Cardiac Cachexia: Pathophysiology and Clinical Implications

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Abstract

Cardiac cachexia (i.e. body wasting) has long been recognised as a serious complication of chronic heart failure (CHF) which affects many body systems and remains an important and increasing public health problem. The occurrence of wasting in CHF has been known for many centuries but little investigated. Independently of functional disease severity, age, and measures of exercise capacity and cardiac function, cardiac cachexia is associated with poor prognosis. Cachectic CHF patients are weaker and fatigue earlier because of a general loss of fat tissue, lean tissue and bone tissue as well as impaired muscle quality. There is a shift of understanding of pathophysiology of cardiac cachexia with increasing evidences that metabolic, neurohormonal and immune abnormalities may play a significant role as well the degree of body wasting is dependent on such changes. It has been shown that cardiac cachexia is linked to raised plasma levels of tumor necrosis factor alpha and other inflammatory cytokines and increased concentration of epinephrine, norepinephrine, and cortisol. Furthermore, they also present high plasma renin activity and increased plasma aldosterone level. Cardiac cachexia may be the result of a multifactorial neuroendocrine and metabolic disorder and of a complex imbalance of different body systems.

Key words: body wasting, chronic heart failure, cytokines, immune activation, neurohormones, nutrition.

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Chronic heart failure (CHF) is an important cause of morbidity and mortality with a poor prognosis, comparable to many malignant cancers [81]. Weight loss and body wasting are important features of advanced heart failure. The earliest report dates back 2300 years to classical Greece (Hippocrates, about 460-377 BC) [40, 66].

Cardiac cachexia as a serious complication of CHF has been little investigated [7]. There is still no accepted global definition of cachexia even though several research groups have extensively explored the wasting process in different conditions. In studies with heart failure patients, patients were classified as "malnourished" when the body fat content was <22% for women and <15% for man or when the percentage of ideal weight was <90% [32]. Other groups defined patients with CHF prospectively as "cachectic" when the body fat content was <29% (women) or <27% (men) [80], or when the ideal body weight was <85% [70] or <80% [92].

Freeman and Roubenoff recommended in 1994 [50] a documented loss of at least 10% of lean tissue as the cut-off to define cardiac cachexia. There are some disadvantages of such a definition. Some patients may suffer from fat tissue loss (i.e. lipolysis) but little or no lean tissue loss. Additionally, this definition is muscle focused; it does not consider that lean tissue may be replaced by fat with no general weight loss. Furthermore, many physicians may not have easy access to facilities that allow prospective measurement of lean body mass and such measurement would cause fairly large additional cost.

Our definition of 'clinical cardiac cachexia' is more simple and quickly applicable: in patients with CHF without signs of other primary cachectic states (like cancer), cardiac cachexia can be diagnosed when weight loss of >7.5% of the previous normal weight is observed over a period of >6 months. The latter would be the average body weight prior to the onset of heart disease. The development of the cachectic state in CHF patients is a dynamic process and it can only be proven by documentation of dry weight loss measured in a non-edematous state.

This article will focus on the available knowledge relating the presence of general weight loss in CHF patients, its clinical implications, the influence of neurohormonal and immunologic abnormalities and potential treatment strategies.

Epidemiology

The prevalence of CHF rises with increasing age to >10% in subjects older than 80 years and, it is about 1% in middle-aged people [37]. This has been attributed to improved survival in patients with coronary artery disease [65] as the most important aetiological factor for the development of CHF [79]. The natural and perioperative morbidity and mortality in patients with cardiac cachexia are higher than that of non-cachectic patients [1, 92]. But there is no correlation between disease morbidity and mortality in cachectic CHF patients and the New York Heart Association (NYHA) class [23]. Cardiac cachexia also occurs in childhood in relation to malnutrition and/or malabsorption diseases like kwashiorkor or marasmus [19].

The first prospective study on the frequency and prognostic importance of weight loss in 171 CHF outpatients identified 28 cachectic patients (16%) [13] with an observed weight loss of 6-30 kg and an 18-month mortality of 50% (Fig. 1). That is worse than the prognosis for some forms of cancer. Furthermore, cardiac cachexia may be more common as previously thought. In the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial the incidence of new edema-free weight loss (>7.5% of the previous normal weight) was 35% over three years [11].

