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CARDIAC CACHEXIA: A SYSTEMATIC OVERVIEW

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ABSTRACT

Cardiac cachexia as a terminal stage of chronic heart failure carries a poor prognosis. The definition of this clinical syndrome has been a matter of debate in recent years. This review describes the ongoing discussion about this issue and the complex pathophysiology of cardiac cachexia and chronic heart failure with particular focus on immunological, metabolic, and hormonal aspects at the intracellular and extracellular level. These include regulators such as neuropeptide Y, leptin, melanocortins, ghrelin, growth hormone, and insulin. The regulation of feeding is discussed as are nutritional aspects in the treatment of the disease. The mechanisms of wasting in different body compartments are described. Moreover, we discuss several therapeutic approaches. These include appetite stimulants like megestrol acetate, medroxyprogesterone acetate, and cannabinoids. Other drug classes of interest comprise angiotensin-converting enzyme inhibitors, beta-blockers, anabolic steroids, beta-adrenergic agonists, anti-inflammatory substances, statins, thalidomide, proteasome inhibitors, and pentoxifylline.
LIST OF ABBREVIATIONS


KEY WORDS
Cachexia, heart failure, nutrition, treatment
I. INTRODUCTION

The treatment of chronic heart failure (CHF) has made significant advances over the last two decades. This applies likewise for the establishment of the diagnosis of this syndrome using different single and multi-biomarker approaches (Cowie et al., 1997, von Haehling et al., 2007c, Kempf et al., 2007). Even more so, our understanding of the disease has developed from the rather simplistic model of mere pump failure to that of a complex disease that affects multiple body systems. Despite this, the clinical perspective remains poor, because about half of the patients with CHF die within four years of diagnosis (Remme et al., 2001). This truly devastating prognosis is comparable to that of some types of cancer (Stewart et al., 2001). Overall, the incidence of CHF is steadily increasing in most European countries and in the United States. Current estimates amount to an incidence of 0.1-0.5% per year, and the numbers are doubling with each decade to reach 3% in those over the age of 75. The prevalence of CHF has been estimated at around 0.3-2.4%, which implies that 5 million people in the United States are affected (American Heart Association, 2005). Heart failure accounts for 970,000 hospitalizations and 12-15 million outpatient office visits in this country per year. This causes health-care associated costs of 28 billion US-dollar.

The situation worsens considerably once cardiac cachexia has been diagnosed. Although the definition of this clinical entity has been subject to debate over years (see below), all researchers have unanimously agreed on the poor prognosis of the cachectic patient. In unselected patients with CHF, mortality rates were as high as 50% in the cachectic subset compared to 17%
in the non-cachectic subset at 18 months of follow-up (Anker et al., 1997). Cachexia is not a unique feature of CHF, but is also seen in terminal stages of other chronic illnesses, including cancer, sepsis, rheumatoid arthritis, and acquired immunodeficiency syndrome (AIDS).

Cachexia is not only associated with poor outcomes, but also with an unfavourable response to drug treatment and poor quality of life. It has been observed in patients with cancer that survival is impaired already at a weight loss of 5% (Dewys et al., 1980). Weight loss exceeding 30% is incompatible with life (Fearon et al., 1992). It is among the most common misconceptions that one of the underlying causes of cachexia is anorexia, i.e. loss of appetite. Although anorexia is certainly a common feature of the diseases leading to the development of cachexia, this feature alone cannot explain the metabolic changes observed during this perturbation. Importantly, nutritional supplementation cannot reverse the process of losing weight in patients with genuine cachexia, which is possible in patients who suffer from starvation or anorexia. Still, nutritional aspects have to be considered when treating patients with cachexia.

Weight loss in the cachectic patient predominantly affects muscle protein, however, bone and fat tissue are likewise affected later in the course of the disease. The factors that trigger the progression from clinically and body weight stable, ambulatory CHF to cardiac cachexia remain poorly understood. The timelines differ widely between patients. The aim of this review is to provide a broad overview of the current knowledge of cardiac cachexia. This
II. DEFINITION OF CARDIAC CACHEXIA

Body weight is a dynamic parameter, and it has a certain rhythm over the lifespan (Wallace et al., 2002). Currently, public opinion is more concerned with weight gain than weight loss, and therefore most of the programs in adults are aiming at the reduction of body size (Dansinger et al., 2007). However, weight loss due to body wasting may reflect serious disease and has to be considered with particular attention. Cachexia (Greek: kakós – bad; hexis - condition) constitutes its terminal phase and develops in advanced stages of various chronic illnesses, e.g. CHF, chronic obstructive pulmonary disease, or cancer. The syndrome of body wasting has been recognized for centuries. A picturesque clinical description of cachexia was provided by Hippocrates already in the ancient Greece: “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… The illness is fatal.” (Doehner et al., 2002a). This description is still used for didactic purposes whilst its applicability in everyday clinical practice is being challenged. Nowadays, and also in line with evidence based medicine, clear cut definitions are of major importance for identification and management of certain diseases or medical conditions. However, in the field of body wasting
and cachexia, the important question of a universal definition is still debated [Springer et al., 2006b, Lainscak et al., 2008, Evans et al., 2008].

