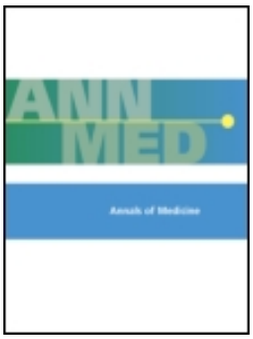

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# Cardiac cachexia

*Stefan D Anker[1,2], Wolfram Steinborn[1] and Sabine Strassburg[2]*

**Chronic heart failure (CHF) remains an important and increasing public health care problem. It is a complex syndrome affecting many body systems. Body wasting (i.e., cardiac cachexia) has long been recognised as a serious complication of CHF. Cardiac cachexia is associated with poor prognosis, independently of functional disease severity, age, and measures of exercise capacity and cardiac function. Patients with cardiac cachexia suffer from a general loss of fat tissue, lean tissue, and bone tissue. Cachectic CHF patients are weaker and fatigue earlier, which is due to both reduced skeletal muscle mass and impaired muscle quality. The pathophysiologic alterations leading to cardiac cachexia remain unclear, but there is increasing evidence that metabolic, neurohormonal and immune abnormalities may play an important role. Cachectic CHF patients show raised plasma levels of epinephrine, norepinephrine, and cortisol, and they show high plasma renin activity and increased plasma aldosterone level. Several studies have also shown that cardiac cachexia is linked to raised plasma levels of tumour necrosis factor alpha and other inflammatory cytokines. The degree of body wasting is strongly correlated with neurohormonal and immune abnormalities. The available evidence suggests that cardiac cachexia is a multifactorial neuroendocrine and metabolic disorder with a poor prognosis. A complex imbalance of different body systems may cause the development of body wasting.**

**Keywords:** body wasting; chronic heart failure; cytokines; immune activation; neurohormones; nutrition

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From the [1]Department of Clinical Cardiology, National Heart & Lung Institute, Imperial College, London UK, [2]Applied Cachexia Research, Department of Cardiology, Charité, Campus Virchow-Klinikum, Berlin, Germany.

**Correspondence:** Stefan Anker, MD, PhD, Division of Applied Cachexia Research, Dept. of Cardiology, Charité, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin Germany. Tel: +49-30-450553463. Fax: +49-30-450553951. E-mail: s.anker@imperial.ac.uk

## Introduction

Chronic heart failure (CHF) is a leading cause of morbidity and mortality world-wide and associated with a poor prognosis, comparable to many highly malignant cancers (1). It was recognised a long time ago that significant weight loss and wasting are important features of advanced CHF. The earliest report dates back 2300 years to classical Greece and the school of medicine of Hippocrates (about 460–377 BC) on the island of Cos (2). Hippocrates wrote that "the flesh is consumed and becomes water,… the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away…. This illness is fatal". The term cachexia is of Greek origin, derived from the words *kakós* = bad and *hexis* = condition or appearance.

Cardiac cachexia is a serious complication of CHF which has been too little investigated (3, 4). This article will focus on the available knowledge concerning the presence of general weight loss in CHF patients, its clinical implications, and the potential importance of immunologic and neurohormonal abnormalities in its development and progression and the potential treatment strategies.

## Definition of cardiac cachexia

Research groups have extensively investigated the wasting process in different conditions, but there is still no accepted global definition of cachexia. In heart failure studies, patients were classified as 'malnourished' when the body fat content was <15% for men and <22% for women, or when the percentage of ideal weight was <90% (5). Other groups defined CHF patients prospectively as 'cachectic' when the body fat content was <27% (men) or <29% (women) (6), or when the ideal body weight was <85% (7) or even <80% (8).

As the cut-off to define cardiac cachexia, Freeman and Roubenoff suggested in 1994 (9) a documented loss of at least 10% of lean tissue. This definition may

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**Abbreviations and acronyms**

| | |
|---|---|
| ACE | angiotensin converting enzyme |
| ANP | atrial natriuretic peptide |
| BNP | brain natriuretic peptide |
| CHF | chronic heart failure |
| GH | growth hormone |
| IGF-1 | insulin-like growth factor 1 |
| IL | interleukin |
| LVEF | left ventricular ejection fraction |
| NYHA | New York Heart Association |
| sTNF-R1 | soluble TNF receptor 1 |
| TNFα | tumour necrosis factor alpha |
| TGF-β | transforming growth factor β |

**Key messages**

- **Cardiac cachexia is a common complication of CHF with a poor prognosis, in which patients suffer from generalised loss of lean, fat and bone tissue.**
- **Inflammatory cytokine activation and neuro-endocrine abnormalities play a significant role in the pathogenesis of the wasting process in CHF.**
- **There is no established, proven therapy of cardiac cachexia. Further research is needed to develop new effective and safe treatments for cardiac cachexia.**

not be ideal as it is muscle focused. Additionally, it does not consider that fat tissue replacement may take place with no general weight loss. Furthermore, some patients may suffer from fat tissue loss but little or no lean tissue loss. Finally, focusing on body composition to define cachexia (particularly when done with dual energy x-ray absorptiometry (DEXA) scanning) could cause fairly large additional cost and many physicians may not have easy access to such machines.

It is important to note that the development of the cachectic state in CHF is a dynamic process that can only be proven by documentation of dry weight loss measured in a non-oedematous state. We suggest the use of a relatively broad definition of 'clinical cardiac cachexia': In CHF patients without signs of other primary cachectic states (e.g., cancer, thyroid disease, or severe liver disease), cardiac cachexia can be diagnosed when 'weight loss of >6.0% of the previous normal weight is observed over a period of >6 months'. This definition is simple and quickly applicable. In general, the previous normal weight of a heart failure patient would be the average weight prior to the onset of heart disease (e.g., before the diagnosis of idiopathic dilated cardiomyopathy). On the time axis, it would be important to note the last time point when the patient had this weight without being oedematous.

## Epidemiology

The incidence and prevalence of CHF is about 1% in middle-aged people, but it rises with increasing age to >10% in subjects older than 80 years (10). It is important to note that the prevalence of CHF is still increasing. Mainly, this is due to improved treatment and survival of patients with coronary artery disease (11), which is the most important etiological factor for the development of CHF (12). In patients with cardiac cachexia, natural and perioperative morbidity and mortality are higher than in non-cachectic patients (8, 13). The New York Heart Association (NYHA) class does not correlate with disease morbidity or mortality in cachectic CHF patients (14).

In the first prospective study on the frequency and prognostic importance of cachexia in CHF outpatients, 28 patients (16%) were identified as being cachectic (15). The observed weight loss amounted to 6–30 kg. The 18-month mortality was 50% in the cachectic patients, which is worse than the prognosis for some types of cancer (Fig 1). Cardiac cachexia is not as rare as previously thought. In the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial the incidence of new oedema-free weight loss >6.0% was more than 35% over three years with a cross-sectional prevalence of this degree of weight loss between 12% and 14% (16).

## Etiology

Three different mechanisms have been proposed to be responsible for the development of cardiac cachexia: 1) dietary deficiency, 2) malabsorption and metabolic dysfunction and 3) loss of nutrients *via* the urinary or digestive tracts (17). Already in 1964, Pittman and Cohen were the first to analyse extensively the pathogenesis of the syndrome of cardiac cachexia (18). An increased catabolism (protein loss) and reduced anabolism due of cellular hypoxia were proposed as the principal pathogenic factors.