Etiology

Three distinct mechanisms are thought to be responsible for the development of cardiac cachexia: (a) malabsorption and metabolic dysfunction, (b) dietary deficiency and (c) loss of nutrients via the urinary or digestive tracts [15]. The first to analyse extensively the pathogenesis of cardiac cachexia were Pittman and Cohen [94]. They proposed the development of cellular hypoxia as being the principal pathogenic factor, leading to less efficient intermediary metabolism followed by an increased catabolism (protein loss) and reduced anabolism.

The genesis from heart failure to cardiac cachexia is not yet clarified. Neither cellular hypoxia nor malabsorption were of pathogenic importance in a group of 11 cachectic patients with NYHA class IV mitral valve disease [31]. In another study it has been demonstrated that only fat

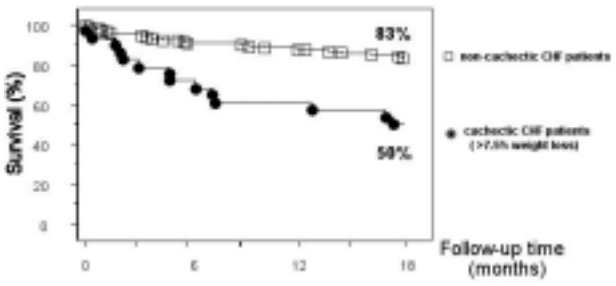

Figure 1. Kaplan-Meier survival curve for 18 month survival of 171 patients with chronic heart failure (CHF) subgrouped to cachectic and non-cachectic CHF patients. Adapted from Ref. [13].

malabsorption occurs (but not protein losing gastroenteropathy) in elderly ambulatory patients with cardiac cachexia [67]. Starvation and anorexia are often contemplated to be the main cause of cardiac cachexia. They would generally lead to a loss of fat tissue and cause reduced plasma albumin levels. Cachectic CHF patients suffer from muscle, fat and bone tissue loss. These indicate the presence of a general wasting process. But albumin and liver enzyme plasma levels are not decreased in these patients [4]. This argues against a major contribution of starvation, anorexia, gastrointestinal malabsorption, or liver synthetic dysfunction in these patients. However, only intervention studies can tell us whether abnormal food intake is of pathophysiologic relevance in the genesis of cardiac cachexia. Such studies are needed.

Additionally, physical inactivity is unlikely to have significant importance in the development of cardiac cachexia. Histological evidence suggests that the atrophy in states of reduced physical activity is very different from the muscle atrophy observed in CHF [111, 121].

Neuroendocrine Abnormalities

A multitude of secondary changes is related to CHF. Most of them are mainly a response to the impaired cardiac function and include general neurohormonal activation via stimulation of the sympathetic nervous system, the renin-angiotensin-aldosterone axis and the natriuretic peptide system. At the onset of cardiac heart failure, these systems are thought to be beneficial, but finally they contribute to increased vascular resistance and afterload, ventricular enlargement and remodeling [49]. The neurohormonal hypothesis postulates the heart failure progresses as a result of activation of endogenous neurohormonal systems, which exert deleterious effects on the heart and circulation [93].

Both, norepinephrine and epinephrine can cause a catabolic metabolic shift [4, 95], and lead to graded increase in resting energy expenditure in CHF patients [75, 89]. Furthermore, the clinical severity of CHF illness corresponds to the degree of the increase in resting energy demands [89]. Plasma norepinephrine may reflect overall sympathetic activity [54], but no study has investigated catecholamine levels specifically in cachectic CHF patients until recently. We found that cachectic CHF patients have markedly increased norepinephrine and epinephrine levels in contrast to near-normal levels of non-cachectic CHF patients (Fig. 2) as we stratified 53 CHF patients for left ventricular ejection fraction (LVEF), NYHA class and presence of cachexia [4]. None of the other subclassifications revealed significant differences between groups of CHF patients.

