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Review

Vascular Dysfunction in Cardiac Cachexia: Molecular Mechanisms and Pharmacotherapies

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Abstract

Severe heart failure (HF) is accompanied by cardiac cachexia (CC), defined as significant weight loss, muscle atrophy, and metabolic abnormalities. Muscle wasting in patients with CC is closely associated with hormonal changes. Previous studies on the pathogenesis of CC have focused on the imbalance between catabolic and anabolic processes. Thus, this review focused on the role of endothelial dysfunction in CC. We summarized how inflammatory cytokines and neurohormonal factors cause vascular dysfunction, leading to reduced nutrient delivery and perfusion. Furthermore, we discuss both conventional and emerging therapeutic strategies that may ameliorate CC by targeting the vasculature. These include ghrelin, the vascular benefits of foundational HF drugs (angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor-neprilysin inhibitors (ARNIs), and beta-blockers), and the promise of novel agents, such as BTB and CNC homology 1 (BACH1) inhibitors and fibroblast growth factor 21 (FGF21) agonists. We also summarize the existing animal models of CC and discuss advanced imaging and omics technologies for future research. This review provides a novel perspective on CC pathogenesis and highlights promising avenues for therapeutic intervention.

Keywords: cardiac cachexia; muscle atrophy; vascular dysfunction; ghrelin; tumor necrosis factor-alpha; therapeutics

1. Introduction

Heart failure (HF) is a major socioeconomical burden, with a prevalence of 2% in Western countries [1]. A serious complication of HF is cardiac cachexia (CC), a profound state characterized by substantial involuntary weight loss that is unresponsive to nutritional intervention. CC also occurs in other chronic diseases, including malignant cancer, AIDS and rheumatoid arthritis [1]. CC is estimated to affect 10% of all symptomatic patients with HF [2]. The annual mortality rate associated with CC ranges from 20 to 40% [3].

The clinical manifestations of cachexia include anemia, anorexia, fatigue, and weight loss [4]. However, the weight loss cutoff for diagnosing cachexia remains controversial [2]. Definitive diagnosis also requires the absence of edema, a prerequisite that complicates assessment, particularly in populations with HF. Furthermore, other etiologies of weight loss (e.g., malignant tumors, acute infection, or hyperthyroidism) must also be excluded. Earlier HF studies adopted the percentage of weight loss (>7.5% [5] or >6.0% [6]) as criterion for diagnosing cachexia. A recent study enrolled a broad cohort of ambulatory patients with chronic HF. In that study, cachexia was found in 16.4% of participants [5]. During the 18 months of follow-up, mortality was markedly higher in cachectic patients (50%) relative to those who were not (17%) [5]. Even after statistical adjustments for age and HF classification (e.g., New York Heart Association [NYHA] functional class), cachexia remained a strong and independent predictor of mortality. A retrospective analysis of the Study of Left Ventricular Dysfunction (SOLVD) and Vasodilator-Heart Failure Trial (V-HeFT) II databases applied multiple weight loss thresholds (≥5.0%, ≥6.0%, ≥7.5%, ≥10.0%, and ≥15.0%) [6]. In the SOLVD study, 42% of 1929 patients experienced ≥5% weight loss, which remained an independent predictor of mortality after 8 months, even after adjusting for age, sex, NYHA class, left ventricular ejection fraction (LVEF), and treatment (enalapril vs. placebo) [6]. Furthermore, a weight loss more than 6% (observed in 36% of the patients) was strongly associated with increased mortality during a mean

follow-up of 35 $\pm$ 13 months. According to a consensus statement, CC can be diagnosed with >5% weight loss (or BMI <20 kg/m^2) within 12 months or less. Diagnosis of CC requires meeting $\geq$3 of the following criteria: decreased muscle strength, loss of appetite and fatigue, lack of fat mass index, and abnormal biochemistry (e.g., inflammation markers increase, anemia, decreased albumin) [2].

The pathogenic mechanism of CC involves increased inflammation, neurohormonal activation, and imbalance in metabolic hormones [7]. It exhibited a stronger correlation with hormonal alterations than with the severity of chronic heart failure (CHF). CC patients usually have increased plasma levels of tumor necrosis factor-alpha (TNF-α), interleukin 1 and 6, norepinephrine, epinephrine, renin, angiotensin II (ANG II) and progesterone [8,9]. Activation of the systemic sympathetic nerve induces a decrease in peripheral blood flow caused by vasoconstriction and reduces the perfusion of exercised muscles. Endothelial dysfunction and capillary rarefaction may precede muscle atrophy and contribute to wasting [9]. In the experimental rabbit model, HF was induced by coronary artery ligation. Progressive vascular thinning and increased apoptosis are observed over time [10]. Endothelial cell apoptosis precedes muscle cell apoptosis in norotaline-induced CHF rats [11]. This suggests that the microcirculation is a potential target for the treatment of muscular atrophy in patients with CC.

