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Cardiac cachexia: *hic et nunc*☆

"*hic et nunc*" — here and now

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ABSTRACT

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

1. Epidemiological aspects of cardiac cachexia

Through prevalence of chronic disease, lack of specific therapies or non-implementation of existing and evidence based management, cachexia evolved to a public health issue [1]. Most of epidemiological figures are based on different cachexia definitions and derived from heterogeneous populations [2]. One would hope this would change with a consensus cachexia definition published in 2008 [3]. However, literature speaks for itself as we are still in need of quality and quantity on this topic [4]. For heart failure (HF), as for other chronic diseases, only few studies were published and they remain heterogenous in cachexia definition. The recent study in HF again used the old definition, namely unintentional non-edematous weight loss of >5% over at least 6 months. By applying this definition, cachexia was found in 19/238 (10%) HF patients [5]. In fact, new definition was tested in a single HF study [6]. In 137 patients, the obligatory criterion of weight loss was met by 42 (31%) but when additional 3 criteria were requested, significantly fewer patients met the cachexia definition (30 (22%) patients, $p = 0.0006$). Interestingly, no difference in survival was seen between those two patient groups. The authors therefore challenged the added value of new cachexia definition, more precisely the addition of criteria on top of obligatory weight loss.

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

Abbreviations: ActRIIB, Activin type II B receptors; AET, Aerobic exercise training; BCAA, Branched chain amino acid; C6M, MMP-generated degradation fragment of collagen 6; CAF, C-terminal agrin fragment; CC, cardiac cachexia; GDF15, growth differentiation factor 15; HF, heart failure; IC6, type VI collagen N-terminal globular domain epitope; IGF-1, Insulin-like growth factor 1; P3NP, *N*-terminal propeptide of type III procollagen; RAAS, renin–angiotensin–aldosterone axis; SNS, sympathetic nervous system; sTNFRs, Soluble tumor necrosis factor receptors (sTNFRs); TNF-α, tumor necrosis factor alpha; UPP, ubiquitin–proteasome pathway.

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source of information should be the Studies Investigating Comorbidities Aggravating Heart Failure (SICA-HF) that has included HF patients, diabetics and healthy controls [8]. After an extensive baseline assessment that allows for cachexia diagnosis, they were seen at regular intervals and followed-up for mortality. First reports from this study include muscle wasting aspect which was frequent and associated with reduced physical performance [9]. Along with cachexia definition, health professionals' attitudes across the chronic disease need to be changed. Screening for nutritional aspects, weight loss, and correlates in terms of physical performance and quality of life should be part of routine assessment [10] as many of abnormalities may be managed in an easy way.

2. Advances in patophysiology of cardiac cachexia

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

2.1. Immune activation

Increased circulating levels of pro-inflammatory cytokines characterized HF, namely tumor necrosis factor alpha (TNF-α), interleukin-1, and interleukin-6 [14–17]. The rise of these inflammatory mediators seems to be combined with inadequately raised or even decreased levels of anti-inflammatory mediators such as interleukin-10 and transforming growth factor beta 1 [18]. The cause of immune activation is still uncertain [19].

2.2. Metabolic abnormalities

Evidence is mounting that the abnormal and imbalanced metabolism represents an intrinsic aspect of HF pathophysiology, with fundamental symptomatic and prognostic implications [11]. The concept of metabolic failure in HF include both impaired myocardial energy utilization and metabolic inefficiency at the systemic level. The key points in this concept are global anabolic blunting and insulin resistance and catabolic overactivity [20,21]. Anabolic deficiency in HF patients induce loss of skeletal muscle mass and function [22]. Men with HF showed reduced circulating testosteron and dehydroepiandrosterone sulphate, and its relation with decreased exercise capacity [23,24]. It is well-known that anabolic steroids have significant role in the quantitative and qualitative regulation of muscle fibre content, leading to increases in muscle mass and strength, as well as improvement in physical performance [25].The major anabolic hormones modulating protein metabolism in skeletal muscle include insulin, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [16]. It has been previously proven that that insulin resistance may play an important role in skeletal muscle dysfunction in HF [20,26]. Since IGF-1 has been shown to stimulate protein synthesis and to reduce protein degradation, changes in the GH/IGF-1 axis may impact the anabolic/catabolic balance in the wasting syndrome [27]. Patients with HF-related systolic or diastolic dysfunction have significantly lower plasma levels of total IGF-1, but free IGF-1 is significantly higher than in healthy controls. Recently, the role of leptin and other adipokines in the process of body wasting has been questioned [28–30]. Adiponectin, an adipokine with multiple metabolic actions, increases both locally and globally with HF severity and is highest in cachectic patients [31,32]. Our recent findings may indicate a cross-sectional metabolic association of increased serum adiponectin with reduced peripheral muscle mass and muscle strength in non-cachectic, non-diabetic, elderly HF patients [33]. Recent reports suggest the role of changes in small and large intestine function in HF in the pathogenesis of wasting [34,35]. Furthermore, in patients with stable HF, the blood flow in the intestinal arteries is reduced and relates to CC [36].

