Review article

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Imbalance of catabolic and anabolic pathways in chronic heart failure

Implications for the treatment of cardiac cachexia

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Abstract

Chronic heart failure (CHF) is a complex metabolic disorder with multiple interactions between the immune, neurohormonal and cardiovascular systems. That the progression of CHF is due to neurohormonal abnormalities is now considered to be established and has led to major therapeutic benefits. Many current therapies are also thought to exert a variety of immunological effects and this has been much less studied. This review aims to discuss interactions between immune pathways and neurohormonal abnormalities relevant to disease progression in CHF and to the development of cardiac cachexia. Cytokines, in particular tumour necrosis factor-α, have many interactive opportunities within a regulatory network of energy metabolism, immune function and neuroendocrine function. Inflammatory cytokines are known to contribute to the progression of CHF, being related to patients' prognosis. Advanced CHF can be considered to be a state of chronic (low-grade) inflammation and catabolism. Anti-cytokine therapy could be successful in patients with proven immune abnormalities as in cardiac cachexia. In addition, anabolic therapies appear to be indicated in cachectic CHF patients. These novel approaches are certainly not without some risk and many of them are very expensive, which may limit their application to certain subgroups of patients. In the future it may not be enough to monitor only the cardiac function of patients; rather, the immune and neurohormonal status of patients may also need to be included to perform a complete assessment.

Keywords: *Chronic heart failure*, *cachexia*, *wasting*, *hormones*, *cytokines*, *endotoxin*.

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Introduction

Chronic heart failure (CHF) is a clinical syndrome with features of cardiac dysfunction as well as extracardiac manifestations that are consequent on damage to the heart. Advances in our understanding of the pathophysiology of CHF have moved us away from seeing it in purely haemodynamic terms to an appreciation of its multisystemic nature. Patients with CHF have evidence of neurohormonal and inflammatory cytokine activation, which may play a crucial role in the pathogenesis of this syndrome (1, 2). Many patients with advanced CHF develop a wasting syndrome termed cardiac cachexia which is associated with a particularly poor prognosis (3) and marked endocrine and immune abnormalities (4). This review article will present the current evidence on the importance of neurohormonal and immune pathways in patients with CHF that lead to an imbalance of catabolic and anabolic metabolism and hence to cachexia. Therapeutic implications will be highlighted.

Immune activation in chronic heart failure

Many studies have shown that CHF is associated with increased circulating levels of proinflammatory cytokines. Cytokines are low molecular weight proteins that can be released by most cell types. Unlike hormones, cytokines are not stored but are secreted in response to specific stimuli. Cytokines have autocrine and paracrine actions. The cytokines considered the most relevant for the pathogenesis of CHF are tumour necrosis factor-α (TNF) and interleukin-6 (IL-6), which have therefore been the most extensively studied in this disease.

Tumour necrosis factor-α

TNF is a 51 kDa trimeric molecule with a half-life of around 30 min. TNF can be quantified in the serum or plasma using commercially available assays. Elevated levels of TNF have been documented not only in the circulation (5) but also in the myocardium of patients with CHF (6). TNF is capable of promoting left ventricular remodelling

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(7) and it is known to be negatively inotropic (8). TNF levels are particularly elevated in cachectic CHF patients (5, 9–10) and have been found to be the strongest predictors of the degree of previous weight loss (9). Apoptosis is frequently found in the skeletal muscle of CHF patients and is related to an impairment of exercise capacity (11). Animal experiments have shown that TNF is capable of inducing skeletal muscle wasting and apoptosis (12, 13). These properties of TNF, therefore, make it an important factor in the pathogenesis of catabolism in CHF, and hence in the development of weight loss (i.e. cachexia).

The actions of TNF are mediated by binding to specific receptors (TNF receptors 1 and 2) that are present on most cell types (14). The extracellular domain fragments of both receptors shed from cell surfaces can be detected as soluble forms (sTNFR-1 and -2). At physiological concentrations, sTNFRs appear to stabilize the TNF molecule, thereby prolonging its actions (15). However, at higher concentrations sTNFRs can inhibit the activity of TNF. In addition, sTNFRs are indicators of long-term immune status. sTNFR-1 is already elevated in stable, non-cachectic CHF patients (16) and has been shown to vary over time to a lesser degree than TNF and IL-6 (17).

Concerning energy metabolism, TNF is known to influence directly thermogenesis, and to contribute to elevated insulin and leptin levels, the latter being a common feature in patients with CHF (18). It has been suggested that leptin levels are not elevated in patients with cardiac cachexia when corrected for the amount of fat tissue (19).

