

Cardiac cachexia: hic et nunc

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Abstract

Cardiac cachexia (CC) is the clinical entity at the end of the chronic natural course of heart failure (HF). Despite the efforts, even the most recent definition of cardiac cachexia has been challenged, more precisely, the addition of new criteria on top of obligatory weight loss. The pathophysiology of CC is complex and multifactorial. A better understanding of pathophysiological pathways in body wasting will contribute to establish potentially novel treatment strategies. The complex biochemical network related with CC and HF pathophysiology underlines that a single biomarker cannot reflect all of the features of the disease. Biomarkers that could pick up the changes in body composition before they convey into clinical manifestations of CC would be of great importance. The development of preventive and therapeutic strategies against cachexia, sarcopenia, and wasting disorders is perceived as an urgent need by healthcare professionals. The treatment of body wasting remains an unresolved challenge to this day. As CC is a multifactorial disorder, it is unlikely that any single agent will be completely effective in treating this condition. Among all investigated therapeutic strategies, aerobic exercise training in HF patients is the most proved to counteract skeletal muscle wasting and is recommended by treatment guidelines for HF.

Keywords Cachexia; Heart failure; Prevalence; Diagnosis; Treatment

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Epidemiological aspects of cardiac cachexia

Through the prevalence of chronic disease, lack of specific therapies, or non-implementation of existing and evidence-based management, cachexia evolved to a public health issue.¹ Most of the epidemiological figures are based on different cachexia definitions and derived from heterogeneous populations.² One would hope this would change with a consensus cachexia definition published in 2008.³ However, literature speaks for itself as we are still in need of quality and quantity on this topic.⁴ For heart failure (HF), as for other chronic diseases, only few studies were published, and they remain heterogeneous in cachexia definition. The recent study in HF again used the old definition, namely, unintentional non-edematous weight loss of >5% over at least 6 months. By applying this definition, cachexia was found in 19/238 (10%) HF patients.⁵ In fact, a new definition was tested in a single HF study.⁶ In 137 patients, the obligatory criterion of

weight loss was met by 42 (31%), but when additional three criteria were requested, significantly fewer patients met the cachexia definition [30 (22%) patients, $P=0.0006$]. Interestingly, no difference in survival was seen between those two patient groups. The authors therefore challenged the added value of new cachexia definition, more precisely, the addition of criteria on top of obligatory weight loss.

Nonetheless, it needs to be acknowledged that cachexia is representing a major burden for patients and the healthcare system. In the 1 year analysis of the USA Nationwide Inpatient Sample, cachexia as a primary or secondary diagnosis was reported for 32 131 (0.41%) of all admissions.⁷ Cachexia patients were older, had longer length of stay (6 vs. 3 days), and required an average of \$4641 more per hospital stay. HF was recorded for 19% of cachexia admissions and was the third most common chronic comorbidity (after malignancy, 34%, and chronic obstructive pulmonary disease, 29%). Based on burden in terms of costs and outcome, well-conducted cross-sectional or longitudinal epidemiological studies are urgently needed. An important source of

information should be the Studies Investigating Comorbidities Aggravating Heart Failure that has included HF patients, diabetics, and healthy controls.⁸ After an extensive baseline assessment that allows for cachexia diagnosis, they were seen at regular intervals and followed-up for mortality. First reports from this study include muscle wasting aspect, which was frequent and associated with reduced physical performance.⁹ Along with cachexia definition, health professionals' attitudes across the chronic disease need to be changed. Screening for nutritional aspects, weight loss, and correlates in terms of physical performance and quality of life should be part of routine assessment¹⁰ as many of abnormalities may be managed in an easy way.

Advances in pathophysiology of cardiac cachexia

The pathophysiology of cardiac cachexia (CC) is complex and multifactorial including several factors interacting in a complex system with immune, metabolic, and neurohormonal consequences, which induce catabolic and anabolic imbalance.³ The overall net catabolic dominance in HF provokes systemic tissue wasting.¹¹ Skeletal muscle loss may be the most clinically relevant aspect, as it determines physical capacity and symptomatic severity of HF. However, bone and fat compartment are also affected by global catabolic dominance.^{11–13} The final event in progressive tissue wasting in HF is a life-threatening CC.

Immune activation

Increased circulating levels of pro-inflammatory cytokines characterized HF, namely, tumour necrosis factor alpha (TNF- α), interleukin-1, and interleukin-6.^{14–17} The rise of these inflammatory mediators seems to be combined with inadequately raised or even decreased levels of anti-inflammatory mediators such as interleukin-10 and transforming growth factor beta 1.¹⁸ The cause of immune activation is still uncertain.¹⁹

