Review Article

Catabolism in chronic heart failure

C. Berry and A. L. Clark

Department of Cardiology, Western Infirmary, North Glasgow Hospitals University NHS Trust, Glasgow, U.K.

Introduction

Why can chronic heart failure be a catabolic state? The resting metabolic rate of some[1–3], but not all[4,5] patients with heart failure is increased. Resting metabolic rate may account for up to 70% of daily energy expenditure in heart failure[6], and increases with NYHA functional class[6]. Resting energy expenditure accounts for a greater proportion of daily energy expenditure in heart failure patients, although there may be no difference in absolute resting energy expenditure, when compared with healthy controls. Paradoxically, average daily energy expenditure in heart failure patients falls with increased severity of disease[4]. These facts may be explained through greater energy conservation, as a result of a reduction in physical activity rather than energy loss through an increase in resting metabolic rate.

Factors which contribute to an increased resting metabolic rate in heart failure may be increased cardiac and ventilatory work[7], and increased resting peripheral oxygen consumption[8]. Oxidative lipid metabolism is activated in heart failure and free fatty acid levels are reported to be higher in heart failure than normal[3]. In these patients, left ventricular ejection fraction is inversely correlated with rates of free fatty acid oxidation, whereas plasma norepinephrine and growth hormone are positively related to free fatty acid oxidation rates[3]. Increased norepinephrine stimulates hormone-sensitive lipase which results in increased lipolysis and loss of body fat stores. Loss of muscle bulk happens early in the course of chronic heart failure[9], as a consequence of both the disease process and physical inactivity[10]. Reduced bone mass is common in heart failure and is related to low levels of serum vitamin D and secondary hyperparathyroidism[11]. Ultimately, cardiac cachexia may develop in some patients, and is an adverse prognostic feature[12].

Recent research has emphasized the potential importance of peripheral changes in the development and progression of heart failure[13]. Neurohormonal and immune system activation have been linked with weight loss and the development of cardiac cachexia (Fig. 1). In this article, we will review the evidence for catabolic/anabolic imbalance and its relationship with cachexia in heart failure. These abnormalities have important potential roles both pathophysiologically and as potential therapeutic targets.

Neurohormonal activation

In chronic heart failure activation of the sympathetic nervous system[14,15], and renin angiotensin system is a counter-regulatory response directed at maintaining renal and major body organ perfusion[16,17]. Hyperreninaemia results in elevated circulating concentrations of stress hormones such as angiotensin II, aldosterone and norepinephrine[17–19]. Circulating concentrations of endothelin may also be elevated in heart failure[20] and constitute an adverse prognosis[21]. The increase in plasma levels of some of these hormones in asymptomatic left ventricular dysfunction[22,23], the further increase with severity of heart failure[23], their prognostic significance in both asymptomatic left ventricular dysfunction[24–26], and heart failure[22,27] and the reduction in hormone levels with therapy[24,26], all implicate neurohormonal activation in the pathophysiology of disease.
How may these hormones promote catabolism in heart failure? Increased circulating catecholamines contribute to a rise in basal metabolic rate in healthy subjects and may contribute to the increase in resting energy expenditure observed in some patients. Furthermore, angiotensin II has a centrally acting anorexic effect. In experimental animals, chronic infusion of angiotensin II induced anorexia and weight loss, independent of any vasopressor effect. Both angiotensin II and norepinephrine also have other catabolic effects; for example they may exert cytotoxic effects on cardiocytes in vitro. The hypertensive effect of angiotensin II in animal models appears to be contributed to in part by increased vascular superoxide production. Angiotensin II has recently been demonstrated to increase superoxide production in human arteries by an angiotensin type 1 receptor-specific mechanism. The mechanism for this appears to be an angiotensin II-mediated activation of vascular NAD(P)H oxidase by increased transcription of the p22phox active subunit of this enzyme. It is plausible that activation of the renin angiotensin system contributes to oxidative stress in heart failure (Fig. 2). Neurohormonal mechanisms may also contribute to apoptosis in heart failure (see below). Angiotensin II induces apoptosis in both cardiomyocytes and endothelial cells in vitro. Angiotensin II induced apoptosis may be triggered by an AT1 receptor-mediated dephosphorylation and inactivation of Bcl-2, which is an inhibitor of apoptosis, or by an angiotensin II type 1 receptor mediated elevation in cytosolic calcium. Beta-adrenergic receptor stimulation may also trigger tumour necrosis factor (TNF) alpha production in vitro and beta-blockade can improve abnormal immune responses in heart failure patients.

