



Sarcopenia in heart failure: mechanisms and therapeutic strategies

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Abstract

Chronic heart failure (CHF) is a highly prevalent condition among the elderly and is associated with considerable morbidity, institutionalization and mortality. In its advanced stages, CHF is often accompanied by the loss of muscle mass and strength. Sarcopenia is a geriatric syndrome that has been actively studied in recent years due to its association with a wide range of adverse health outcomes. The goal of this review is to discuss the relationship between CHF and sarcopenia, with a focus on shared pathophysiological pathways and treatments. Malnutrition, systemic inflammation, endocrine imbalances, and oxidative stress appear to connect sarcopenia and CHF. At the muscular level, alterations of the ubiquitin proteasome system, myostatin signaling, and apoptosis have been described in both sarcopenia and CHF and could play a role in the loss of muscle mass and function. Possible therapeutic strategies to impede the progression of muscle wasting in CHF patients include protein and vitamin D supplementation, structured physical exercise, and the administration of angiotensin-converting enzyme inhibitors and β -blockers. Hormonal supplementation with growth hormone, testosterone, and ghrelin is also discussed as a potential treatment.

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1 Introduction

Chronic heart failure (CHF) affects approximately 2% of the population in Western countries.^[1] Noticeably, the prevalence of CHF increases dramatically with age, doubling approximately every 10 years in men and every seven years in women past the age of 55 years.^[2] As a result, elderly people represent over 80% of all CHF patients. The disproportionate prevalence of CHF in late life is largely attributable to long-term exposure to cardiovascular risk factors. In addition, intrinsic cardiovascular aging, defined as the development of structural and functional alterations during aging, may render the heart more vulnerable to various stressors, which ultimately favors the development of CHF.^[3] It is also worth mentioning that the implementation of more effective therapeutics has increased life expectancy in individuals with CHF, with the result that a larger share of these patients survive into old age.^[4]

Heart dysfunction is a major factor limiting physical performance in CHF patients. Skeletal muscle abnormalities, which often accompany CHF, may also contribute to fatigue and dyspnea.^[5] In old age, the superimposition of “cardiac skeletal myopathy” with age-dependent muscle decline may lead to more severe functional impairment.^[6] To further complicate the matter, 10%–15% of CHF patients develop cardiac cachexia, a condition characterized by the loss of body weight due to muscle wasting and adipose tissue demise.^[7] Cardiac cachexia has a dramatic prognostic impact in CHF patients, with an 18-month mortality rate of up to 50%.^[8] Besides, cardiac cachexia worsens the functional capacity of patients with CHF above and beyond the deterioration that might be predicted by the assessment of cardiac dysfunction.^[8]

While the loss of body weight is a defining component of cachexia, sarcopenia (i.e., the age-related loss of muscle mass and strength/function) is not necessarily associated with changes in body weight, because declining muscle mass can be masked by proportional increases in adipose tissue. Such a phenomenon may hinder the clinical detection of sarcopenia and requires the use of imaging techniques, including dual-energy X-ray absorptiometry, computed tomography or magnetic resonance imaging, for muscle mass

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quantification. From a clinical perspective, it is virtually impossible to distinguish between sarcopenia and cachexia-related muscle wasting in advanced stages of CHF. Yet, it should be noted that muscle mass is lost earlier than adipose tissue during the progression of CHF. As such, older patients with CHF may develop sarcopenia before becoming cachectic, by progressing along a theoretical “wasting continuum.”^[6] Although sarcopenia is primarily an age-dependent phenomenon, its course is accelerated by the co-occurrence of disease conditions, including among others CHF.^[9] Indeed, sarcopenia affects approximately 20% of older adults with CHF, which exceeds the prevalence observed in individuals of the same age without CHF.^[10] Remarkably, older CHF patients with sarcopenia show a lower exercise capacity than those with preserved muscle mass and function.^[10] This finding suggests that the recognition of sarcopenia in the context of CHF and the implementation of *ad hoc* therapeutic strategies may help ameliorate the patients’ functional capacity, before the wasting disorder enters its later stages.

This review focuses on sarcopenia and “cardiac skeletal myopathy” in CHF patients, highlighting common pathophysiological mechanisms and shared therapeutic strategies.