Metabolic abnormalities

Evidence is mounting that the abnormal and imbalanced metabolism represents an intrinsic aspect of HF pathophysiology, with fundamental symptomatic and prognostic implications.¹¹ The concept of metabolic failure in HF include both impaired myocardial energy utilization and metabolic inefficiency at the systemic level. The key points in this concept are global anabolic blunting and insulin resistance and catabolic overactivity.^{20,21} Anabolic deficiency in HF patients induce loss of skeletal muscle mass and function.²² Men with HF showed reduced circulating testosterone and dehydroepiandrosterone sulfate, and its relation with decreased exercise capacity.^{23,24} It is well known that anabolic steroids have a significant role in the quantitative and qualitative regulation

of muscle fibre content, leading to increases in muscle mass and strength, as well as improvement in physical performance.²⁵ The major anabolic hormones modulating protein metabolism in skeletal muscle include insulin, growth hormone (GH), and insulin-like growth factor 1 (IGF-1).¹⁶ It has been previously proved that insulin resistance may play an important role in skeletal muscle dysfunction in HF.^{20,26} Since IGF-1 has been shown to stimulate protein synthesis and to reduce protein degradation, changes in the GH/IGF-1 axis may impact the anabolic/catabolic balance in the wasting syndrome.²⁷ Patients with HF-related systolic or diastolic dysfunction have significantly lower plasma levels of total IGF-1, but free IGF-1 is significantly higher than in healthy controls. Recently, the role of leptin and other adipokines in the process of body wasting has been questioned.^{28–30} Adiponectin, an adipokine with multiple metabolic actions, increases both locally and globally with HF severity and is highest in cachectic patients.^{31,32} Our recent findings may indicate a cross-sectional metabolic association of increased serum adiponectin with reduced peripheral muscle mass and muscle strength in non-cachectic, non-diabetic, elderly HF patients.³³ Recent reports suggest the role of changes in small and large intestine function in HF in the pathogenesis of wasting.^{34,35} Furthermore, in patients with stable HF, the blood flow in the intestinal arteries is reduced and relates to CC.³⁶

Neurohormonal abnormalities

The hallmark of HF pathophysiology, as a response to impaired cardiac function, is a general neurohormonal activation via stimulation of the sympathetic nervous system, the renin–angiotensin–aldosterone axis, and the natriuretic peptide system.^{37,38} Chronic autonomic sympathetic/parasympathetic imbalance is a crucial element of HF pathophysiology. Both epinephrine and norepinephrine can cause a catabolic metabolic shift, leading to graded increase in resting energy expenditure in HF patients with CC.^{37,38} Sustained sympathetic stimulation, as is seen in HF, activates the renin–angiotensin–aldosterone axis.³⁹ Studies have shown that Angiotensin II induces muscle wasting through multiple mechanisms: (i) increased oxidative stress via activation of NADPH oxidase; (ii) increased protein breakdown via reduced IGF-1 and increased cytokine signaling such as glucocorticoid and IL-6; (iii) reduced appetite via alteration in orexigenic/anorexigenic neuropeptide expression in the hypothalamus; (iv) impaired energy balance via inhibition of AMPK; and (v) inhibition of satellite cell function and muscle regeneration.⁴⁰

Molecular basis of cachexia

The molecular basis of cachexia is still poorly understood, and the lack of therapies is evident.^{41–43} Better understanding of molecular mechanisms of cachexia has provided potentially new treatment targets. Skeletal muscle wasting is

a consequence of protein synthesis and degradation imbalance. Recent studies in CC have evaluated the ubiquitin–proteasome pathway (UPP) and autophagy/lysosomal proteolytic pathways to better understand the process of muscle atrophy in HF.^{43–45} The UPP plays a critical role in skeletal muscle wasting. Studies from many groups over the past years have indeed identified many components in the UPP that are induced in atrophying skeletal muscle.⁴⁶ The UPP plays a crucial role in the breakdown of myofibrillar proteins.^{12,47} The overactivation of the UPP in the skeletal muscle of HF patients has been attributed to increased oxidative stress.^{48,49} Transcription factors activating the proteasome pathway include particularly the forkhead box class O and nuclear factor- κ B (NF- κ B) that drive increased expression of the E3 ubiquitin ligases muscle RING-finger protein (MuRF-1) and muscle atrophy F-box.⁴⁶ Thus, inhibition of forkhead box class O was found to induce hypertrophy by increasing protein synthesis.⁵⁰ Additionally, one recent study demonstrated that angiotensin II induces skeletal muscle atrophy in part by increased muscle-enriched E3 ubiquitin-ligase muscle RING-finger (MuRF-1) expression, which may involve protein kinase-D.⁵¹ Along with overactivated UPP, autophagy and lysosomal protein breakdown are also increased.⁵² Unlike UPP, which removes short-living cytosolic and nuclear proteins, the autophagy–lysosome system accounts for degradation of long-living proteins and protein aggregates. There is direct evidence that autophagy signaling is increased in a CC rat model.⁴⁵ Some other important molecular mechanisms of controlling muscle mass include: PI3K–AKT signalling, NF- κ B, SMAD2 and SMAD3 in myostatin-enhanced and activin A-enhanced proteolysis.⁴³

Myostatin

Myostatin, a member of the transforming growth factor beta superfamily, is an extracellular cytokine dominantly expressed in skeletal muscles, which is known to play the important role in the negative regulation of muscle mass.^{53,54} Myostatin appears to be a key player in the integrated physiology of muscle, fat, and bone.⁵⁵ It is unclear whether myostatin directly affects fat and bone, or indirectly via muscle. Myostatin has high affinity to the activin IIB receptor, and it has been shown that administration of soluble activin IIB receptor resulted in an improvement in body and muscle weights in mice.⁵⁶ However, myostatin and the muscle atrophy F-box expression remained unaffected by both the HF and age.⁵⁷

Regenerative capacity of skeletal muscle

Skeletal muscle has a remarkable ability to maintain its homeostasis against injury or wasting by activating a well orchestrated regenerative response to repair damaged myofibers.⁵⁸ Injury leads to activation and proliferation of mitotically quiescent mononuclear cells; satellite cells, which form myoblasts, terminally differentiate and fuse to form

multinucleated myotubes.⁵⁹ Trials in aged muscle clearly indicate that systemic changes in chronic disease states strongly affect satellite cell regenerative capacity. Therefore, identifying mechanisms whereby chronic diseases lead to lower satellite cell function would have the therapeutic potential to reverse the reduction in muscle regeneration seen in cachexia conditions.