The mechanisms of the transition from heart failure to cardiac cachexia are not yet clarified. Neither malabsorption nor cellular hypoxia was of importance in a group of 11 cachectic patients with NYHA class IV mitral valve disease (19). In contrast to this study, King *et al*. demonstrated presence of fat malabsorption but not protein malabsorption in elderly ambulatory patients with cardiac cachexia

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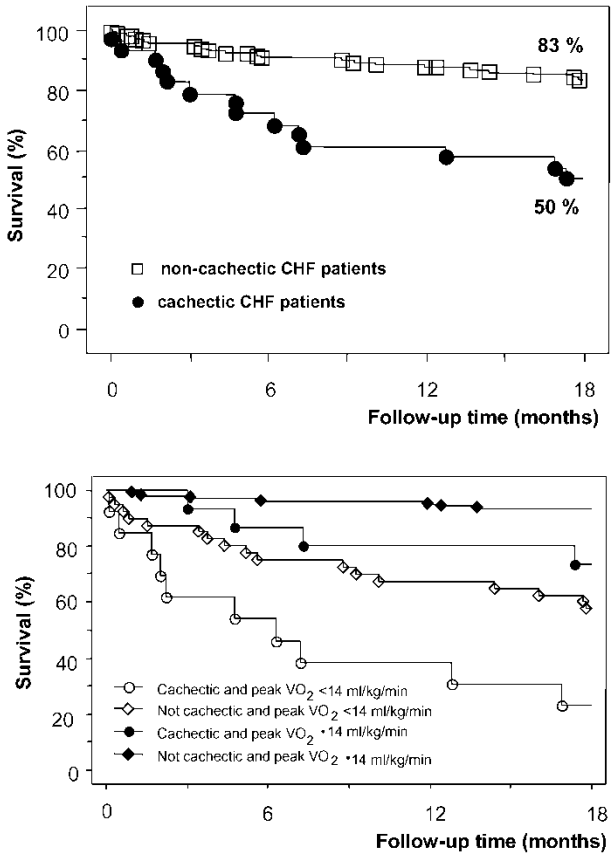


**Figure 1. Top**: Kaplan-Meier survival curve for 18-month survival of 171 patients with chronic heart failure (CHF) subgrouped to cachectic and non-cachectic CHF patients. **Bottom:** The influence of peak oxygen consumption (peak $VO_2$) <14 ml/kg/min. The effect of both, presence of cardiac cachexia and peak $VO_2$ is independent and additive. Adapted from reference (15).

(20). Another aspect is a higher resting metabolic rate, which was demonstrated in patients with heart failure. (21, 22) and increases with the severity of the disease (23). Interestingly, the resting metabolic rate correlates with increasing concentrations of catecholamines in older individuals (24), but it is not known if this holds true for heart failure patients.

## Body composition alterations

It has long been known, that patients with CHF suffer from muscle atrophy (25) being present in up to 68% of patients (26). Two of the main symptoms of CHF patients are early fatigue and muscle weakness. We found that both mainly occur in patients with NYHA class III and IV (27), and in cachectic subjects (28). A direct relationship between loss of lean body mass and impaired prognosis, as it is known to exist in cancer and AIDS, has not yet been documented, in CHF (29).

CHF patients do not only suffer from significant loss of lean tissue (i.e., skeletal muscle) but also show a reduced fat tissue mass (i.e., energy reserves) and evidence of decreased bone mineral density (i.e., osteoporosis) (28). We found that cachectic CHF patients have a reduction in total body fat, lean tissue mass, and bone mineral density (30–32) (Fig 2). Others (33) have confirmed these findings. Loss of limb muscle tissue together with impaired peripheral blood flow seen in CHF patients (28, 34) contribute to decreased oxidative capacity as the main cause of the decreased exercise capacity of CHF patients. Patients with cardiac cachexia also show particularly abnormal baro- and chemoreflex function and increased slope of ventilation to carbon dioxide production (VE/VCO2-slope) (35), which are all known to be related to poor prognosis (36, 37). Finally, in addition to these peripheral changes, cardiac wasting also occurs in cachectic CHF patients (38).

## Neuroendocrine abnormalities

The precise mechanisms of these body composition changes are not entirely clear. It is known that plasma levels of inflammatory cytokines and catabolic hormones correlate significantly with the reduced muscle, fat and bone tissue mass (30, 32). Moreover the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis plays an important role in the pathogenesis of the wasting process (39, 40). High TNFα, an abnormal GH/IGF-1 ratio and low testosterone levels all correlate with the degree of weight loss in cachectic CHF patients (41).

Whilst plasma norepinephrine may reflect overall sympathetic activity (42), both norepinephrine and epinephrine can cause a catabolic metabolic shift (24, 41). Catecholamines can lead to an increase in resting energy expenditure in CHF patients (43, 44). There is a relation between the clinical severity of illness and the degree of the increase in resting energy demands (44). Until recently no study has investigated catecholamine levels specifically in cachectic CHF patients. When we stratified 53 CHF patients for LVEF, NYHA class and presence of cachexia, we found cachectic CHF patients to have markedly increased norepinephrine and epinephrine levels, while non-cachectic CHF patients have near-normal levels (Fig 3) (41).

The specific association between cachexia and neuroendocrine activation in CHF is also reflected in abnormal aldosterone plasma levels and plasma renin activity. Both variables are increased in patients with cardiac cachexia although treatment characteristics (ACE inhibitors and diuretics) as well as the time since diagnosis of CHF were similar (41). Renin is a stimulator of the production of angiotensin II and norepinephrine (45). The activity of angiotensin II