In this review, we aimed to (i) discuss the mechanisms by which inflammation and neurohormonal changes cause vascular dysfunction-associated muscle wasting in patients with CC, (ii) provide an overview of current animal models of CC, and (iii) summarize possible therapeutic interventions.

2. Muscle Wasting Promotes Cardiac Cachexia

Chronic HF and cardiac cachexia are "waste diseases". Evidence indicates that muscle wasting (sarcopenia) often precedes the development of cachexia and may occur independently of weight loss [2]. Fülster *et al.* [12] reported that among 200 patients with HF (mean age, 67 years), 19.5% experienced muscle wasting. In another study, non-cachectic patients with CHF exhibited reduced lean tissue in their legs compared with healthy controls. Cachectic patients also demonstrated a significant reduction in lean mass compared to both non-cachectic CHF individuals and control subjects [13].

3. Possible Mechanism of Muscle Wasting in CC

The pathogenesis of muscle wasting in CC is multifactorial and involves neurohormonal activation, inflammation, metabolic hormonal imbalances, and gastrointestinal alterations [14]. Factors contributing to muscle wasting include persistent activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS), and elevated plasma pro-inflammatory cytokines [15]. Cachectic HF patients were demonstrated to have elevated inflammatory cytokine TNF-α as well as epinephrine and norepinephrine when compared to non-cachectic patients [16]. These alterations lead to decreased vascular function, which is likely to contribute to reduced blood flow and nutrient delivery to the skeletal muscle in patients with CC, thus impairing skeletal muscle anabolism [9]. A decrease in the number of capillaries in the skeletal muscle induces inadequate blood supply [10], which is one of the causes of muscle wasting. In addition to elevated inflammatory cytokines and neurohormones, a recent study showed that the expression profile of high circulating miRNA-628 (occurred in 90.6% of cachectic patients) concurrent with low miRNA-6803 (observed in 96.9% of cachectic patients) strongly predicts cachexia prevalence [17]. Table 1 (Ref. [17–20]) summarizes the altered components observed in patients with HF and CC compared with those without CC.

3.1 TNF-α

Immune activation, especially TNF-α is thought to play a causal role in promoting muscle wasting and anorexia [21]. TNF-α causes vascular dysfunction [22], which might contribute to decreased exercise tolerance. Elevated plasma levels of inflammatory cytokines are linked to the loss of muscle, fat, and bone tissue characteristics during CC [23]. In an animal study, implantation of TNF-α-producing cells into the skeletal muscle caused cachexia, whereas implantation of the same cells into the brain caused anorexia [24]. In an animal study, implantation of TNF-α-producing cells into skeletal muscle caused cachexia, while implantation of the same cells into the brain caused anorexia [25], which suggests that TNF-α is closely related to cachexia. Plasma TNF-α levels most strongly predict the extent of weight loss in CHF patients [26]. In this study, significant correlations between accumulated TNF-α and loss of lean, fat or bone mass were demonstrated. In addition, in patients with CHF, impaired endothelium-dependent vasodilation in the forearm is associated with elevated TNF-α levels [27].

The mechanism of how TNF-α regulates peripheral blood flow has not been fully elucidated. In experimental models, short-term exposure to TNF-α markedly impairs endothelium-dependent relaxation [28]. Cell culture experiments further reveal that TNF-α rapidly stimulates reactive oxygen free radical production, leading to nitric oxide inactivation [29]. Moreover, TNF-α suppresses endothelial nitric oxide synthase (eNOS) activity through inhibition of Protein Kinase B (Akt) phosphorylation [30]. Besides the post-transcriptional inactivation of eNOS, TNF-α further promotes the degradation of eNOS mRNA [31]. Elevated serum levels of TNF-α correlate with increased endothelial cell apoptosis [32]. This correlation supports experimental evidence demonstrating that TNF-α triggers the apoptotic signaling cascade in endothelial cells [33].

Table 1. Biomarkers of HF patients with or without cardiac cachexia (CC).

Biomarkers	HF patients with CC	HF patients without CC	The effect on blood vessels	References
Epinephrine (pg/mL)	61 ± 9	44 ± 4	vasoconstriction	[18]
Norepinephrine (pg/mL)	849 ± 128	597 ± 50	vasoconstriction	[18]
Angiotensin II (pg/mL)	123 ± 20	74 ± 10	vasoconstriction	[18]
GH/IGF-1	1.68 ± 0.16	2.80 ± 0.14	vasodilatation	[19]
Ghrelin (pg/mL)	50.6 (30.8–63.2)	36.7 (24.3–63.6)	vasodilatation	[20]
TNF-α (pg/mL)	5.1 ± 0.5	3.3 ± 0.3	vasoconstriction	[18]
↑miRNA-628-3p+↓miRNA-6803-3p	90.6% + 96.99%	36.4% + 40.79%	Not determined	[17]

HF, heart failure; GH, growth hormone; IGF-1, insulin-like growth factor 1; TNF-α, tumor necrosis factor-alpha.
↑ represents an increase, and ↓ represents a decrease.