2.3. Neurohormonal abnormalities

The hallmark of HF pathophysiology, as a response to impaired cardiac function, is a general neurohormonal activation via stimulation of the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone axis (RAAS) and the natriuretic peptide system [37,38]. Chronic autonomic sympathetic/parasympathetic imbalance is a crucial element of HF pathophysiology. Both epinephrine and norepinephrine can cause a catabolic metabolic shift, leading to graded increase in resting energy expenditure in HF patients with CC [37,38]. Sustained sympathetic stimulation, as is seen in HF, activates the RAAS [39]. Studies have shown that Angiotensin II induces muscle wasting through multiple mechanisms: (1) increased oxidative stress via activation of NADPH oxidase; (2) increased protein breakdown via reduced IGF-1 and increased cytokine signaling such as glucocorticoid and IL-6; (3) reduced appetite via alteration in orexigenic/anorexigenic neuropeptide expression in the hypothalamus; (4) impaired energy balance via inhibition of AMPK; and (5) inhibition of satellite cell function and muscle regeneration [40].

2.4. Molecular basis of cachexia

The molecular basis of cachexia is still poorly understood and the lack of therapies is evident [41–43]. Better understanding of molecular mechanims of cachexia has provided potentially new treatment targets. Skeletal muscle wasting is a consequence of protein synthesis and degradation imbalance. Recent studies in CC have evaluated the ubiquitin–proteasome pathway (UPP) and autophagy/lysosomal proteolytic pathways to better understand the process of muscle atrophy in HF [43–45].The UPP plays a critical role in skeletal muscle wasting. Studies from many groups over the past years have indeed identified many components in the UPP that are induced in atrophying skeletal muscle [46] The UPP plays a cricial role in the breakdown of myofibrillar proteins [12,47]. The overactivation of the UPP in the skeletal muscle of HF patients has been attributed to increased oxidative stress [48,49]. Transcription factors activating the proteasome pathway include particularly the forkhead box class O (FoxO) and nuclear factor-kB (NF-kB) that drive increased expression of the E3 ubiquitin ligases muscle RING-finger protein (MuRF-1) and muscle atrophy F-box (MAFbx) [46]. Thus, inhibition of FoxO was found to induce hypertrophy by increasing protein synthesis [50]. Additionally, one recent study demonstrated that angiotensin II induces skeletal muscle atrophy in part by increased muscle-enriched E3 ubiquitin-ligase muscle RING-finger (MuRF 1) expression, which may involve protein kinase-D [51]. Along with overactivated UPP, autophagy and lysosomal protein breakdown are also increased [52]. Unlike to the UPP which removes short-living cytosolic and nuclear proteins, the autophagy–lysosome system accounts for degradation of long-living proteins and protein aggregates. There is direct evidence that autophagy signaling is increased in a CC rat model [45]. Some other important molecular mechanisms of controlling muscle mass include: PI3K–AKT signalling, NF-κB, SMAD2 and SMAD3 in myostatin- and activin A enhanced proteolysis [43].

2.5. Myostatin

Myostatin, a member of the transforming growth factor beta superfamily, is an extracellular cytokine dominantly expressed in skeletal muscles which is known to play the important role in the negative regulation of muscle mass [53,54]. Myostatin appears to be a key player in the integrated physiology of muscle, fat, and bone [55]. It is unclear whether myostatin directly affects fat and bone, or indirectly via muscle.