Cardiac cachexia as a clinical entity is acknowledged as a complex syndrome, which is associated with poor outcomes (Anker et al., 2004a, Morley et al., 2006). No single reason for cachexia exists. Patients usually experience progressive weight loss with body composition alterations and disturbed homeostasis of several body systems. There is evidence for activation of neuroendocrine and inflammatory systems, increased lipolysis, muscle wasting, lack of appetite, and malabsorption whilst the importance of individual pathways and the exact interplay remain unknown (see below) (von Haehling et al., 2007b, Strassburg et al., 2005). Additional confusion is caused by several terms used when describing body wasting. Indeed, descriptive terms such as “cachexia”, “anorexia”, “sarcopenia”, “malnutrition” and even “hypercatabolism”, are being (mis)used by researchers and clinicians and are frequently regarded as synonyms. Again, important differences exist and one should be careful how and when to use individual terms. The process of sarcopenia, which is regarded as age associated “normal” muscle wasting (Evans, 1995), may not result in significant weight changes, because loss of muscle and increases in fat mass are frequently balanced. In contrast to cachexia, malnutrition and anorexia are reversible with adequate food intake. Loss of appetite or anorexia causes loss of fat mass rather than muscle tissue. Malnutrition is also associated with body wasting, predominantly of fat tissue. Both anorexia and malnutrition can be cured by adequate nutrition alone, which, however, is insufficient to treat
cachexia (Springer et al., 2006b). Lastly, the term hypercatabolism cannot be evaluated during clinical examination and neglects the other side of the coin, the anabolic processes (Springer et al., 2006a).

Several definitions have been used in different studies. Most of them focused on weight loss alone, and only a few acknowledged the importance of body composition or temporal components of weight change. Regarded from a historical point of view, the first reports focused on body fat content and defined a cut-off at a body fat content <15% for men and <22% for women or as the percentage of ideal weight <90% (Carr et al., 1989). In 1994, the loss of body weight was acknowledged and cachexia was considered in patients with loss of ≥10% of lean tissue (Freeman & Roubenoff, 1994). This definition is hampered mainly by the requirement for dual energy X-ray absorptiometry (DEXA), which even today is not usually part of a clinical work-up. In cardiac cachexia, one has to consider the presence of oedema, and only non-oedematous weight loss can be considered appropriate.

In view of the significant prevalence and devastating prognosis once cachexia is present, the authors are proponents for a clinical definition of cachexia rather than relying on complicated tests or devices. The definition should embrace all the elements of evidence-based medicine, should be validated for the prognostic significance but should be feasible for use in clinical practice (Lainscak et al., 2008). Of the reported definitions, the one derived from the SOLVD (Studies of Left Ventricular Dysfunction) database is the most appropriate (Anker et al., 2003). In this observational study, a cut-off of non-
oedematous weight loss of >6% of total body weight over a period of 6 or more months turned out to be strongest predictor of mortality among cut-offs from 5% to 15%. The strength of this analysis is adoption of two critical issues in cachexia, namely weight loss and its dynamics, frequently neglected in earlier reports. At this stage it is important to add that the severity of cardiac cachexia may not always correlate with classical criteria of disease severity as New York Heart Association (NYHA) functional class, left ventricular ejection fraction, or exercise duration (Anker et al., 1997a). Cardiac cachexia even may not be associated with morphological cardiac changes as seen by magnetic resonance imaging or echocardiography (Florea et al., 2002, Florea et al., 2004).