**Immune activation**

Increased circulating cytokines, including TNFalpha, IL-1, IL-6, and IL-8, their receptors and leucocyte chemokines all appear important to the pathophysiology of heart failure. In the studies of left ventricular dysfunction (SOLVD), there were significant correlations between both plasma TNFalpha and IL-6 and NYHA functional class. In patients with severe heart failure, elevated levels of soluble tumour necrosis factor receptor (sTNFRII) are a stronger predictor of early mortality than plasma norepinephrine, atrial natriuretic peptide or NYHA class. Furthermore, elevated plasma cytokines (IL-6 and IL-8) and soluble adhesion molecules (sVCAM-1 and sL-Selectin) fall to near normal when patients with decompensated heart failure are stabilized by mechanical circulatory support.

The clinical use for measurement of cytokines and neurohormones has been limited as their concentrations can vary markedly between patients. Factors which may contribute to this variability are aetiology, severity of disease, differences in treatments, altered renal function, haematocrit and co-morbidity. Some cytokines have pro-inflammatory effects (e.g. TNFalpha, IL-1, IL-2, IL-6 and IL-8) whereas others, such as IL-4, IL-10 (which may be reduced in heart failure) and IL-13, are anti-inflammatory.
How might immune activation occur in heart failure? There is increased endothelial production of soluble adhesion molecules (sVCAM-1, sE, sL and sP-selectin)[48,54]. These molecules are important mediators of both endothelial–leucocyte adhesion and inflammatory responses[53]. Endothelial cell injury may be important in heart failure as elevated plasma ICAM-1 levels are associated with an adverse prognosis[21].

Leyva et al. recently demonstrated correlations between elevated TNFα receptors (sTNFR) (0.74, \( P<0.001 \)), IL-6 (0.66, \( P<0.001 \)) and ICAM-1 (0.44, \( P<0.01 \)), and uric acid in heart failure patients[56]. In hypoxia IL-6 and ICAM-1 are produced by injured endothelial cells[57,58], and vascular xanthine dehydrogenase enzyme is converted from its native state into xanthine oxidase. This enzyme catalyses the production of uric acid, with superoxide being produced as a byproduct of this reaction[59]. Leyva et al. hypothesized that the injured microvascular endothelium in heart failure may be a source of increased free radical production thus triggering leucocyte activation and increased cytokine production. This novel hypothesis requires further investigation. Soluble CD14 levels, specific for endotoxin exposure, are also elevated in heart failure[50]. This finding led Anker et al. to suggest that mesenteric congestion may facilitate systemic endotoxin release from the gut, triggering immune activation. Which cytokines may contribute to catabolism in heart failure?

### Tumour necrosis factor

Tumour necrosis factor α is a pleiotropic polypeptide cytokine elaborated by activated monocytes and macrophages in response to systemic disease[50]. Its biological effects include anorexia, pyrexia, increased metabolic rate and immune activation[61]. TNFα exerts its biological effect on binding to one of two cell membrane receptors, TNFR1 and TNFR2[62]. Extracellular release of the receptors as soluble proteins may neutralize the bioactivity of circulating TNFα[63], or may act as a reservoir for TNFα with levels of the receptor reflecting the bioactivity of TNFα.

Levine et al. first described elevated levels of TNFα in severe chronic heart failure[41]. Circulating concentrations of TNFα may rise during a period of acute clinical decompensation[64], and may remain elevated despite treatment. TNFα plasma concentrations are higher in heart failure patients with weight loss[42,65], and are also inversely related to body mass index in those patients of normal body weight[67].

TNFα, sTNFR1 and sTNFR2 plasma concentrations typically increase with the severity of disease[49,53,66,67], although may be normal in clinically stable patients. TNFα concentrations are increased within the heart, whereas both myocardial protein and mRNA levels of TNFR1 and TNFR2 are decreased[68]. As TNFα induces shedding of its cellular receptor, it may be that in the failing heart, elevated myocardial TNFα results in a depletion of the receptors[68].

