Heart Failure-Induced Cachexia

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Abstract
Heart failure patients often develop cachexia, which is an independent factor for survival reduction. Cachexia can be diagnosed when there is loss of more than 6% of the body weight, in the absence of other diseases. Even though its pathophysiology has not yet been completely clarified, various factors seem to be involved, such as reduction in food consumption, gastrointestinal tract abnormalities, immunologic and neuro-hormonal activation and changes in the relationship between anabolic and catabolic processes. Since there is no specific therapy for heart failure-induced cachexia, management is based on nutritional support, neuro-hormonal blockade, control of edema and anemia and exercise. Drugs with anabolic and immunomodulating properties are being evaluated and clinical and non-clinical trials.

Introduction
Heart failure is caused by functional and/or structural heart abnormalities, which can be acquired or hereditary and lead to worsening of ventricular ejection and filling capacity. In the last decades, with better understanding of its pathophysiology, it has become clear that pathological changes involve not only the cardiovascular system, but also the renal, neuroendocrinological, immunological, musculoskeletal, hematologic and gastrointestinal systems, as well as nutritional status. Currently, studies are being carried out in order to clarify the pathophysiology of the systemic complications related to heart failure and to propose treatments that improve quality of life and increase survival. Among them, we highlight the research on heart failure-induced cachexia. In this review article, we will discuss the definition, prevalence, causes, clinical impact and therapeutic alternatives to heart failure-induced cachexia.

Cachexia is an important predictive factor in the reduction of survival in heart failure, independent from important variables such as age, functional status, ejection fraction and capacity to perform physical activity. The importance of cachexia development to the prognosis of heart failure became more evident with the description of the reverse epidemiology of obesity in this condition. In normal subjects, the increase in the body-mass index (BMI) is associated to an increased risk of developing cardiovascular disease. However, in heart failure patients, there is a positive correlation between BMI and survival. The protection factor of BMI increase in these patients has been well documented in a post hoc analysis of the multicentric trial DIG (Digitalis Investigation Group), which showed increased mortality in patients with the smallest BMI values, and decreased mortality in patients with the largest BMI values.

Definition of heart failure-induced cachexia
The noun cachexia is of Greek origin and is formed by the junction of kakós, which means bad, and hexis, meaning condition. Some patients lose so much weight that this diagnosis becomes evident. However, it is often difficult to diagnose cachexia in heart failure patients, since edema impairs body weight evaluation and other anthropometric measures. Besides, the interpretation of laboratorial methods for nutritional status evaluation, such as nutritional markers levels or body composition determination by bioelectric impedance, is difficult. Bioelectric impedance can overestimate mass without fat because of excessive extracellular fluid effect.

In order to facilitate the diagnosis of cachexia, Anker et al. proposed in 1997 an easily applicable definition for the evaluation of heart failure patients. According to the authors, cachexia should be diagnosed when there is body weight reduction superior to 7.5% of the usual weight, non intentional and not attributable to edema, in the absence of other diseases that may cause undernourishment such as, for example, neoplasias, infection or hypothyroidism. The weight loss must have occurred over six months. Steep losses in shorter time periods can also be derived from heart failure itself, but other severe diseases must be investigated. The weight before development of the heart condition must be considered. Later, the same authors demonstrated that losing as much as 6% of the body weight is associated to a worse prognosis. Thus, heart failure-induced cachexia is now defined as loss of 6% of the body weight.

It must be emphasized, however, that this definition is not universally used in general studies on cachexia. In 2006, in the Cachexia Consensus Conference, the condition was defined as weight loss ≥ 5% in < 4 month or BMI < 20 kg / m² plus chronic disease and at least three of the following criteria: 1) reduced muscle strength; 2) fatigue; 3) anorexia; 4) reduction of the fat free mass index and 5) biochemical abnormalities such as inflammation, anemia or low serum protein levels.

Keywords
Cachexia; Heart Failure; Prognosis; Anorexia.
albumin. It must be emphasized that, contrary to anorexia and malnutrition, conditions that can resolve with adequate food ingestion, cachexia is hardly ever reversible.  

**Epidemiology**

Defining cachexia as a weight loss status equivalent to 6% of the body weight, Anker et al.\(^\text{8}\) noted that 34% of the heart failure patients treated in outpatient clinics presented cachexia during the 48-month follow-up period. Other studies showed that an annual incidence of cachexia of approximately 10% in patients class III or IV of the New York Heart Association, and a prevalence between 12 and 15% in classes II to IV.\(^\text{11,12}\)

**Pathophysiology of heart failure-induced cachexia**

The pathophysiologic mechanisms involved in heart failure-induced cachexia have not yet been completely unveiled. We will present next the various factors considered at the root of its development.