The current state-of-the-art approach to define cardiac cachexia will probably be adopted sometime in the future. It might be necessary to add some laboratory, clinical and functional parameters to be able to identify cachexia and body wasting in an early phase. Ideally, patients at risk for the development of cachexia should be identified as early as possible, however, no effective treatment of manifest cachexia is available yet (Springer et al., 2006a). A recent report of a 3-factor profile in cancer patients (weight loss ≥10%, food intake ≤1500 kcal/day, and C-reactive protein level ≥10 mg/dl) has shown better prognostic yield than weight loss alone (Fearon et al., 2006). These findings are in line with a recently reported score of clinical and laboratory parameters in patients with heart failure (Anker et al., 2003a) and could set the stage for an agreement upon the critical issues of a universal cachexia definition. The quest for such a definition is still ongoing and great
efforts have been made in recent years. We took part in the initiation of the first Cachexia Conference that was held in the year 2000. One of the principal topics of the third meeting in 2005 was the definition of cachexia, but no conclusive statement was adopted. The efforts to reach a consensus on the definition of cachexia peaked at the Cachexia Consensus Conference in December 2006 (Evans et al., 2008). A group of eminent scientists and clinicians met to work on an operational definition applicable for basic and clinical science. Although immense effort was invested, some disagreement remained. Nonetheless, the conference has advanced the field substantially through endorsed definition, which should enable reliable identification of cachexia in clinical practice as well as planning and initiation of interventional trials. According to a recently published consensus document (Evans et al., 2008), cachexia has to be considered in adult patients with chronic illness, who experience weight loss of 5% in 12 months or less (or have a body mass index <20) and comply with at least three out of five clinical or laboratory criteria (Table 1). With emerged definition of cachexia, the interventional trial results will be more applicable to cachexia of different etiology, and the quest for an effective treatment may be reaching some landmarks in the near future.

III. IMMUNE ACTIVATION

One key aspect of CHF and cardiac cachexia like many other forms of cachexia is inflammatory immune activation. This has been first described by Levine and associates in 1990 (Levine et al., 1990). Indeed, it may well be
that activation of the pro-inflammatory mediator tumour necrosis factor-α (TNFα) is the final common pathway that links all forms of cachexia. Since the initial description of TNFα activation in CHF, at least five different hypotheses have been suggested to explain the origin of immune activation in this disease (Anker et al., 2004b). In most cases, the production of pro-inflammatory cytokines has been attributed to secretion by mononuclear cells, although the myocardium seems to be another important source. However, it appears that only the failing myocardium is capable of TNFα production (Mann et al., 2001). Some evidence suggests that catecholamines augment myocardial cytokine release. The concepts trying to explain increased production of pro-inflammatory mediators comprise response to myocardial injury (Matsumori et al., 1994) and underperfusion of peripheral tissues (Tsutamoto et al., 1998). Since lipopolysaccharide (LPS), a cell wall component from Gram-negative bacteria, is one of the strongest inducers of pro-inflammatory cytokines and especially TNFα, it has been proposed that increased bowel wall oedema may cause translocation of this substance from the gut. This eventually yields pro-inflammatory cytokine secretion from monocytes in the bloodstream and other tissues (Anker et al., 1997b). Indeed, it has been shown that very small (pathophysiological) amounts of this substance are capable of inducing TNFα secretion (Genth-Zotz et al., 2002). Moreover, it has been demonstrated that cellular desentization may be present in patients with advanced stages of CHF, which suggests a previous LPS-challenge (Sharma et al., 2005a).
Only indirect evidence is currently available to buttress the aforementioned hypotheses. The elevation of plasma levels of pro-inflammatory mediators in acute myocarditis and acute myocardial infarction may hint toward the tissue injury hypothesis (Matsumori et al., 1994b). Moreover, peripheral IL-6 spillover data drawn from arterial and venous plasma samples indicated peripheral cytokine production (Tsutamoto et al., 1998). This has not been demonstrated for TNFα. Soluble CD14, a marker of LPS-cell interaction and shedding from the cell membrane, was found to be increased in some patients with CHF (p=0.0048), especially in those with cardiac cachexia (Anker et al., 1997b). This finding has been interpreted as a sign of a previous LPS challenge. Later studies revealed elevated LPS levels in the bloodstream of patients with CHF during oedematous decompensation (p<0.05) (Niebauer et al., 1999). It is well possible that the aforementioned hypotheses rather complement than exclude one another, but it is certainly true that inflammatory activation is much more than an epiphenomenon in CHF.

**Intracellular Signal Transduction**

One of the most important signal transducers of many inflammatory stimuli is nuclear factor-κB (NF-κB). It was first described in 1986 as being necessary for immunoglobulin kappa light chain transcription in B cells (Sen & Baltimore, 1986), hence its name. NF-κB is a key signal integrator in virtually any cell type. Depending on the stimulus and the cell type, it orchestrates diverse processes ranging from development over differentiation, inflammation,
immunity to apoptosis by the direct regulation of over 150 genes (Pahl, 1999).

Interestingly, over-activity of the NF-κB system has been shown to occur in patients with CHF (Jankowska et al., 2005). Regression analyses in this study showed that peak oxygen consumption (r=0.53, p=0.025), presence of peripheral oedema (r=0.37, p<0.05) and serum C-reactive protein (r=0.40, p=0.02) were the major determinants of NF-κB over-activity.