3.2 Neurohormonal Activation

Patients with cachectic HF have higher circulating levels of aldosterone, cortisol, norepinephrine and epinephrine than those with HF but without cachexia [16,34]. Activation of the RAAS is a key mechanism in CC [35]. Although short-term RAAS activation can enhance cardiac output, chronic activation has deleterious effects, promoting cardiac overload and subsequent structural remodeling of the heart [16]. Administration of Angiotensin II, the primary RAAS effector, causes skeletal muscle atrophy in rodents [16]. Ang II induces muscle wasting via multiple mechanisms. Ang II promotes skeletal muscle atrophy via the transcriptional activation of muscle-specific RING-finger protein 1 (MuRF1) by transcription factor EB (TFEB) [36]. Ang II activates the ubiquitin-proteasome system (UPS) by inducing the expression of the muscle-specific E3 ubiquitin ligase MuRF1, driving muscle protein degradation and ultimately leading to a decrease in muscle mass. The basic helix-loop-helix TFEB is a transcriptional regulator that potently induces MuRF1 expression. TFEB is activated via the Ang II/protein kinase D1 (PKD1)/histone deacetylase-5 (HDAC5) signaling pathway, and its inhibition consequently abolished Ang II-induced muscle atrophy *in vitro* [36]. Activation of the RAAS contributes to reduced tissue perfusion and resultant cellular hypoxia. These conditions are associated with a shift in muscle metabolism characterized by elevated catabolic activity and suppressed anabolic processes [16]. Angiotensin II causes vascular smooth muscle cell (VSMC) dysfunction, including increased oxidative stress, inflammation, migration, hyperplasia, and hypertrophy [37,38]. Angiotensin II also destroys endothelial function. Murugan *et al.* [39] showed that angiotensin II increases endoplasmic reticulum stress, reduces nitric oxide (NO) utilization, and impairs endothelium-dependent relaxations through activation of the eukaryotic initiation factor 2α (eIF2α) and activating transcription factor 6 (ATF6) pathways.

According to clinical guidelines, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and beta-blockers (BB) are foundational therapies for HF. These medications prevent cardiac remodeling [40]. Clinical trials have verified the efficacy of the neurohormonal inhibitors in preventing the development of CC [41,42]. Specifically, ACEIs reduce weight loss in patients with cachectic HF by blocking the conversion of angiotensin I into angiotensin II [6]. In a study by Anker *et al.* [6], enalapril, an ACE inhibitor, lowered the risk of significant weight loss by 19%. It also delays the onset of cachexia by approximately eight months [6]. Additionally, an effect of beta-blockers is weight gain, which may confer protection against progression to cardiac cachexia [42]. According to Hryniewicz *et al.* [43], long-term therapy with beta blockers, such as carvedilol and long-acting metoprolol, leads to increased body weight, decreased plasma norepinephrine levels, and partial reversal of cachectic status.

4. Therapeutic Interventions

Although there is no specific therapeutic strategy for CC, some interventions may alleviate wasting associated with advanced HF. The interventions target its underlying drivers, including hormonal imbalances, neurohormonal activation, chronic inflammation, and metabolic dysfunction, ranging from appetite-stimulating hormones like ghrelin and foundational neurohormonal blockers to newer heart failure drugs and emerging anti-inflammatory and metabolic agents.

4.1 Ghrelin

Ghrelin is an anticatabolic hormone secreted by the gut. Ghrelin is the only circulating hormone that stimulates food intake and appetite by binding to the growth hormone (GH)-secretagogue receptor (GHS-R), ghrelin acts as the only circulating hormone that stimulates food intake and appetite [44]. Plasma ghrelin levels are elevated in patients with HF [18]. Ghrelin secretion is thought to serve as a compensatory response to cachexia-associated weight loss, negative energy balance, decreased appetite, and inflammation [45]. A small, uncontrolled study involving 10 patients with CC showed that ghrelin administration exhibited beneficial cardiovascular effects, including increased GH levels, increased lean body mass, and improved LVEF [46]. Furthermore, chronic ghrelin treatment improves both left ventricular function and the course of CC in animal models

Table 2. Animal models of cardiac cachexia.