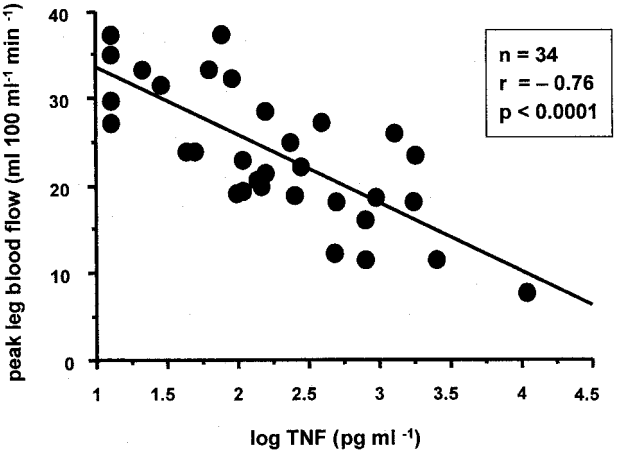

Fig. 1. Relationship between plasma tumour necrosis factor (TNF) levels and peak leg postischaemic blood flow in chronic heart failure patients. [Adapted from Anker et al. (21).]

Peripheral vasoconstriction is another important pathophysiological phenomenon: as CHF worsens it may contribute to the deterioration in left ventricular function by increasing afterload. TNF may have a pathophysiological role as serum levels are inversely related to peripheral blood flow in patients with CHF both during stable disease (21; Fig. 1) and at times of decompensation (22). Peak leg blood flow is also the best predictor of exercise capacity in cachectic patients with heart failure (Fig. 2) (20). Several mechanisms contribute to peripheral vasoconstriction and many treatment strategies in CHF are targeted towards these pathways. The links between TNF and a number of the pathological processes underlying the development of CHF suggest that the development of anti-TNF therapies may be of benefit. These therapeutic approaches are discussed later in this review.

Interleukins-1 and -6

The presence of IL-1β mRNA in the coronary arteries and myocardium of patients with dilated cardiomyopathy has been demonstrated, whereas patients with ischaemic heart disease express much less IL-1β (23). IL-1 has important negative inotropic effects as it has been shown to depress myocardial contractility by stimulating nitric oxide synthase (23). In addition, IL-1 and TNF both inhibit cardiac myocyte β-adrenergic responsiveness (24). Interleukin 6 (IL-6) is another proinflammatory cytokine which has been implicated in the pathogenesis of CHF. Patients with CHF have raised circulating IL-6 levels (25, 26) which are associated with a worse New York Heart Association (NYHA) functional class, increased length of hospital stay and poorer left ventricular function (27–30). Furthermore, IL-6 may be important in the development of osteoporosis, which is known to occur in CHF patients (31).

Immune parameters and prognosis in chronic heart failure

The search for accurate and independent prognostic markers in CHF is important with regard to monitoring treatment and selecting appropriate patients for transplantation. Studies have shown that elevated levels of plasma TNF, sTNFR-1 and -2, IL-6 and soluble CD14 (the receptor for endotoxin) are markers of impaired survival in patients with CHF (32, 33). In particular, sTNFR-1 appears to be the strongest and most accurate predictor of survival in CHF independent of established parameters (32) (Fig. 3). In research settings and

