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Pharmacological management of cardiac cachexia: a review of potential therapy options

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Abstract

Cardiac cachexia is a syndrome of progressive skeletal muscle and fat loss affecting a significant number of congestive heart failure patients. With the potential detrimental effects of cardiac muscle wasting, greater attention is needed to understanding the prevention and treatment of the condition. Potential therapeutic approaches are aimed at the various mechanisms for the pathogenesis of cardiac cachexia including neurohormonal abnormalities, immune activation and inflammation, metabolic hormonal imbalance, and gastrointestinal abnormalities. While there are no current guideline-recommended treatments for the prevention of cardiac cachexia, targeting an imbalance of the renin-angiotensin-aldosterone system with beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers appears to be the most well-studied therapeutic approaches. Treatment of inflammation with monoclonal antibodies, hormonal imbalance with testosterone, and nutritional deficiencies with appetite stimulants has also been suggested. Proposed therapies may prove beneficial in heart failure patients; however, further studies specifically focusing on the cardiac component of cachexia are needed before definitive therapy options can be established.

Keywords Cachexia · Heart failure · Weight loss · Inflammation

Introduction

Cardiac cachexia is a syndrome of progressive skeletal muscle and fat loss induced by the functional abnormalities of the heart in patients with congestive heart failure. The term is derived from the Greek words *kakos* and *hexis* which together mean "bad condition" [1] and is often associated with increases in insulin resistance, anorexia, and inflammation [2]. As heart failure (HF) affects an estimated 6.5 million Americans over the age of 20 [3], the appropriate treatment of the condition as well as its deleterious effects is of utmost importance. Cardiac cachexia is thought to affect between 8 and 42% of patients with HF [4]. It is considered a risk factor for mortality independent of age, functional status, and ejection fraction [5] with a mortality rate in cachectic HF patients being as high as 20 to 30% at 1 year [6]. This makes cardiac cachexia an important factor to address when developing a treatment plan for HF patients.

Cachexia is defined by the 2008 Cachexia Consensus Conference as a metabolic syndrome resulting in the loss of muscle mass with or without fat loss in the presence of chronic illness. A diagnosis requires weight loss of at least 5% within 12 months (or BMI < 20 kg/m^2) as well as three out of five clinical factors (decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry (e.g., increased inflammatory markers, anemia, decreased albumin)) [7]. In most cardiology literature however, the definition of cardiac cachexia proposed by Anker et al. in 1997 is more commonly accepted. They define cardiac cachexia as unintentional weight loss of > 7.5% of dry body weight over at least a 6-month period in the absence of any other underlying cause [8]. Regardless of the definition used, there is consensus of the potential detrimental effects of cardiac-associated muscle

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wasting and the need for greater attention to treatment of the condition as cachexia has been linked to decrease in left ventricular mass, anemia, and gastrointestinal changes [4]. This review aims to discuss the various contributing factors to the development of cardiac cachexia and the available pharmacologic agents used for their prevention and treatment.

Therapeutic approaches and pharmacotherapy of cardiac cachexia

As many mechanisms for the pathogenesis of cardiac cachexia have been proposed, numerous potential targets for drug therapy exist. While no current treatment guidelines or definitive treatment options have been established for cardiac cachexia management, many potential therapeutic options have been studied, aimed at the various pathophysiologic components of the syndrome (Table 1).

Neurohormonal changes

An increase in the renin-angiotensin-aldosterone system (RAAS) is a hallmark characteristic of chronic heart failure. The compensatory mechanism is activated in response to a decrease in cardiac output and leads to increases in heart rate, vasoconstriction, and sodium reabsorption. While the short-term effects of RAAS activation result in an increase in cardiac output, continued activation is detrimental, resulting in overworking of the heart and consequent heart remodeling [23]. Sodium and subsequent water retention can lead to volume overload and congestive symptoms, vasoconstriction to decreased peripheral organ perfusion, and overactivity of the heart muscle to increased resting energy expenditure [24, 25].