### Table 1 Effects of TNFα which may contribute to catabolism in heart failure

<table>
<thead>
<tr>
<th>Effects of TNFα</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Apoptosis</td>
<td>↓Bax, ↑Bcl₂, ↑iNOS, ↓eNOS</td>
</tr>
<tr>
<td>2. Cardiotoxicity</td>
<td>↑O₂⁻, ↑Mn SOD, ↑iNOS</td>
</tr>
<tr>
<td>3. Activation of nuclear transcription factors e.g. NFκB</td>
<td>↑fas, ↑Bcl₂</td>
</tr>
<tr>
<td>4. Induction of iNOS</td>
<td>↑Ubiquitin proteosome activity</td>
</tr>
<tr>
<td>5. Increased free radical activity</td>
<td>↑IL-6</td>
</tr>
</tbody>
</table>

Table 2 Summary of the catabolic effects of TNFα in heart failure

<table>
<thead>
<tr>
<th>Catabolic effects of TNFα in heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vascular dysfunction</td>
</tr>
<tr>
<td>2. Oxidative stress</td>
</tr>
<tr>
<td>3. Apoptosis</td>
</tr>
<tr>
<td>4. Proteolysis</td>
</tr>
<tr>
<td>5. Immune activation</td>
</tr>
<tr>
<td>6. Negative inotrope</td>
</tr>
<tr>
<td>7. Basal metabolic rate</td>
</tr>
<tr>
<td>8. Anorexia</td>
</tr>
</tbody>
</table>

**Table 2** Summary of the catabolic effects of TNFα in heart failure

- **Neopterin** is a metabolite of tetrahydrobiopterin which is required for the interaction of TNFα with its receptor. Concentrations of neopterin correlate with plasma TNFα[47] and sTNFR[70]. Levels of neopterin, sTNFR and sIL-2R are higher in NYHA groups III–IV when compared with groups NYHA I–II[70].

In the early stages of disease, elevated TNFα may have beneficial effects. In vitro, TNFα induces nitric oxide synthase (iNOS) expression in both endothelial and vascular smooth muscle cells resulting in enhanced nitric oxide (NO) production from these cells[71,72]. In vivo, TNFα levels correlate with enhanced forearm blood flow responses to both endothelial-dependent and independent vasodilatation in heart failure patients[73]. This suggests activation of a counter-regulatory mechanism of TNFα-enhanced peripheral blood flow. What properties of TNFα could contribute to catabolism and weight loss?

### Catabolic effects of TNFα in heart failure (Table 1 and Fig. 2)

(A) Apoptosis

TNFα triggers cardiocyte apoptosis, or pre-programmed cell death, by a TNFR1 dependent increase in intracellular sphingosine[74,75]. Elevated plasma TNFR1, but not TNFα, is related to sFas which is an endogenous inhibitor of apoptosis[76,77]. A causal relationship between increased myocardial production of TNFα and increased apoptosis in heart failure (see below) has not been established.

- **Bcl₂** is an intracellular membrane protein which inhibits apoptosis[79]. Bcl₂ homodimers maintain organelle membrane integrity whereas heterodimerization with a protein such as Bax promotes apoptosis. In vitro,
genes[82]. Cellular production of NF
promotes the expression of many in
fl
ported in septic shock patients [80]. In vitro, TNF
cox-2 compared with controls [95].
ure and die prematurely[84,85]. This directly implicates
Transgenic mice with cardiac over-expression of TNF
(C) Nuclear factor kappa B (NF
ubiquitin proteosomes)[79]. Activation of intracellular proteolytic systems (e.g.
resulting from cells within the vascular wall and in leucocytes that sympathetic nervous system activation may induce cardiac dysfunction[82]. Altered calcium homeostasis within the myocyte may contribute to the negative inotropic effects of TNF[83]. Transgenic mice with cardiac over-expression of TNF develop impaired cardiac function, congestive heart failure and die prematurely[84,85]. This directly implicates myocardial production of TNFα in the pathogenesis of cardiomyopathy and congestive heart failure[86].