It was demonstrated that cortisol level as part of the general stress response with a catabolic action increased manifestly (2.5-fold) in untreated CHF patients with severe disease [2] and particularly in cachectic CHF patients (Fig. 2) [4], probably due to an increase in the release of adrenocorticotropic hormone [85]. The level of the anabolic steroid dehydroepian-

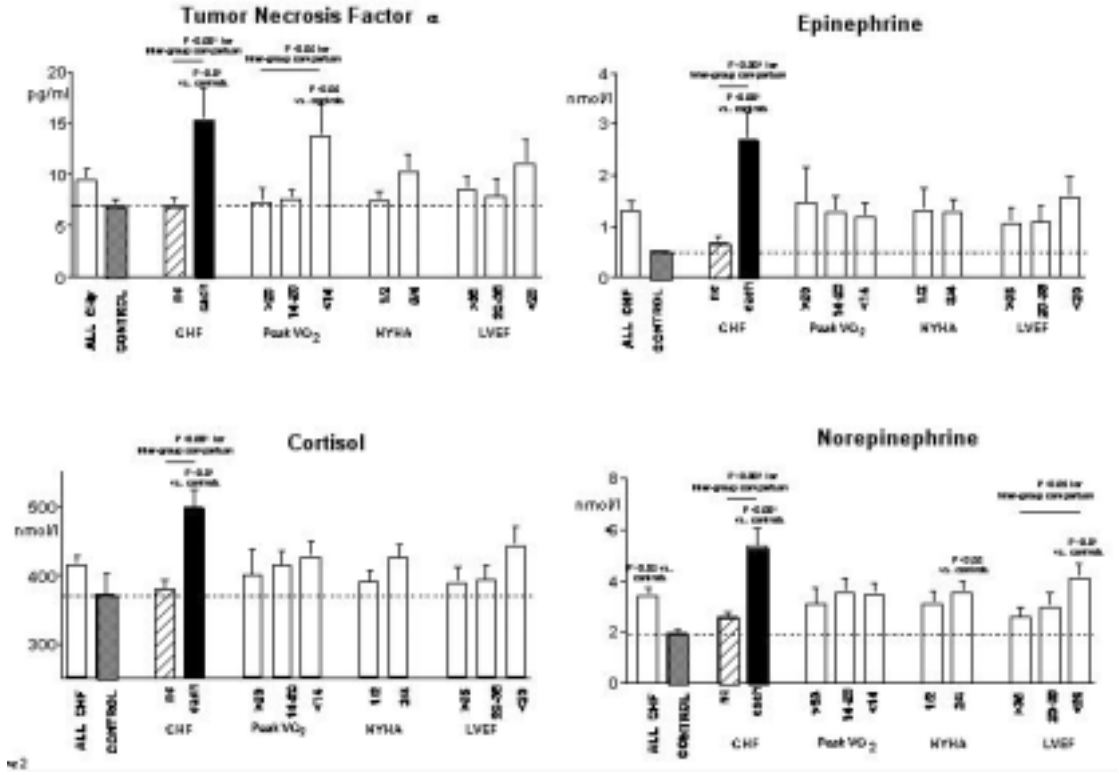

Figure 2. Norepinephrine, epinephrine, tumor necrosis factor alpha (TNFα) and cortisol plasma levels in 53 chronic heart failure (CHF) patients and 16 healthy controls. Patients are sub-grouped according to: (1) cachectic state (nc: non-cachectic, n=37: cach: cachectic, n=16): (2) maximal oxygen consumption [peak VO_2] (<14 (n=17) vs. 14-20 (n=24) vs. >20 ml/kg per min (n=12); (3) New York Heart Association class [NYHA] (class 1/2 (n=16) vs. class 3/4 (n=37)); (4) left ventricular ejection fraction [LVEF] (<20% vs. 20-35% (n=17) vs. >35% (n=12)). Data presented as mean ± S.E.M. P-values for Fisher's test are given if ANOVA showed significant inter-group variation. Adapted from Ref. [24].

drosterone, which was lowest in cachectic CHF patients in our study [4], may be a hint of a catabolic/anabolic imbalance. Furthermore, the immune activation seen in cachectic CHF patients is directly related to abnormalities of sex steroid metabolism [5].

