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Review

Recent insights on the molecular mechanisms and therapeutic approaches for cardiac cachexia

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ABSTRACT

Cardiac cachexia (CC) affects a large proportion of patients with chronic heart failure, a major public health issue in western countries. The pathophysiology of CC is complex and multifactorial, resulting from several factors interacting in a complex system with metabolic, immune and neurohormonal consequences, triggered to protect the heart and the circulation from damage. Despite the adverse clinical effects, CC diagnosis is not straightforward and has not specifically been targeted, with therapeutic strategies only comprising interventions with appetite stimulants, and anti-inflammatory substances. Here we review the molecular pathways underlying CC-related muscle wasting aiming to provide clues for the definition of CC-specific biomarkers and for the development of drugs that prevent and/or counteract muscle impairment, which will certainly impact the management of cardiovascular disorders.

Contents

Abbreviations: 4E-BP1, Eukaryotic translation initiation factor 4E binding protein; ACE, Angiotensin-converting enzyme; ANP, Atrial natriuretic peptide; BMD, Bone mineral density; BMI, Body mass index; BNP, Brain natriuretic peptide; CC, Cardiac cachexia; CHF, Chronic heart failure; cNOS, Constitutive nitric oxide synthase; CT, Computed tomography; DHEA, Dehydroepiandrosterone; eIF-4E, Inhibitor of the eukaryotic translation initiation factor 4E; ESR, Erythrocyte sedimentation rate; FOXO, Forkhead box O; GC, Glucocorticoids; GFR, Glomerular filtration rate; GH, Growth hormone; HF, Heart failure; IGF, Insulin-like growth factor; IGFBP-3, Insulin-like growth factor binding protein 3; IGFBPs, Insulin-like growth factor binding proteins; IL-1, Interleukin 1; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; IL-10, Interleukin 10; LPS, lipopolysaccharide; MRI, Magnetic resonance imaging; NOS, Nitric oxide synthase; NPS, Natriuretic peptide system; NT-proBNP, N-terminal pro-BNP; p70S6K1, p70 ribosomal protein S6 kinase 1; PI3K, Phosphatidylinositol 3-kinase; PNS, Parasympathetic nervous system; PRA, Plasma renin activity; RAAS, Renin–angiotensin–aldosterone system; ROS, Reactive oxygen species; SNS, Sympathetic nervous system; sTNFR, Soluble form of tumor necrosis factor receptor; TGF-β1, Transforming growth factor beta 1; TNF-α, Tumor necrosis factor alpha; TNFRs, Tumor necrosis growth factor receptors; UPP, Ubiquitin–proteasome pathway.

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Introduction

Chronic heart failure (CHF) is a major public health issue in western countries, and the associated high morbidity and mortality makes this clinical condition comparable to some types of malignant cancers [1–5]. Initially, this syndrome was linked to the malfunction of the heart as a pump, usually caused by dysfunction of the ventricular myocardium [6]. However, there is now mounting evidence that CHF is a systemic state, which begins with an abnormality of the heart, but involves the dysfunction of most body organs [3,6–11], including cardiovascular, musculoskeletal, renal, neuroendocrine, immune, haemostatic and inflammatory systems [6]. The etiology of CHF is diverse with causes such as ischemic heart disease, idiopathic dilated cardiomyopathy, and valvular dysfunction [12]. At advanced states, cardiac cachexia (CC) can occur [10].

CC is a serious complication in patients with advanced CHF, characterized by a significant weight loss (>7,5%) and body wasting [13,14]. The presence of general weight loss in patients with heart failure (HF) can misleadingly be termed CC [13], and it is important to differentiate cachexia from malnutrition and anorexia [5]. In contrast to cachexia, malnutrition and anorexia are reversible once food is supplied [5,15]. According to Anker and Coats [13], when weight loss is higher than 7.5% of the previous normal weight is observed in patients with CHF of at least six months duration and without signs of other primary cachectic states (like cancer, thyroid disease, or severe liver disease), cachexia should be considered. When weight loss is greater than 66% of ideal body weight patients usually die from cachexia.

There are several possible approaches to evaluate a cachectic state and the methods used include: body composition analysis with fat and lean tissue estimation along with anthropometric measurements (e.g. skinfold thickness and arm muscle circumference); calculations of the ideal percentage of mass matched for sex, age, and height; scores including serum albumin concentrations, cell-mediated immunity changes, weight/height index or body mass index (BMI), and the history of weight loss [13]. Additionally, characterization of lean tissue is made possible by studying urinary creatinine excretion rates, skeletal muscle protein turnover, bioelectrical impedance, and total body potassium content, or via skeletal muscle size measurement by magnetic resonance imaging (MRI), computed tomography (CT) or body densitometry [13,16].

CHF-related muscle wasting is not due to a single factor, but rather it is influenced by many factors, interacting in a complex system with metabolic, immune and neurohormonal consequences [17]. Moreover, weight loss in CC results not only from the loss of lean tissue, but also from reductions in the fat mass and in bone mineral density (BMD) [5]. Loss of adipose tissue in patients with cachexia seems to be mediated by increased lipolysis or reduced lipogenesis [18]. Increased levels of catecholamines and cortisol could be the cause for increased lipolysis in cachectic patients and might also contribute to the increased resting metabolic rate that has been described in CHF patients [19].