Emerging biomarkers of cardiac cachexia

Despite the high morbidity and mortality associated to CC, there are no universally accepted specific biomarkers for this condition, which makes its diagnosis and treatment difficult.^{60–62} Currently, wasting assessment is limited only to quantification of muscle mass based on imaging and functional tests to quantify muscle function. However, all are expensive and only available at medical centers equipped to do so. In addition, such tests only allow for wasting detection, but not for patients at risk of developing muscle atrophy.^{63,64} Thus, the identification of reliable biomarkers that can be used in a cost-effective manner and could guide diagnosis and therapy in routine clinical practice and clinical trials is warranted. Several inflammatory, hormonal, and oxidative stress molecules have been suggested as serological markers of prognosis in CC but with doubtful success. As individual biomarkers may have limited sensitivity and specificity, multimarker strategies involving mediators of the biological processes modulated by CC may importantly contribute for the diagnosis and management of the disease, as well as for the establishment of new therapeutic targets.^{16,60,62} After a brief reminder on biomarkers, which were evaluated in the past (biomarkers of immune activation, metabolic biomarkers, and neurohormonal biomarkers), we will focus in this review on the analysis of the emerging biomarkers for CC/cachexia/sarcopenia proposed recently (Table 1), briefly highlighting the biological processes to which they are related.

Biomarkers of immune activation

Several markers of immune activation have been investigated in the syndrome of cachexia such as TNF- α , soluble tumour necrosis factor receptors (sTNFRs), interleukin 1 beta, interferon γ , and interleukin 6.^{16,60,65} CC is related to increased circulating levels of TNF- α ^{66,67}, which are involved in the activation of catabolic pathways, in particular of NF- κ B signaling that up-regulates the transcription of members of the proteolytic UPP.¹⁶

Metabolic biomarkers

Among multiple metabolic disturbances already evaluated in the previous section of this review, this paragraph will focus on adipokines known to be of high importance for regulation of body weight in CC. Plasma levels of the adipokines,

Table 1. Biomarkers of cardiac and non-cardiac cachexia

| | Biomarker | Cardiac cachexia | References | Non-cardiac cachexia | References |
|--|----------------------|------------------|----------------|----------------------|-------------------|
| Biomarkers of immune activation | | | | | |
| | TNF- α | ↑ | 16,38,60,65,68 | ↑ | 171–175 |
| | sTNFRs | ↑ | 38,42 | ↑ | 40 |
| | IL-1 | ↑ | 38,42 | ↑ | 171,175 |
| | IL-6 | ↑ | 38,42,68 | ↑ | 176,177 |
| Metabolic biomarkers | | | | | |
| | Adiponectin | ↑ | 31,33,68 | ↑ | 178,179 |
| | Leptin | ↑ | 28,69–71 | ↑ | 180 |
| | Insulin | ↑ | 11,26,181,182 | ↑ | 183,184 |
| | Testosterone/DHEA | ↓ | 22–24 | ↓ | 185 |
| | Growth hormone | ↑ | 79,181,186,187 | ↑ | 188,189 |
| | IGF-1 | ↓ | 27,79,181 | ↓ | 189,190 |
| | Uric acid | ↑ | 11,191 | ↑ | 192 |
| Neurohormonal biomarkers | | | | | |
| | Norepinephrine | ↑ | 16,37,38 | ↑ | 193 |
| | Epinephrine | ↑ | 16,37,38 | ↑ | 193 |
| | Angiotensin II | ↑ | 40,72,73 | ↑ | 74,75 |
| | Natriuretic peptides | ↑ | 11,60 | ↑ | 77,194 |
| | Cortisol | ↑ | 60,67,79,195 | ↑ | 196 |
| Emergent biomarkers | | | | | |
| | Ghrelin | ↑ | 61,83,84 | ↑ | 80,197,198 |
| | CAF | - | - | ↑ | 85,86 |
| | GDF15 | - | - | ↑ | 88 |
| | IC6 and C6M | - | - | ↑ | 89,93 |
| | P3NP | - | - | ↓ | 90 |
| | Myostatin | ↑↓ | 5,199–204 | *↓ **↑ = | *205 **55,206–209 |
| Markers of muscle mass | | | | | |
| | Serum creatinine | - | - | ↓ | 93,210,211 |
| | Urinary creatinine | - | - | ↓ | 95 |
| | Gelsolin | - | - | ↓ | 96 |

C6M, MMP-generated degradation fragment of collagen 6; CAF, C-terminal agrin fragment; CC, cardiac cachexia; DHEA, Dehydroepiandrosterone; GDF15, growth differentiation factor 15; IC6, type VI collagen N-terminal globular domain epitope; IGF-1, Insulin-like growth factor 1; IL-1, Interleukin 1; IL-6, Interleukin 6; P3NP, N-terminal propeptide of type III procollagen; sTNFRs, Soluble tumour necrosis factor receptors (sTNFRs); TNF- α , tumour necrosis factor alpha.