Abnormal aldosterone plasma levels and plasma renin activity (a stimulator of the production of angiotensin II and norepinephrine [114]) reflect also a specific association between cachexia and neuroendocrine activation in CHF. Both parameters are increased in patients with cardiac cachexia although treatment characteristics as well as the time since diagnosis of CHF were similar [4]. The reduction of circulating insulin-like growth factor-1 (IGF-1) as well as the fibrosis of smooth muscle cells are results of the activity of angiotensin II and aldosterone [28]. Similar hormonal changes are also observed in adult patients with congenital heart disease [25].

Inflammatory Cytokine Activation

Recent findings have shifted the understanding of the pathophysiology of CHF to an increasingly complex approach involving neurohormonal and immunological aspects [7, 22, 105, 108]. Levine and colleagues reported that tumor necrosis factor alpha (TNFα) is increased in patients in cardiac cachexia [70] and, it is the strongest predictor of the degree of previous weight loss (r=0.78, p=0.0003; Fig. 2) [4]. Subsequently, these findings were confirmed by other groups [44, 80].

There are three hypotheses about the main stimulus for the immune activation in CHF. One hypothesis assumes that the heart itself is the main source of inflammatory cytokines [104] because the failing myocardium is capable of producing TNFα [115]. But there is no long-term beneficial anti-inflammatory effect after treatment with ventricular assist devices [34]. The second hypothesis suggests hypoxia as the main stimulus for increased TNFα production in CHF patients [59].

The endotoxin hypothesis [9] proposes bacterial translocation to occur due to bowel wall edema. Bacterial endotoxin, as the strongest known natural inflammatory stimulus [123], may enter the circulation because of altered gut permeability caused by acute venous congestion. Subsequently, endotoxin-stimulated inflammatory cytokine production may take place. Elevated plasma concentrations of endotoxin are present in CHF patients during an acute edematous exacerbation, and they can be normalised by diuretic therapy [87]. Interestingly, raised lipopolysaccharide (LPS)-levels have also been

detected in severely diseased children with grown-up congenital heart disease [7].

The biologically relevant LPS concentration to stimulate significant cytokine production of CHF patients ex vivo has been identified in vitro to be approximately 0.6-1.0 EU/mL [52]. The LPS-sensitivity of peripheral monocytes is increased in non-edema CHF patients [124].

The endotoxin hypothesis opens various options for novel therapeutic strategies against endotoxin and its binding to cells of the immune system or directly against the bacteria in the gut. Endotoxin-mediated inflammation may also be of importance in cardiogenic shock [30]. LPS-stimulated cytokine production of mononuclear cells of CHF patients and control in vitro can be reduced by interleukin-10 (IL-10) [26]. An explanation for the inverse relationship between high lipoprotein levels and low plasma levels of TNF and other inflammatory cytokine parameters [103] may be the beneficial role of lipids in patients with CHF by binding to and detoxifying the effects of endotoxin [101].

In the development of catabolism TNF plays an important role together with interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ and transforming growth factor-β (TGF-β). Proteolysis, weight loss and muscle atrophy can be prevented by IL-6 antibody therapy in animal models [118]. Furthermore, Barton suggested in 1997 that IL-6 can lead to the development of osteoporosis [20], but we were unable to find a significant correlation between serum IL-6 levels and bone mineral density in our patient cohort [6].

Additionally, TNF exerts effects on endothelial cells including rearrangement of the cytoskeleton and increased permeability to albumin and water. TNF also can cause induction of surface procoagulant activity, enhanced expression of activation antigens and IL-1 release [24] as well as reduction of the constitutive nitric oxide synthase mRNA in vascular endothelial cells [126]. A long-term detrimental effect of increased TNF concentrations could be reduction of peripheral blood flow in CHF patients [17].

Many of the TNF-effects could contribute (directly or indirectly) to cardiac cachexia in CHF [33]. But there are differences between the site of production and action of TNFα as animal experiments have shown. In skeletal muscle implanted TNF-producing cells cause cachexia, whereas TNF-producing cells implanted in the brain resulted in profound anorexia [117]. Furthermore, apoptosis as an important factor for cachexia development can be triggered by TNF [33].

