reduced muscle anabolism, increased muscle catabolism or both⁽¹⁴⁾. Such imbalance may yield histological changes in the muscles' ultrastructure, finally leading to increased degradation of myofibrils and myocyte apoptosis. Indeed, TNF has been shown to be able to induce myocyte apoptosis⁽¹⁰⁾, but is also able to stimulate myofibril degradation via the ubiquitin-proteasome pathway⁽⁴⁶⁾. Therefore, the balance between anabolic players such as testosterone, growth hormone or insulin-like growth factor-1 and the catabolic factors TNF, IL-1 β , interferon- γ , myostatin or glucocorticoids is of major importance in this regard⁽¹⁴⁾. Lack of anabolic growth factors inside of skeletal muscles and reduced physical activity have also been found to be involved in an increased rate of apoptosis⁽⁴⁷⁾. Interestingly, apoptosis activity has been shown to inversely relate to muscle weight, suggesting a causative relationship⁽²⁹⁾. The predominant mechanism of myofibril degradation involves the adenosine triphosphate-dependent ubiquitin-proteasome pathway, which is responsible for the degradation of myofibril proteins from the intracellular compartment. However, it appears that an overactivity of this pathway does not play a major role in the development of sarcopenia in healthy elderly subjects, whereas it does play a prominent role in patients with chronic inflammatory syndromes such as HF^(10,48).

Muscle loss in heart failure

Peripheral loss of skeletal muscle tissue is a general finding in patients with HF and occurs early in the course of the disease⁽⁴⁹⁾. Muscle mass is the major determinant of both resting energy expenditure⁽⁵⁰⁾ and exercise capacity⁽⁵¹⁾. The muscle hypothesis⁽⁵²⁾ holds that many factors are involved in the development of reduced peak oxygen uptake (peak VO₂) in HF. Besides physical inactivity, the muscle itself is affected by ultrastructural abnormalities, alterations in mitochondrial structure and function, oxidative stress and a shift in fibre distribution^(14,53). All these factors play a role not only in the reduced exercise capacity in patients with HF, but also in the development of sarcopenia. Among male non-cachectic patients with HF, lean tissue in the legs was reduced by 9.1 % compared with healthy male control subjects of similar age⁽²¹⁾. The thirty-six patients with HF in the present study were (mean (SEM)) age 58.9 (1.3) years, weighed 83.8 (2.0) kg, their mean New York Heart Association class was 2.7 (0.1), and their mean left ventricular ejection fraction was 25 (2)%. Study participants' total lean tissue was 57.4 (1.0) kg⁽²¹⁾. However, patients in the present study were not investigated for the presence or absence of sarcopenia. A later study from my group in a significantly larger cohort of patients from the studies investigating comorbidities aggravating heart failure, conducted among 200 male and female patients with stable ambulatory HF (mean (SD), age 66.9 (10.4) years, weight 86.7 (16.9) kg, New York Heart Association class 2.3 (0.5),

left ventricular ejection fraction 38.9 (13.5 %) found that the patients' mean lean mass was 54.6 (10.8) kg and thus similar to that seen in the study published one and half decades earlier⁽²⁰⁾. The prevalence of sarcopenia in the present study was 19.5 %, and thus too high to be simply attributed to advanced age, since these patients had, on average, not reached 70 years. Sarcopenia, however, was associated with lower hand grip strength, lower quadriceps strength, lower gait speed and 6-min walk distance as well as lower left ventricular ejection fraction and peak oxygen consumption as assessed using spirometry⁽²⁶⁾.