	Experimental animal	Processing mode	Experimental period	Model success indicator	References
The monocrotaline (MCT) model	C57BL/6 mice	MCT was injected subcutaneously every week (600 mg/kg)	6 weeks	compared with the control group, MCT mice loss body weight, increased lung weight, increased heart weight and right ventricular (RV) hypertrophy	[76]
	male C57/BL6 mice		8 weeks	the RV: left ventricle (LV) plus septal weight ratio was significantly increased in MCT mice compared with the control group	[77]
	male Sprague-Dawley rats	intraperitoneal injection of MCT (30 mg/kg)	3 weeks	when MCT-injected animals had lost $\geq$8.5% of their peak body weight or had not eaten in the previous 24 h, the animal was killed	[68]
Dahl salt-sensitive rats	male Dahl salt sensitive rats	fed with high-salt (8% NaCl)	2–5 weeks	heart tissue shows muscle loss and inflammation	[78]
	male Dahl salt sensitive rats	fed with high-salt (8% NaCl)	5–7 weeks	compared with the control group, the Dahl rats fed with high-salt diet had lower food intake and body weight	[79]
Surgical models	Male Sprague Dawley rats (280–300 g)	Left Anterior Descending Coronary Artery Ligation	4 weeks	the left ventricular ejection fraction is reduced by more than 20% and body weight is reduced by more than 6%	[80]
Transgenic mouse model	CSQ-overexpressing mice	calseqestrin (CSQ)-overexpressing	8 weeks	cardiac-specific CSQ-overexpressing	[81]

[47]. Nagaya *et al*. [47] investigated the effect of ghrelin on body weight and indicated that, when given a dose of 100 microg/kg *bis in die*, CHF rats treated with ghrelin showed a significantly greater increase in body weight than those given placebo. In addition, Studies in CHF rats with coronary ligation demonstrated that subcutaneous ghrelin attenuates cardiac cachexia, improves left ventricular function, and increases cardiac output [48].

Ghrelin enhances cardiac function by decreasing vascular resistance [49]. Ghrelin augments eNOS expression in both humans and animal models, ghrelin has been shown to augment eNOS expression [50]. In vascular endothelial cells, ghrelin binds to the cell surface receptor growth hormone secretagogue receptor-1a (GHSR-1a). Activated GHSR-1a activates phosphatidyqinositol-3 kinase (PI3K) phosphorylation [51]. PI3K catalyzes the phosphorylation of phosphatidylinositol 4,5 biphosphate lysate (PI (4,5)) to phosphatidylinositol 3,4,5 trisphosphate (PI (3,4,5) P3). PIP3 binds and activates PDK-1. PDK-1 phosphorylates and activates the intracellular kinase, Akt. Akt phosphorylates eNOS, enhances its activity, and promotes NO release from the ECs. An increase in NO causes vasodilation and increases the blood supply [52]. Therefore, ghrelin increases skeletal muscle blood flow by increasing NO bioactivity [53] (Fig. 1).

Ghrelin also inhibited the expression of inflammatory cytokines by inhibiting NF-κB activation. A study verified that ghrelin inhibits basal and TNF-α-induced chemotactic cytokine and monocyte adhesion in HUVECs [54]. Ghrelin protects against CC by increasing skeletal muscle blood flow and inhibiting inflammation.

4.2 Neurohormone Inhibitor

SOLVD database analysis revealed that the administration of enalapril, an ACEI, significantly reduced the risk of substantial weight loss (>6%) compared to placebo [6]. While Angiotensin I and II activate the ubiquitin-proteasome system, the ACEI imidapril blocks its activity, thereby reducing protein degradation. Consistently, imidapril ameliorates weight loss in a murine CC model [55].

Like ACEIs, β-blockers may ameliorate muscle loss independently of their cardioprotective role. This effect, observed in burn patients and animal models, is linked to a decrease in energy expenditure that facilitates the accretion of skeletal muscle mass. Correspondingly, clinical data from COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) and CIBIS-II (Cardiac Insufficiency Bisoprolol Study) trials demonstrated that β-blocker treatment brought significant weight gain in participants [56] (Fig. 2).

4.3 ARNIs, SGLT2is and MRAs

In addition to the conventional ACEIs and β-blockers, the therapy for heart failure with reduced ejection frac-