Elevated plasma levels of cytokines and soluble cytokine receptors are suitable to predict the impaired survival in patients with CHF [46]. Levels of soluble TNF receptor 1 (sTNF-R1) appear to be very strong predictors of mortality. They have the highest specificity and

Table 1. Body composition in cachectic and non-cachectic patients with chronic heart failure (CHF) compared with healthy controls as determined by dual x-ray absorptiometry. All results mean ± SEM (ranges given in brackets). The derived measures were indented. Adapted from [16].

Total body results	cachectic CHF patients n=18	non-cachectic CHF patients n=36	Controls n=15
Lean tissue (kg)	46.0±1.2 ### ****	57.4±1.0	58.2±1.4
	(37.9 - 53.1)	(45.8 - 74.9)	(50.4 - 72.0)
- Body lean tissue content (%)	73.6±1.3 **	69.0±0.9	70.8±1.5
	(66.7 - 88.9)	(56.9 - 79.4)	(57.5 - 78.8)
- Body lean tissue / height (g/cm)	269±6 ### ****	331±5	331±7
	(226.9 - 305.1)	(283.3 - 423.0)	(292.1 - 389.2)
Fat tissue (kg)	13.6±0.8 ### ****	21.6±1.2	20.3±1.9
	(7.4 - 19.7)	(11.2 - 36.6)	(11.3 - 37.6)
- Body fat tissue content (%)	21.6±1.1	25.3±1.0	23.9±1.5
	(13.8 - 116.3)	(15.5 - 37.8)	(16.2 - 36.7)
- Body fat tissue / height (g/cm)	80±5 ## ***	124±7	116±11
	(43.7 - 116.3)	(63.9 - 212.9)	(63.3 - 225.0)
Bone mineral content (g)	2628±58 ### ****	3126±56	3184±107
	(2240 - 3020)	(2503 - 4059)	(2563 - 3915)
- Bone mineral content / height (g/cm)	15.4±0.3 ### ****	18.0±0.3	18.1±0.6
	(13.0 - 23.1)	(14.7 - 23.1)	(14.6 - 21.2)
Bone mineral density (g/cm^2)	1.16±0.02 ≠ **	1.23±0.01	1.22±0.02
	(1.033 - 1.286)	(1.065 - 1.509)	(1.055 - 1.380)

≠ p<0.05 vs controls ** p<0.01 vs non-cachectic CHF patients
p<0.01 vs controls *** p<0.001 vs non-cachectic CHF patients
p<0.0001 vs controls **** p<0.0001 vs non-cachectic CHF patients

sensitivity amongst all cytokine parameters [102].

Leptin as a product of the ob gene is involved in the regulation of food intake and energy balance [127]. TNF can lead to an increase in the plasma concentration of the hormone leptin in a dose dependent fashion [128]. Plasma leptin levels have been reported to be increased in CHF patients [71]. But the importance of leptin for cardiac cachexia pathophysiology is doubtful [41, 47, 84].

One important observation is the strong correlation between serum uric acid and circulating markers of inflammation in CHF patients [72] and particular in cachectic patients [42]. Recently, it has been shown that serum uric acid appears to be a potent and independent marker of impaired prognosis in CHF patients [14]. The therapeutic application of allopurinol in CHF patients to reduce uric acid levels has been shown to improve endothelial function and blood flow in arms and legs [43]. The elevation of the erythrocyte sedimentation rate as an inflammatory marker also relates adversely to prognosis [109].

Body Composition Alterations

Two of the main symptoms of CHF patients are early fatigue and muscle weakness, predominantly in patients with NYHA class III and IV [58], or in cachectic subjects [16]. CHF patients suffer from muscle atrophy [73] being present in up to 68% of patients [76]. A direct relationship between loss of lean body mass and impaired prognosis is known in cancer and AIDS [68], but it has not as yet been documented in CHF.