*Circulating myostatin levels in non-cardiac cachexia;

**Local myostatin expression in non-cardiac cachexia.

-, no trials to date.

adiponectin, and leptin may have a role in the detection of muscle, fat, and bone wasting processes.^{12,32} *Adiponectin* may play a role in the pathogenesis of body wasting among HF patients.^{13,33,68} The catabolic effects of *leptin* include inhibition of insulin signaling and enhanced lipid oxidation, thus inhibiting anabolic pathways and reducing energy storage.⁶⁹ These effects may have catabolic effects promoting the development of CC in HF patients.⁷⁰ Interestingly, leptin levels decrease in CC, but remain higher than in healthy individuals.⁷¹ This decrease in leptin concentrations may be due to the reduction of fat tissue in these patients.^{70,71}

Neurohormonal biomarkers

Both *norepinephrine* and *epinephrine*, as mediators of activated sympathetic nervous system, cause a metabolic shift towards catabolism, leading to a graded increase in resting energy expenditure in patients with CC.¹⁶ *Ang II*-induced body wasting is due to both anorexigenic and catabolic effects.^{72,73} Recently, Cichello *et al.*⁷⁴ showed a direct effect of *Ang II* infusion on appetite impairment and body weight loss mostly due to adipose tissue wasting. Sanders *et al.*⁷⁵ have reported a direct catabolic effect on skeletal muscle

by *Ang II* with increased intracellular protein degradation in murine myotubes through an increased expression of the UPP. Increased plasma levels of atrial *natriuretic peptide* and brain natriuretic peptide were found in cachectic HF patients when compared with non-cachectic patients and healthy volunteers.^{60,66} The role of the heart in metabolism is highlighted by the lipolytic activity of natriuretic peptides, as well as by its actions on slowing gastric emptying and absorption.^{76,77} The inverse correlation reported between natriuretic peptides and body weight index seems to be explained by the increased energy utilization and thermogenesis induced by these peptides.⁷⁸ Plasma *cortisol* levels are increased in CC patients.^{60,67,79} Cortisol is known to induce muscle atrophy by decreasing protein synthesis and increasing proteolysis by four distinct mechanisms.

Novel biomarkers for cardiac cachexia/cachexia

Ghrelin

Ghrelin is a 28-amino acid peptide hormone monal tissues.⁸⁰ It stimulates the release of growth hormone from the

pituitary gland and stimulates food intake.^{80,81} Ghrelin is a strong adipogenic and orexigenic molecule, inducing weight gain and adiposity.⁸² Ghrelin not only suppresses the production of the pro-inflammatory cytokines tumour necrosis factor, interleukin-1 β , and interleukin-6, but also stimulates the anti-inflammatory cytokine interleukin-10.⁶⁰ In general, the metabolic changes induced by ghrelin lead to an increase not only in body weight and body fat mass, but also in lean tissue mass, the latter possibly mediated by a reduction in myostatin plasma levels.⁶¹ The resistance of HF patients to the effects of appetite-stimulating peptide ghrelin may be one of the contributing factors in the development of CC.⁸³ Patients with HF and CC have higher plasma ghrelin levels than in those without CC and healthy subjects, which may suggest a compensatory mechanism under the conditions of anabolic/catabolic imbalance, countering further energy deficit and defending against starvation.⁸⁴

C-terminal agrin fragment (CAF): CAF, derived from the peptide agrin, is a synaptically located key player during the initial formation and maintenance of neuromuscular junctions.⁴⁶ In humans, serum CAF levels have recently been shown to be inversely related to appendicular lean mass in men where lower appendicular lean mass was associated with higher CAF.⁸⁵ In addition, serum CAF concentrations have been shown to be increased in older adults with sarcopenia compared with aged-matched controls.⁸⁶ Resistance exercise training significantly improves muscle strength and quality in older adults and results in an increase of CAF in older adults.⁸⁷ It has been proposed as a novel diagnostic marker for muscle wasting in HF patients, which may be useful in identifying patients with CC.⁴²

Growth differentiation factor 15 (GDF-15): Several studies have shown that GDF-15 plays an important role in the pathways of muscle wasting and cachexia.^{46,88} Recent findings suggest that GDF-15 induces weight, fat, and muscle wasting, as well as that it decreases activity in mice and may be a promising target for therapeutic interventions in the field of cachexia.⁸⁸

IC6 and C6M

One recent study showed that type VI collagen turnover-related peptides (IC6 and C6M) represent novel biomarkers of muscle mass or change in muscle mass in young men.⁸⁹ Type VI collagen is a basement membrane protein expressed in most tissues, but highly abundant in muscle sarcolemma.⁹⁰

P3NP

This collagen fragment N-terminal propeptide of type III procollagen (P3NP) is a measure of skeletal muscle status and a biomarker candidate for muscle anabolism.⁸⁷ It is released into circulation during collagen synthesis in soft lean tissue, and its levels have been associated with changes in the lean mass of elderly patients.^{63,91}

Myostatin

Although it seems a natural candidate for an atrophy biomarker, as it directly mediates catabolic signaling, the data of a recent study in CC could not confirm the role of circulating myostatin as a biomarker for muscle wasting in humans.^{12,63,92}