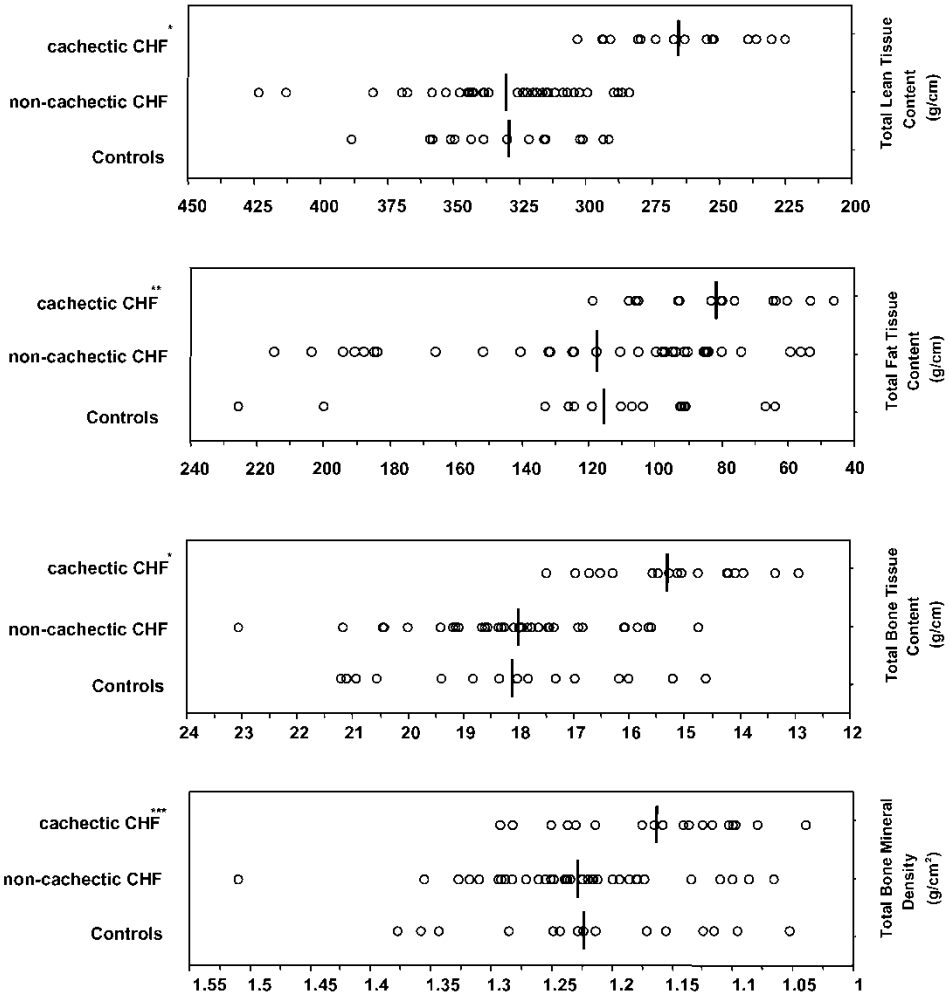


**Figure 2.** Body composition of 18 cachectic chronic heart failure (CHF) patients and 36 non-cachectic CHF patients compared to 15 healthy controls as determined by dual X-ray absorptiometry. Cardiac cachexia is defined as presence of documented non-oedematous and non-intentional weight loss of more than 7.5% compared to previous normal weight. The results of the assessment of total fat, lean and bone tissue were standardised for body height (g/cm). The total body mineral density is given in g/cm$^2$. * iP < 0.0001 *versus* non-cachectic patients. ** $P < 0.001$ *versus* non-cachectic patients. *** $P < 0.01$ *versus* non-cachectic patients. Adapted from reference (25).

and aldosterone can explain the fibrosis of smooth muscle cells as well as the reduction of circulating IGF-1 (46). Recently, very similar hormonal changes were described in adult patients with congenital heart disease (47).

Anand and colleagues demonstrated a 2.5-fold increase in cortisol (48) in untreated CHF patients with severe disease. Cortisol is a hormone considered to be part of the general stress response with a catabolic action. This rise is probably due to an increase in the release of adrenocorticotropic hormone (49). Cortisol levels are particularly increased in cachectic CHF patients (Fig 3) (41). In addition, in our study the anabolic steroid dehydroepiandrosterone was lowest in cachectic CHF patients, suggestive of a catabolic/anabolic imbalance (41). Abnormalities of sex steroid metabolism are strongly and directly related to the immune activation seen in cachectic CHF patients (50).

### *Inflammatory cytokine activation*

Already in 1990, Levine and colleagues reported that tumour necrosis factor alpha (TNFα) is increased in patients with cardiac cachexia (7). Other groups subsequently confirmed this (6, 51). The strongest predictor of the degree of previous weight loss is the TNFα plasma level (Fig 3) (41).

The main stimulus for the immune activation in CHF is not known. But there are three hypotheses. One hypothesis suggests hypoxia as the main stimulus for increased TNFα production in CHF patients (52). The second hypothesis assumes that the heart itself is the main source of inflammatory cytokines (53). It has been shown that the failing myocardium is capable of producing TNFα (54). However, treatment of patients with ventricular assist devices has no long-term beneficial anti-inflammatory effects (55).

The third hypothesis (the endotoxin hypothesis

(56)) suggests that bowel wall oedema that occurs in CHF is responsible for bacterial translocation with subsequent endotoxin release and endotoxin-stimulated inflammatory cytokine production. A first argument for this hypothesis is that there are elevated concentrations of endotoxin in patients during an acute oedematous exacerbation, which can be normalised by diuretic therapy (57). Acute venous congestion can lead to altered gut permeability for bacteria and endotoxin, which may subsequently enter into the circulation. Bacterial endotoxin is the strongest known natural inflammatory stimulus (58). In any healthy person the gut contains >1 kg of gram-negative bacteria. Therefore, intact gut barrier function is of importance to protect against endotoxin translocation.

Additionally, the lipopolysaccaride (LPS) sensitivity of peripheral monocytes has been found to be increased in some CHF patients without oedema (59). Raised LPS levels have also been found in severely diseased adolescents with congenital heart disease (3). We have also found that the LPS levels detected *in vivo* (0.6–1.0 EU/ml) are biologically relevant to stimulate significant cytokine production in whole blood of CHF patients ex vivo (60).

The endotoxin hypothesis opens up the possibility for novel therapeutic strategies directed against the bacteria in the bowel, against endotoxin itself, or the binding of endotoxin to cells of the immune system. For instance, IL-10 can reduce LPS-stimulated cytokine production of mononuclear cells of CHF patients as well as in healthy controls *in vitro* (61). Also in cardiogenic shock we found evidence that endotoxin-mediated inflammation may be of importance (62). In 2000, we have hypothesised that lipids play a beneficial role in patients with CHF by binding to and detoxifying the effects of endotoxin (63). This may explain why high lipoprotein levels were found to relate inversely to low plasma levels of TNF and other inflammatory cytokine variables (64), and why low but not high serum lipoprotein levels are related to poor prognosis in CHF patients (65, 66).