Pathophysiology of cardiac cachexia

Little is known about HF-related mechanisms that result in CC [13,16]. In 1964, Pittman and Cohen [reviewed in 16] extensively analyzed the pathogenesis of the CC syndrome and pointed cellular hypoxia as a leading pathogenic factor, causing less efficient intermediary metabolism, therefore inducing catabolism and reducing anabolism. Nowadays it is known that this catabolic/anabolic imbalance is caused by a series of immunological, metabolic, and neurohormonal processes [20], most of which are activated early in the development of CHF. Many of these pathways are triggered to protect the heart and the circulation from damage and to compensate for impaired myocardial function [5].

Immune activation in CHF

Many studies have referred to the association of CHF with increased circulating levels of pro-inflammatory cytokines, namely tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) [21–25]. Importantly, the rise of these inflammatory mediators seems to be combined with inadequately raised or even decreased levels of anti-inflammatory mediators such as interleukin-10 (IL-10) and transforming growth factor beta 1 (TGF-β1) [26]. The origin of immune activation is still uncertain [6]. Some hypotheses about the main stimulus for the immune activation in CHF have been put forward [1]. One hypothesis assumes that the heart itself is the main source of inflammatory cytokines [1,8], since the failing myocardium is capable of producing TNF-α [27]. Although some authors [6] suggest myocardial production of cytokines as a localized phenomenon, Tsutamoto et al. [28] have found increased levels of TNF-α in the coronary sinus when compared to the aortic root, supporting that the elevated plasma TNF-α is partly derived from the failing heart. Not only cardiomyocytes, but also other cells within the failing heart such as endothelial cells, fibroblasts and infiltrating inflammatory cells may contribute to the myocardial inflammation in CHF. Moreover, several extramyocardial tissues and cells – circulating leukocytes, blood platelets, endothelial cells, liver, lungs and tissue macrophages – also seem to contribute to the systemic inflammation that characterize this disorder [11]. Nevertheless, the direct stimuli underlying their activation are unknown [6].

The second hypothesis postulates that extramyocardial cytokine production due to tissue hypoxia may be the primary stimulus for increased TNF-α production in patients with CHF [8]. It is assumed that the bowel wall edema and ischemia, which occur in CHF as a result of venous congestion, are responsible for bacterial translocation, leading to endotoxin (lipopolysaccharide, LPS) release and subsequent activation of the circulating immune cells [6,8]. Indeed, endotoxin is one of the strongest inducers of TNF-α and other pro-inflammatory mediators. Very small amounts of this substance are capable of inducing TNF-α secretion [3]. Jankowska et al. [6] have proposed another theory. According to these authors, CHF-related immune activation is a consequence of long-term neurohormonal overactivation and exaggerated stimulation of the sympathetic nervous system (SNS), and that the initial mechanism triggering inflammatory processes in CHF is secondary to the central suppression of parasympathetic nervous system (PNS).

Cytokines-related signaling pathways underlying muscle wasting

Muscle wasting results from a chronic imbalance in the activation of anabolic or catabolic pathways and TNF-α is one of the candidates that have been suggested as a common mediator in all forms of cachexia [5,29]. TNF-α activates proteasome-dependent protein breakdown in striated muscle and other tissues, thus maintaining the wasting process [5]. The major catabolic pathways involve cytokine-induced activation of NF-κB signaling (Fig. 1) that up-regulates the transcription of members of the proteolytic ubiquitin–proteasome pathway (UPP). This up-regulation can be mediated by forkhead box O (FOXO) transcription factors. TNF-α induces the cytosolic release of NF-κB from its inhibitory IκB proteins, allowing the translocation of NF-κB into the nucleus and subsequent transcription of proteolytic pathway components [29]. Proteins to be degraded by this mechanism are first conjugated to multiple molecules of ubiquitin, and then degraded in the 26S proteasome complex in an ATP-dependent process [30]. However, the proteasome is not able to degrade intact myofibrils [15], so actin and myosin need to dissociate from myofibrils before they can be ubiquitinated and degraded [30]. Thus, there are other proteolytic enzymes that act upstream UPP, namely m-calpain, cathepsin-L and/or caspase-3 [29].

Protein ubiquitination is regulated by at least three different enzymes: ubiquitin activating enzyme, E1; ubiquitin conjugating enzyme, E2; and ubiquitin ligase, E3 [30]. Initially, ubiquitin is activated by E1, in an energy-dependent step; it is then transferred by E2 to E3, that finally catalyzes the binding of ubiquitin chains to different substrate proteins [31]. In addition to the activity of enzymes involved in the ubiquitination and deubiquitination of proteins, certain features of a protein can make it susceptible to degradation [30]. According to the N-end rule, the in vivo half-life of a protein is related to the identity of