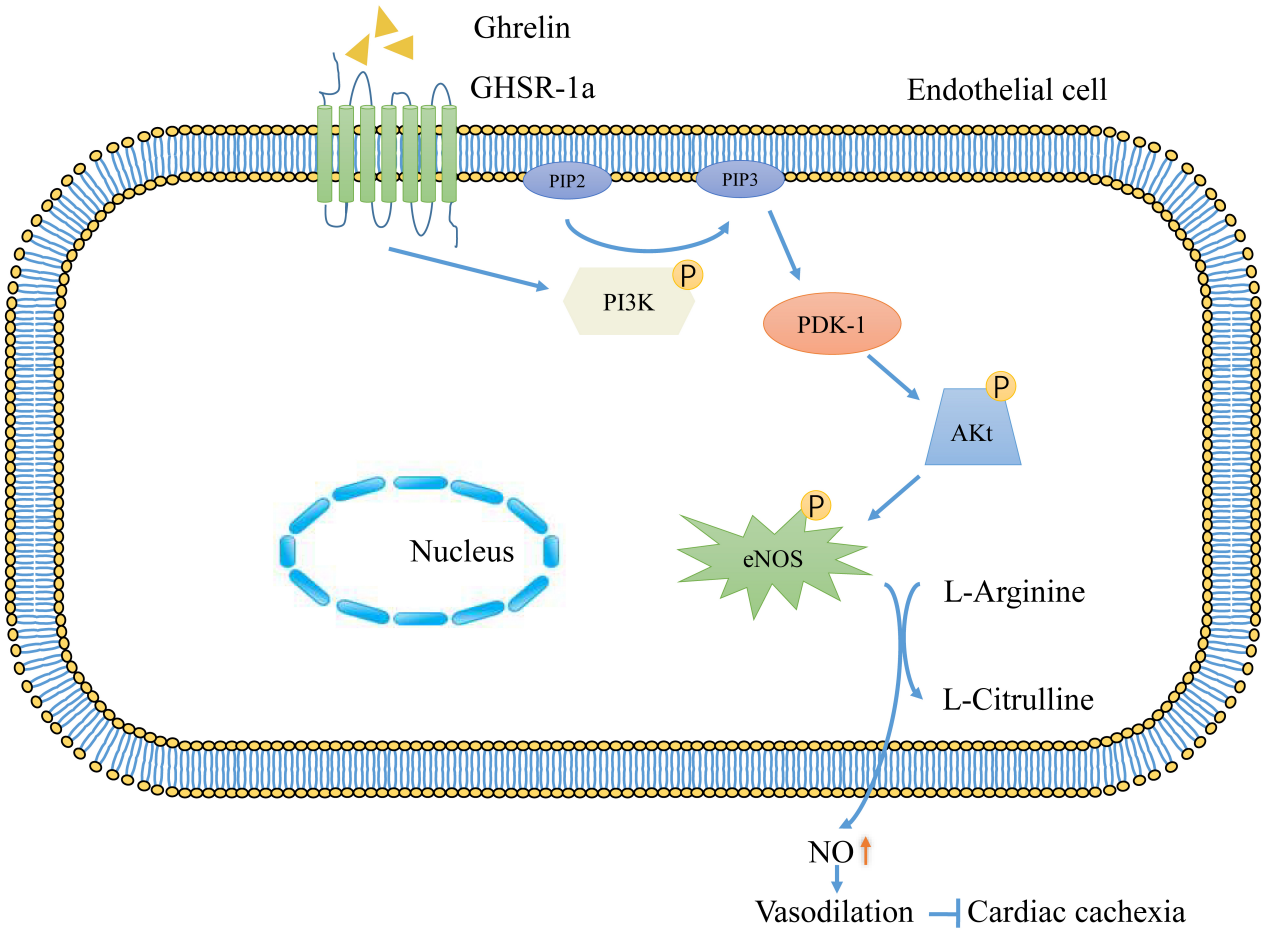

Fig. 1. Ghrelin promotes the production of NO in endothelial cells. Ghrelin binds to GHS-R1a and activates PI3K/AKT pathway, which promotes the activity of eNOS via phosphorylation. Increased NO relaxes the blood vessels and improves the problem of insufficient blood supply in patients with cachexia. NO, nitric oxide; GHS-R1a, growth hormone secretagogue receptor 1a; PI3K, phosphatidylinositol 3-kinase; AKT, Protein Kinase B; eNOS, endothelial nitric oxide synthase.

tion (HFrEF) has evolved to include angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and mineralocorticoid receptor antagonists (MRAs) [57]. These agents greatly benefit the natural history of HFrEF through distinct and complementary vascular and metabolic mechanisms.

ARNIs (e.g., Sacubitril/Valsartan) target both Angiotensin II Type 1 receptor and neprilysin, an enzyme that breaks down endogenous vasoactive peptides, such as natriuretic peptides. Accordingly, ARNIs not only block RAAS-mediated vasoconstriction, but also preserve the vasodilation effects of natriuretic peptides. This leads to improved endothelial function and vascular compliance [58], which could ameliorate the tissue hypoxia and anabolic resistance seen in cachexia. However, natriuretic peptides also stimulate lipolysis and adipose tissue browning [59], which may cause the loss of adipose tissue in the state of advanced HF.