Previous studies had studied skeletal muscle mass and came to different conclusions, because no stringent cut-off criteria for sarcopenia were used. Rather, the respective authors described skeletal muscle mass reduction *per se*. Mancini *et al.*⁽⁵⁴⁾, for example, found that 68 % of their fifteen patients with chronic HF had reduced skeletal muscle mass compared with healthy controls, as evidenced by a decrease in the creatinine: height ratio and/or a reduced upper arm circumference of <5 % of normal. Using MRI, the authors also demonstrated that the patients' calf muscle volume was reduced, whereas fat mass was largely preserved⁽⁵⁴⁾. Drexler *et al.*⁽⁵⁵⁾ studied fifty-seven patients with chronic HF and eighteen healthy control subjects and found that patients with HF had by 20 % reduced density of mitochondria in their skeletal muscle. Importantly, the fibre-type distribution was shifted towards type II fibres in patients with HF and their capillary length density of skeletal muscle was also reduced⁽⁵⁵⁾. Most importantly, the density of mitochondria was strongly associated with the patients' peak oxygen consumption⁽⁵⁵⁾. Using quadriceps biopsies from nine patients with severe chronic HF, Lipkin *et al.*⁽⁵⁶⁾ found increased acid phosphatase, increased interstitial cellularity, excess intracellular lipid accumulation, atrophy of both type I and II fibres and variation in size with hypertrophy and atrophy of fibres. Completing the pathophysiological portfolio of sarcopenia development in HF, increased skeletal myocyte apoptosis has been observed in affected patients⁽⁵⁷⁾. Adams *et al.*⁽⁵⁸⁾ studied thirty-four patients with mild-to-moderate chronic HF and detected apoptosis in skeletal muscle biopsies from the vastus lateralis muscle in sixteen of these patients (47 %). Patients with skeletal muscle apoptosis showed significantly lower peak oxygen consumption as assessed by spirometry (12.0 (SD 3.7) *v.* 18.2 (SD 4.4) ml/kg per min, $P = 0.0005$). Lower peak VO_2 was also described when Harrington *et al.*⁽⁵⁹⁾ studied 100 patients with chronic HF and compared them with thirty-one healthy controls (18 (SD 0.6) *v.* 33.3 (SD 1.4) ml/min per kg, $P < 0.0001$). Computed tomography-measured cross-sectional area in the quadriceps at mid-thigh and in the total leg were lower in patients with HF than in controls (both $P < 0.05$). Overall, patients were weaker than the control subjects as assessed by quadriceps maximal isometric strength ($P < 0.005$), even after correcting strength for the cross-sectional area⁽⁵³⁾.

Just as in patients with ageing-associated sarcopenia, mitochondria-released cytochrome c has been implicated in the development of muscle wasting in HF⁽⁵⁷⁾.

Cytochrome c release into the cytosol is a consequence of the intracellular balance of the regulatory proteins Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic). Cytochrome c release in turn activates caspase-9, which initiates a cascade of events that leads to apoptosis⁽²⁹⁾. Gielen *et al.*⁽⁶⁰⁾ have recently shown that MuRF-1 expression in vastus lateralis muscle biopsies was elevated among sixty patients with chronic HF when compared with sixty healthy controls of similar age, suggesting clinically relevant activation of the ubiquitin-proteasome system, for which MuRF-1 acts as an important transcription factor. Subjects were randomised to 4 weeks supervised endurance exercise training or a control group. Exercise training reduced the expression of MuRF-1 mRNA by more than 30 % in a repeat biopsy at 4 weeks follow-up^(14,21). Other local factors appear to play important roles in HF as well as evidenced by reduced expression of local skeletal muscle expression of the anabolic insulin-like growth factor-1⁽⁶¹⁾. As reviewed in detail elsewhere⁽¹⁴⁾, insulin-like growth factor-1 is a key regulator of protein kinase B, also known as Akt, whose downstream target is called mammalian target of rapamycin, a pivotal regulator of translation initiation and overall muscle size. It appears that basal protein kinase B phosphorylation is decreased in patients with HF compared with age- and physical-activity-matched controls⁽⁶²⁾. Pro-inflammatory cytokines such as TNF do not only play a role in the induction of proteasome-activity and apoptosis, but they can also induce a state of growth hormone resistance⁽⁶³⁾. Indeed, many pro-inflammatory mediators have been shown to be overexpressed in patients with HF⁽⁶⁴⁾ and their levels are associated with poor survival^(65,66). Ventricular assist device implantation in patients with advanced HF has been shown to enhance skeletal muscle expression of insulin-like growth factor-1, to increase protein kinase B phosphorylation, and to increase the fibre cross-sectional area⁽⁶⁷⁾.