2 Shared pathophysiological pathways between sarcopenia and CHF

Patients with severe CHF exhibit multiple histological abnormalities in skeletal muscle, collectively referred to as “cardiac skeletal myopathy.”^[11] Two thirds of cases of advanced CHF experience myofiber atrophy and decreased muscular capillary density. Type I to type II fiber switch is also commonly observed.^[12] Such an inversion, together with reductions in mitochondrial cristae surface area, cytochrome C oxidase activity and mitochondrial volume density, contributes to impairing exercise tolerance.^[12] Finally, myofiber roundness secondary to intra-fibrillar edema and the deposition of fibrotic and adipose tissue alter muscular structure and fiber orientation, further reducing force-generating capacity.^[12,13]

The nature of muscular changes in sarcopenia is quite different. During aging, as a consequence of selective denervation and the loss of fast motor units, type II fibers are more prone to atrophy than type I fibers, with a 26% reduction of the cross sectional area of fast-twitch fibers in individuals aged 80 years compared to 20-year-olds. From approximately the age of 80 onwards, both types of fibers are lost. The denervation and loss of fast motor units begins at the age of 60 years at a rate of 3% annually, which leads to a 60% loss of fibers by the age of 80 years. The infiltration of

fat and connective tissue is another important contributor to declining muscle quality.^[14]

The frequent coexistence of sarcopenia and CHF is likely the result of their shared pathophysiological pathways involving altered nutrient intake and absorption, inflammatory processes and metabolic and autonomic disturbances. These combined processes result in ultra-structural muscle abnormalities, alterations of mitochondrial structure and function, enhanced oxidative stress, and a shift in fiber distribution, eventually leading to reduced exercise capacity.

The following paragraphs provide an overview of the major mechanisms involved in the development of sarcopenia in the context of CHF (Figure 1), including malnutrition, inflammation, humoral factors, the ubiquitin proteasome system (UPS), myostatin signaling, apoptosis, and oxidative stress.

2.1 Malnutrition

Patients with CHF frequently develop anorexia as a result of dysgeusia, nausea and gastroenteropathy, the latter being secondary to intestinal edema which also causes malabsorption. Moreover, several drugs prescribed to treat CHF can lead to a reduction in appetite [e.g., digoxin, angiotensin-converting enzyme (ACE) inhibitors, and β -blockers]. In addition, diuretics may favor a loss of nutrients through urination. Collectively, an insufficient intake or absorption of primary nutritional elements, or their loss, predisposes patients with CHF to malnutrition and paves the way for muscle depletion.

2.2 Inflammation

Inflammatory markers are typically elevated in individuals with CHF. Inflammation is also involved in the pathogenesis of sarcopenia, therefore representing a fundamental point of contact between the two conditions. Notably, tumor necrosis factor alpha (TNF- α) and its soluble receptors have been associated with declines in muscle mass and strength over five years of follow-up in a sample of more than 2000 older adults participating in the Health, Aging and Body Composition (Health ABC) study.^[15]

The mechanisms whereby inflammation impacts muscle physiology are multifold. TNF- α induces apoptosis of myonuclei,^[16] while the transcription factor NF- κ B stimulates proteolysis and inhibits the transcription of genes coding for myosin heavy chain.^[17] TNF- α also stimulates the local synthesis of other pro-inflammatory cytokines through a paracrine effect. Sato, *et al.*^[18] demonstrated that the TNF-like weak inducer of apoptosis (TWEAK) decreased mitochondrial content and oxidative phosphorylation, and inhibited angiogenesis in skeletal muscle.