Biomarkers of muscle mass

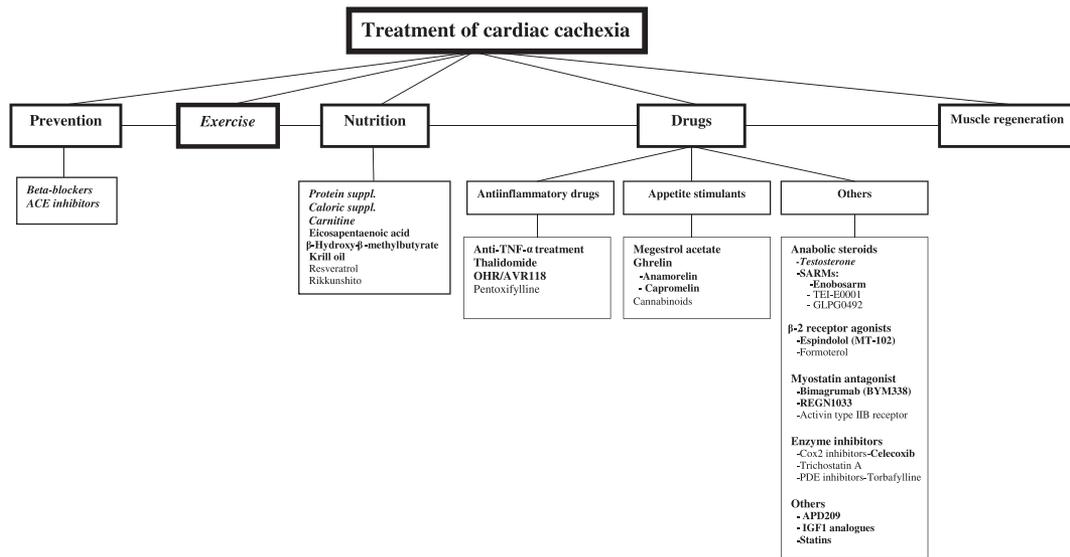
Serum *creatinine* levels are understood to be an unspecific marker of muscle wasting.⁹³ Most studies show that serum creatinine correlate well with measures of skeletal muscle mass.^{93,94} Low urine creatinine excretion, as an indirect measure of low muscle mass, is associated with major adverse cardiac events and all-cause mortality in the general population.⁹⁵ Plasma *gelsolin* is an actin-binding protein mainly produced and secreted by myocytes.⁹⁶ Recent data demonstrated the prognostic ability of low plasma gelsolin concentrations in hemodialysis patients suggesting that its levels incorporate the degree of systemic inflammation and muscle wasting.^{96,97} Plasma gelsolin has been suggested as a marker of muscle mass in haemodialysis patients.^{93,98}

Therapeutic strategies for cardiac cachexia

The development of preventive and therapeutic strategies against cachexia, sarcopenia, and wasting disorders is perceived as an urgent need by healthcare professionals.^{99,100} However, the treatment of skeletal muscle wasting remains an unresolved challenge to this day. As CC is a multifactorial disorder, it is unlikely that any single agent will be completely effective in treating this condition; thus, it will be necessary to target different pathways. Figure 1 summarizes some potential therapeutic strategies in the management of CC.

Preventive strategies for body wasting and cardiac cachexia

Heart failure (HF) management improved over the last decades, and key pharmacological agents are now prescribed to most patients.¹⁰¹ We, however, keep under treating our patients, particularly with beta blockers but also with ACE inhibitors. When considering the landmark report of *ACE inhibitor* associated prevention of weight loss,¹⁰² the adequate daily dose should be pursued. For *beta blockers*, the disproportion is even greater as less than 20% of patients receive target daily dose.¹⁰¹ As weight gain is the class effect of beta blockers, it is not surprising that in HF, carvedilol was associated with prevention of 6% weight loss (risk reduction vs placebo: 33%) and with >5% weight gain (37% vs. placebo). Recently, some ACE inhibitors and beta blockers have been

Figure 1 Therapeutic strategies in the management of cardiac cachexia

* **Bolded terms:** investigated in clinical trials (finished or ongoing). Non-bolded terms: investigated only in animal models or in vitro studies.

* *Terms in italics:* studies in patients with HF or HF animal models.

tested for the potential of muscle mass gain. Imidapril, a highly lipophilic ACE inhibitor, was tested in a mice tumour model. At a daily dose of 10 mg/kg body weight, it attenuated the weight loss.⁷⁵ Similar effects were observed in another experiment performed in the murine cancer cachexia model, where imidapril attenuated the muscle and adipose tissue depletion.¹⁰³ Transfer to patients with cancer cachexia was already conducted in a randomized placebo controlled trial, but the findings were not published yet.¹⁰⁴ Another attractive concept for prevention of body wasting is the *exercise* training that is expanding over a variety of chronic disease, including the cachexia patients.¹⁰⁵

Exercise training

Being a part of daily living, exercise is the easiest way to preserve and increase muscle mass; also, it is the most effective anabolic agent with many ancillary effects delivered at no or low costs. Data are now emerging for patients with chronic kidney disease^{106–108} and cancer,¹⁰⁹ while there are already existing guidelines for HF¹¹⁰ and chronic obstructive pulmonary disease.¹¹¹ The current gold standard against muscle wasting is exercise training.¹¹² Among all investigated therapeutic strategies, aerobic exercise training (AET) in HF patients is the most proved to counteract skeletal muscle wasting and is recommended by treatment guidelines for HF.^{58,113} However, in the paper of Moreira *et al.*, the benefits of AET on skeletal muscle mass, metabolic capacity, and proteasome activity changes were remarkably similar between

protocols.¹¹⁴ Thus, future efforts are warranted to evaluate the AET protocols (e.g. durations, types, different intensities) in order to optimize the effects of AET on CC.