Cachectic HF patients have been shown to have elevated levels of epinephrine, norepinephrine, cortisol, and aldosterone when compared to non-cachectic patients, implicating RAAS activation as one of the most important targets in

Table 1 summarizes the available evidence for the management of patients with cardiac cachexia

Therapeutic target	Potential therapy	Effects	Patient population	Reference
Neurohormonal imbalance	Beta-blockers	↑ weight gain ↓ plasma NE Partial reversal of cachexia	HF patients	Hryniewicz et al. [9]
	ACE inhibitors	↓ risk of weight loss and delayed cachexia development ↓ muscle strength decline, protective effect against muscle deterioration	HF patients Rat model	Anker et al. [10] Marzetti et al. [11]
	ARB	↓ left ventricular wall thinning ↓ plasma levels of proinflammatory cytokines	Mouse Model	Scherrer-Crosbie [12]
Immune activation and inflammation	Biologics	No benefit of etanercept over placebo No clinical benefit seen with infliximab	HF patient HF patient	Mann et al. [13] Chung et al. [14]
	Pentoxifylline	↓ TNF-α concentrations ↑ functional capacity ↑ LVEF ↓ skeletal muscle mass loss ↓ ubiquitin proteasome pathway activation	HF patients Rat model	Sliwa et al. [15] Steffen et al. [16]
Metabolic hormonal imbalance	Ghrelin	↑ food intake ↑ GH level ↑ left ventricular mass and LVEF ↑ muscle strength and lean muscle mass ↑ left ventricular function ↓ cardiac cachexia development	HF patients Rat model	von Haehling et al. [17] Nagaya et al. [18]
	Testosterone	↑ exercise capacity Improvement in NYHA functional class ↑ exercise capacity ↓ insulin resistance	HF patient (men) HF Patient	Malkin et al. [19] Toma et al. [20]
	Enobosarm	↑ lean body mass No adverse effects normally associated with testosterone	Cancer cachexia	von Haehling et al. [21]
Gastrointestinal abnormalities	Appetite stimulants	Megestrol acetate not effective in the treatment of non-cancer cachexia	Non-cancer cachexia (HIV, COPD, renal failure, geriatric cachexia)	Taylor et al. [22]

NE, norepinephrine; *HF*, heart failure; *ACE*, angiotensin converting enzyme; *ARB*, angiotensin receptor blocker; *TNF-α*, tumor necrosis factor-alpha; *LVEF*, left ventricular ejection fraction; *GH*, growth hormone; *NYHA*, New York Heart Association; *HIV*, human immunodeficiency virus; *COPD*, chronic obstructive pulmonary disease

combating cardiac cachexia [5]. Vasoconstriction from RAAS activation leads to decreased tissue perfusion and cellular hypoxia, inducing catabolism and preventing anabolism in muscle tissue [26]. Decreased perfusion to gastrointestinal organs additionally contributes to intestinal edema and malabsorption [5]. As stated by Okoshi et al., treatment of HF with neurohormonal blockade is able to "reverse cachexia independently of nutritional support" [4]. While therapies such as beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB) are guideline-recommended therapies for the treatment of HF for the prevention of cardiac remodeling [27], studies have shown that their effects can also result in the prevention of cachexia development [9–12].

Beta blockers Beta blockers exert their effects by binding to beta-1 adrenergic receptors of the heart, preventing their activation by catecholamines (epinephrine and norepinephrine) [23]. Beta-1 blockade results in decreased inotropic and chronotropic effects on the heart leading to a decrease in resting energy expenditure and lipolysis [9]. In cachectic HF patients, Hryniewicz et al. showed that long-term use of beta-blockers (carvedilol and long-acting metoprolol) was associated with an increase in weight gain, reduction of plasma norepinephrine, and partial reversal of cachexia. The increase in weight gain seen with beta-blockers may be associated with the decrease in catecholamines as well as the overall improvement in hemodynamics and functional capacity that result from therapy [9].

ACE inhibitors and ARBs Angiotensin II (ANGII) is the main molecule that produces the effects of the renin-angiotensin-aldosterone system. The well-known effects of ANGII to increase blood pressure and sodium retention are associated with the worsening of HF [23]. However, ANGII has been shown to be an important molecule in the development of cardiac cachexia. ANGII induces muscle wasting via several mechanisms including decreasing protein anabolism by decreasing insulin-like growth factor I (IGF-1), increasing reactive oxygen species (ROS) in skeletal muscle, reducing appetite, and increasing intermediate molecules (TNF-α, IL-6, glucocorticoids) which contribute to muscle degradation [28].

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II and are associated with attenuation of weight loss in cachectic HF patients [28]. Anker et al. demonstrated that treatment with the ACE inhibitor enalapril reduced risk of weight loss by > 19% and delayed the development of cachexia by about 8 months [10]. Studies performed in aged rat models demonstrated an attenuation in muscle strength decline and a protective effect against age-related muscle deterioration when treated with enalapril [11].

Angiotensin receptor blockade also has the potential to reduce ANGII-induced muscle breakdown by preventing interaction with the ANGII type 1 receptor. Mouse models of cachexia have shown that treatment with the ARB losartan prevented left ventricular wall thinning and decreased plasma levels of proinflammatory cytokines [12]. Further studies are needed to establish a definitive relationship between ARB treatment and cachexia reduction.