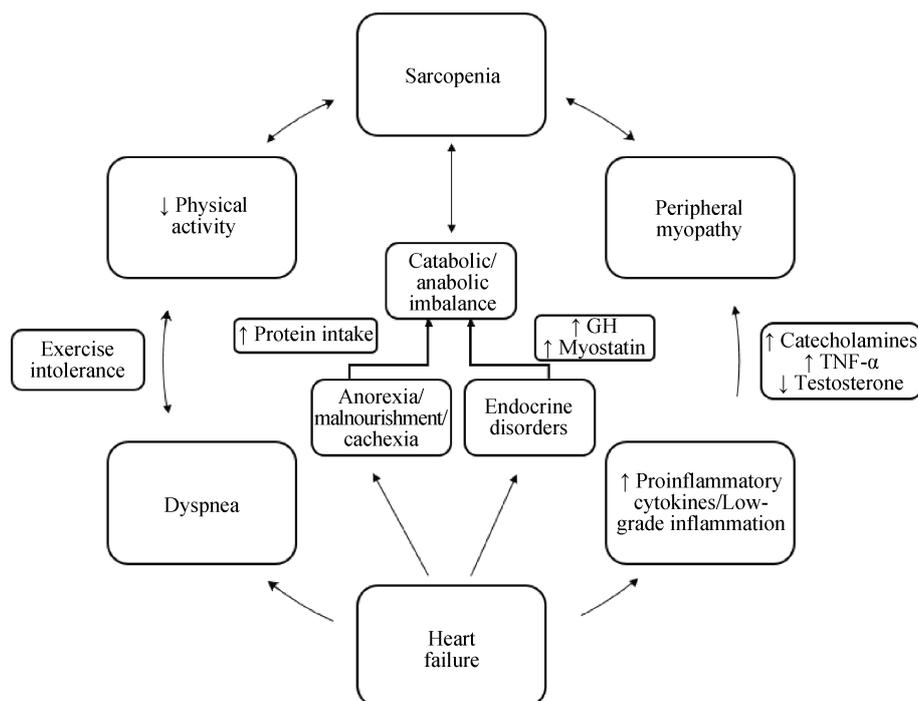


Figure 1. Interaction and common pathways between sarcopenia and heart failure. GH: growth hormone.

Among the possible causes of TNF- α elevation in CHF is the endotoxin hypothesis. It suggests that bowel wall edema, a common condition in CHF, would alter gut permeability to endotoxin-like lipopolysaccharide (LPS), a potent inflammatory stimulator and inducer of monocyte activation.^[19] Finally, even if TNF- α production is mostly controlled by mononuclear cells, its overexpression is also sustained by catecholamines, the concentrations of which are usually elevated in CHF patients as a response to myocardial injury and peripheral tissue hypoxia.^[20]

Schaap, *et al.*^[21] demonstrated that higher levels of interleukin (IL) 6 and C-reactive protein (CRP) increased the risk of muscle strength loss in the longitudinal aging study of Amsterdam. Finally, IL-1, IL-6 and TNF- α are linked to the activation of the UPS and may induce anorexia and lipolysis, thus contributing to weight loss.^[22]

2.3 Humoral factors

A decline in anabolic hormones has been described in sarcopenia. Indeed, age-related decreases in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels are linked to reduced muscle mass and function.^[23] In CHF patients, the expression of IGF-1 in muscle is blunted in the face of normal serum IGF-1 levels, possibly contributing to muscle mass loss.^[24] However, attempts to manage sarcopenia through IGF-1 and GH supplementation have produced conflicting results.^[25] The administration of GH at high doses in rats with HF decreased not only muscle

atrophy but also serum levels of TNF- α and the number of apoptotic myonuclei, possibly through IGF-1 over-expression.^[26] Conversely, IGF-1 administration to old rats did not produce any sizeable changes in muscle mass or strength.^[27]

Ghrelin is a peptide hormone produced primarily in the fundus region of the stomach with pleiotropic actions, including GH secretagogue effects. Ghrelin has recently gained attention since it appears to inhibit sympathetic nerve activity through a vasodilative effect, in order to regulate appetite via GH-independent mechanisms and to inhibit pro-inflammatory cytokine production.^[22] Moreover, ghrelin negatively controls the secretion of leptin, a product of the *ob* gene, which decreases food intake, increases resting energy expenditure, and upregulates transforming growth factor beta 1 (TGF- β 1), augmenting the fibrogenic response and leptin-induced cytokine expression.^[28]

Testosterone has been investigated as a possible factor involved in sarcopenia.^[29] Furthermore, low testosterone levels, a common finding in CHF patients, is thought to contribute to the progression of cardiac dysfunction through altered peripheral vascular resistance, increased cardiac afterload, and decreased cardiac output.^[30]