Nutritional interventions

The influence of nutrition on protein kinetics in patients with cachexia is poorly understood.⁴⁶ Nutritional therapy alone has no effect on the underlying catabolic process of cachexia, but it would be interesting to know the potential synergistic effect from nutritional therapy in conjunction with different drugs. There is increasing evidence that *protein supplementation* acts to increase muscle synthesis and that this effect is increased in conjunction with exercise.¹¹⁵ The international study group to review dietary protein needs with aging (The PROTAGE study group) has supported the need for 1–1.5g/kg of high-quality protein to restore muscle in persons with sarcopenia.¹¹⁶ Additionally, *caloric supplementation* in HF patients enhanced weight and improved quality of life.¹¹⁷ Skeletal and cardiac muscle creatine content is reduced in HF, largely because of reduced expression of the creatine–sodium co-transporter.¹¹ Although there is some evidence of improved skeletal muscle function and exercise duration with chronic oral *carnitine* administration, there is no evidence of improved cardiac function.¹¹⁸ Some nutritional interventions such as eicosapentaenoic acid, β -Hydroxy- β -methylbutyrate, and resveratrol may counteract body wasting and muscle loss in animal models, without proved effects in humans.¹¹⁹

Rehabilitation nutrition

The concept of rehabilitation nutrition as a combination of both rehabilitation and nutrition care management may improve muscle mass and physical performance in disabled elderly.¹²⁰ One recent study in HF patients showed that the combination of branched chain amino acid (BCAA) supplementation and resistance exercise can manage sarcopenia and cachexia.¹²¹ The authors found that clinical and physical improvements were caused by the resistance exercise independently from branched chain amino acid supplementation. In general, there is consensus that sarcopenia requires appropriate physical therapy and nutrition management in addition to treatment for primary disease.¹²⁰

Drugs for cardiac cachexia

Clinical trials with drugs in the field of cachexia remain small, and most are performed in oncology patients.⁶¹ Investigations of drugs that counteract body wasting in HF patients are scarce. About 19 drugs that can regulate muscle mass have been reported in the literature so far.¹¹⁹ These therapeutic interventions include use of anti-inflammatory substances and appetite stimulants. Except megestrol, no other drug has yet been recommended by the FDA to prevent or treat muscle atrophy.

Anti-inflammatory drugs

Anti-TNF- α treatment

Use of antibodies against pro-inflammatory cytokines could be beneficial in regulating loss of skeletal muscle. There are many studies that have highlighted the beneficial effect of some of these antibodies such as anti-TNF α , anti-IL-1, and anti-IL-6 on preserving the muscle loss and restoring their function.¹¹⁹ Some of these antibodies are under phase I/II/III trials predominantly in patients with cancer cachexia. One animal study showed that anti-TNF α treatment reduces the skeletal muscle wasting in cardiac cachexia and preserves the body mass.¹²²

Thalidomide has shown its anti-cachectic property in cancer patients by down-regulating the TNF α mRNA expression. It also prevents the nuclear translocation of NF- κ B along with reduction of serum levels of IL-6 and CRP in the cancer-cachexia patients.^{123,124}

Pentoxifylline is also known as suppressor of TNF production, and this property makes it helpful in prevention of skeletal muscle wasting in cancer, sepsis, trauma, and AIDS models.^{125,126}

OHR/AVR118 is a broad-spectrum peptide-nucleic acid immune-modulator with anti-inflammatory activity that targets both cellular pro-inflammatory chemokine and cytokine synthesis (such as TNF- α and IL-6). A phase II trial of this drug

on patients with advanced cancer and cachexia achieved stabilization of body weight, body fat, and muscle mass with a significant increase in appetite without showing any adverse effect.¹²⁷ Additionally, this drug has also been used for treatment of AIDS cachexia patients.¹¹⁹

Appetite stimulants

Megestrol acetate

Previous studies have shown beneficial results in humans with cancer cachexia using appetite stimulants such as megestrol acetate (with or without thalidomide, formoterol, and L-carnitin) to improve skeletal muscle mass and strength.^{128–130} Beginning in 1993, megestrol acetate was approved in the USA and in several European countries for the treatment of the anorexia–cachexia syndrome.¹³¹ The precise mechanism by which weight gain is mediated is unknown, but studies suggest the role of neuropeptide Y, the inhibition of pro-inflammatory cytokines, and the modulation of calcium channels in the ventromedial hypothalamus.^{132–134}

Cannabinoids are known to stimulate appetite as well.⁶⁵ The mechanism by which cannabinoids exert their effects is not elucidated, but it was suggested that they may act via endorphin receptors, by inhibiting prostaglandin synthesis, or may suppress cytokine production and/or secretion.^{135,136}