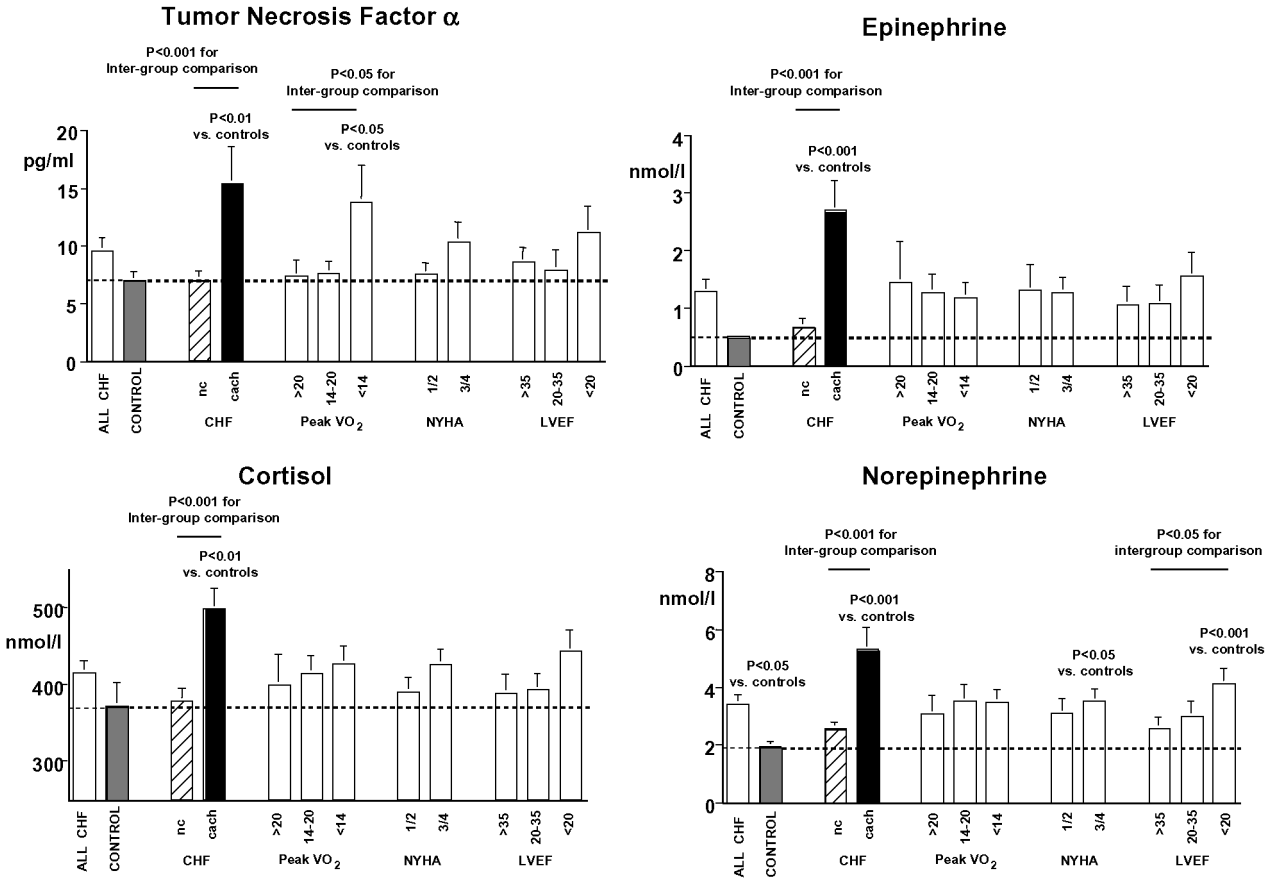


**Figure 3.** Tumor necrosis factor alpha (TNFα), epinephrine, norepinephrine and cortisol plasma levels in 53 chronic heart failure (CHF) patients and 16 healthy controls. Patients are sub-grouped according to: **1**) cachectic state (nc = non-cachectic, $n = 37$; cach = cachectic, $n = 16$): **2**) maximal oxygen consumption (peak $VO_2$) (<14 ($n = 17$) *versus* 14–20 ($n = 24$) *versus* >20 ml/kg per min ($n = 12$); **3**) New York Association class (NYHA) (class 1/2 ($n = 16$) *versus* class 3/4 ($n = 37$)); **4**) left ventricular ejection fraction (LVEF) (<20% *versus* 20%–35% ($n = 17$) *versus* >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 reference (38).

TNFα is one of the key cytokines important to the development of catabolism together with interleukin-1 (IL-1), interleukin-6 (IL-6), interferon-γ and transforming growth factor-β (TGF-β). In animal models, proteolysis, muscle atrophy and weight loss were prevented by IL-6 antibody therapy (67). Additionally, it has been suggested that IL-6 can lead to the development of osteoporosis (68). We were unable to find a significant correlation between serum IL-6 levels and bone mineral density (30).

Many of the TNF-effects can directly or indirectly contribute to body wasting in CHF (69). Animal experiments have shown a difference between the site of production and action of TNFα. Cachexia occurs when TNFα producing cells are implanted in skeletal muscle, whereas TNF producing cells implanted in the brain cause profound anorexia (70). This shows that increased levels of TNFα may indeed play a causative role in the genesis of cachexia. TNFα also can induce apoptosis, which may be important in the development of the cachectic state (70).

Furthermore, TNFα exerts effects on endothelial cells including rearrangement of the cytoskeleton, increased permeability to albumin and water, enhanced expression of activation antigens, induction of surface procoagulant activity and IL-1 release (71) and reduction of the constitutive nitric oxide synthase mRNA in vascular endothelial cells (72). The strong inverse relationship between maximal peripheral blood flow and TNFα levels in CHF patients could support the idea of detrimental effects of long-term increased TNFα-effects (73).

Leptin, the product of the *ob* gene, is a protein involved in the regulation of food intake and energy balance (74). It acts centrally to decrease food intake and increase resting energy expenditure. Although it has been reported that plasma levels of leptin are increased in CHF (75), it is doubtful that leptin is important for cardiac cachexia pathophysiology (76–78).

To predict the impaired survival of patients with CHF, elevated plasma levels of cytokines and soluble cytokine receptors are suitable (79). In particular, soluble TNF receptor 1 (sTNF-R1) levels appear to be the most accurate predictors of mortality, with the highest sensitivity and specificity amongst all immune variables (80).

The elevation of other inflammatory markers (like the erythrocyte sedimentation rate) also relates adversely to prognosis (81). There is a strong correlation between serum uric acid and circulating markers of inflammation in CHF patients (82). Uric acid is more elevated in CHF with cachexia than in patients without cachexia (33). Additionally, serum uric acid appears to be a strong and independent marker of impaired prognosis in patients with CHF (83). The serum uric acid also can be more easily and inexpensively assessed than cytokine levels. Lowering uric acid (with therapeutic application of allopurinol) has been shown to improve endothelial function and blood flow in arms and legs in CHF patients (84, 85). In a pilot study allopurinol was shown to improve myocardial efficiency (86).

## Clinical implications

Cardiac cachexia is a multifactorial neuroendocrine and metabolic disorder. It is characterised by an imbalance of catabolic and anabolic body system, which may cause the development of body wasting (Fig 4). It appears unlikely that any single agent will be completely effective in treating this condition. Fortunately, it is not difficult to detect the wasting process in heart failure. It is important to document the weight history and changes (weight taken regularly in a non-oedematous state) for all CHF patients. This is an easy, time-effective and cost-effective task.

### *Nutritional support*

Except for preoperative and postoperative nutritional support of patients with cardiac cachexia, there are no controlled studies of nutritional strategies in cardiac cachexia. Treatment studies are limited by poor compliance of patients with nutritional regimes. In patients with heart failure, studies have either failed to quantify nutrient and caloric intake (5), or have involved small numbers of patients without cachexia being assessed (87).

It is important to note that healthy older people have a high incidence of inadequate nutritional intake (88). As diseases causing cachexia are more common in the elderly, many patients will be predisposed to cachexia by pre-existing inadequate nutrition. Furthermore, protein-energy malnutrition is common in those with chronic illness (89). In stable CHF patients with no signs of severe malnutrition, nutritional support alone does not have a significant effect on clinical status of heart failure (87). Intensive nutritional support can lead to an increase in the amount of lean tissue (90). This strategy is of great importance in the preoperative and postoperative phases. Immediate postoperative intravenous hyperalimentation alone did not improve survival in one study (13), whereas in another study, when cachectic patients with heart failure received preoperative nutritional support, there was an improvement in the operative mortality rate in the treatment group (17% *versus* 57%, $P < 0.05$) (8).