SGLT2is (e.g., Empagliflozin, Dapagliflozin) promote the excretion of glucose and sodium through the kidneys. Glucose excretion transforms the heart and muscles from utilizing glucose to utilizing ketone bodies as an energy source [60,61], which is more efficient and may spare protein catabolism in the context of cachexia. SGLT2 inhibitors (SGLT2is) exert pleiotropic effects in heart failure. In murine models, empagliflozin improved skeletal muscle mitochondrial fatty acid oxidation and exercise tolerance [62], and luseogliflozin prevented muscle atrophy via enhanced fatty acid metabolism [63]. Concurrently, empagliflozin promotes erythropoiesis, which may increase oxygen delivery [64].

MRAs directly counteract the proteolysis effects of aldosterone on skeletal muscle [65]. MRAs also improve insulin sensitivity of the muscle [66] and improve vascular tone by inhibiting aldosterone-induced endothelial dysfunction, vascular inflammation, and oxidative stress [67].

In conclusion, the vascular and metabolic beneficial effect of the newer guideline agents (ARNIs, SGLT2is, and MRAs) suggest the therapeutic potential for cachexia.

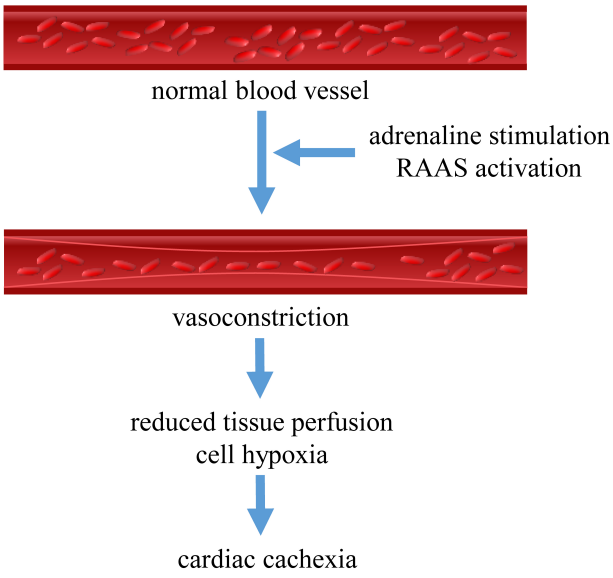

Fig. 2. Schematic of the effect of RAAS on cardiac cachexia. Adrenaline stimulation and activation of the RAAS system leads to vasoconstriction. Reduced tissue perfusion and hypoxia of cells contributes to cardiac cachexia. RAAS, renin-angiotensin-aldosterone system.

4.4 Anti-Inflammatory Agents

The concentration of TNF-α in HF is sufficient to cause endothelial dysfunction, which is partly responsible for reduced blood supply to skeletal muscles [22]. Therapies using anti-inflammatory agents are mechanistically appealing. Pentoxifylline is a known inhibitor of TNF-α production. Although pentoxifylline has not been evaluated in human cardiac cachexia, Steffen *et al.* [68] reported that it significantly attenuated skeletal muscle wasting in rats with monocrotalin (MCT)-induced CC. Etanercept, a recombinant TNF-α receptor, can bind to TNF-α and functionally inactivate TNF-α, profoundly improving systemic endothelial vasodilator capacity in patients with advanced HF [69] (Fig. 3). Though elevated TNF-α levels have been correlated to increase in muscle loss, trials of anti-TNF-α therapies in HF patients have shown mixed results [70]. Large-scale clinical trials (e.g., RENEWAL, ATTACH) with etanercept and infliximab caused neutral or harmful outcomes to the failing heart. Several reasons may explain the failure of anti-TNF trials. First, TNF receptor 1 (TNFR1) is considered to mediate the pro-inflammatory effect, while TNFR2 is related to the beneficial effect of TNF on host defense and tissue repair [71,72]. Broad inhibition of TNF-α may disrupt its essential homeostatic functions. Second, the patients enrolled into the trials are not well classified. HF patients at acute inflammatory phase should be included. Third, the time and dose for the treatment may need optimization. It is preferably to intervene with smaller doses of infliximab before severe irreversible heart failure occurs. Last, inhibiting only TNF is insufficient to suppress the complex inflammation network. Other cytokines, such as IL-1 and IL-6 may compensate. Considering the complexity of inflammation modulation in HF, a multi-faceted strategy instead of merely impeding TNF-α signaling is more conducive to repair the precisely regulated internal environment.