Mechanisms of wasting: fat

Fat tissue wasting in HF has been far less extensively studied than muscle wasting. Using a highly selected group of hospitalised patients with HF, Melenovsky *et al.*⁽⁶⁸⁾ found that fat wasting was more prevalent among patients with right than left ventricular dysfunction. Indeed, fat-mass index was 6.7 (SD 3.9) *v.* 7.8 (SD 3.6) kg/m² ($P = 0.005$), respectively. This was also true for absolute fat mass as assessed by dual-energy X-ray absorptiometry scan (25 (SD 10) *v.* 30 (SD 11) kg, $P = 0.002$). No such difference was found for fat-free mass index ($P = 0.21$) or absolute fat lean mass (54 (SD 9) *v.* 55 (SD 10) kg, $P = 0.64$), suggesting equivalent muscle loss in the two groups. Christensen *et al.*⁽⁶⁹⁾ followed thirty-eight patients with chronic HF, nineteen of whom were cachectic, for 12 months and found that neither group showed a difference in absolute lean mass from baseline to 12 months; however, a statistically significant increase in fat mass was noted in the cachectic subgroup (from 15.7 (SD 1.6) to 17.1 (SD 1.6) kg, $P < 0.05$), but not

in the non-cachectic subgroup. Percentage lean mass decreased in the cachectic subgroup from baseline to follow-up. It is noteworthy that fat mass in both groups was rather at the low end of the spectrum in the first place and also that the change in fat mass was not linked to an increase in body weight, possibly related to a relative decrease in muscle mass. It remains a matter of speculation why and when fat loss becomes evident in patients with HF, but it seems that natriuretic peptides, pro-inflammatory cytokines and possibly catecholamines play a role. Indeed, both sarcopenic and cachectic patients have been found to present with lower fat mass in cross-sectional studies^(20,21). From a pathophysiological standpoint, natriuretic peptides such as atrial and B-type natriuretic peptide have been implicated in lipolysis, as adipocytes are sensitive to both peptides⁽⁷⁰⁾. In addition, natriuretic peptides have been shown to enhance the secretion of adiponectin from adipocytes⁽⁷¹⁾.

Adiponectin is an adipose tissue-derived factor that appears to improve insulin sensitivity and inhibit vascular inflammation⁽⁷²⁾. Even though adiponectin is primarily produced by adipose tissue, human plasma adiponectin levels show, counterintuitively, an inverse relation with BMI and percentage body fat⁽⁷³⁾. Therefore, it has been suggested that adiponectin secretion could aid in weight loss, which in the setting of HF could be considered as a cardiac unloading action⁽⁴⁹⁾. Conversely, Lavie *et al.*⁽⁷⁴⁾ studied 209 ambulatory patients with chronic HF who were referred for a cardiac rehabilitation programme, showing that the total fat is a strong and independent predictor of event-free survival. For every 1 % of absolute increase in percentage body fat in this population, there was a reduction in major clinical events. Improved survival is therefore consistently associated with higher BMI, and this, in turn, is linked to body fat in patients with HF.

Altogether, it appears that fat loss occurs predominantly late in the course of HF and that it plays an important role in the development of cachexia. Both patients with sarcopenia and cachexia present with lower fat mass in cross-sectional studies, but longitudinal studies suggest that alterations are possible and that increases in fat mass are possible but associated with decreases in muscle mass. Patients with right ventricular failure are more prone to develop fat loss than those with left ventricular failure.

Treatment approaches to wasting in heart failure

Muscle mass, muscle strength and muscle wasting

It is important to understand that muscle wasting and fat wasting follow different pathophysiological pathways. Therefore, sarcopenia and cachexia may require different therapeutic approaches, even though these can show overlap to some extent. The only clinically meaningful therapeutic approach to muscle wasting in HF that has sufficient evidence is exercise training, because it is able to reduce oxidative stress, pro-inflammatory cytokine production, tissue expression of myostatin and the overall activity of the ubiquitin-proteasome system^(60,75-77).

Exercise training is also being advocated for patients with cancer in order to improve their exercise capacity and quality of life^(78,79). The present guidelines for HF management by the European Society of Cardiology state that 'it is recommended that regular aerobic exercise is encouraged in patients with HF to improve functional capacity and symptoms'⁽⁸⁰⁾. This is a class I recommendation with a level of evidence grade A as at least one randomised controlled study has proven its efficacy⁽⁸¹⁾. Effects of exercise training include improved quality of life and exercise capacity and ultimately beneficial effects on mortality and hospitalisations⁽⁸²⁾. Detailed recommendations can be found in a consensus statement issued by the European Society of Cardiology⁽⁸²⁾.