Immune activation and inflammation

Proinflammatory cytokines IL-6, IL-1, and TNF-α have been implicated in protein catabolism and are an important predictor of muscle and fat loss [29]. As HF is an inflammatory disease, these mediators are elevated in HF patients with even greater elevations seen in cachexia. Their increase in HF is multifactorial and may be attributed to hypoxia from decreased muscle perfusion, direct tissue injury, increased adrenergic activation, and bowel wall edema and bacterial translocation [30]. The most widely studied is TNF-α which has been shown to act directly on skeletal muscles to cause protein loss [31]. TNF-α binds to its receptor, stimulating an increase in reactive oxygen species which activates nuclear factor-κB and leads to an increase in the ubiquitin proteasome pathway resulting in increased protein degradation [31]. The implication in protein and muscle catabolism makes TNF-α a potential target in the treatment of cardiac cachexia. Though elevated TNF-α levels have been correlated to increase in muscle loss and worsening of HF, trials of anti-TNF-α therapies in HF patients have shown mixed results [13, 14].

Etanercept and infliximab Two large-scale clinical trials investigating the effect of direct TNF-α inhibition in HF patients have been completed. Both the RENEWAL and ATTACH trials were stopped early as neither was able to show benefit to decrease mortality or hospitalizations due to HF.

Etanercept is a fusion protein linked to a human IgG1 antibody which binds to TNF-α, preventing its interaction with cell surface receptors [30]. RENEWAL was a large-scale clinical trial, composed of a European and North American arm, that investigated the use of etanercept at doses of either 25 mg once, twice, or three times weekly in patients with NYHA class II to IV HF. It was stopped early in March of 2001 due to a lack of clinical benefit seen in the etanercept group compared to placebo [13].

The ATTACH trial also looked at anti-TNF-α therapy in HF patients. Infliximab, a chimeric monoclonal antibody, binds to and inactivates TNF-α, preventing its binding to cell receptors and downstream immunologic effects. ATTACH studied 150 patients with NYHA classes III and IV HF and compared infliximab, given at doses of either 5 mg/kg or 10 mg/kg, to placebo. The trial failed to show a clinical benefit of the administration of infliximab with the high-dose infliximab group trending toward adverse outcomes [14].

Pentoxifylline Pentoxifylline is an erythrocyte phosphodiesterase inhibitor used in the treatment of peripheral vascular disease to decrease blood viscosity and improve circulation [32]. The xanthine derivative also possesses immunomodulatory properties including the downregulation of TNF-α synthesis, making it a potential therapeutic option to attenuate the immune activation in HF and cachexia. Studies with pentoxifylline in patients with HF have shown mixed results in regard to improvements in cardiac function [15, 16, 33]. Early studies with small study populations suggested an association with decreases in TNF-α concentrations and improvements in functional capacity as results showed treatment with pentoxifylline lead to increased LVEF and improvements in NYHA functional class [15, 33]. Later studies were not able to replicate these results, reporting no improvements in LVEF or decrease in TNF-α concentrations in pentoxifylline versus placebo. This is likely due to the implementation of beta-blockers as standard HF treatment after the conduction of the initial studies [32]. While human studies of pentoxifylline in the setting of cardiac cachexia have yet to be conducted, Steffen et al. evaluated the administration of pentoxifylline to rats with monocrotaline-induced cardiac cachexia and was able to show an attenuation in skeletal muscle mass loss and reduction in ubiquitin proteasome pathway activation [16]. Pentoxifylline has also been shown to reduce muscle wasting in the setting of cancer and AIDS-associated cachexia [2], making it a potential therapeutic option in cardiac cachexia following further investigations.

Metabolic hormonal imbalance

The catabolic state of HF that results from neurohormonal activation is augmented by a metabolic hormonal imbalance. Cachectic patients have altered levels of ghrelin, growth hormone (GH), insulin-like growth factor 1 (IGF-1), leptin, adiponectin, and testosterone [2]. These alterations lead to decreased food intake as well as impaired ability for protein synthesis seen in patients with cardiac cachexia [32].

Growth hormone and ghrelin Growth hormone is an anabolic hormone involved in protein synthesis and associated with increases in muscle mass. Its effects on skeletal and myocardial growth are mediated mainly via IGF-1 [32]. Ghrelin is a GH-releasing peptide thought to have many potential actions including stimulating food intake and weight gain as well as having effects on gastric motility, taste, stress, glucose metabolism, and inflammation [34]. Patients with cardiac cachexia are thought to have an inherent GH resistance as levels of GH and ghrelin have consistently shown to be elevated while IGF-1 are decreased. Regardless of this resistance, ghrelin continues to be studied in the setting of cardiac cachexia, likely for its effects independent of GH release [35].