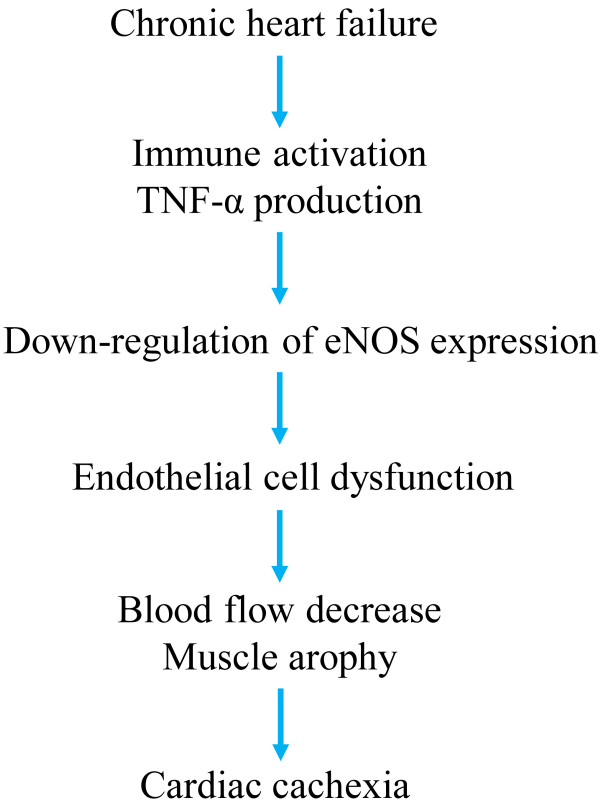

Fig. 3. Role of TNF-α in cardiac cachexia. Chronic heart failure leads to immune activation, which induces the production of TNF-α. Elevated TNF-α down-regulates the expression of eNOS in endothelial cells, which leads to endothelial dysfunction, reduced blood supply to skeletal muscle, and decreased muscle mass and finally the development of cardiac cachexia. TNF-α, tumor necrosis factor-alpha.

4.5 Emerging Therapeutic Strategies

Recently, studies are revealing novel mechanisms in angiogenesis and cardiac energy allocation with therapeutic potential for CC. First, as a transcriptional repressor, BACH1 antagonizes NRF2 and inhibits the Wnt/β-catenin pathway, leading to impaired angiogenesis and exacerbated oxidative stress in ischemic myocardium and skeletal muscle. BACH1 inhibition, by relieving its transcriptional repression of pro-angiogenic and antioxidant genes, has emerged as a core strategy to improve tissue perfusion. Small-molecule inhibitors of BACH1 (such as BI033) can specifically bind to the BTB domain of BACH1 and

block its DNA binding. This leads to increased expression of genes including vascular endothelial growth factor A (VEGFA) and heme oxygenase 1(HMOX1), which promotes microcirculatory reconstruction, and significantly improves blood flow perfusion in models of myocardial infarction and limb ischemia [73]. Secondly, activating the FGF21 pathway is key to reprogramming whole-body energy metabolism and prioritizing cardiac energy supply. The stress hormone FGF21 binds to its receptor complex (FGFR/β-Klotho) and activates downstream PI3K/AKT and ERK1/2 signaling. It enhances cardiac glucose uptake and fatty acid oxidation to improve mitochondrial function. Systemically, it inhibits white adipose tissue inflammation and promotes brown adipose tissue activation [74]. In addition, FGF21 mediates the mobilization of energy substrates from the liver and adipose tissue via circulation to maintain sufficient cardiac energy availability when under stress [75]. In the future, combining BACH1 inhibitors with FGF21 agonists is expected to synergistically improve myocardial energy supply and peripheral tissue perfusion.

5. Animal Model of CC

The main animal models of CC are surgical, pharmacological, and genetic. We retrieved data on CC and animal models to generate the following Table 2 (Ref. [68,76–81]).

The most commonly used surgical model is the permanent ligation of the anterior descending branch of the left coronary artery to induce myocardial infarction (MI), which has been used in mice and rats [47,81]. Eight weeks after surgery, the mice showed increased heart weight, cardiac hypertrophy [82], and a cachectic state, including decreased food intake, weight loss, decreased fat and skeletal muscle mass, leading to impaired exercise performance [81].

In addition to surgical models, the pharmacological MCT mouse model is a model of CC [76]. Monocrotalin (MCT) is a macrocyclic pyrrolizidine alkaloid found in the seeds of Crotalaria spectabilis [83]. C57BL/6 mice (aged 8 weeks) were subcutaneously injected weekly with MCT (600 mg/kg) for 6 weeks, and CC was induced to CC due to pulmonary hypertension and subsequent right ventricle dysfunction [77]. MCT mice showed a significant decrease in body weight compared with the control group. In addition, MCT mice exhibit pulmonary congestion, increased heart weight, and right ventricular hypertrophy [77].