Ghrelin administration has therapeutic appeal for its anabolic activities.¹³⁷ Ghrelin agonists such as *anamorelin* carry potential in the treatment of cachexia as they mimic a natural ligand for the growth hormone secretagogue receptor and thus stimulate food intake and appetite.²¹ The single study in humans showed that repeated administration of ghrelin improved left ventricular function, exercise capacity, and muscle wasting in patients with HF.¹³⁸ In the recent study in patients with lung carcinoma and cachexia, anamorelin significantly increased body weight, improved muscle strength and quality of life, and had an overall favourable safety/tolerability profile.¹³⁹ The largest human trial with anamorelin intervention ROMANA 2 phase III trial that included 495 patients with non-small cell lung cancer was recently finished, but results have not been reported so far.¹⁴⁰ Another study have shown that the ghrelin agonist, *capromelin*, increased lean mass and physical performance over one year in older sarcopenic individuals.¹⁴¹

Other drugs for treatment of cardiac cachexia/non-cardiac cachexia

Anabolic steroids including testosterone have been effectively used to treat muscle wasting in HF.²² The problem with the administration of anabolic steroids are adverse events that outweigh their potential benefits. Selective androgen receptor modulators (*SARMs*) belong to a relatively new class of therapeutics currently under development that possesses anabolic properties without adverse effects on prostate, skin, or hair frequently associated with testosterone treatment.^{56,142}

Enobosarm, an orally bioavailable non-steroidal SARM with tissue-specific anabolic and androgenic activity, has shown amelioration in lean mass and physical function in healthy younger as well as in healthy elderly men and postmenopausal women.^{143,144} In patients with cancer, treatment with enobosarm confirmed its beneficial effect on skeletal muscle mass and physical performance.¹⁴⁵ Dobs *et al.* established a SARM, enobosarm, as a new drug for the prevention and treatment of muscle wasting in cancer patients.¹⁴⁶ Takagi *et al.* recently presented another new SARM (*TEI-E0001*) as a novel long acting SARM.¹⁴⁷ In the animal model, they demonstrated that TEI-E0001 has potent anabolic activity on the muscle and bone, while reducing androgenic side effects. *GLPG0492*(galapagos) is another non-steroidal SARM that has shown its efficacy on muscle by increasing muscle fibre size and skeletal muscle function in the hind limb of immobilized mice and in Duchenne muscular dystrophy patients, respectively.^{148,149}

β-2 receptor agonists

β-2 receptor agonism is involved in the regulation of skeletal muscle proliferation and differentiation programmes, and these properties make this receptor signaling pathway a novel therapeutic target for controlling the skeletal muscle wasting.^{150,151} A novel anabolic agent *espidolol* (*MT-102*) has recently been established. Animal experiments in 19-month-old male Wistar Han rats have shown that espidolol can abolish the effects of ageing-related body and muscle wasting.¹⁵² It appears to possess three potential pharmacological targets in cancer cachexia: (i) reduced catabolism through non-selective β-blockade, (ii) reduced fatigue and thermogenesis through central 5-HT1a antagonism, and (iii) increased anabolism through partial β-2 receptor agonism.¹⁵³ The ACT-ONE trial has recently demonstrated that MT-102 counteracted body wasting and some aspects of physical performance in 87 patients with cancer cachexia.^{46,154} Another β-2 receptor agonist, *formoterol*, induced reduction of muscle weight loss in cachectic tumour-bearing rats and showed no influence on heart weight and seems to improve heart function.¹⁵⁵ Thus, MT-102 and formoterol seem to be prospective new drugs to treat patients with cancer cachexia, especially if they present signs of declined cardiac function.⁴⁶

Myostatin antagonist

REGN1033 and *Bimagrumab* (*BYM338*) are two human mono-clonal antibodies against myostatin.¹¹⁹ The administration of myostatin antagonist (*REGN1033*) induced increase of muscle mass, force, and physical performance outcomes in aged mice and prevents the loss of muscle mass.¹⁵⁶ The treatment with *BYM338* enhances differentiation of primary human skeletal myoblasts and increases skeletal muscle mass in mice by blocking the activin type II B receptors (*ActRIIB*).¹¹⁹ A soluble form of the *activin type IIB receptor* (*ActRIIB/Fc*; *ACVR2B-ACE031*) can inhibit myostatin signalling and

significantly increases muscle growth in mice bearing cancer.¹⁵⁷ Overall *BYM338*, *REGN1033*, and soluble *ActRIIB/Fc* are promising drugs that have the ability to regulate muscle wasting/cachexia by blocking myostatin/activin signaling under diverse pathological conditions including cancer.

Enzyme inhibitors

Several enzyme inhibitors (*Cox2* inhibitors, *Trichostatin A*, *PDE* inhibitors—*torbafylline*) showed promising results in suppressing muscle loss in animal models of cachexia.¹¹⁹ Additionally, *Cox2* inhibitor, *celecoxib* has showed a beneficial effect against muscle loss in patients with cancer and arthritis-induced cachexia.