1) **Reduced food ingestion**

Reduced food consumption can be secondary to anorexia, and its mechanisms have not yet been discovered. Various factors may be involved, such as tasteless diets, particularly due to the low sodium content, severe depression and passive visceral congestion. Drugs frequently prescribed for treating the disease can inadvertently contribute to reduced food ingestion. Digitalis intoxication can lead to anorexia, nausea and vomiting. Some angiotensin converting enzyme inhibitors, particularly captopril, can affect taste and exacerbate anorexia.\(^\text{11}\) The chronic and vigorous use of diuretics can lead to depletion of the body’s storage of zinc, causing taste alterations, and of potassium, promoting intestinal hypomotility. Inflammatory cytokines, as we will see later, and inadequate concentrations of leptin also lead to anorexia.\(^\text{14,15}\)

Besides all these factors, there seems to be also an intrinsic disorder of appetite regulation. The main appetite regulation site is the hypothalamus. Two areas were identified in the hypothalamus: a lateral area, which induces appetite when stimulated, and a medial area, which leads to satiety. Various neuropeptides are involved in the control of food ingestion. It is thought that in heart failure, there is an imbalance between the action of neuropeptides, with anorexic agents, that act on the satiety center, prevailing over orexigenic.\(^\text{3}\)

Besides anorexia, other factors may lead to the reduction of food ingestion, such as early fullness due to significant hepatomegaly and reduced energy ingestion due to low lipid ingestion. The reduction of fat ingestion, with its high energy density, may not be compensated with a proportional increase in carbohydrate ingestion. Finally, it is important to highlight that, in class IV heart failure patients, dyspnea at rest can also limit food ingestion.

2) **Gastrointestinal tract abnormalities**

The role of the gastrointestinal tract in the genesis of cachexia has been studied in detail recently.\(^\text{14,17-19}\) A number of structural changes have been detected in the gastrointestinal tract of heart failure patients, such as thickened intestinal wall, suggesting mucous edema, increased collagen content in the intestinal wall and increased distance between capillary wall and enterocytes.\(^\text{20,22}\) It is now believed that these changes lead to worsened enterocyte nutrition and to the development of intestinal malabsorption. Functional changes were also described, such as decreased absorption of protein and fat and increased paracellular permeability.\(^\text{20,21,23}\) Additionally, an increase in bacteria concentration in the mucous biofilm and in its adherence to the intestinal wall was observed. The increased paracellular intestinal permeability and increased intestinal bacterial colonization are to be held responsible for the inadequate absorption of bacterial constituents such as endotoxins, a process known as bacterial translocation. Bacterial endotoxins, also known as lipopolysaccharides, are considered one of the most powerful inducers of tumor necrosis factor-α (TNFα) and other pro-inflammatory substances.\(^\text{24,25}\) These data strongly suggest that, in heart failure, gastrointestinal tract abnormalities are involved not only in cachexia development but also in systemic inflammatory activation.

3) **Neurohumoral and immunological activation**

Immunologic and neuroendocrinologic changes have important roles in the development of cachexia. The article published by Levine et al.\(^\text{16}\) in 1990 was a landmark in the study of immunologic changes in heart failure. The authors observed that patients, particularly those with cachexia, presented high serum TNFα concentrations. These findings were remarkable for the understanding of the pathophysiology of heart failure and its systemic complications. It soon became clear, in large clinical studies, such as SOLVD\(^\text{27}\) and VEST,\(^\text{28}\), that TNF-α is a good prognostic marker that correlates to functional class, cardiac performance and survival. In experimental studies, the increase in TNF-α leads to a heart failure phenotype, with cachexia and skeletal muscle changes.\(^\text{29,30}\) It was verified later that other cytokines are implicated in heart failure. Among pro-inflammatory cytokines, we highlight interleukin (IL)-6 and the IL-1 family. Among anti-inflammatory cytokines, the IL-10 family and transforming growth factorβ play a crucial role.