The most widely accepted transgenic mouse model was obtained by heart-specific overexpression of calsequestrin (CSQ) [84]. Mice with cardiac-specific CSQ overexpression showed physical signs of cachexia at eight weeks. These include reduced body weight, skeletal muscle mass, and left ventricular ejection fraction. In addition, transgenic mice exhibit exercise intolerance [55,84].

The core differences in heart cachexia models originate from pathological driving mechanisms, which in turn lead to specificity in vascular and muscular outcomes. Right heart failure models are often induced by pulmonary hypertension, characterized by systemic venous congestion, which triggers vascular endothelial inflammation and oxidative stress through elevated venous pressure, exacerbating lower limb edema and thrombosis risk. At the same time, gastrointestinal congestion leads to loss of appetite and insufficient blood supply to muscles, accelerating muscle atrophy [85]. In the left heart failure model, pulmonary circulation congestion is the main manifestation. Increased pulmonary capillary pressure leads to increased endothelial permeability and pulmonary edema, which restricts respiratory function and reduces physical activity, promoting muscle degradation through disuse mechanisms and chronic hypoxia [86]. The pulmonary hypertension model directly targets the pulmonary vascular endothelium, leading to increased right heart load through pulmonary small artery contraction and remodeling. Its vascular outcomes focus on elevated pulmonary vascular resistance and endothelial dysfunction, while muscle wasting is secondary to systemic hypoxia related to right heart failure [87]. Ischemic heart failure models result from coronary endothelial lesions leading to insufficient myocardial blood supply. Vascular outcomes primarily involve coronary stenosis and myocardial ischemia, while muscle atrophy is mainly related to reduced perfusion and limited activity [88,89]. Pulmonary hypertension models are an ideal choice for mechanism research because they directly simulate pulmonary vascular endothelial injury [87].

6. Emerging Tools to Clarify Vascular to Muscle Causality

The emergence of imaging and molecular profiling technologies provides an opportunity to clarify vascular to muscle causality. Advanced imaging tools, including superb microvascular imaging (SMI) [90] and contrast-enhanced ultrasound (CEUS) [91], enable the quantitative and non-invasive assessment of muscle perfusion and metabolism. Positron emission tomography/computed tomography (PET/CT) is used to measure perfusion, vascular inflammation, muscle viability and substrate utilization (e.g., glucose uptake) [92]. These tools can establish whether impaired nutrient and oxygen delivery is the primary limiting factor for muscle metabolic function and exercise capacity. At the cell and molecular levels, single-cell and spatial transcriptomics identify the initiating cell types and molecular signals within the vascular and muscle niches [93,94]. Furthermore, metabolomic analysis of muscle tissue and serum may identify the downstream biochemical metablics of vascular impairment that directly lead to the muscle [95]. Joint use of these tools favors the systematic study of the role and mechanism of vascular dysfunction in cachexia.

7. Conclusion

Malnutrition and cachexia are frequently observed in patients with advanced HF, leading to reduced quality of

life and increased mortality. The mechanisms underlying CC have not yet been elucidated and require further research. This review proposes vascular dysfunction as a pivotal mechanism, potentially preceding and driving the progression of muscle wasting in CC. TNF-α and neurohormonal factors induce endothelial apoptosis, capillary rarefaction and impaired vasodilation. Vascular dysfunction impedes the perfusion and nutrient acquisition in the skeletal muscle. There are no specific approved treatments for CC. However, HF therapies including ACEIs, β-blockers, and the newer ARNIs, SGLT2is, and MRA indirectly ameliorates the neurohormonal and metabolic drivers of vascular dysfunction and cachexia. Furthermore, ghrelin and anti-inflammatory agent demonstrate therapeutic potential by directly enhancing endothelial function and skeletal muscle perfusion. hold mechanistic promise by directly improving endothelial function and skeletal muscle perfusion, though their clinical translation requires further validation. Emerging imaging tools and multi-omics technologies will facilitate the investigation of vascular-muscle causality. Biomarkers such as circulating miRNAs may predict CC in the early stage. Emerging targets like BACH1 and FGF21 provide a new choice to improve perfusion and energy balance. While this review synthesizes current knowledge on vascular dysfunction in CC, there are several limitations. The causal relationship between vascular dysfunction and subsequent muscle wasting is primarily supported by correlative clinical data and animal models. The mechanistic pathways involved in ghrelin, BACH1 and FGF21 are largely based on preclinical evidence. Their direct translation to human CC is largely speculative.

Author Contributions

HH searched for the literature and drafted the manuscript. JM provided effective guidance and suggestion on the draft conception and made the figures. YG made the tables and reviewed the manuscript critically. JingL and JuL conceived, supervised and revised the review. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Javdat Muratkhodjaev is an employee of GENEX LLC Pharmaceutical Company, the judgments in data interpretation and writing were not influenced by this relationship.

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