(C) Nuclear factor kappa B (NFκB)
NFκB is a ubiquitous nuclear transcription factor which promotes the expression of many inflammatory genes[87,88]. Cellular production of NFκB can be triggered by multiple stimuli, such as IgG and intracellular reactive oxidant species, such as superoxide[89]. TNFα increases superoxide production and may alter cellular redox status[90]. TNF promotes the activation of cell adhesion molecules, such as the vascular adhesion molecule (VCAM), through free radical mediated up-regulation of NFκB in vitro. NFκB is also important in the activation of iNOS[91]. In vitro, NFκB is an important intermediary signal in the TNFα related induction of cyclo-oxygenase-2 gene expression[92,93]. This enzyme is responsible for the synthesis of prostanooids, such as thromboxane and prostaglandin F2α, which cause vasospasm and are prothrombotic, negatively inotropic and cardiotoxic[94]. Immunohistochemical staining of cardiac tissue from heart failure patients stains strongly for both NFκB and cox-2 compared with controls[95].

(D) Anorexia
Experimental evidence suggests that tissue wasting may arise for reasons which may not simply be explained through physical inactivity[96]. TNFα may directly stimulate loss of appetite when locally produced within the brain[97]. Although there is no direct evidence of TNFα-induced anorexia in chronic heart failure, it may contribute to weight loss in humans through down-regulation of the β-3 adrenergic receptor, induction of leptin expression in adipose tissue and reduction in body fat stores[98,99].

**Interleukins**
The interleukins (IL), particularly IL-1, IL-2, and IL-10, may be activated in chronic heart failure[44-46]. IL-1 is released from activated T lymphocytes and is the trigger for macrophage activation. IL-2 production and the acute phase inflammatory response within the liver[100]. IL-1 may be involved in the pathogenesis of dilated cardiomyopathy. IL-1 attenuates cardiomyocyte hypertrophy by inhibiting transcription of the alpha-actin gene promoter in vitro[101]. There is increased expression of mRNA in IL-1 in the coronary arteries and myocardium of patients with dilated cardiomyopathy when compared to those with ischaemic heart failure, whereas expression of other cytokines such as TNFα, IL-6 and IL-10, are similar[102].

IL-6 is proinflammatory, increases endothelial vaso-active peptides[103], is proteolytic[104] and enhances the catabolic actions of TNFα[105]. Triggers for IL-6 production from cells within the vascular wall and in leucocytes are hypoxia, sympathetic nervous system activation, endothelin and TNFα (Fig. 2)[106]. The proteolytic effect of TNFα is thought to be mediated through IL-6[106]. Chronic overproduction of IL-6 in transgenic mice results in protein breakdown, muscle atrophy and weight loss. These effects may be prevented by treatment of these animals with IL-6 receptor antibody[107]. The arteriovenous ‘spillover’ of interleukin-6, as measured by the increment in IL-6 concentration between femoral artery and femoral vein, is increased in patients with heart failure[107]. Treatment with beta-blockers correlated negatively with IL-6 arteriovenous ‘spillover’ concentrations[107]. This supports the concept that sympathetic nervous system activation may induce IL-6 release within the vasculature. Circulating IL-2 and IL-10 levels can be elevated in patients with dilated cardiomyopathy[46]. IL-2 may be elevated as a result of abnormal lymphocyte function, whereas the anti-inflammatory cytokine IL-10 may be increased as a counter-regulatory response.

**Oxidative stress**
Oxidative stress may be defined as increased tissue activity of oxygen free radicals, in excess of normal cellular homeostatic anti-oxidant systems. In heart failure, there is both increased superoxide production by leucocytes[52] and reduced levels of plasma thiol anti-oxidants[106].
How is oxidative stress related to the pathophysiology of heart failure? Experimental mice lacking the gene for manganese superoxide dismutase have deficient mitochondrial scavenging of superoxide anion which is produced as a byproduct of oxidative phosphorylation. Increased cellular superoxide activity causes enhanced oxidative free radical tissue injury and heart failure in these animals. Plasma malondialdehyde, a marker of oxidative stress, is elevated in chronic heart failure and is related to exercise-intolerance. Keith et al. measured plasma lipid peroxides, malondialdehyde, glutathione, vitamin C and E and demonstrated that oxidative stress correlates with both NYHA functional class and TNFR levels. Oxidative stress may also contribute to increased rates of cardiomyocyte apoptosis in chronic heart failure (see below).