Angiotensin II, besides being involved in blood pressure control and cardiac remodeling, may also play a role in muscle wasting. Brink, *et al.*^[31] showed that the infusion of angiotensin II resulted in the loss of body weight and muscle mass in rats. In such a model, muscle wasting was pri-

marily attributed to UPS-mediated protein degradation. Other preclinical studies showed that the administration of ACE-inhibitors or angiotensin II type 1 receptor blockers (ARBs) reduced the extent of myocyte apoptosis and mitochondrial free radical generation, while improving nitric oxide (NO) signaling and the expression of the mammalian target of rapamycin (mTOR) in old rats.^[32,33]

2.4 The UPS

Muscle protein breakdown in patients with CHF has been primarily attributed to overactivation of the UPS pathway.^[34] The UPS involves a multi-subunit protease that specifically degrades ubiquitin-conjugated proteins through the action of three enzymes, the ubiquitin-activating enzyme, the ubiquitin-conjugating enzyme and ubiquitin ligases (atrogin-1 and MuRF-1).^[34] Elevated levels of MuRF-1 have been detected in skeletal muscle of patients with CHF.^[35] Inducers of MuRF-1 expression are pro-inflammatory cytokines such as TNF- α , IL-6, and IL1 β . Whether the UPS is activated in sarcopenic muscle is still under debate with some studies showing a marked increase in UPS activity,^[36] others finding only a small degree of UPS activation,^[37] and others still failing to demonstrate any connection at all.^[38]

2.5 Myostatin signaling

Myostatin, also known as growth differentiation factor 8, is a negative regulator of muscle mass. Myostatin is primarily expressed in skeletal muscle where it acts as an inducer of muscle atrophy.^[39] Myostatin is further expressed in the myocardium where it exerts an anti-hypertrophic, but pro-fibrotic effect.^[39] It has been demonstrated that myostatin gene and protein expression is increased in older men relative to younger individuals.^[40] The downregulation of myostatin's gene expression leads to muscle hypertrophy and hyperplasia and myostatin-null mice show an increase in the cross-sectional area of type II fibers.^[41] It is interesting to note that the baseline expression of myostatin mRNA was found to be about 50% higher in vastus lateralis muscle biopsies from patients with CHF than in those obtained from healthy age-matched controls.^[35] Shyu, *et al.*^[42] showed that myocardial myostatin expression was also up-regulated in a rat model of volume overload-induced HF. Interestingly, Heineke, *et al.*^[43] demonstrated that myostatin released from cardiomyocytes induced muscle atrophy in HF. These authors also showed that the infusion of the myostatin-blocking antibody JA-16 promoted greater maintenance of muscle mass in mice with HF, paving the way for myostatin inhibition as a candidate therapeutic target. However, myostatin-blocking agents need to be tested thoroughly in preclinical models before their safety and

effectiveness can be evaluated in clinical studies of patients with CHF.^[39]

2.6 Apoptosis in myocytes

In recent years, the accelerated elimination of myonuclei through an apoptosis-like process (myonuclear apoptosis) has been proposed as a mechanism contributing to sarcopenia.^[44] Several apoptotic pathways have been linked with age-related muscle atrophy. In particular, the death receptor-mediated pathway of apoptosis, triggered by TNF- α , has been shown to be activated in the skeletal muscle of older rodents,^[27] suggesting its possible involvement in age-related muscle loss. Marzetti, *et al.*^[45] showed that aging is associated with decreased IL-15 signaling in rat gastrocnemius muscle, which may contribute to sarcopenia partly through enhanced TNF- α mediated apoptosis. Notably, TNF- α -related and mitochondrion-mediated apoptotic signaling was found to predict low muscle mass and slow gait speed in a sample of older adults.^[46]

A higher frequency of myonuclear apoptosis has also been found in the muscle of patients with CHF relative to age-matched healthy controls.^[47] In this same study, cardiac cachexia was not accompanied by the elevation of myocyte apoptosis, but was instead associated with increased fibrosis, suggesting a divergent mechanism of muscle wasting in CHF and cachexia.