Patients with heart failure have a number of risk factors for micronutrient deficiency. They are usually elderly and prone to excess urinary losses of, for example, thiamine due to diuretic therapy. But

 

deficiencies of specific micronutrients such as selenium and thiamine can also cause heart failure (91). Many micronutrients have, as part of their function, the ability to scavenge free radicals. The presence of elevated levels of markers of oxidative stress in heart failure patients correlates with functional class, reduced exercise tolerance, lower antioxidant levels and indices of worse prognosis including cachexia (92, 93). The stimuli for free radical production, such as catecholamines and cytokine activation, are elevated in heart failure. Antioxidants and free radical scavengers like vitamin C and E can suppress the elevated production of free radicals in leucocytes (94). To achieve a balanced, sufficient nutrition the consultation of dietitians could be very helpful in the management of cachectic CHF patients.

*Exercise*

Exercise rehabilitation training improves the exercise capacity. It reverses the muscular metabolic abnormalities and atrophy as well as impaired blood flow and neurohormonal abnormalities (95). It has been suggested that moderate exercise training could safely be applied to cachectic CHF patients in NYHA class I to III (96). The best correlate of impaired exercise capacity in cachectic CHF patients is the peak leg blood flow, whereas the muscle strength and age are the best predictors of exercise intolerance in non-cachectic patients (28). Whether this has implications for a potential systematic rehabilitation programme has not been studied yet.

*Drug therapy*

State-of-the-art CHF therapy is based on modulation of neurohormonal systems, particularly with ACE inhibitors, beta blockers and aldosterone antagonists. However, there is no specific therapy for cachexia in CHF available. Several options are potentially available.

ACE inhibitors have a favourable effect on catecholamines and other neurohormones and endothelial function in patients with chronic heart failure, which might prevent tissue damage and apoptosis through improved nutritional status of tissues and reduction of ischaemia and oxidative stress. This auspicious effect of ACE inhibitors in cachectic heart failure patients (enalapril in addition to conventional treatment) was affirmed by a 19% reduction of the risk of weight loss of 6% or more. (97) Reduction of the immune activation might be a further mechanism by which ACE inhibitors reduces mortality.

Fish oil (n-3 polyunsaturated fatty acids) has been shown to reduce TNF$\alpha$ and IL-1 concentrations in healthy volunteers (98) and patients with rheumatic disease (99). Furthermore, it improves cachexia in dogs with congestive heart failure (100).

For the management of rheumatoid arthritis and Crohn's disease specific anti-cytokine therapies have

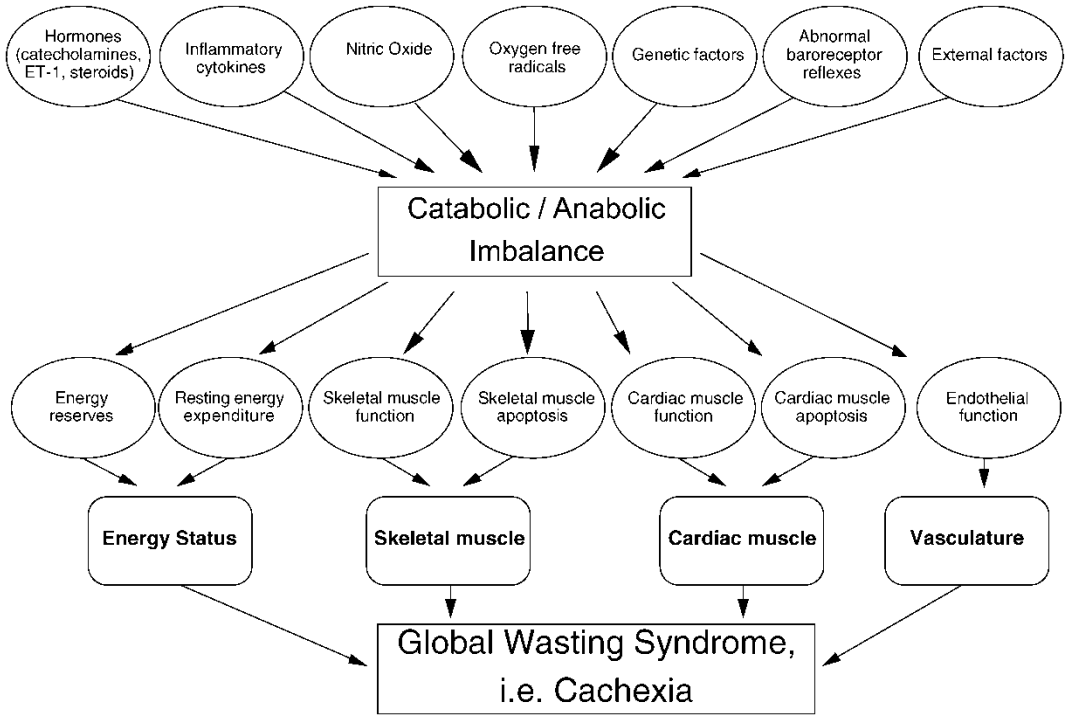


**Figure 4.** The development of cachexia due to a complex interaction of different body systems and an imbalance of catabolic and anabolic systems. Adapted from reference (17). ET-1 = Endothelin-1.

been established (101–103). The value of such treatment in the management of CHF is highly controversial (104).

Some large scale studies – RENAISSANCE and RECOVER (combined the renewal programme) (105) – were initiated in CHF patients in NYHA class II to IV. These studies had to be stopped prematurely in 2001 because of a lack of benefit from etanercept (106). A phase II study using the TNFα antibody remicade for 6 weeks in CHF patients in NYHA III and IV (ATTACH) was also stopped earlier because of an increase in mortality in patients on the highest dose of active therapy (107). Therefore, the future of anti-TNF therapy in CHF patients is uncertain. Possibly, only patients with proven high TNFα levels (like patients with cardiac cachexia) could benefit from this type of therapy (108).

It has been suggested that the phosphodiesterase inhibitor pentoxiphylline can reduce TNFα plasma concentrations in CHF patients (109). However, in a well-controlled study Skudicky *et al*. have shown that in CHF patients treated with ACE inhibitors and beta-blockers, therapy with pentoxifylline did not reduce TNF levels (110). Furthermore, other phosphodiesterase inhibitors (e.g., amrinone, vesnarinone, pimobendan), which have short-term hemodynamic benefits in heart failure, can inhibit the production of TNFα and other cytokines from stimulated human lymphocytes (111). Whether simultaneous treatment with beta-blockers changes the adverse prognosis of phosphodiesterase inhibitors in CHF is currently under investigation.

On the anabolic side, the use of anabolic steroids to increase muscle mass in cardiac cachexia may be an option, but their side effects on kidney function and potential to induce prostate hyperplasia may limit their potential (17, 112). Furthermore, recombinant human growth hormone can be considered as an option for the treatment of cardiac cachexia. In fact, normal doses (2 IU per day given daily) did not cause significant clinical benefits after 3 months of treatment compared to placebo (113), but two case reports involving three cachectic patients demonstrated an increases of muscle mass and strength and improvement of exercise capacity (114, 115). Both of the latter studies used high dose GH therapy (70–98 IU per week) for a short period (1 week to 3 months) with no reported side effects. These high doses of GH may be necessary to overcome GH resistance, which is present in patients with cardiac cachexia (40).