A number of treatment approaches have been pursued for the treatment of muscle wasting and in order to increase muscle strength and exercise capacity in patients with HF^(83,84). No study has so far specifically investigated therapeutic effects in sarcopenic patients with HF, very few have studied cardiac cachexia. Interventions include essential amino acid supplementation in order to provide elements for the growth of skeletal muscle⁽⁸⁵⁾, recombinant human growth hormone, synthetic ghrelin, testosterone replacement therapy, β -blockers, fish oil and β -receptor agonists⁽⁸³⁾. Included patient cohorts, however, rarely exceeded fifty patients. Growth hormone application has seen tremendous trial activity in the past, but clinical benefit could not be demonstrated⁽⁸⁶⁾. β -Receptor agonists have been tested in the management of muscle wasting⁽⁸⁷⁻⁸⁹⁾, for example fenoterol or clenbuterol, but despite its pathophysiological attractiveness, this approach may be dangerous in patients with HF. Nutritional administration of essential amino acids appears to be promising, as an investigator-blinded, randomised study in thirty-eight patients with HF has shown that improvements in peak VO_2 and 6-min walk distance are possible with this approach within 2 months of treatment⁽⁹⁰⁾, but larger studies are required to confirm these results. Banerjee *et al.*⁽⁹¹⁾ used another interesting approach. Testing the effects of electrical stimulation using a 6-week training programme during which patients were exposed to electrical stimulation of the major leg muscles for a minimum of 1 h, for 5 d each week. Peak VO_2 increased from 19.5 (SD 3.5) to 21.2 (SD 5.1) ml/kg/min ($P < 0.05$), walking distance from 415 (SD 57) to 455 (SD 55) m ($P < 0.005$) and quadriceps strength increased from 378 (SD 110) to 405 (SD 109) N ($P < 0.005$). No change in BMI was noted⁽⁹¹⁾.

Testosterone administration has been associated with improvements in exercise capacity, and, indeed, testosterone deficiency is a phenomenon that is frequently observed in patients with HF⁽⁹²⁾. Reduced serum levels are associated with muscle myopathy⁽⁹³⁾ as well as poor survival⁽⁹⁴⁾. Caminiti *et al.*⁽⁹⁵⁾ studied seventy male patients with stable chronic HF, who were randomly assigned to receive either intramuscular injection of testosterone every 6 weeks or placebo (n 35 per group). Baseline peak VO_2 was directly related to the serum testosterone level and improved significantly after 12 weeks of treatment from 13.4 ± 4.4 to 16.3 ± 1.7 ml/kg/min ($P < 0.05$). Likewise, testosterone-treated patients'