**Apoptosis**

Apoptosis, or genetically programmed cell death, is an important process in the pathophysiology of hypertension, coronary heart disease and possibly heart failure. Narula et al. reported that apoptosis affected 5–35% of myocytes in explanted cardiac tissue of patients with heart failure. Olivetti et al. described an increased number of apoptotic cells (by a magnitude of 232-fold) in heart failure patients. This equated to a prevalence of 0.23% of apoptotic cells within the failing heart. The discrepancy between these two figures may be related to an over-estimation in the initial report through experimental error.

Apoptosis within the heart may be triggered by hypoxia, and ischaemia–reperfusion (Fig. 2). Increased free radical activity in hypoxic cardiomyocytes triggers stress-activated protein kinases in vitro. These enzymes are important in the intracellular signalling events involved in apoptosis. In vitro evidence from models of mechanical-stretch induced cardiocyte apoptosis, suggests that pressure-overload within the heart in vivo may upregulate apoptosis. In dogs, pacing-induced heart failure is associated with an increased cardiocyte apoptosis.

Atrial natriuretic peptide (ANP), another peptide which is increased in many patients with heart failure, causes an increase in the prevalence of apoptotic cardiomyocytes from 4.8% to 19% in vitro. Insulin like growth factor-1 (IGF-1) is an important cell survival factor which inhibits cardiac myocyte apoptosis in vivo. Levels of IGF-1 (see below) are reduced in some patients in heart failure, suggesting another mechanism by which apoptosis might be induced in heart failure.

Fas and Fas ligand (Fas-L) are cell-membrane proteins which are important activators of apoptosis whereas soluble Fas (sFas) and soluble Fas-ligand (sFas-L) inhibit apoptosis. sFas is increased in heart failure and is related to severity of disease but not aetiology, which is in contrast to initial reports. sFas is related to plasma sIL-2R and leucocyte activation in heart failure. Furthermore, cardiomyocyte production of sFas is increased in hypoxia. This suggests that increased sFas may be a counter-regulatory phenomenon. More research is required to elucidate just how important the process of apoptosis is in the pathophysiology of heart failure.

**Catabolic: anabolic hormone disturbance**

*(A) Steroid metabolism*

Catabolic steroids such as cortisol are disproportionally elevated in untreated heart failure patients. In treated patients, there is an increase in cortisol (catabolic) relative to dehydroepiandrosterone (anabolic). Increased catabolic steroids may augment basal metabolic rate, induce insulin resistance and free fatty acid oxidation, all of which may contribute to catabolic:anabolic imbalance (Fig. 2).

*(B) Growth hormone*

Growth hormone is anabolic and promotes skeletal muscle and cardiac hypertrophy. It is secreted in a circadian rhythm with plasma levels being highest at night, and secretion can be depressed in cardiac failure. Giustina et al. found a linear correlation $r=0.813, P<0.01$ between ejection fraction and mean plasma growth hormone concentration, although others have found growth hormone to be strikingly elevated in heart failure.

Growth hormone mediates its anabolic effects through insulin-like growth factor 1 (IGF-1). Whilst many patients display normal levels of IGF-1, there is a subgroup of patients with low levels of IGF-1 relative to growth hormone. In fact, growth hormone may be strikingly elevated in some heart failure patients, who have normal IGF-1 concentrations. These patients may be growth hormone resistant. Growth hormone resistance is associated with loss of muscle bulk and muscle strength, independent of aerobic capacity, left ventricular ejection fraction or NYHA classification. Growth hormone resistant patients may also have higher levels of TNFα and an elevated cortisol:DHEA ratio. The reduction in IGF-1 may have adverse consequences; TNF-induced cell killing is prevented by IGF-1 alone and expression of IGF-1 may protect cells, including cardiocytes, from apoptosis.

