Expert Perspective

Cardiac Cachexia: Is it Time to Legalise Anabolic Agents?

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Heart failure is the final outcome of all diseases of the cardiovascular system. In spite of the great progress that has been made in the therapeutic management of the syndrome, its morbidity and mortality remain at high levels. For this reason great efforts have been made in recent years to find new treatments based on a better understanding of the pathophysiology of the syndrome.

Many investigators have observed over the centuries that some patients with heart failure exhibit clinical manifestations similar to those of the chronic inflammatory or neoplasmatic diseases that are known as cardiac cachexia.[1-11] It has been known since the time of Hippocrates that these patients have the worst prognosis. In recent years, clinical follow up studies have confirmed that the presence of cardiac cachexia should trigger an alarm for the cardiologist, because it has a significant adverse effect on prognosis, independently of other prognostic parameters, such as age, NYHA functional class, left ventricular ejection fraction and peak oxygen consumption.[8] Twenty-nine percent of patients with cardiac cachexia will die within 6 months. The combination of cardiac cachexia with peak oxygen consumption <14 ml/kg/min means 77% mortality at 18 months, while the absence of these two parameters predicts very good survival, with mortality below 7% over the same period.[8]

Definition

Cardiac cachexia is effectively a new syndrome within the wider realm of heart failure and is characterised by a significant loss of body weight, which is often accompanied by anorexia and a variety of biochemical changes compatible with malnourishment (anaemia, hypoalbuminaemia), and inflammation (increased erythrocyte sedimentation rate and acute phase proteins).

The most important problem in daily clinical practice is that there is no generally accepted definition of cardiac cachexia in the international literature. Hippocrates, who first described it, identified the basic characteristics of cardiac cachexia as "consumption of the flesh and conversion of the flesh to water." Kotler et al defined cachexia as "accelerating loss of skeletal muscle through a chronic inflammatory reaction."[11] The trouble with this definition is that it cannot be used in research or in the clinical evaluation of the patient. Various clinical characteristics have been used to distinguish cardiac cachexia. Formerly, cachexia was defined in terms of anthropometrical characteristics, biochemical parameters, body fat, muscle mass, connective tissue or the percentage of ideal weight.[2-6] According to the newest clinical definition, cardiac cachexia is a condition in which, in patients

Table 1. Circumstances in which cachexia is encountered, apart from heart failure.

Infections
Cancer
AIDS
Rheumatoid arthritis
Cystic fibrosis
Diabetes mellitus
Chronic obstructive pulmonary disease
Inflammatory bowel diseases
Thyroid diseases
Liver failure
Elderly subjects with no obvious disease

with heart failure, there is a proven and involuntary loss of weight in excess of 6-7.5% of the previous norm and not due to oedema, over a period of at least 6 months.[8] This assumes that other causes that can lead to weight loss have been ruled out (Table 1).

The incidence of cachexia in patients with heart failure varies from study to study in the range 16-50%.[2,8-10] However, these data are from small studies and the real extent of the problem has not been assessed by a large epidemiological study.

Pathogenesis of cardiac cachexia

Cardiac cachexia has a multifactorial basis and three main components are involved in its pathophysiology: disturbances of basic metabolism, activation and overproduction of neurohormonal factors, and the presence of a low level inflammatory process in the cardiovascular system of patients with heart failure.[11-34] The relative contribution of each factor and their interaction have not been adequately investigated so far. It is also not known which is the parameter that signals the transition from heart failure to cachexia, or even whether there is a genetic predisposition to the syndrome.

Initially, it was thought that anorexia and the malabsorption of fat and other nutritional constituents by oedematous gastrointestinal mucosa were responsible for the malnutrition of patients with end-stage heart failure.[18,21] This view was supported by the observation that cachectic patients with heart failure did not differ from non-cachectic patients as regards the classical haemodynamic parameters used to assess the severity of heart failure, such as left ventricular ejection fraction,[18-21] while they had higher pressures in the right cardiac cavities.[2,8,20] Right heart failure may indeed accelerate cardiac cachexia, since it is correlated with protein loss enteropathy,[21] while intestinal oedema exacerbates these patients' anorexia.[7] However, cachexia also appears in patients who have no apparent right heart failure and cachexia differs from the weight loss resulting from a reduced intake or deprivation of food,[11] in that the total protein synthesis in cachexia does not change substantially, whereas in food deprivation it is reduced. In cardiac cachexia there is an increase in the synthesis of acute phase proteins, whereas muscle protein synthesis decreases.[14] Finally, disturbances due to food deprivation are usually reversible when feeding is recommenced, in contrast to cardiac cachexia where nutritional support brings no material improvement.[15]