Another option to treat cardiac cachexia may be ghrelin which in animal studies has been proven to improve ventricular function and increase body weight (116). Possibly, ghrelin is better suited to overcome growth hormone resistance in CHF than growth hormone itself (117).

Circulating levels of atrial and brain natriuretic peptides (ANP, BNP) (118, 119), TNFα (120) and IL-6 (121) are all reduced following treatment with ACE inhibitors. Additionally, it has been shown that ACE inhibitors, likely by reduction of the angiotensin II activity, can restore depressed levels of circulating IGF-1 in CHF patients (122). Angiotensin II is a potent stimulator of the immune and neurohormonal axis. In a study of Tsutamato and colleagues it was demonstrated that therapy with candesartan – an angiotensin II type 1 receptor antagonist – resulted in reduced plasma levels of TNFα, IL-6 and BNP (123). We now have evidence that ACE inhibitors (16) as well as beta blockers (124) can prevent the development of cachexia in CHF. However, these drugs cannot reverse cardiac cachexia. Future trials need to focus on cachexia in CHF.

## Conclusions

Chronic heart failure has a prevalence of about 1%–2% in the population (10, 125). Because of general progress in health care and improved survival after myocardial infarction the incidence of new-onset CHF cases appears to increase. Significant proportions of CHF patients are cachectic patients (10%–15%), with this condition being readily detectable. The immune and neurohormonal abnormalities play a significant role in the pathogenesis of the wasting process and hopefully further research will lead to the development of new treatments for this aspect of cardiac cachexia. Finally, major research is needed to obtain the ability to predict the development of cardiac cachexia and to stop the wasting process before the onset of significant weight loss. All of this will have a significant influence on the quality of life of many patients and may improve the long-term prognosis of CHF in general.

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## References


1. McMurray JJ, Stewart J. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000;833:596–602.
2. Doehner W, Anker SD. Cardiac cachexia in early literature: a review of research prior to Medline. Int J Cardiol 2002;85:7–14.
3. Anker SD, Coats AJS. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999;115:836–47.
4. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJ, et al. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. J Card Fail 2003;9:29–35.
5. Carr JG, Stevenson LW, Walden JA, Heber D. Prevalence and haemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1989;63:709–13.
6. McMurray J, Abdullah I, Dargie HJ, Shapiro D. Increased concentrations of tumor necrosis factor in 'cachectic' patients with severe chronic heart failure. Br Heart J 1991; 66:356–8.
7. Levine B, Kalman J, Mayer L, Fillit H, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236–41.
8. Otaki M. Surgical treatment of patients with cardiac cachexia. An analysis of factors affecting operative mortality. Chest 1994;105:1347–51.
9. Freeman LM, Roubenoff R. The nutrition implications of cardiac cachexia. Nutr Rev 1994;52:340–7.
10. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, et al. The epidemiology of heart failure. Eur Heart J 1997;18:208–25.
11. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J 1994;72 (Suppl):S3–9.
12. McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, et al. Recent trends in acute coronary heart disease: mortality, morbidity, medical care, and risk factors. N Engl J Med 1996;334:884–90.
13. Abel RM, Fischer J, Buckley MJ, Barnett GO, Austen WG. Malnutrition in cardiac surgical patients. Arch Surg 1976; 111:45–50.
14. Blackburn GL, Gibbons GW, Bothe A, Benotti PN, Harken DE, McEnany TM. Nutritional support in cardiac cachexia. J Thorac Cardiovasc Surg 1977;73:489–96.
15. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, et al. Wasting as independent risk factor for mortality in chronic heart failure. Lancet 1997; 349: 1050–3.
16. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361:1077–83.
17. Anker SD, Sharma R. The syndrome of cardiac cachexia. Int J Cardiol 2002;85:51–66.
18. Pittman JG, Cohen P. The pathogenesis of cardiac cachexia. N Engl J Med 1964;271:403–9.
19. Buchanan N, Keen RD, Kinsley R, Eyberg CD. Gastrointestinal absorption studies in cardiac cachexia. Intensive Care Med 1977;3:89–91.
20. King D, Smith ML, Chapman TJ, Stockdale HR, Lye M. Fat malabsoprtion in elderly patients with cardiac cachexia. Age Ageing 1996;25:144–9.
21. Poehlman ET, Scheffers J, Gottlieb S, Fisher ML, Vaitekevicus P. Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med 1994;121:860–2.
22. Riley M, Elborn JS, McKane WR, Bell N, Stanford CF, Nicholls DP. Resting energy expenditure in chronic heart failure. Clin Sci (Lond) 1991;80:633–9.
23. Obisesan TO, Toth MJ, Kendall D. Energy expenditure and symptom severity in men with heart failure. Am J Cardiol 1996;77:1250–2.
24. Poehlman ET, Danfort E. Endurance training increaes metabolic rate and norepinephrine appearance rate in older individuals. Am J Physiol 1991;261:E233–9.
25. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. Int J Cardiol 1988;18:187–95.
26. Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation 1992;85:1364–73.
27. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski PP, Poole-Wilson PA, et al. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. J Am Coll Cardiol 1997;30:1758–64.
28. Anker SD, Swan JW, Volterrani M, Chua TP, Clark AL, Poole-Wilson et al.. The influence of muscle mass, strength, fatigability and blood flow on exercise capacity in cachectic and non-cachectic patients with chronic heart failure. Eur Heart J 1997;18:259–69.
29. Kotler DP, Tierney AR, Wang J, Pierson RN. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. Am J Clin Nutr 1989;50:444–7.
30. Anker SD, Clark AL, Teixeira MM, Hellewell PG, Coats AJ. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1998;83:612–5.
31. Anker SD, Ponikowski PP, Clark Al , Leyva F, Rauchhaus M, Kemp M, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. Eur Heart J 1999;20:683–93.
32. Toth MJ, Gottlieb SS, Goran MI, Fisher ML, Poehlman ET. Daily energy expenditure in free-living heart failure patients. Am J Physiol 1997;272:E469–75.
33. Doehner W, Rauchhaus M, Florea VG, Sharma R, Bolger AP, Davos CH, et al. Uric acid in cachectic and noncachectic patients with chronic heart failure: relationship to leg vascular resistance. Am Heart J 2001;141:792–9.
34. Volterrani M, Clark AL, Ludman PF, Swan JW, Adamopoulus S, Piepoli M, et al. Predictors of exercise capacity in chronic heart failure. Eur Heart J 1994;15:801–9.
35. Ponikowski P, Piepoli M, Chua TP, Banasiak W, Francis D, Anker SD, et al. The impact of cachexia on cardiorespiratory reflex control in chronic heart failure. Eur Heart J 1999;20: 1667–75.
36. Ponikowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, et al. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. Circulation 1999;100:2418–24.
37. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 2001; 103:967–72.
38. Florea VG, Henein MY, Rauchhaus M, Koloczek V, Sharma R, Doehner W, et al. The cardiac component of cardiac cachexia. Am Heart J 2002;144:45–50.
39. Niebauer J, Pflaum CD, Clark AL, Strasburger CJ, Hooper J, Poole-Wilson PA, et al. Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition,