There are various sources of cytokines in the body.\(^\text{31}\) Structurally damaged myocardium itself can express and produce increased levels of inflammatory mediators. Circulating leukocytes, platelets, endothelial cells and liver and lung cells also seem to be involved in the production of cytokines. Among the stimulus to cytokine production, we emphasize: hemodynamic overload, neurohormonal activation, hypoxemia and tissue hypoperfusion, low density lipoprotein oxidation, autoantibodies and immunological stimulation caused mainly by the absorption of intestinal endotoxin, as mentioned before.\(^\text{31}\)

Besides largely known cardiac alterations, cytokines also induce cachexia, endothelial dysfunction, erythropoiesis inhibition, intestinal permeability changes, free radical scavenger enzymes activity reduction, blood flow reduction to skeletal muscle, contractile muscle protein functional changes, skeletal muscle cell apoptosis and muscle atrophy and proteolysis.\(^\text{32}\) Since they result in proteolysis and loss of muscle mass, skeletal muscle alterations have a main role in cachexia development.
Regarding neurohormonal activation, its reflections are mainly related to the increase in basal energy expenditures and the additional activation of inflammatory mediators. Heart failure patients with cachexia have increased plasma concentration of norepinephrine, epinephrine, cortisol and aldosterone, compared to heart failure patients without cachexia, suggesting the systemic neurohormonal activation is implicated in the genesis of cachexia\textsuperscript{1,2}. Indeed, clinical trials show that using angiotensin converting enzyme inhibitors\textsuperscript{3} or beta-blockers\textsuperscript{4} may decrease the odds of losing weight. In vitro studies have demonstrated that angiotensin II, aldosterone and catecholamines can induce inflammatory cell activation and cytokine production increase\textsuperscript{5,6}. Additionally, adrenergic stimulation promotes vasoconstriction leading to worsened intestinal perfusion\textsuperscript{7}, which may enhance bacterial endotoxin translocation.

**Altered relationship between anabolic and catabolic processes**

The imbalance between anabolic and catabolic processes is important in the genesis of cachexia, particularly regarding skeletal muscle proteolysis\textsuperscript{7,8}. Nuclear factor-kappaB (NF-κB) participates in one of the main induction routes for catabolism and muscle proteolysis. The immunological and neurohormonal activation in heart failure, as well as the increased reactive oxygen species, stimulate NF-κB in muscle, activating ubiquitin-proteasome route and leading to muscle proteolysis. The ubiquitin system can be activated myoosin and inhibited by myoosin antagonists, such as follistatin, insulin and IGF-1\textsuperscript{9}. In rats with heart failure, muscle atrophy is associated to changes in the expression of proteins of the myoosin/follistatin route\textsuperscript{10,11}.

**Clinical consequences of cachexia**

Clinical manifestations of cachexia derive both from weight loss and the systemic inflammatory process. Steep drops in body weight, even with absent systemic inflammation, cause deleterious effects in virtually all organs and systems. Among cachexia consequences, we emphasize cardiac alterations, respiratory function abnormalities, reduced muscle and bone mass, reduced urinary concentration and acidification, impaired skin healing, predisposition to pressure ulcers in bedridden patients, gastrointestinal tract changes, anemia, and immunity reduction leading to increased infection risk.

The cardiac impairment makes it difficult to study cachexia effects on the heart itself, due to the underlying heart disease structural and functional changes. Experimental studies evaluate the cardiac effects of cancer cachexia unrelated to cardiac disease. These studies demonstrated molecular changes that are characteristic of the heart remodeling process and worsened ventricular function\textsuperscript{12}. In our lab, we evaluated cardiac impairment in normal and hypertensive rats subject to major feeding reduction. We verified that body weight reduction was associated to cardiac muscle mass decrease. In normotensive animals, we found morphologic and ultrastructural myocardial abnormalities and mild functional changes\textsuperscript{42-44}. However, in hypertensive rats' hypertrophied hearts, ultrastructural changes characterized by disorganization and loss of myofilaments and myofibrils, mitochondrial degeneration and numerous plasma membrane invaginations\textsuperscript{45} were more evident and widely spread in the myocardium. We observed evident myocardial and ventricular systolic dysfuction, probably caused to more intense ultrastructural changes\textsuperscript{46-48}. Sugizaki et al\textsuperscript{49} and Gut et al\textsuperscript{50,51} observed that the functional changes after inotropic myocardial stimulation are compatible with abnormalities in proteins involved in calcium intracellular transport. Thus, feeding restriction leads to morphological and functional changes in normal hearts, which are aggravated by mechanical overload.