Another parameter that contributes to the loss of muscle mass in patients with heart failure is the reduction in physical activity. However, this mechanism does not explain the syndrome, given that the weight loss in cardiac cachexia is due to the loss not only of muscle tissue but also of fat and bone mass.[11-14]

The most important pathogenetic mechanism in cardiac cachexia is the increased catabolism and/or the reduced anabolic response to the pathophysiological changes brought about by the deterioration in cardiac function.[15-18]

The progression of heart failure is accompanied by the generalised activation of neurohormonal mechanisms, of which the main ones are stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone axis, and an increase in the activity of the natriuretic peptide system. Patients with cardiac cachexia show increased neurohormonal activation compared to heart failure patients without cachexia. Elevated levels of epinephrine, norepinephrine, aldosterone and growth hormone have been found in patients with heart failure and cachexia.[18,22,23]

Growth hormone has an anabolic action and acts via insulin growth factor 1 (IGF-1) in protein synthesis and cell proliferation. The increase in growth hormone in cachectic patients with heart failure is not accompanied by a proportional increase in IGF-1. Consequently, cardiac cachexia is characterised by resistance to growth hormone, resulting in the persistence of catabolic activity. Furthermore, cachectic patients with heart failure show reduced levels of most anabolic hormones and especially of dehydroepiandrosterone.[18,19]

The precise role of natriuretic peptides in cachexia has not been investigated. There are, however, experimental indications that B-type natriuretic pep-

Table 2. Possible mediators of cachexia (modified from reference 1).

Protein	Effect on appetite	Relation with cachexia in animals	Relation with cachexia in humans
Tumor necrosis factor α (TNF-α)	reduction	positive	positive
Interleukin 6	reduction	positive	unknown
Interleukin 1	unknown	positive	negative
Cilliary neurotrophic factor (CNTF)	reduction	positive	unknown
Interferon-γ	reduction	positive	negative
Lipid mobilizing factor (LMF)	none	positive	positive
Proteolysis inducing factor (PIF)	none	positive	positive

tide (BNP), apart from its beneficial actions, also increases lipolysis.[3]

It is therefore clear nowadays that the excessive activation of neurohormonal mechanisms contributes to the worsening of heart failure syndrome and is actively involved in the pathogenesis of cardiac cachexia. What happens in cardiac cachexia is a tilting of the anabolism/catabolism balance in the direction of catabolic activity.[18]

A recent discovery is that disturbances of anabolic hormone metabolism are directly related with the anomalous activation of the immune system in patients with cardiac cachexia. The immunological-cytokinetic activation is considered to occupy a central role in the pathophysiology of cardiac cachexia. Levine, in 1990, first revealed the relationship between tumour necrosis factor α (TNF-α) and the severity of heart failure.[4] From later studies it emerged that levels of cytokines, and particularly TNF-α, were directly related with weight loss in cachectic patients. TNF-α is a cytokine that promotes inflammation, has a catabolic action on most tissues and contributes to worsening of the syndrome. According to experimental data, it caused proteolysis, muscle atrophy, weight loss and osteoporosis.[22] In recent years it has been shown that other proinflammatory cytokines, such as interleukin (IL) 1β and IL-6 have a significant role in the manifestation of the syndrome. Table 2 shows the principal moderators that have been found to play a part in the pathophysiology of cachexia syndrome.

Cytokines and neurohormonal activation are also powerful stimuli for the induction of apoptosis and necrosis of myocardial, endothelial and skeletal muscle cells in patients with heart failure, resulting in dysfunction of the heart muscle, endothelium and peripheral musculature.[20-33]

In recent years two other proteins, leptin and ghrelin, have been implicated in the pathophysiology of cardiac cachexia. The role of leptin in cardiac cachexia has not yet been elucidated. Although it has been maintained that heart failure is generally characterised by hyperleptinaemia,[32] it appears that in cachexia leptin levels are not elevated.[9,33] Ghrelin, a peptide that has been isolated from the stomach, plays a part in the release of growth hormone through a route independent of the hypothalamic. Its action consists of an increase in nutritional uptake and an increase in fatty tissue, thus creating a positive energy balance.[17] Elevated ghrelin levels have been found in cardiac cachexia, linked with increased levels of growth hormone and TNF-α. It has been hypothesized that ghrelin may well represent a balancing mechanism against the hypercatabolic activity of cardiac cachexia.[17,34]

Treatment of cardiac cachexia

To date there is no particular treatment for cardiac cachexia that is of proven efficacy. Understanding of the pathophysiology of cardiac cachexia has led to the development of drugs aimed at controlling neurohormonal and cytokinetic activation and to the designing of clinical studies involving the administration of anabolic substances. Table 3 shows the therapeutic approaches to cachexia that are currently being tested at an experimental or clinical level.[35-49]

However, older therapeutic approaches involving nutritional support and controlled physical exercise have not been abandoned. A hypercaloric diet in cachexia of non-cardiac aetiology, such as acquired immune deficiency syndrome (AIDS) or lymphoma, did not produce the expected results, since the balance of protein synthesis was not affected beneficia-

Table 3. Agents that are being tested in experimental and/or clinical studies for the treatment of cachexia.