2.7 Oxidative stress

Under physiological conditions, aerobic metabolism generates small amounts of reactive oxygen species (ROS) which are rapidly detoxified by endogenous antioxidant systems. When an imbalance between pro-oxidants and antioxidants exists, oxidative stress occurs. ROS production increases as an organism ages and is postulated to be one of the factors leading to senescence.^[48] ROS can accelerate skeletal muscle degeneration since they accumulate during contractile activity, while the muscle enzymatic scavenger systems (such as catalase, glutathione transferase, and superoxide dismutase) decline with age.^[49]

Elevated levels of oxidative stress markers have been documented in CHF patients and have correlated with NYHA class, reduced exercise tolerance, lower antioxidant levels, and other indices of worse prognosis.^[50] The underlying mechanisms could be related to endothelial dysfunction, tissue ischemia and hypoxia, and alterations of the xanthine oxidase system.^[51] Further research on these pathways may possibly lead to the development of new strategies targeting ROS generation systems and antioxidant agents to maintain muscle homeostasis in CHF.

The following provide an overview of the major mecha-

nisms involved in the development of sarcopenia in the context of CHF (Figure 1), including malnutrition, inflammation, humoral factors, the ubiquitin proteasome system (UPS), myostatin signaling, apoptosis, and oxidative stress.

3 Treatment

As of now, no treatment is available to specifically prevent muscle wasting or restore muscle health in CHF. ACE-inhibitors, β -blockers, and mineralocorticoid-receptor antagonists at their maximal tolerated doses should be offered to all patients with CHF. It is interesting to note that, besides their beneficial effect on survival, some of these agents, in particular ACE-inhibitors, may offer therapeutic advantage in sarcopenic patients irrespective of CHF. Apart from cardiological treatments, nutritional support and physical activity seem to convey remarkable benefits on muscle function and physical performance in patients with CHF. Anti-inflammatory agents, appetite-stimulating drugs, inhibitors of proteolysis and apoptosis, and specific hormonal supplementation regimens are currently under study as possible future therapeutic options. The following subsections provide an overview of treatment strategies that can simultaneously target cardiac dysfunction and sarcopenia.

3.1 Nutritional supplementation

In order to maintain muscle mass, restore energy reserves and improve exercise capacity, an adequate nutritional status must be achieved and maintained in all CHF patients. The relationship between protein/caloric intake and muscle mass has been actively investigated in the context of sarcopenia.^[52] It is widely acknowledged that the provision of adequate amounts of protein and several other nutrients is instrumental to preserving muscle homeostasis in older adults.^[53]

Although evidence is still preliminary, available data suggest that specific dietary regimens or nutrient supplementations may offer therapeutic gain in CHF patients with sarcopenia. For instance, Rozenryt, *et al.*^[54] performed a clinical, randomized, double-blind, placebo-controlled pilot study in which 29 patients with CHF and cachexia were allocated to either a high-caloric (600 kcal) high-protein (20 g) oral nutritional supplement in addition to usual food intake or placebo for six weeks. The active intervention group experienced increased body weight (70% fat tissue, 30% muscle tissue) during treatment and the subsequent 12-week follow-up period, and showed reduced systemic TNF- α levels. The quality of life of patients was significantly improved during the first six weeks of the intervention, but decreased somewhat in the follow-up. Moreover, in a ran-

domized, placebo controlled, double-blind trial conducted in 38 stable CHF patients with severe muscle depletion, supplementation with essential amino acids improved exercise output, peak oxygen consumption and walking capacity during two months of follow-up.^[55]

3.2 Physical activity

The effectiveness of physical activity in achieving and maintaining cardiorespiratory, musculoskeletal, and neuro-motor fitness is undisputed.^[56] In patients with CHF, engaging in aerobic exercise with or without a resistance training component has been associated with a reduced hospitalization rate and an improved health-related quality of life.^[57] As such, the European Society of Cardiology recommends CHF patients engage in regular aerobic exercise to improve functional capacity and symptoms.^[58]