In addition to significant loss of lean tissue (skeletal musculature), CHF patients also show an evidence of decreased bone mineral density (i.e. osteoporosis) and reduced fat tissue mass (i.e. energy reserves) [16]. We [6, 10, 12] and others [116] have shown this for cachectic CHF patients (Table 1). Impaired peripheral blood flow as well as loss of limb muscle tissue both have been seen in cachectic CHF patients [16, 122]. These factors contribute to decreased oxidative capacity, that is the main reason of the impaired exercise capacity of CHF patients.

To assess the clinical outcome of cachectic CHF patients, peripheral chemosensitivity and cardiorespiratory reflex control are also suitable. Abnormal baro- and chemoreflex function and increased VE/VCO_2-slope have been found in patients with cardiac cachexia [98], which are all known to be related to impaired prognosis [96, 97]. Finally, also cardiac wasting occurs in cachectic CHF patients [48].

The precise mechanisms of body composition changes in CHF are not clear. Plasma levels of catabolic hormones and inflammatory cytokines correlate significantly with the reduced fat, muscle and bone tissue mass [6, 12]. The pathogenesis of the wasting process is influenced by the growth hormone (GH) / IGF-1 axis [18, 86]. High TNFα, an abnormal GH/IGF-1 ratio and low testosterone levels all correlate with the degree of weight loss in cachectic CHF patients [4].

Clinical Implications

Drug therapy

It has been shown that fish oil as kind of n-3 polyunsaturated fatty acids supplementation reduce levels of TNFα and IL-1 in healthy volunteers [45] as well as in patients with rheumatic disease [69]. Using fish oil, Freeman et al. have shown an improving of cachexia in dogs with congestive heart failure [51]. In this study the reduced IL-1 levels were predictors of survival. Hence, unspecific anti-cytokine therapy may be of benefit in cardiac cachexia.

Specific anti-cytokine therapies have been established for the treatment of rheumatoid arthritis [53, 82] and Crohn's disease [100]. However, the benefit of this therapy in the management of CHF is controversial [106].

Because of the success of in vivo pilot animal studies with a TNFα receptor fusion protein, which has showed a trend for reversal in depression of LV function and dilatation [27], human studies were started. In an important pilot study, a small CHF patient group with NYHA class III and elevated TNFα concentration received the soluble p75 TNF receptor fusion protein etanercept, which blocks the effects of TNFα [39]. This study demonstrated a decrease in the levels of biologically active TNFα as well as trends for increases in left ventricular ejection fraction, 6-min walk distance and quality of life scores [39].

To test this therapy in patients with CHF and NYHA class II to IV large scale studies (called RENAISSANCE and RECOVER [3]) were initiated. However, these studies had to be stopped prematurely in 2001. There was no benefit of the use of etanercept [63]. Also the phase II trial ATTACH (Anti-TNFα Therapy Against Congestive Heart Failure) using the TNFα antibody infliximab was stopped early [64]. In this trial, patients receiving the highest dose of active treatment showed increased mortality and hospitalisation rate. It has been suggested that only patients with proven high TNFα levels (like patients with cardiac cachexia) could benefit from this type of therapy [8] but this hypothesis remains to be tested.

Using an intravenous immunoglobulin as immunomodulating therapy in patients with CHF, Gullestad et al. demonstrated an increase in anti-inflammatory markers (IL-10 and IL-1 receptor antagonist) and a reduction of inflammatory cytokines like IL-1β [55]. There were no clinical benefit in terms of NYHA class or peak oxygen consumption, but a trend for a small improvement in left ventricular ejection fraction (LVEF+5%, p=0.08 vs. placebo) was found.

Repeatedly, it has been suggested that pentoxifylline can reduce TNFα plasma concentrations in CHF patients by phosphodiesterase inhibitors [113]. In a well-controlled study, Skudicky et al. have shown that in CHF patients treated with ACE inhibitors and beta-blockers, pentoxifylline (which is a phosphodiesterase inhibitor) did not reduce TNF levels [112]. Other phosphodiesterase inhibitors like amrinone, vesnarinone, or pimobendan

have short-term hemodynamic benefits in heart failure. They can inhibit the production of TNFα and other cytokines from stimulated human lymphocytes [77]. The influence of simultaneous treatment with beta-blockers to prevent the adverse prognosis of phosphodiesterase inhibitors in CHF is currently under investigation.