As above mentioned, heart failure induces gastrointestinal tract changes. Body weight loss causes additional deleterious effects, promoting enterocyte atrophy, loss of villous structure and increased bacterial translocation risk\textsuperscript{52}.

Impairment of skeletal muscle system is common in heart failure and worsened by cachexia. Muscle mass reduction consequently to atrophy, apoptosis or necrosis,\textsuperscript{39,40,54,55} more frequent in cachetic patients\textsuperscript{52,53}, is frequently cited. Other muscular changes include reduced capillary density, reduced mitochondrial number, metalloprotease and myofibril composition modification, increased oxidative stress and calcium intracellular transport and metabolism abnormalities\textsuperscript{56-59}. There are strong evidences that metabolic abnormalities are intrinsic and independent from tissue hypoperfusion, as previously thought\textsuperscript{60,61}. Consequently, there is a reduction in muscle strength capacity, even after adjusting for muscle mass\textsuperscript{62}.

Finally, anemia, a frequent complication of heart failure, can be exacerbated by cachexia\textsuperscript{63}. Despite its multifactorial etiology, factors related to cachexia, such as reduced food ingestion, reduced intestinal absorption and the chronic inflammation status, have an important role in its genesis\textsuperscript{64}. Despite not having been systematically evaluated in large studies, iron deficiency has been described in rates ranging from 1 to 44% of the cases, depending on the studied sample and heart failure severity\textsuperscript{65,66}. This deficiency, besides impairing erythropoiesis, can also compromise cardiac function, inducing sympathetic nervous system activation, ventricular dilation, mitochondrial and ultrastructural heart changes and thrombocytosis\textsuperscript{67}.

**Treatment of heart failure-induced cachexia**

Since there is no specific treatment, various options have been proposed for prevention and treatment of cachexia: nutritional therapy, neurohormonal blockade, edema reduction, intestinal translocation reduction, appetite stimulants, immunomodulation, anemia correction, anabolic steroids and physical activity.

Nutritional therapy is now one of the mainstays for prevention and treatment of cachexia\textsuperscript{1,14,68}. The aims of nutritional therapy are to achieve and maintain, without edema, body weight within the ideal range, or, according to some authors, a little below ideal weight. The aims include the recovery of energy reserves, such as fat tissue and, more difficult to achieve, recovery of lean mass and bone mass. There are no specific recommendations for protein
and calorie supply in heart failure-induced cachexia. According to Heymsfield and Casper, the administration of 35 kcal/kg/day, by enteral route, is a safe and effective manner to increase lean mass. However, it is recommended that caloric supply does not exceed 28 kcal/kg/day. Nutritional support must be started in smaller amounts and gradually increased, if possible, to achieve and maintain the desired weight. Energy excess must be avoided, since it is associated to increased physiological stress with increased insulin and catecholamine concentrations in plasma and hepatic dysfunction. The increased circulating insulin levels may lead to greater sodium and water resorption by the kidneys and worsening heart failure. Protein must be prescribed according to normal adult recommendation (1.0 to 1.2 g/kg/day). Protein need can be larger if there are losses due to renal disease or intestinal malabsorption.

Some electrolytes must receive special attention. The sodium intake depends on heart failure’s functional classification. Three to 4 grams are recommended in moderate cases. Sodium consumption must be in the 0.5 to 2.0 grams/day range in severe cases; in these settings, it is important to educate the patients about sodium content in food. Due to chronic and often high diuretic doses, patients can present potassium and magnesium depletion with their corresponding associated symptoms. With increased supply of carbohydrates and amino acids and increased serum insulin levels, potassium, phosphorus and magnesium migrate from extracellular from intracellular space, with severe potential clinical manifestations, such as arrhythmias and sudden death. Water restriction is not always needed, depending on the severity of the disease. If the patients’ sodium intake is smaller, they are less thirsty; thus, it is not necessary to restrict fluid intake. In more advanced cases with intense neurohormonal activation leading to thirst center stimulation and sodium and water retention by the kidneys, water restriction can be necessary. Water restriction is mandatory if hyponatremia is present. It is important to emphasize that the increase in sodium and carbohydrate intake can be associated to greater sodium and water retention by the kidneys and worsening heart failure. Thus, it is important to weight the patient daily in order to individually adjust diuretic therapy.