Is growth hormone supplementation in heart failure clinically beneficial? Growth hormone replacement therapy increases ventricular wall thickness and improves left ventricular ejection fraction. Growth hormone exerts a hypertrophic effect in the myocardium of both experimental animals and humans with heart failure. In contrast to earlier reports, a recent study...
randomized, double-blind, placebo-controlled trial of recombinant growth hormone treatment in 50 patients with dilated heart failure did not report any clinical benefits with growth hormone therapy\(^{[140]}\).

(C) Insulin resistance

Insulin is natriuretic, antilipolytic, antiglycogenolytic and promotes protein anabolism. Swan et al. were the first to describe increased stimulated insulin release and insulin resistance in heart failure patients\(^{[128]}\). Insulin resistance may have an antidiuretic effect and thus contribute to salt and water retention. Insulin resistance in chronic heart failure is related to severity of disease, independent of plasma catecholamine levels and left ventricular ejection fraction\(^{[143]}\). Insulin selectively enhances blood flow within skeletal muscle\(^{[142]}\) and hyperinsulinaemia, at least in this context, may be beneficial in enhancing impaired regional blood flow in chronic heart failure\(^{[143]}\). By contrast, Anker et al. reported normal insulin levels in cachectic heart failure patients\(^{[12]}\).

(D) Leptin

Leptin is a hormone product of the obesity (ob) gene in adipocytes. In animal models, circulating leptin induces anorexia and weight loss\(^{[144,145]}\). It is reported to exert its effects via inhibition of hypothalamic release of neuropeptide Y and reduction in appetite\(^{[140]}\), rather than by any direct reduction of peripheral adipocyte number\(^{[147]}\). Neuropeptide Y is elevated in heart failure\(^{[148]}\), perhaps paradoxically. However, as it is co-released with noradrenaline from sympathetic nerve terminals\(^{[149]}\), the paradox may be related to activation of the sympathetic nervous system. The novel relationship between insulin resistance, sympathetic nervous system activation and leptin metabolism in heart failure merits further study.

(E) Thyroxine

Thyroid dysfunction may occur in severe chronic heart failure\(^{[129]}\) and may be due to impaired thyroid hormone synthesis or peripheral tissue resistance\(^{[150]}\). Thyroid hormone is anabolic and may increase muscle protein synthesis\(^{[155]}\). Thyroid hormones are positively inotropic\(^{[158]}\) and may enhance myocardial oxidative metabolism\(^{[159]}\). In euthyroid heart failure patients thyroxine supplementation improved cardiac output, the cardiac inotropic state (left ventricular ejection fraction/ end systolic stress), peak oxygen consumption and exercise time. These effects were independent of any beta-adrenergic improvements and did not cause overt biochemical or clinical hyperthyroidism\(^{[160]}\). Further studies are required to evaluate the role of thyroxine supplementation in heart failure.

Nutrition

Investigations into the nutritional status of heart failure patients have either failed to quantify nutrient and caloric intake\(^{[161]}\), or have involved small numbers of patients\(^{[162]}\). As yet there has been no large-scale study which has formally assessed nutrient intake in a population of heart failure patients. Malaise, lethargy, nausea, lack of motivation and poor mobility may all contribute to inadequate nutrition which can be present in some patients.

Malabsorption

Gastrointestinal malabsorption may be a cause of impaired nutrition in chronic heart failure patients. Fat malabsorption may affect elderly patients with cardiac cachexia\(^{[163]}\), although gastrointestinal protein loss does not seem important\(^{[168]}\). In these studies, tests for bacterial overgrowth were negative and any malabsorption may have occurred as a result of gastrointestinal congestion.

Cachexia in cardiac failure

Cardiac cachexia was originally described by Hippocrates: ‘The flesh is consumed and becomes water . . . the
abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thigh melt away. Weight loss may be a problem in some heart failure patients, some of whom may ultimately develop cardiac cachexia. By definition, cachexia is the depletion of the metabolically active lean body mass. Weight loss resulting in cachexia can arise from a combination of inadequate protein intake, impaired enteral nutrient absorption, catabolic processes resulting in excessive nitrogen excretion, inadequate anabolism and physical inactivity. Stable isotope studies of muscle protein turnover have reported increased protein catabolism in heart failure patients with cardiac cachexia. As yet, there are no data on fat or carbohydrate metabolism in these patients.