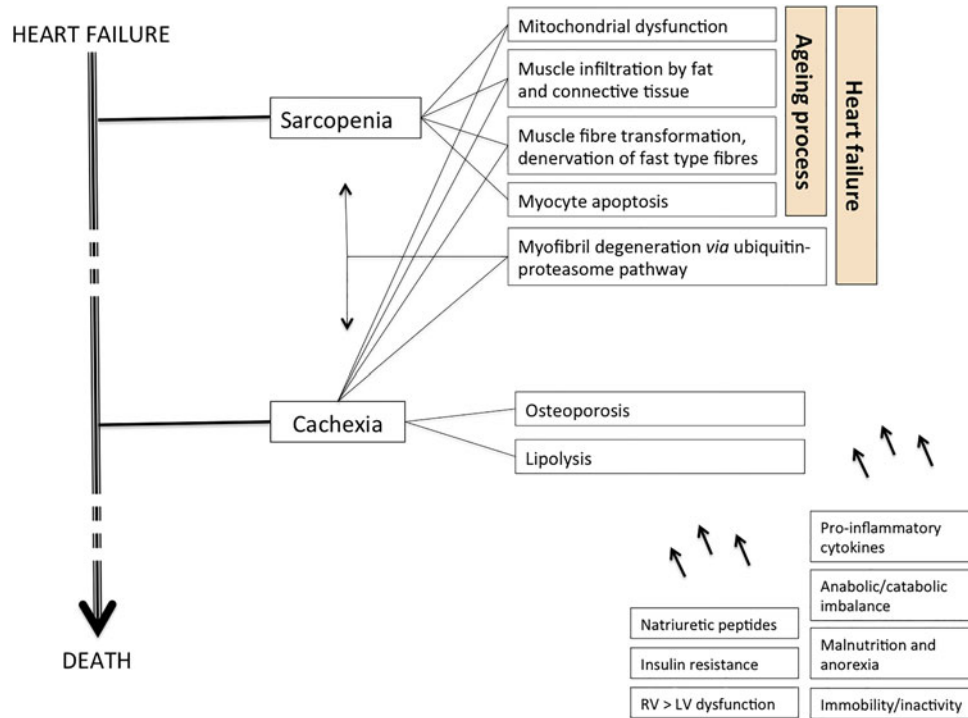


Fig. 1. (Colour online) The wasting continuum in heart failure (HF). Mitochondrial dysfunction, infiltration by fat and connective tissue, muscle fibre transformation, denervation of fast type fibres and myocyte apoptosis all play a role in muscle wasting (sarcopenia) that develops early in HF. Overactivity of the ubiquitin–proteasome system leads to myofibril degeneration. Cachexia is less prevalent than muscle wasting. It is associated with muscle and adipose tissue wasting; osteoporosis affects up to 50 % of patients but has been studied least well in HF.

6-min walk distance increased from 387 (SD 121) to 473 (SD 138) m ($P < 0.05$). Body weight increased from 63.5 (SD 13.7) to 66.8 (SD 11.4) kg ($P < 0.05$). No such change was noted in the placebo group⁽⁹⁵⁾. A similar study from the same group of workers was published 1 year later, performed in thirty-six elderly female patients with chronic HF of ischaemic aetiology, twenty-four of whom were randomised to a testosterone transdermal patch or to placebo⁽⁹⁶⁾. After 6 months treatment, their peak VO_2 had increased from 10.5 (SD 1.0) to 13.2 (SD 1.8) ml/kg/min and their 6-min walk distance from 261 (SD 52) to 357 (SD 43) m (both $P < 0.05$). Altogether, testosterone therapy was well tolerated; only one patient left the study for generalised prurigo. Virilisation was not noted in any of the patients⁽⁹⁶⁾. A novel class of drugs, selective androgen receptor modulators, has recently received tremendous research endeavour for their ability to increase muscle mass in clinical studies; however, their effects on muscle strength or exercise capacity are not yet convincing^(97–101). Studies in HF are not available.

Cachexia

Treatment studies to tackle cachexia and thus body rather than muscle wasting are different and require different approaches. Strategies include nutritional advice, appetite stimulants such as megestrol acetate, cyproheptadine and dronabinol anabolic steroids, ghrelin, or myostatin

antibodies⁽¹⁰²⁾. However, most experience stems from cancer cachexia studies, and studies into the treatment of cardiac cachexia remain a rarity. This is surprising, considering an estimated prevalence of 2 % for HF in European countries alone. Even though 80 % of these patients are at risk to develop cardiac cachexia, approximately only 10 % are in fact cachectic⁽¹⁰³⁾. But even this comparatively low prevalence translates into approximately 1.2 million patients with cardiac cachexia in Europe⁽¹⁰³⁾. One small study evaluated the anabolic steroid oxymetholone, administered for 3 months at a dose of 5–10 mg daily to patients with idiopathic dilated cardiomyopathy; however, these patients were not cachectic. Treatment led to significant decreases in left ventricular end-diastolic and end-systolic diameters and decreased left ventricular mass. Rozenyrt *et al.* studied the effects of a nutritional intervention of 6 weeks duration in twenty-nine patients with cardiac cachexia⁽¹⁰⁴⁾. A diet containing 2512 kJ (600 kcal)/d with relatively high fat content increased body weight during the treatment and the subsequent 12-week follow-up period and had anti-inflammatory effects in that it reduced serum levels of TNF. Patients' quality of life of patients improved for the 6 weeks of the period of the nutritional intervention, but decreased somewhat in the follow-up period⁽¹⁰⁴⁾.

Ghrelin is a peptide hormone that was originally identified in 1999⁽¹⁰⁵⁾ and is mainly produced in the fundus region of the stomach⁽¹⁰⁶⁾, but also in other organs⁽¹⁰²⁾.