anabolic deficiency, cytokine and neurohormonal activation. J Am Coll Cardiol 1998;32:393–7.
40. Anker SD, Volterrani M, Pflaum CD, Strasburger CJ, Osterziel KJ, Doehner W, et al. Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. J Am Coll Cardiol 2001; 38:443–52.
41. Anker SD, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, et al. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. Circulation 1997;96:526–34.
42. Goldstein DS. Plasma norepinephrine as an indicator of sympathetic neural activity in clinical cardiology. Am J Cardiol 1981;48:1147–54.
43. Lommi J, Kupari M, Yki-Jarvinen H. Free fatty acid kinetics and oxidation in congestive heartfailure. Am J Cardiol 1998; 81:45–50.
44. Obisesan TO, Toth MJ, Donaldson K, Gottlieb SS, Fisher ML, Vaitekevicius P, et al. Energy expenditure and symptom severity in men with heart failure. Am J Cardiol 1996;77: 1250–2.
45. Staroukine M, Devriendt J, Decoodt P, Verniory A. Relationships between plasma epinephrine, norepinephrine, dopamine and angiotensin II concentrations, renin activity, hemodynamic state and prognosis in acute heart failure. Acta Cardiol 1984;39:131–8.
46. Brink M, Wellen J, Delafontaine P. Angiotensin II causes weight loss and decreases circulating insulin-like growth factor I in rats through a pressor-independent mechanism. J Clin Invest 1996;97:2509–16.
47. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002;106:92–9.
48. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin. Studies of body water and sodium renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1989;80:299–305.
49. Nicholls MG, Espiner EA, Donald RA, Hughes H. Aldosterone and its regulation during diuresis in patients with gross congestive heart failure. Clin Sci Mol Med 1974;47: 301–15.
50. Anker SD, Clark AL, Kemp M, Salsbury C, Teixeira MM, Hellewell PG, et al. Tumor necrosis factor and steroid metabolism in chronic heart failure: possible relation to muscle wasting. J Am Coll Cardiol 1997;30:997–1001.
51. Dutka DP, Elborn JS, Delamere F, Shale DJ, Morris GK. Tumor necrosis factor alpha in severe congestive heart failure. Br Heart J 1993;70:141–3.
52. Hasper D, Hummel M, Kleber FX, Reindl I, Volk HD. Systemic inflammation in patients with heart failure. Eur Heart J 1998;19:761–5.
53. Seta Y, Shan K, Bozkurt B, Oral H, Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. J Card Fail 1996;3:243–9.
54. Torre-Amione G, Kapadia S, Lee J, Durand JB, Bies RD, Young JB, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 1996;93:704–11.
55. Clark AL, Loebe M, Potapov EV, Egerer K, Knosalla C, Hetzer R, et al. Ventricular assist device in severe heart failure: effects on cytokines, complement and body weight. Eur Heart J 2001;22:2275–83.
56. Anker SD, Egerer KR, Volk HD, Kox WJ, Poole-Wilson PA, Coats AJ. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol 1997;79: 1426–30.
57. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999;353:1838–42.
58. Von Haehling S, Genth-Zotz S, Anker SD, Volk HD. Cachexia: a therapeutic approach beyond cytokine antagonism. Int J Cardiol 2002;85:173–83.
59. Vonhof S, Brost B, Stille-Siegener M, Grumbach I, Kreuzer H, Figulla H. Monocyte activation in congestive heart failure due to coronary artery disease and idiopathic dilated cardiomyopathy. Int J Cardiol 1998;63:237–44.
60. Genth-Zotz S, von Haehling S, Bolger AP, Kalra PR, Coats AJS, Anker SD. Pathophysiological quantities of endotoxin induce tumor necrosis factor release in whole blood from patients with chronic heart failure. Am J Cardiol 2002;90: 1226–30.
61. Bolger AP, Sharma R, von Haehling S, Doehner W, Oliver B, Rauchhaus M, et al. Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic heart failure. Am J Cardiol 2002;90:348–9.
62. Brunkhorst FM, Clark AL, Forycki ZF, Anker SD. Pyrexia, procalcitonin, immune activation and survival in cardiogenic shock: the potential importance of bacterial translocation. Int J Cardiol 1999;72:3–10.
63. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. Lancet 2000;356:930–3.
64. Rauchhaus M, Koloczek V, Volk H, Kemp M, Niebauer J, Francis DP, et al. Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure. Int J Cardiol 2000;76:125–33.
65. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216–24.
66. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003;42:1933–40.
67. Tsujinaka T, Fujita J, Ebisui C, Yano M, Kominami E, Suzuki K, et al. Interleukin 6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin 6 transgenic mice. J Clin Invest 1996;97:244–9.
68. Barton BE. IL-6: insights into novel biological activities. Clin Immunol Immunopathol 1997;85:16–20.
69. Cicoira M, Bolger AP, Doehner W, Rauchhaus M, Davos C, Sharma R, et al. High tumor necrosis factor-alpha levels are associated with exercise intolerance and neurohormonal activation in chronic heart failure patients. Cytokine 2001; 15:80–6.
70. Tracey KJ, Morgello S, Koplin B, Fahey TJ, Fox K, Aledo A. Metabolic effects of cachectin/tumor necrosis factor are modified by site of production: Cachectin/tumor necrosis factor-secreting tumor in skeletal muscle induces chronic cachexia, while implantation in brain induces predominantly acute cachexia. J Clin Invest 1990;86:2014–24.
71. Bolger AP, Anker SD. Tumor necrosis factor in chronic heart failure: a peripheral view on pathogenesis, clinical manifestations and therapeutic implications. Drugs 2000;60:1245–57.
72. Yoshizumi M, Perrella MA, Burnett JC, Lee ME. Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. Circ Res 1993;73: 205–9.
73. Anker SD, Volterrani M, Egerer KR, Felton CV, Kox WJ, Poole-Wilson PA, et al. Tumor necrosis factor alpha as a predictor of impaired peak leg blood flow in patients with chronic heart failure. Q J Med 1998;91:199–203.
74. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L,