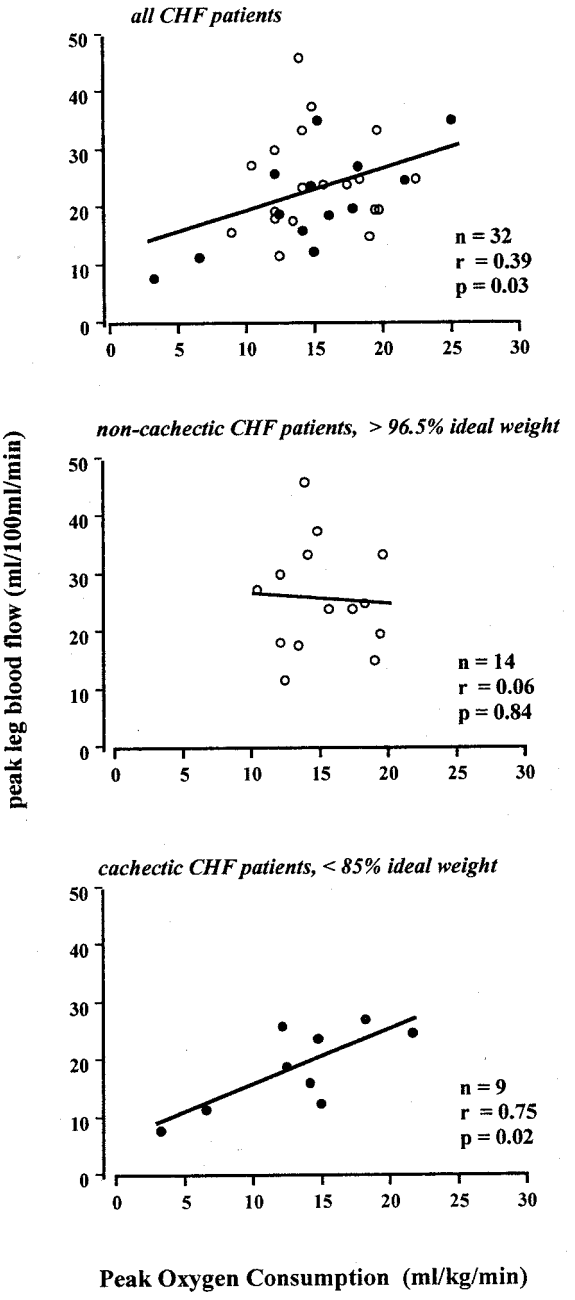

Fig. 2. Relationship between peak leg postischaemic blood flow and exercise capacity (peak Vo_2) in chronic heart failure (CHF) patients with (●) and without (○) cachexia. [Adapted from Anker et al. (20).]

with regard to focused clinical trials, the measurement of soluble TNF receptors may be an ideal measure to define patients who are likely to benefit from anti-TNF treatment. However, such assessments are not available in routine clinical practice as they remain relatively expensive and time consuming. Therefore, most would aim to use biochemical surrogate markers of inflammation instead. The latter could be C-reactive protein (34), serum uric acid (35) or the erythrocyte sedimentation rate (36).

Cause(s) of inflammatory immune activation in chronic heart failure

The main stimulus for the immune activation in CHF is not known, and at present there are three main theories as to why this occurs. One hypothesis is that the heart is the main source of proinflammatory cytokines. In support of this, it has been shown that the failing myocardium is capable of producing TNF (6), and *in vivo* studies have reported that haemodynamic pressure overloading is capable of stimulating TNF mRNA synthesis (37).

The second hypothesis is that the bowel wall oedema and ischaemia, which occur in CHF as a result of venous congestion, are responsible for bacterial translocation, leading to endotoxin release and subsequent immune activation (38). In support of this it has been reported that monocytes from patients with heart failure are more sensitive than normal to stimuli such as lipopolysaccharides (LPS) (39–41). The evidence for this hypothesis is further supported by the finding that there are elevated concentrations of endotoxin (LPS) and inflammatory cytokines in patients during an acute oedematous exacerbation (42). Endotoxin levels are normalized by intensive diuretic therapy in these patients (42). Endotoxin is also known to be able to induce synthesis of TNF mRNA in the myocardium *in vivo* (43). If this hypothesis holds true, it opens up a variety of possibilities for novel therapeutic strategies directed against the bacteria in the bowel wall, endotoxin itself or the binding of endotoxin to cells of the immune system (14, 42). Because lipoproteins can form micelles around endotoxin and block its bioactivity, according to the endotoxin–lipoprotein hypothesis, lipoproteins of all types [including low-density lipoprotein (LDL)] may have direct beneficial effects in CHF patients (44). In correlation studies, this idea has been supported (45).

The third proposed hypothesis postulates that extramyocardial cytokine production due to tissue hypoxia may be the primary stimulus for increased TNF production in CHF patients (46, 47). This is supported by the finding that tissue hypoxia and free radical production are potent stimuli for the generation of cytokine release via nuclear factor-κB (NF-κB) dependent pathways (14). It may, of course, be the case that more than one mechanism is involved in causing the immune activation that occurs in heart failure.

Neurohormonal activation

Several neurohormonal changes, including raised catecholamine levels, overactivity of the renin–angiotensin–aldosterone system and elevation of natriuretic peptides, occur when heart failure becomes chronic (48). According to the neurohormonal hypothesis (49), heart failure progresses owing to the deleterious effects of the activated endogenous neurohormonal system on the heart and circulation. Several studies have found neurohormonal activation to be strongly related to mortality (50, 51). Nevertheless, a drug's ability to reduce plasma catecholamine levels is not directly related to a mortality benefit of such a drug (52). Both adrenaline (epinephrine) and noradrenaline (norepinephrine) can cause increases in metabolic rate (53), with levels being markedly raised in CHF patients with cardiac cachexia (9). In addition, plasma levels of cortisol and aldosterone as well as plasma renin activity are particularly elevated in CHF patients with cardiac cachexia (9). These data suggest a specific association between the development of body wasting and the presence of neurohormonal activation in CHF patients.