Physical exercise is also recognized as one of the most effective interventions for sarcopenia.^[59] Consequently, it is reasonable to believe that exercise training may provide a remarkable therapeutic advantage in the management of muscle wasting in the context of CHF. Indeed, physical exercise has been shown to act on most of the pathways proposed to underlie CHF-associated muscle decline, including the UPS pathway,^[60] inflammation,^[61] and myostatin signaling.^[62] In addition, physical exercise may enhance vagal tone and decrease sympathetic activity, thereby improving endothelial function in CHF patients.^[63,64] As a result, a consensus statement produced by the European Association for Cardiovascular Prevention and Rehabilitation recommends practicing regular physical activity for the prevention of body wasting in CHF.^[65] Future, large-scale clinical trials are needed to establish the type, duration and frequency of physical exercise needed to maximize the benefits and reduce the risk of adverse events.

3.3 Hormonal treatment

3.3.1 Testosterone

Testosterone deficiency is frequently observed in patients with CHF and is associated with muscle wasting, reduced functional capacity, and increased mortality.^[66,67] Caminiti, *et al.*^[68] studied 70 men with stable CHF who were randomly assigned to receive either intramuscular injections of testosterone every six weeks or a placebo. In the intervention group, peak VO₂, walk distance and body weight improved significantly after 12 weeks of treatment. Similar results were obtained in a related study that tested the effect of testosterone transdermal patches versus placebo in older women with CHF.^[69] Other reports showed that testosterone administration increased both strength and walking distance in patients with CHF.^[70,71]

While testosterone has been utilized as a therapeutic agent since the 1940s, there is a fear that it may produce excessive side effects.^[72] A meta-analysis of controlled studies of testosterone supplementation in older men found no increase in mortality.^[73] However, there is still some controversy surrounding potentially adverse cardiovascular effects, particularly during the first three months of treatment.^[74,75] Selective androgen receptor modulators (SARMs) have therefore been explored as an alternative option since they may theoretically be safer. These agents are emerging as a new class of anabolic therapies for a number of clinical indications, including sarcopenia, osteoporosis, CHF, and cachexia. Preclinical studies and small clinical trials have shown positive effects of SARMs on sarcopenia and cachexia, but their efficacy and safety need to be definitively established through larger-scale trials.^[76]

3.3.2 GH

GH administration for the management of sarcopenia in CHF patients has seen significant trial activity in the past, but its clinical benefits are still disputed. Improvements in cardiac function and exercise capacity were observed in a small-scale, open-label trial in patients with idiopathic dilated cardiomyopathy and moderate-to-severe HF.^[77] Similar benefits were achieved in 22 patients with CHF of different etiologies and reduced ejection fraction treated with recombinant human GH for three months.^[78] Conversely, no symptomatic or functional improvements were observed in patients with dilated cardiomyopathy by Osterziel, *et al.*^[79] in the largest clinical trial on GH supplementation conducted thus far.

Despite these conflicted findings, interest in GH as a treatment option in sarcopenic patients with CHF has not disappeared, but more research is needed to properly assess its safety profile and efficacy.

3.3.3 Ghrelin

Ghrelin is a peptide hormone mainly produced in the fundus region of the stomach that promotes gastric motility, stimulates appetite, and induces GH release.^[80] Due to its anabolic, orexigenic, and anti-inflammatory properties, ghrelin represents a promising treatment option for muscle wasting associated with aging and various disease conditions. A small, uncontrolled study of intravenous infusion of ghrelin in 10 patients with CHF showed improvements in left ventricular function, exercise capacity, muscle strength, and lean body mass.^[81] The main disadvantages of ghrelin as a therapeutic agent are its short half-life and need for intravenous administration. These limitations have been overcome by the development of ghrelin receptor agonists

with longer half-lives and the opportunity for oral administration. Some ghrelin agonists have already shown promising results in animal models of HF-related body wasting, reducing, for example, the expression of myostatin in skeletal muscle and increasing lean and fat mass.^[82,83]

3.3.4 Vitamin D

Low serum levels of vitamin D have been associated with reduced muscle mass and physical performance in older people with and without CHF.^[84,85] As such, vitamin D supplementation is regarded as an appealing strategy to manage sarcopenia also in the setting of CHF. A recent study showed that a 13-week supplementation with vitamin D and leucine-enriched whey protein improved appendicular muscle mass and lower-extremity function among sarcopenic older adults.^[86] Along the same lines, another recent study carried out in post-menopausal women demonstrated that vitamin D increased muscle strength and prevented the loss of muscle mass during nine months of follow-up.^[87]