 *ISSN 0785-3890*

Friedmann JM. Positional cloning of the mouse ob gene and its human homologue. Nature 1994;372:425–32.
75. Leyva F, Anker SD, Egerer K, Stevenson JC, Kox WJ, Coats AJ. Hyperleptinaemia in chronic heart failure. Relationships with insulin. Eur Heart J 1998;19:1547–51.
76. Murdoch DR, Rooney E, Dargie HJ, Shapiro D, Morton JJ, McMurray JJ. Inappropriately low plasma leptin concentration in the cachexia associated with chronic heart failure. Heart 1999;82:352–6.
77. Filippatos GS, Tsilias K, Venetsanou K, Karambinos E, Manolatos D, Kranidis A, et al. Leptin serum levels in cachectic heart failure patients. Relationship with tumor necrosis factor-alpha system. Int J Cardiol 2000;76:117–22.
78. Doehner W, Pflaum CD, Rauchhaus M, Godsland IF, Egerer K, Cicoira M, et al. Leptin, insulin sensitivity and growth hormone binding protein in chronic heart failure with and without cardiac cachexia. Eur J Endocrinol 2001;145:727–35.
79. Ferrari R, Bachetti T, Confortini R, Opasich C, Febo O, Corti A, et al. Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. Circulation 1995;92:1479–86.
80. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060–7.
81. Sharma R, Rauchhaus M, Ponikowski PP, Varney S, Poole-Wilson PA, Mann DL, et al. The relationship of erythrocyte sedimentation rate to inflammatory cytokines and survival in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2000;36:523–8.
82. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, et al. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J 1998;19:1814–22.
83. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991–7.
84. Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002;105:2619–24.
85. Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation 2002;106:221–6.
86. Cappola TP, Kass DA, Nelson GS, Berger RD, Rosas GO, Kobeissi ZA, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. Circulation 2001;104:2407–11.
87. Broquist M, Arnquist H, Dahlström U, Larsson J, Nylander E, Permert J. Nutritional assessment and muscle energy metabolism in severe chronic congestive heart failure-effects of long-term dietary supplementation. Eur Heart J 1994;15:1641–50.
88. McGandy RB, Russel RM, Hartz SC, Jacob RA, Tannenbaum S, Peters H, et al. Nutritional status survey of healthy non-institutionalized elderly: energy and nutrient intake from three-day diet records and nutrient supplements. Nutr Res 1986;6:785–98.
89. Moriwaki H, Tajika M, Miwa Y, Kato M, Yasuda I, Shiratori Y, et al. Nutritional pharmacotherapy of chronic liver disease: from support of liver failure to prevention of liver cancer. J Gastroenterol 2000;35(Suppl 12):13–7.
90. Heymsfield SB, Casper K. Congestive heart failure: clinical management by use of continuous nasoenteric feeding. Am J Clin Nutr 1989;50:539–44.
91. Witte KKA, Clark AL, Cleland JGF. Chronic heart failure and micronutrients. J Am Coll Cardiol 2001;37:1765–74.
92. Belch JJF, Bridges AB, Scott N, Chopra M. Oxygen free radicals and congestive heart failure. Br Heart J 1991;65:245–8.
93. Nishiyama Y, Ikeda H, Haramaki N, Yoshida N, Imaizumi T. Oxidative stress is related to exercise intolerance in patients with heart failure. Am Heart J 1998;135:115–20.
94. Herbaczynska-Cedro K, Kosiewicz-Wasek B, Cedro K. Supplementation with vitamins C and E suppresses leukocyte oxygen free radical production in patients with myocardial infarction. Eur Heart J 1995;16:1044–9.
95. Coats AJ, Adamopoulos S, Meyer TE, Conway J, Sleight P. Effects of physical training in chronic heart failure. Lancet 1990;335:63–6.
96. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation 1992;85:2119–31.
97. Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361:1077–83.
98. Endres S, Ghorbani R, Kelly VE, Georgilis K, Lonnemann G, van der Meer JW, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of IL-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265–71.
99. Kremer JM, Jubiz W, Michalek A, Rynes RI, Bartholomew LE, Bigaoutte J, et al. Fish-oil fatty acid supplementation in active rheumatoid arthritis: a double-blinded, controlled, crossover study. Ann Intern Med 1987;106:497–503.
100. Freeman LM, Rush JE, Kehayias JJ, Ross JN Jr, Meydani SN, Brown DJ, et al. Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. J Vet Intern Med 1998;12:440–8.
101. Goldenburg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther 1999;21:75–87.
102. Moreland LW. Inhibitors of tumor necrosis factor for rheumatoid arthritis. J Rheumatol 1999;26:7–15.
103. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–405.
104. Sharma R, Anker SD. Cytokines, apoptosis and cachexia: the potential for TNF antagonism. Int J Cardiol 2002;85:161–71.
105. Anker SD. Has the time arrived to use anticytokine therapy in chronic heart failure? Dial Cardiovasc Med 2000;5:162–70.
106. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
107. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
108. Anker SD, Coats AJS. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123–30.

 *ISSN 0785-3890*

109. Sliwa K, Skudicky D, Candy G, Wisenbaugh T, Sareli P. Randomised investigation of effects of pentoxiphylline on left-ventricular performance in idiopathic dilated cardiomyopathy. Lancet 1998;351:1091–3.
110. Skudicky D, Bergmann A, Sliwa K, Candy G, Sareli P. Beneficial effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy treated with angiotensin-converting enzyme inhibitors and carvedilol: results of a randomized study. Circulation 2001;103:1083–8.
111. Matsumori A, Shioi T, Yamada T, Matsui S, Sasayama S. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. Circulation 1994;89:955–8.
112. Sharma R, Anker SD. Immune and neurohormonal pathways in chronic heart failure. Congest Heart Fail 2002;8:23–8.
113. Osterziel KJ, Strohm O, Schuler J, Friedrich M, Hanlein D, Willenbrock R, et al. Randomised, double-blind, placebo-controlled trial of human recombinant growth hormone in patients with chronic heart failure due to dilated cardiomyopathy. Lancet 1998;351:1233–7.
114. Cuneo RC, Wilmshurst P, Lowy C, McGauley G, Sonksen PH. Cardiac failure responding to growth hormone. Lancet 1989;1:838–9.
115. O'Driscoll JG, Green DJ, Ireland M, Kerr D, Larbalestier RI. Treatment of end-stage cardiac failure with growth hormone. Lancet 1997;349:1068.
116. Nagaya N, Kangawa K. Ghrelin improves left ventricular dysfunction and cardiac cachexia in heart failure. Curr Opin Pharmacol 2003;3:146–51.
117. Cicoira M, Kalra PR, Anker SD. Growth hormone resistance in chronic heart failure and its therapeutic implications. J Card Fail 2003;9:219–26.
118. Sigurdsson A, Swedberg K, Ullmann B. Effects of ramipril on the neurohormonal response to exercise in patients with mild or moderate congestive heart failure. Eur Heart J 1994;15:247–54.
119. Van Veldhuisen DJ, Genth-Zotz S, Brouwer J, Boomsma F, Netzer T, Man In'T Veld AJ, et al. High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. J Am Coll Cardiol 1998;32:1811–8.
120. Liu L, Zhao SP. The changes in circulating tumor necrosis factor levels in patients with congestive heart failure influenced by therapy. Int J Cardiol 1999;69:77–82.
121. Gullestad L, Aukrust P, Ueland T, Espevik T, Yee G, Vagelos R, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol 1999;34:2061–7.
122. Corbalan R, Acevedo M, Godoy I, Jalil J, Campusano C, Klassen J. Enalapril restores depressed circulating insulin-like growth factor 1 in patients with chronic heart failure. J Card Fail 1998;4:115–9.
123. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Hisanaga T, et al. Angiotensin II type 1 receptor antagonist decreases plasma levels of tumor necrosis factor alpha, interleukin-6 and soluble adhesion molecules in patients with chronic heart failure. J Am Coll Cardiol 2000;35:714–21.
124. Coats AJS, Anker SD, Roecker EB, Schultz MK, Staiger C, Shusterman N, et al. Prevention and reversal of cardiac cachexia in patients with severe heart failure by carvedilol: results of the COPERNICUS study. Circulation 2001;104:II–437 (abstract).
125. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993;22:6A–13A.

 *ISSN 0785-3890*