In studies of non-cachectic HF patients, ghrelin administration over a 3-week period increased food intake, GH level, left ventricular mass, LVEF, muscle strength, and lean muscle mass [17]. Animal studies have also shown chronic ghrelin administration can improve left ventricular function and reduce the development of cardiac cachexia [18]. Despite the GH resistance seen in cachectic HF patients, administration of ghrelin to 10 patients with cardiac cachexia in a small, uncontrolled study showed beneficial cardiovascular effects including additional increases in GH, increases in lean body weight, and LVEF [36]. As ghrelin has been shown to have anti-inflammatory effects and cause increases in appetite independently of GH stimulation, these may help to explain the beneficial effect in cardiac cachexia despite the GH resistance [35]. While the multifaceted effects of ghrelin show potential in cardiac cachexia treatment, further, well-controlled studies are needed.

Testosterone Patients with HF have decreased circulating levels of testosterone which may contribute to loss of skeletal and left ventricular muscle mass and decreases in exercise tolerance [37]. Administration of testosterone has long been shown to induce muscle growth and is also associated with increased release of IGF-1 and decreases in peripheral vascular resistance and inflammatory cytokines in patients with HF [19]. Of the treatments under investigation for management of cardiac cachexia, testosterone has shown to have the strongest evidence [17], receiving a mention in the European Society of Cardiology heart failure treatment guidelines as a potential treatment option in cachectic patients [38].

Malkin et al. studied the effect of testosterone administration in 76 men with stable HF and impaired exercise tolerance. Patients received either a 5-mg daily testosterone patch or placebo for a period of 12 months. At the end of the study, those receiving testosterone had increases in exercise capacity as shown by improvements in the incremental shuttle walk test, as well as improvements in NYHA functional class versus placebo. No serious adverse effects were reported; however, the patch system of administration was not well-tolerated [19]. A meta-analysis from 2012 which included four studies of testosterone replacement in patients with HF, one study completed in women, concluded that testosterone replacement in both men and women with HF increases exercise capacity and improves insulin resistance [20]. While numerous trials have been conducted on the use of testosterone in HF, most trials use small sample sizes and do not specifically study the cachectic HF patient [17].

One of the limiting factors in testosterone replacement is the potential downstream side effects. Long-term administration of testosterone has been shown to cause salt and water retention [20] and decreased left ventricular dysfunction in healthy individuals [17]. Harmful side effects have not been reported to date from replacement studies in HF, likely due to

the lower levels administered for replacement. However, follow-up periods in these studies have been short, ranging only from 12 weeks to 1 year [20]. More recently, the selective androgen receptor modifier, enobosarm, has been studied in patients with cancer cachexia and was shown to increase lean body mass without the adverse effects normally associated with testosterone [21].

Gastrointestinal abnormalities

Decreased intestinal blood flow along with increased sodium and water reabsorption in HF leads to peripheral and gastrointestinal edema. This results in complex gastrointestinal changes including increases in bowel wall thickness and intestinal permeability. The increase in bowel wall thickness decreases absorptive capacity contributing to nutritional deficiencies seen in cachectic patients. Gastrointestinal symptoms such as nausea, early satiety, burping, and anorexia can also develop, leading to decreased nutrient intake, further exacerbating the catabolic/anabolic imbalance [6, 39, 40].

Appetite stimulants Decreases in food intake associated with gastrointestinal symptoms of edema contribute to decreases in physical activity and the overall catabolic state of the patient and lack of capacity for protein synthesis [25]. Appetite stimulants such as megestrol acetate have been studied in patients with cancer cachexia to increase weight gain and skeletal muscle mass. Studies have been completed using megestrol acetate alone or in combination with thalidomide, formoterol, or L-carnitine, all showing effects on weight gain [2]. None of these trials however looked at use in patients with cardiac cachexia. A more recent meta-analysis from 2015 looking at megestrol acetate use in non-cancer cachexia (HIV, COPD, renal failure, geriatric cachexia) concluded that progesterone therapy (megestrol acetate or medroxyprogesterone) was not effective in the treatment of non-cancer cachexia and any effect on weight gain is small and insignificant [22]. Appetite stimulants have not been studied specifically for cardiac cachexia treatment. Potential may still exist for use in this patient population as the etiology of cachexia can differ between disease states and increased nutritional intake may help to neutralize the imbalance in the metabolic state [41].