Since micronutrient requirement in heart failure have not been established, the usual recommendations must be followed. Reduced intake and chronic diuretic use can lead to water-soluble vitamin deficiency. Particular attention must be given to thiamine, whose deficiency can increase severity of underlying heart disease. In cases of poor intestinal absorption, supplementation of fat soluble vitamins (A, D, E and K) may be required.

For nutritional support administration, the oral route is often effective, and voluntary food intake can revert negative energy and protein imbalance. However, it is not always possible to provide the desired food amount using only the oral route and it is necessary to initiate dietary support by nasoenteral route, usually well accepted by patients. Meals (provided by oral or enteral route) must be frequent and in small amounts. Factors such as hepatic congestion, gastric distention and ascites cause intolerance to the intake of large amounts of food. When the gastrointestinal tract cannot be used, or in perioperative settings, the intravenous route can be used for parenteral nutrition (total or supplementary to diet provided by gastrointestinal route). Since heart failure patients are intolerant to large fluid administrations, parenteral nutrition is more frequently provided via central central lines, allowing the infusion of smaller volumes of hypertonic concentrated solutions.

It is important to point out that doubt still exist whether cachexia can be reversed with adequate implementation of nutritional support, in spite of its recognized importance in heart failure.

Another mainstay in heart failure-induced cachexia is neurohormonal blockade, which must be done according to current guidelines. Due to its importance in neurohormonal activation in cachectic states, the blockade of the renin system is being investigated in a multicentric study evaluating the effects of imidapril on gastrointestinal cancer patients with non-cardiogenic cachexia.

Since systemic venous congestion is associated to gastrointestinal tract changes, patients must present as little edema as possible. Although experimental studies have demonstrated reduction of intestinal translocation with antibiotic therapy, it is not yet known if intestinal microbiota modulation can be useful for systemic inflammatory process control. Thus, selective intestinal decontamination is not indicated in heart failure.

Appetite stimulants, such as megestrol or medroxyprogesterone, have been used in cachexia associated to other diseases. Due to controversial results, they have not been approved for use in heart failure.

In the last decade, various studies evaluated systemic and cardiac effects of immunomodulatory agents. Taking into account the hazardous effects of TNF-α, drug development was naturally directed to TNF antagonism. Two large studies (Renaissance and Recover) have assessed the effects of etanercept, a TNF-α soluble receptor, in heart failure. Both studies were prematurely interrupted due to lack of clinical benefits. Infliximab, an anti-TNF-α monoclonal antibody, was associated with increased mortality and increased admissions due to heart failure. These results were disappointing for supporters of the hypothesis that it would be possible to improve heart failure survival by modulating inflammatory activity. Pentoxyphylline, a drug that can inhibit cytokine synthesis (particularly TNF-α), was also evaluated. The drug was tested only in small studies, with favorable or nil results. Thalidomide, a drug with potentially immunomodulatory action, presented favorable or nil results. Future perspectives include statins, methotrexate, N-acetylcysteine, immunoglobulin and various immunomodulatory agents (T-cell activation inhibitors, chemokine antagonists, IL-10, IL-1 receptor antagonists) that are currently being investigated experimentally.

Various drugs, such as the anabolic steroid testosterone, growth hormone, myostatin inhibitors and antagonists, bortezomide (a ubiquitin-proteasome route inhibitor), lipopolysaccharide bioactivity inhibitors and melanocortin blockers, are being investigated with the objective of preserving muscle mass. Testosterone was recently evaluated in a randomized double-blind study including
elderly men with heart failure. The administration to testosterone had benecic effects in functional capacity, muscle strength and glucose metabolism, leading to the hypothesis that it can be useful in heart failure.2 Since anemia is associated to decreased tissue oxygen availability, it is thought that its correction can improve tolerance to physical activity and help preserve muscle mass. Though controversial, specific treatment for anemia involve the correction of nutritional deiciencies and the utilization of erthropoeisis-stimulating agents.6

Finally, physical activity is important for maintaining and recovering skeletal muscle and physical conditions.5,8 Physical activity is performed only sporadically, it can lead to peripheral hypoxemia and inamatory cytokine activation. On the other hand, regular physical activity does not induce pro-inflammatory cytokine activation or endothelial damage markers and may yet decrease serum TNF-α and IL-6 levels. Thus, patients must be stimulated to performing physical activity under specialized guidance.

Future developments in heart-failure induced cachexia involve effective treatment development and the capacity of predicting and stopping the process before there is signicant body weight reduction.

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