Ghrelin induces the release of growth hormone from the pituitary gland thereby regulating appetite, but it also has anti-inflammatory properties. Several studies in cancer have shown promising results⁽¹⁰⁷⁾. In patients with HF, ghrelin plasma levels are elevated in cachectic HF compared with non-cachectic patients (237 (SD 18) v. 147 (SD 10) fmol/ml, $P < 0.001$)⁽¹⁰⁸⁾. A small, uncontrolled study of intravenous infusion of ghrelin in ten patients with cardiac cachexia, predominantly patients in New York Heart Association class III, showed promising cardiovascular results⁽¹⁰⁹⁾. Patients received ghrelin at a dose of 2 µg/kg body weight for 30 min twice daily for 3 weeks, thereby inducing a 25-fold increase in growth hormone serum levels and an increase in food intake lean body mass as well as an increase in left ventricular ejection fraction (from 27 (SD 2) to 31 (SD 2) %, $P < 0.05$)⁽¹⁰⁹⁾. Similar results regarding heart function, body weight and body composition have been described in animal models of HF⁽¹¹⁰⁾. Some ghrelin analogues are in development and have shown promising early results in animal models of HF⁽¹¹¹⁾, reducing, for example, the expression of myostatin in skeletal muscle^(112,113). Therapeutic effects included increases in lean mass as well as in fat mass⁽¹¹⁴⁾. Ghrelin receptor agonists such as anamorelin are currently also undergoing clinical testing and can achieve increases in body weight as well as appetite, but studies have so far focused on cancer cachexia, and large-scale studies are still missing^(115–118). Besides, several myostatin antibodies are currently in development and are being tested in clinical trials. No studies in HF are currently available, but animal models have shown that, for example, REGN1033, a fully human anti-myostatin antagonist antibody, increased fibre size, muscle mass and force production in young mice by approximately 20 %, and it improved physical performance outcomes in combination with treadmill exercise in 2-year-old mice⁽¹¹⁹⁾.

Espindolol (MT-102) is another substance that has recently finished a phase II clinical trial, showing good efficacy in patients with cancer cachexia. A total of eighty-seven patients were randomly assigned to espindolol, an anabolic/catabolic transforming agent that has three potential pharmacological targets in cachexia, namely reduced catabolism via non-selective β-blockade, reduced fatigue and thermogenesis through central 5-hydroxytryptamine 1a antagonism and increased anabolism through partial β₂ receptor agonism or placebo⁽¹²⁰⁾. After 16 weeks treatment, patients on espindolol showed beneficial effects on body weight and hand grip strength, i.e. the slope of weight change in the high-dose group of espindolol demonstrated a positive slope compared with a negative slope in the placebo group ($P < 0.0001$)⁽¹²¹⁾.

Conclusions

Sarcopenia and cachexia remain underrecognised and underdiagnosed in patients with HF. This fact has several reasons, which embrace sarcopenia being mostly a diagnosis in the domain of geriatricians, and cachexia being most prevalent in patients with cancer. Anyhow,

the prevalence of sarcopenia in HF, the preferred term being muscle wasting, reaches almost 20 %, that of cachexia probably about 10 %. Another reason for the lack of awareness among cardiologists is the lack of effective treatments. Muscle wasting is best tackled using exercise training, but its effectiveness can probably be improved by nutritional or drug treatments. Essential amino acids and high energetic nutritional supplements have shown some clinical merit. Testosterone and other anabolics have been extensively investigated and have shown clinical benefit, but large-scale studies are still lacking. More recent additions to the wasting treatment portfolio such as appetite stimulants, anamorelin, ghrelin agonists or myostatin antagonists need to be evaluated in clinical trials of HF.

Financial Support

Preparation of this manuscript was partly funded by a grant from the Innovative Medicines Initiative – Joint Undertaking (IMI-JU 115621).

Conflicts of Interest

Stephan von Haehling has been a paid consultant to Thermo Fisher Scientific, Solartium Dietetics, Professional Dietetics, Pfizer, Respicardia, Sorin, Novartis, and Vifor Pharma.

Authorship

Stephan von Haehling presented the content of this manuscript at the Conference on ‘Nutrition and age-related muscle loss, sarcopenia and cachexia’ in London, UK. He wrote the manuscript based on the content of this talk.

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