Diuretics Intestinal ischemia and bowel wall edema are associated with increased gut permeability and bacterial translocation. Patients with edema have higher concentrations of bacterial endotoxins present in systemic circulation leading to increased immune activation and release of proinflammatory cytokines such as TNF-α. As TNF-α can directly contribute to muscle breakdown and decreases in appetite, any further increase in release can worsen a current cachectic state or contribute to cachexia development [42]. A reduction in congestion with the use of loop diuretics such as furosemide and bumetanide have been shown to decrease circulating endotoxin levels in edematous patients [4]. HF patients, especially those with cachexia, should be adequately diuresed to maintain as little peripheral edema as possible paying close attention not to provoke electrolyte disturbances or dehydration [24].

Perspectives for future

The potential for new drugs and targets for cachexia treatment are continually being explored in animal studies. Medications such as the proteasome inhibitor bortezomib and sedative dexmedetomidine have been studied in animal models of cancer and ICU cachexia, respectively. Bortezomib was not shown to be effective in preventing muscle wasting; however, a study of dexmedetomidine showed more promising results [43, 44]. In rats with endotoxemia-induced muscle wasting, dexmedetomidine was shown to alleviate muscle wasting. The effect was attributed to dexmedetomidine's ability to decrease systemic and hypothalamic inflammation [44]. This study provides evidence that hypothalamic peptides may have potential as a target for cachexia treatment and warrant further investigation.

Specific to cardiac cachexia, myostatin has been investigated as a potential target for treatment. A member of the TGF-B superfamily, myostatin, plays a role in the regulation of muscle growth. Myostatin is a negative regulator of muscle mass with the potential to induce skeletal muscle atrophy upon overexpression of the protein. Follistatin regulates myostatin activity, acting as a myostatin antagonist. A recent study utilizing a rat model of myocardial infarction–induced heart failure investigated myostatin and follistatin expression. The authors found the chronic HF rats to have underexpression of follistatin as compared to rats without HF. This finding presents a potential new therapeutic target for the treatment of cardiac cachexia [45]. Further studies are needed to determine the molecular mechanisms behind follistatin downregulation and potential use as a new target in the prevention of muscle wasting.

Pharmacokinetic changes in cachectic patients

While it is imperative to recognize and treat cardiac cachexia to reduce the mortality associated with HF, it is also important to recognize the impact that the cachectic state can bring about in the pharmacological management of HF and associated conditions. While limited studies are available, alterations in drug pharmacokinetics are another potential consequence of cachexia development (Table 2) [46]. Due to increased bowel wall thickness from gut edema, drug absorption may be altered. HF patients were shown to have decreased absorption of

Table 2 describes the pharmacokinetic changes that may occur in cachectic patients

Potential pharmacokinetic changes in cachexia	
Drug absorption	↓
Volume of distribution	↓
Albumin	↓
Cytochrome P450 enzymes	↓
Drug half-life (hepatically metabolized)	↑

the ACEIs enalapril and lisinopril [47]; however, alterations in drug absorption are difficult to predict so changes in dosing strategies are not established or recommended [46]. Volume of distribution in cachexia is generally decreased due to the decrease in both fat and lean muscle mass which decreases distribution of both hydrophilic and lipophilic drugs. As cachectic patients have reduced protein-building capacity, hypoalbuminemia is common. Reduced circulating protein levels can alter free plasma concentrations of drugs that are significantly bound to protein. This includes drugs such as warfarin and digoxin which are commonly used in treatment of atrial fibrillation, a condition that can frequently overlap with HF and can contribute to increases in toxicity such as bleeding risk and digoxin intoxication [46].

Elevated fluid retention in HF can lead to hepatic congestion and subsequent liver dysfunction [6]. Hepatic congestion in HF along with associated reductions in cytochrome P450 enzymes seen in cachectic patients can alter drug metabolism and prolong half-lives of hepatically metabolized drugs. Subsequent reductions in drugs with hepatic metabolism may need to be considered [46]. While minimal studies are available on pharmacokinetic changes in cachexia, and specifically cardiac cachexia, there is evidence available to suggest that alterations exist. Further studies are necessary in order to determine appropriate dosage adjustments.

Conclusion

Cardiac cachexia is a state of protein and fat loss in the presence of heart failure with a multimodal pathogenesis that involves neurohormonal activation, inflammation, metabolic hormonal imbalance, and gastrointestinal changes. While no specific pharmacologic agents have been established for treatment or prevention of cardiac cachexia, many theoretical options are available aimed at the various mechanisms of cachexia development, many with promising results. Combined guideline-recommended pharmacological therapy for heart failure along with exercise and nutritional supplementation is a current staple of therapy; however, with further investigation, establishment of definitive pharmacologic therapies for the treatment and prevention of cardiac cachexia can be found.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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