It is noteworthy that vitamin D influences the pathophysiology of CHF, by modulating the renin-angiotensin system, calcium handling, inflammation, blood pressure, and endothelial function.^[88] Indeed, vitamin D deficiency is common in patients with CHF, especially elderly, obese and black populations, and is associated with adverse outcomes.^[89]

A recent meta-analysis of seven randomized controlled trials affirmed that vitamin D supplementation may decrease serum levels of parathyroid hormone and inflammatory cytokines (i.e., TNF- α and CRP) in CHF patients, whereas no beneficial effects were demonstrated for left ventricular function or exercise tolerance.^[89] These results warrant further investigations to assess whether add-on supplementation therapy including vitamin D, which could have a role in the management of sarcopenic patients with CHF.

3.4 Cardiovascular drugs

3.4.1 ACE-inhibitors and ARBs

ACE inhibitors and ARBs, besides serving as first-line agents for the treatment of CHF, have also been shown to possess a plethora of extracardiac effects, some of which may be harnessed for the management of body wasting.^[90] For instance, Anker, *et al.*^[91] found that, among CHF patients, those taking the ACE-inhibitor enalapril had lower chances of losing weight compared with patients not taking that drug. An analysis of the Women's Health and Aging Study carried out by Onder, *et al.*^[92] showed that participants who had taken ACE-inhibitors continuously over a 3-year period had a lower decline in muscle strength and walk speed compared with those who had used ACE-in-

hibitors intermittently or not at all. The observational nature of these studies does not untangle whether the effects of ACE-inhibitors on physical performance are linked to direct actions on skeletal muscle or are secondary to improvements in hemodynamics. However, preclinical studies suggest that ACE-inhibitors and ARBs possess muscle-protective properties spanning mitochondrial function, oxidative stress, insulin sensitivity, NO signaling, and local inflammation.^[32,33,93]

The enthusiasm surrounding the possibility of using ACE-inhibitors to manage sarcopenia has been tempered by the finding that neither physical performance nor muscle strength were significantly affected after six months of fosinopril use in older persons with high cardiovascular risk profiles enrolled in the TRAIN study.^[94] Furthermore, a recent systematic review and meta-analysis concluded that treatment with ACE-inhibitors did not significantly improve walk distance or muscle strength among older participants in randomized clinical trials.^[95] Given these contrasting findings, specifically designed trials are needed to definitively establish if ACE-inhibitors and ARBs may offer therapeutic gain in the treatment of sarcopenia and CHF-related muscle wasting.

3.4.2 β -blockers

Like ACE-inhibitors, β -blockers represent a fundamental pillar in the treatment of CHF. Previous studies have also shown that carvedilol and bisoprolol reduce the risk of weight loss in patients with CHF.^[96,97] However, improvements in body weight in these patients appeared to be primarily attributable to the inhibition of lipolysis and gains in fat mass, whereas no muscle-specific effects could be demonstrated.^[98,99]

4 Conclusions

The pathophysiology of muscle wasting in CHF is complex and researchers are only beginning to understand the many different mechanisms involved in its pathogenesis. Available evidence suggests that sarcopenia and CHF share several pathways and they could therefore benefit from a common treatment plan. First-line agents for the management of CHF should be offered at their maximal tolerated dosages to all CHF patients, keeping in mind that some of these compounds (e.g., ACE-inhibitors and ARBs) may directly improve muscle homeostasis. A shared treatment plan should also include specific nutritional supplementation regimens, exercise training, vitamin D administration, and possibly the correction of certain hormonal derangements. Preclinical studies have shown that the inhibition of

UPS-dependent muscle protein degradation, myonuclear apoptosis and inflammation may offer therapeutic gain in muscle wasting associated with CHF. Future studies are warranted to establish the effectiveness and safety profile of compounds targeting these biological targets as well as to identify the subset of CHF patients that benefits the most from such treatments.

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