Clinically important cachexia has been defined as non-intentional weight loss of more than 7.5% in a non-oedematous patient over a 6-month period. Little is known with regard to the epidemiology of cardiac cachexia in patients with heart failure. The prevalence has been estimated to range from 16% in outpatients to 61% in hospitalized patients with more severe disease (NYHA III–IV). The presence of cachexia in heart failure is related to the severity of disease and increases the risk of death independent of other factors by a magnitude of at least 2.6. Weight loss in heart failure is related to both symptoms, impaired exercise capacity and physical inactivity.

Therapeutic implications

Therapeutic strategies which modulate the pathophysiology of heart failure may also attenuate catabolism and disease progression. What are the current therapeutic possibilities for the prevention and treatment of cachexia and cachexia in heart failure?

(A) Nutritional support

Routine clinical assessment of the heart failure patient should include both a diet and weight history. Patients should be advised to maintain a minimum recommended daily energy intake of 2800 kCal. The only randomized placebo-controlled trial of a dietary intervention (high protein energy diet) did not show any clinical benefit. However, in this study only two patients fulfilled standard criteria for malnutrition and the small numbers in each group were such that this study was underpowered to detect differences between the two groups.

(B) Exercise training

Training has the potential to reverse at least some of the skeletal muscle abnormalities in heart failure. Initial reports suggest exercise therapy may be beneficial in heart failure. One recent single centre controlled study of exercise rehabilitation in 99 heart failure patients reported improvements in exercise capacity, quality of life, hospital readmissions and all-cause mortality after 14 months therapy and after a further 12 months follow-up. More follow-up data on morbidity and mortality is required before this therapy could be routinely prescribed.

(C) Anabolic enhancement

‘Anabolic support’ may prove to have a role in chronic heart failure. Thyroxine is potentially of benefit (although further clinical trials are required) and a ‘border-line hypothyroid’ heart failure patient should be treated with low-dose thyroxine supplementation. There is insufficient evidence to support the use of growth hormone therapy at present.

(D) Immune modulation

Therapeutic immune modulation is at an early state of development. Evidence from clinical studies in patients with septic shock suggests that anti-TNF therapy may be of benefit in heart failure. There are two phase III clinical trials of recombinant soluble TNF receptor binding proteins (RENAISSANCE and RECOVER) which are currently in progress.

(E) Therapeutic intervention

Beta adrenoceptor antagonists and ACE inhibitors improve prognosis in heart failure. Patients with ischaemic heart disease who take beta-blockers may also gain weight, Experimental evidence suggests that both classes of drugs may not only attenuate neurohormonal activation, but also moderate immune and cytokine activation. For example, beta-blockers reverse sympathetic-induced impaired T cell activation and reduce IL-2 receptor expression. In addition, some beta-blockers such as carvedilol appear to exert potent antioxidant effects and can reduce apoptosis in cardiac ischaemia. ACE inhibitors may attenuate apoptosis in heart failure, and can attenuate neurohormonal activation in patients with asymptomatic and symptomatic left ventricular dysfunction.

Most recently, treatment with aldosterone receptor antagonist, spironolactone, has been shown to reduce morbidity and mortality in patients with severe heart failure.

Conclusions

Neurohormonal and immune activation and catabolic: anabolic imbalance can be important catabolic processes in the pathophysiology of heart failure. These processes
may contribute to symptoms, exercise intolerance, weight loss and disease progression. Assessment of weight loss should be included in the management of heart failure patients. Elevation of hormones such as ANP, aldosterone and norepinephrine constitutes a poor prognosis in patients with left ventricular dysfunction, however variation in plasma concentrations of these hormones is such that their routine measurement is not clinically useful[26].

The exploration of cachexia is at an early stage. The origins of immune activation and weight loss are not yet clear, but given the tremendous impact on patients are important and offer potential new therapeutic targets in chronic heart failure.

References


Zhao SP, Zeng LH. Elevated plasma levels of tumour necrosis factor in chronic heart failure with cachexia. Int J Cardiol 1997; 58: 257–61.


Eur Heart J, Vol. 21, issue 7, April 2000