Anabolic agents	**Hypercaloric feeding**
• Recombinant hGH Recombinant IGF-1	**Appetite stimulants**
• Testosterone	• Megestrol acetate
• Anabolic steroids	• Medroxyprogesterone • Dronabinol
Cytokine inhibition	**Resistance exercise training**
• Pentoxifylline	
• Thalidomide	**n-3 fatty acids**
• Antioxidants	
• Melatonin	
• Medroxyprogesterone	**Metabolic regulators**
• Megestrole acetate	• Insulin-sensitising agents
• Δ-9 tetrahydrocannabinol	• Clenbuterol
• L-Carnitine	• Lipoprotein lipase activators
• Erythropoietin	• Serotonin type 3 receptor antagonists (ondasetron)
• Antisense therapy directed at nuclear factor κ-B	
• Anti-interleukin 6 receptor antibody	
• Anti-tumour necrosis factor antibody	
• Soluble TNF receptor	**Anti-inflammatory agents**
• Interleukin-15	

lly.[11,36-38] In cachectic patients with heart failure who were about to undergo surgical treatment, preoperative support with parenteral nutrition appeared to help reduce mortality.[5]

In patients with chronic heart failure it has been shown that physical rehabilitation through an exercise programme is safe and has satisfactory results.[39,40] The application of an exercise programme may contribute to an improvement in skeletal muscle metabolism and also contributes to a reduction in proinflammatory cytokines while increasing IGF-1.[41] It remains to be proved to what extent an organised exercise programme can offer significant therapeutic benefit to cachectic patients.

An analysis of the results of large clinical studies of heart failure showed that the administration of classical medications (angiotensin converting enzyme inhibitors and β-blockers) reduces the loss of body weight in patients with heart failure.[35,49] It has been shown that in daily clinical practice patients with a severe degree of heart failure do not take full therapeutic treatment for fear of side effects. There are further indications that in severely affected heart failure patients, and especially cachectic patients, an attempt should be made to deliver full drug treatment.

As far as newer therapies are concerned, the evidence from clinical studies to date is limited. Experimental data support the usefulness of fish oil (n-3 polyunsaturated fatty acid) in the treatment of cachexia via a reduction in IL-1 concentrations.[42] In the realm of anti-cytokine treatment the use of anti-TNF antibodies has been tried. It has been reported that the use of etanercept (soluble P75 TNF receptor) improves the cardiac function and the clinical condition of patients with heart failure.[43] The studies that used etanercept (RECOVER, RENAISSANCE) were discontinued prematurely because they failed to show a benefit from the use of the drug. It has been claimed that the results would have been better if the study had been carried out on patients with cardiac cachexia. However, in the studies in question the results do not appear to have been better in the subgroup of patients with weight loss. The failure of those studies has not hindered attempts to administer other anti-cytokine treatments in patients with cachexia (Table 3). The ineffectiveness of a particular drug may be due to the wrong choice of dosage, to the wrong choice of patients, or to the drug's having a different mode of action in the group of patients to whom it was given.

Pentoxifylline is a xanthine derivative that inhibits the production of TNF-α and IL-1. Its addition to the classical treatment for heart failure in small studies has improved the ejection fraction and symptomatology, but there are no specific data for cachex-

ia.[44,45] Also, thalidomide is a drug that selectively inhibits the production of TNF-α, through increased degradation of TNF-α mRNA,[46] but the data relating to cardiac cachexia are limited.[47]

Treatment of cachexia with various appetite stimulants and anabolic agents has been tried mainly for cachexia from cancer and AIDS, with encouraging results. Growth hormone has failed to give satisfactory results, in low dosages, in patients with heart failure from dilated cardiomyopathy.[48] The resistance to growth hormone seen in cardiac cachexia is probably due to blockage of its therapeutic action.[22] There are limited data suggesting that the administration of large doses of growth hormone, or the direct administration of IGF-1, would lead to better results.

To conclude, cardiac cachexia has proved to be a syndrome of complex pathophysiology, in which neurohormonal and cytokine activation play a primary role. The appearance of cardiac cachexia is an unfavourable prognostic factor. For this reason, many research efforts have been made in recent years to find an effective treatment of the syndrome. The efficacy of the treatments available to date has not yet been established.

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