IGF1 analogues

'*Long arginine*' *IGF1* is a modified form of *IGF1* that has a long circulation time, binds to more tissue targets and is more potent than endogenous *IGF1*.⁴³ Its ability to induce myoblast proliferation offers greater therapeutic potential. However, several more potent variants have been developed that have prolonged circulation times and have reduced association with inhibitory *IGF1* binding proteins.¹⁵⁸

APD209

APD209 is an oral, fixed-dose combination of megestrol and formoterol for use in treatment of cancer cachexia at the moment.¹¹⁹

Statins

Along with the primary effect of cholesterol lowering, statins have many ancillary actions that may be relevant for body wasting.⁶⁵ In this context, the fear of muscle-related side effects needs to be put into clinical context and assessed appropriately before statins are either withheld or withdrawn in patients with sarcopenia/cachexia.¹⁵⁹ In fact, several reports suggest statins may even have beneficial effects by preserving or even increasing body compartments (muscle and fat). In an animal model of cancer cachexia, simvastatin vs. placebo attenuated body weight loss (28–48%, depending on dose, $P < 0.05$ for all), mainly because of the preservation of muscle mass.¹⁶⁰ With the improvement of cardiac function, this translated into improved survival with simvastatin. Statins were also associated with an increase of lean mass as measured by DEXA following 12 week resistance training.¹⁶¹ Lean mass gain was higher in those subjects who had higher dietary cholesterol intake and higher serum cholesterol.

Muscle regeneration

One theoretical approach is to use *stem cells* to help replace degenerated muscle tissue.⁹² Recent studies demonstrated different types of stem cells that have been attributed to be endowed with muscle regenerative potential.^{59,162} The possibility to reprogram all the cells of the body to muscle presents a revolutionary concept, importantly widening the range of muscle sources for the treatment of muscle dysfunction.

Ventricular assist device

The improvement of cardiovascular circulatory support by ventricular assist device in terminal HF patients corrects GH/IGF-1 signaling along with amelioration of muscle structure and function with enhancement of oxidative muscle metabolism.¹⁶³

Gaps in evidence-based management of body wasting and cachexia

To improve design of interventional trials, we need to gain better insight into epidemiology, trajectories, and pathways of body wasting in chronic disease. It is not irrelevant how and why the patients die.¹⁶⁴ Knowing the most common causes and also modes of death can lead to application of well-established therapies, e.g. beta blockers or devices for sudden cardiac death. Body wasting and cachexia are usually recognized when patients experience certain limitations in activities of daily living; at this stage, underlying mechanisms are well advanced and tissue damage is already present. Biomarkers that could pick up the changes before they convey into clinical manifestations would be of great importance. For these purposes, blood and/or urine analysis is attractive, with several candidates to assess muscle wasting and quality that are in clinical testing.^{87,89,165} The complex biochemical network related with CC and HF pathophysiology underlines that a single biomarker cannot reflect all of the features of the disease. Consequently, future studies should be focused on the use of a combination of multiple biomarkers in order to establish an optimal network that better reflects all of the characteristic of the syndrome. As there is up-regulation of proteolysis in CC, it is expected an augmentation of cleavage products from proteases as caspases, calpains, or cathepsins.^{60,166} Its measurement may more specifically express cachectic biological processes leading to fatal outcome. In addition to proteolysis, other protein modifications such as oxidation as a result of oxidative stress,^{60,166} which also should be considered in the definition of multimarker strategies. Finally, whether use of *proteomics* and *metabolomics* analysis may contribute in better biomarker evaluation of CC is still unknown as this has not been still assessed in that condition.

A better understanding of pathophysiological pathways in body wasting will contribute to establish potentially novel treatment strategies. Whether the use of *microdialysis* on skeletal muscle may be of help in regard to this aim will be soon evaluated in our study in acutely decompensated HF patients. Microdialysis is a technique designed to explore and monitor the chemistry of extracellular fluid of virtually any tissue or cell culture medium.¹⁶⁷

The intriguing concept to reprogram all the cells of the body to muscle presents a revolutionary idea, importantly widening the range of muscle sources for the treatment of

muscle dysfunction.⁵⁹ Further studies are warranted on the potential of *stem cell therapy* to counteract the muscle wasting including identification of mechanisms whereby chronic disease lead to lower satellite cell function that would have the therapeutic potential to reverse the reduction in muscle regeneration seen in cachexia conditions.

The scientific community is much engaged in interventional trials to find a remedy for muscle wasting and cachexia. It should be emphasized that translation of benefits from the non-cachectic population to cachexia may not be straightforward as drug pharmacokinetics changes with body wasting.^{168,169} Ongoing trials are heterogenous in design and include a wide span of chronic disease.^{94,112} A direct comparison of findings will be difficult as enrolment criteria (including sarcopenia/cachexia definition) vary and because different endpoints are being pursued. On top of that, different analysis plans are used for different regulatory authorities. Many experts have called for a unified approach, and their notion has now materialized in a consensus document.¹⁷⁰ Following this guidance, better use of available resources for adequately powered trials with meaningful clinical endpoints is anticipated. Most of the candidate compounds are newly developed; thus, safety issues deserve particular attention. This should not be limited only to acute side effects but also to drug–drug interactions and long-term safety profile.

Conclusions

Cardiac cachexia (CC) is the clinical entity at the end of the chronic natural course of HF. A simplistic view could be that with effective prevention, incidence of CC would be low or non-existing. In the real world, multiple factors influence disease trajectories in this syndrome. Detection of the pathways that modulate muscle wasting and dysfunction will provide important information for the definition of CC-specific biomarkers and for the development of medications that counteract muscle impairment, which will certainly improve the treatment of this serious disorder.

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Conflict of interest

None declared.

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