Inflammatory cytokines are well known to have significant interactions with neurohormonal pathways in CHF. Insulin resistance is a recognized finding in patients with CHF (54) and has been suggested to be of prognostic value (55). TNF levels correlate positively with the degree of insulin resistance in CHF and may be an important aetiological factor, as has been shown in the context of obesity-related insulin resistance (56). Moreover, there are particular abnormalities of the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis in cachectic CHF patients. GH levels are raised, whereas IGF-I levels are not altered or may even be reduced, implying a picture of acquired GH resistance (9, 57). In addition, the abnormalities of the GH/IGF-I system are closely linked to abnormal plasma levels of inflammatory cytokine in CHF patients (58). Recent studies have been unsuccessful in achieving symptomatic benefits through the administration of GH (in low doses) in CHF patients (59, 60). Anabolic high-dose GH therapy is theoretically considered to be indicated in cachectic CHF patients, but this therapy is not without risk (57).

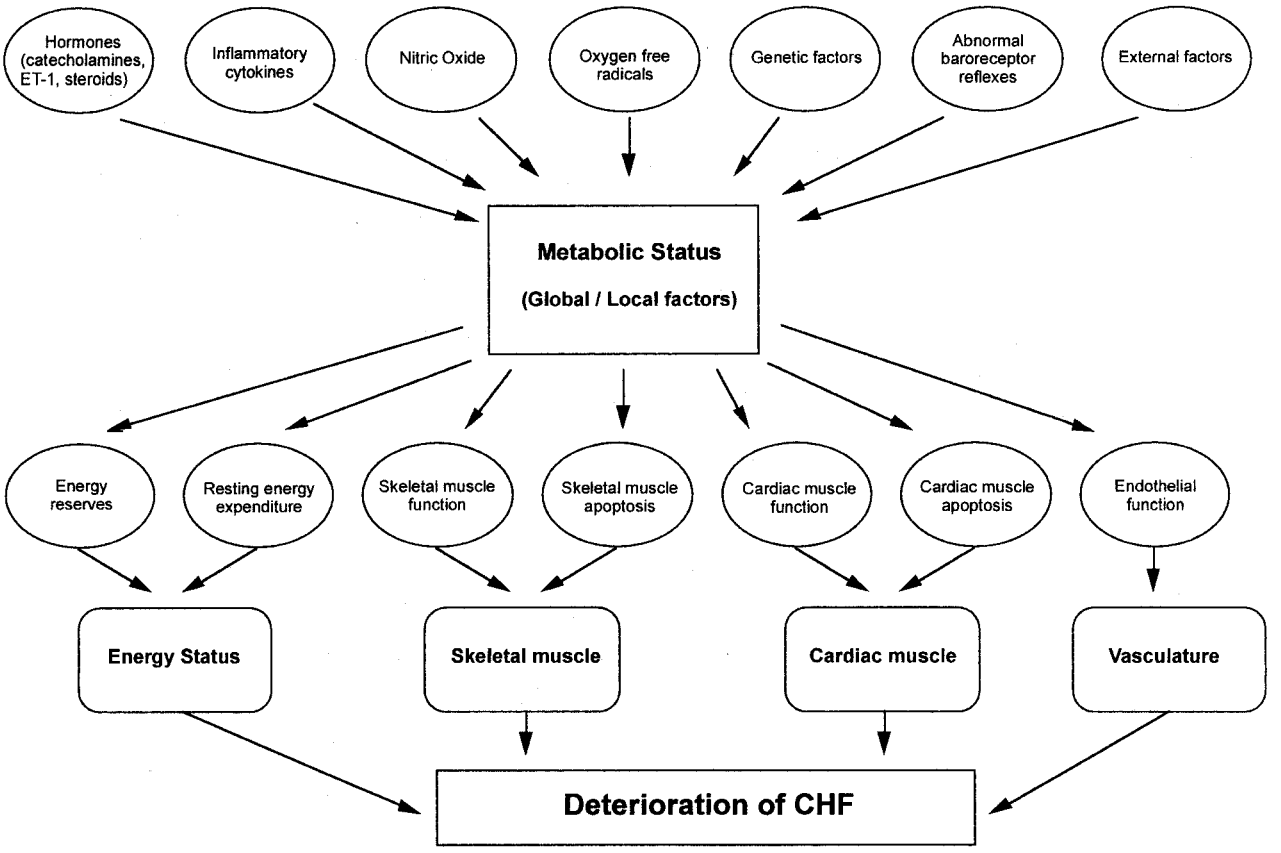

Fig. 3. Metabolic interaction causing catabolic/anabolic imbalance in chronic heart failure (CHF) patients. ET-1: endothelin-1. [Adapted from Sharma et al. (81).]