Treatment with ACE inhibitors can reduce circulating levels of atrial and brain natriuretic peptides (ANP, BNP) [110, 120], TNFα [74] and IL-6 [56]. ACE inhibitors can restore depressed levels of circulating IGF-1 in CHF patients [36]. It has been demonstrated that a therapy with candesartan (angiotensin II type 1 receptor antagonist) results in reduced plasma levels of TNFα, IL-6 and BNP [119] in patients with mild to moderate CHF. Beta-blockers and ACE inhibitors can prevent the development of cachexia in CHF [11, 35], but they can not reverse cardiac cachexia.

The use of anabolic steroids to increase skeletal muscle mass may be an option in cardiac cachexia, however their side effects on kidney function and the risk for development of prostate hyperplasia may limit their potential [15, 107]. Recombinant human growth hormone may be an option for the treatment of cardiac cachexia. To treat patients with cardiac cachexia, high doses of GH may be necessary to overcome GH resistance [18]. In stable CHF, there was no significant clinical benefit of 3 months of treatment with normal doses (2 IU per day) compared to placebo [91]. Short periods (1 week to 3 months) of high dose GH therapy (70-98 IU per week) in three cachectic patients demonstrated an increases of muscle mass and strength and improvement of exercise capacity [38, 90] without major side effects. This treatment approach should be tested in controlled studies.

Nutrition

There are no controlled studies of nutritional strategies in cardiac cachexia except for preoperative and postoperative nutritional support. Nutritional treatment studies in CHF have either failed to quantify nutrient and caloric intake [32], or have involved small numbers of patients without cachexia being assessed [29].

A high incidence of inadequate nutritional intake is found in healthy older people [78]. Therefore, elderly patients are predisposed to cachexia by pre-existing inadequate nutrition. Furthermore, patients with chronic illness often suffer from protein-energy malnutrition [83]. An intensive nutritional support as an important strategy in the preoperative and postoperative phases can lead to an increase in the amount of lean tissue [61]. A study by Otaki et al. has shown a significant improvement in the mortality rate in cachectic heart failure patients who received preoperative nutrition (17 vs. 57%, $p<0.05$) [92], whereas in another study an immediate postoperative intravenous hyperalimentation alone did not improve survival [1]. But there is no significant effect of nutritional support on clinical status of stable heart failure patients without signs of severe malnutrition [29].

Micronutrient deficiency can also cause heart failure, particularly important appear to be selenium and thiamine [125]. One reason for loss of thiamine is diuretic therapy, a standard treatment in virtually all CHF patients. Many micronutrients can also scavenge oxygen free radicals. The increased concentrations of catecholamines and cytokines and tissue hypoxia/ischaemia in heart failure are all stimuli for free radical production. Elevated levels of free radicals are linked to a gradual progression of myocardial dysfunction [57, 99]. Markers of oxidative stress, which are increased in heart failure patients, correlate with functional class, reduced exercise tolerance, lower antioxidant levels and indices of worse prognosis including cachexia [21, 88]. It has been shown that vitamin C and E as antioxidants and free radical scavengers suppress the elevated production of free radicals in leukocytes [60]. Whether antioxidants have anti-cachectic effects in CHF has never been tested.

Conclusions

The incidence of new CHF cases increases due to improvements in health care and improved survival after myocardial infarction. The prevalence of chronic heart failure is about 1-2% in the population [37, 62]. The prevalence of cachexia in CHF patients is about 10-15%. This condition is readily detectable. The understanding of the pathophysiology of CHF has shifted to immune and neurohormonal abnormalities that may also play a significant role in the pathogenesis of the wasting process. Further research on the development of new and effective treatments for cardiac cachexia as well as on the prediction of the development of future cardiac cachexia in CHF (to stop the wasting process before the onset of significant weight loss) is necessary. The major aims are to improve quality of life of many CHF patients and of the long-term prognosis of heart failure overall.

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