Disorders of steroid metabolism are present in patients with CHF and directly relate to the degree of inflammatory cytokine activation in this condition (61). Catabolic stress hormones, such as noradrenaline, adrenaline and cortisol are consistently elevated in patients with cardiac cachexia compared with non-cachectic CHF patients, whereas levels of the anabolic hormone dehydroepiandrosterone (DHEA) are reduced (9). The cortisol/DHEA ratio correlates positively with TNF levels, while both of these indices correlate negatively with the body mass index (61). Steroid hormone alterations as reflected in the cortisol/DHEA ratio are potentially important in regulating patterns of immune activation, influencing the balance of Th1 and Th2 cells (62). It has been proposed that this alteration in the metabolic balance between catabolism and anabolism in CHF, and by association TNF, is a key factor in the development of cardiac cachexia (4).

Modulation of neurohormonal and immune pathways in chronic heart failure patients

Previously, the beneficial effects of drugs used in the treatment of CHF were explained solely by their haemodynamic effects. However, as it is becoming clear that neurohormonal and immune pathways may play an important role in the pathophysiology of CHF, the effects of drugs on these systems are being investigated.

Angiotensin II is a potent stimulator of both the immune and neurohormonal axes, and therefore it may be anticipated that treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor antagonists would have important effects on these pathways. Treatment with ACE inhibitors is known to reduce circulating levels of atrial and brain natriuretic peptides (63, 64), TNF (65) and IL-6 (66), and it has been shown that ACE inhibitors can restore depressed levels of circulating IGF-I in patients with CHF (67). Recently, Tsutamoto et al. investigated the effects of candesartan, an angiotensin II type 1 receptor antagonist, on cytokine parameters in 23 patients with mild to moderate CHF. In this study it was demonstrated that candesartan therapy resulted in reduced plasma levels of TNF, IL-6 and brain natriuretic peptides (68). However, caution must be exercised when trying to interpret the significance of changes in the levels of immune and neurohormonal parameters. For instance, spironolactone (a competitive aldosterone receptor antagonist) is known to be beneficial in patients with CHF in terms of morbidity and mortality (69), but this drug has been shown to augment neurohormonal activity (70). Moxonidine has been shown to reduce neurohormonal activation, but in the MOXCON trial it increased mortality (71).

Phosphodiesterase inhibitors (e.g. amrinone, vesnarinone and pimobendan), which have short-term haemodynamic benefits in heart failure, can inhibit the production of TNF and other cytokines from stimulated human lymphocytes (39, 72). However, it should be noted that phosphodiesterase inhibitors are also related to an adverse prognosis in CHF. Cardiac glycosides can also reduce levels of IL-6 and TNF *in vivo* (73). In a double-blind, randomized, placebo-controlled study in CHF patients treated with ACE inhibitors and β-blockers, therapy with pentoxifylline (dose 400 mg three times per day) did not reduce TNF levels (74).

The value of anticytokine therapy in the management of CHF is highly controversial. Fish oil supplementation decreased plasma concentrations of IL-1β and improved cachexia in dogs with severe congestive heart failure (75). This may seem a rather basic form of anticytokine drug therapy; it suggests that this kind of therapy may be useful in treating patients with advanced CHF. In CHF patients in NYHA class III and IV, initial studies with a TNF receptor fusion protein (etanercept) have suggested short- and medium-term safety (76, 77) as well as haemodynamic and clinical benefits (77). Subsequently, large-scale studies [RENAISSANCE, RECOVER (78)] were initiated in CHF patients in NYHA class II–IV using doses of etanercept that were in some treatment groups higher than those used before. These studies were stopped prematurely because it was unlikely that a benefit could be shown with etanercept (79). Recently, a phase II study in CHF using a TNF antibody (5 or 10 mg kg^{-1} remicade for 6 weeks) was also stopped early because initial analyses indicated an increase in mortality in patients on active therapy (80). The future of anti-TNF therapy in CHF patients is, therefore, very uncertain. Possibly, only patients with proven high TNF levels (such as patients in NYHA class IV or with cardiac cachexia) could benefit from this type of therapy.

Traditional ideas regarding the pathogenesis of chronic heart failure are proving to be inadequate as our understanding of the disease process improves. As a result, this has stimulated the search for other hypotheses to explain the systemic features of this condition. The immune and neurohor-

monal abnormalities present in CHF may play a significant role, particularly in the development of cardiac cachexia. There is currently no specific therapy available for patients with cardiac cachexia. It is hoped that further research into this area will lead to the development of new treatments in the future.

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