The transcription factor family NF-κB (consisting of p65 [Rel A], Rel B, c-Rel, p52, p50) shares an N-terminal Rel homology domain of about 300 amino acids. All subunits may bind to DNA, but only p65, c-Rel and Rel B contain a transactivation domain at the C-terminal region. Homodimers of the transactivation domain-lacking p50 and p52 have been proposed to act as repressors of NF-κB-regulated gene transcription (Graham & Gibson, 2005).

In unstimulated cells, the nuclear localization sequence of NF-κB is masked by one of the seven inhibitory IκB proteins (IκBα, IκBβ, IκBε, IκBγ, Bcl-3, p100, p105). Upon activation of IκB kinase (IKK), IκB is phosphorylated subsequently followed by ubiquitination and degradation via the proteasome, which leads to translocation of NF-κB into the nucleus (see also Figure 3) (Gilmore, 2005).

IV. REGULATION OF FEEDING

BRIEF SUMMARY
In this section, both positive and negative key modulators of appetite will be reviewed. Feeding is a key component of a satiety-hunger homeostatic model (Figure 1). Although a simple but vital daily process, it is influenced by many pathways and/or mechanisms, which are still not completely understood (Table 2) (Brunetti et al., 2005). However, the hypothalamus has been identified as the central regulating site of appetite (Figure 2). Two areas can be differentiated: a lateral “feeding area” and a medial “satiety centre” (Ganong, 1999). Stimulation of the first causes eating behavior, stimulation of the latter cessation of eating. Numerous mediators take part in controlling these centers in the hypothalamus. Neuropeptide Y (NPY) is found in the sympatho-adrenomedullary nervous system and in high concentrations in the hypothalamus, where it co-localized with Agouti related protein (AgRP) and positively modulates food intake. Leptin, an adipocyte-derived hormone, is released proportionally to the fat mass and a direct inhibitor of NPY-action and food intake. Leptin activates pro-opiomelanocortin (POMC) neurons that subsequently activate the melanocortin-4 receptor (MC4R), which does not only lead to a reduced food intake, but also to increased energy expenditure. Melanocortins, cleaved from POMC, may bind to 5 receptors, of which MC4R is critical for appetite regulation, as a loss of function results in obesity. This makes the MC4R an interesting pharmaceutical target in cachexia. The fairly recently identified “hunger hormone” ghrelin is mainly produced in the fundus region of the stomach, and ghrelin positive neurons have been located to the hypothalamus and project to neurons positive for NPY, AgRP, and POMC, which suggests a major role for ghrelin in the regulation of food intake. Ghrelin does not only induced food intake, but also the release of growth hormone via
the growth hormone (GH) secretagogue receptor (GHS-R), thereby acting as an integrator of appetite and anabolic factors. GH is a pleiotropic factor that mediates its effects either directly or indirectly via insulin-like growth factor-1 (IGF-1) and somatomedins. It combines direct lipolytic effects with anabolic effects on muscle, mainly mediated by IGF-1. In CHF and cardiac cachexia a secondary resistance to GH has been described. Interestingly, insulin resistance can also occur secondary to heart failure and both hormone resistances correlate with the severity of the disease. Insulin itself is a strong muscle anabolic factor and hence, an insulin-sensitizing treatment regime seems promising in cachexia.

The hypothalamus is the central area for the regulation of appetite (Figure 2). Stimulation of the lateral area of the hypothalamus causes eating, stimulation of the medial part yields cessation of eating (Ganong 1999). Numerous mediators take part in controlling these centres in the hypothalamus. Excessive fluctuations in feeding cause weight and body composition changes which may develop into medical conditions or disease. Whilst we are encountering an obesity epidemic in both developed and developing countries (Wang & Beydoun, 2007, Prentice, 2006), countries in the so-called third world still have to fight malnutrition and starvation (Muller & Krawinkel, 2005). Nonetheless, body wasting and cachexia accompany a variety of chronic diseases, and due to a significant proportion of affected people worldwide we can regard it as an important public health issue (Kalantar-Zadeh et al., 2007).
Cachexia of chronic illnesses shares several nutritional features. Especially patients with cardiac cachexia experience appetite problems and alterations in food intake, malabsorption of nutrients, metabolic disturbances, and finally an anabolic/catabolic imbalance (see below) (von Haehling et al., 2007b). Malnourishment due to lack of appetite can occur in a variety of chronic diseases and as many as half of the patients can be affected. Hormonal regulation of appetite is still not completely understood, and one of the potential triggers to cause „false satiety“ (i.e. satiety without adequate food intake) might be one or more members of the family of pro-inflammatory cytokines (Inui, 1999). Disturbances in energy expenditure can contribute to anorexia-mediated body wasting and eventually to cachexia. Therefore, it is a key element in treating chronic illnesses that such patients receive adequate nutrition in order to prevent further development of the disease, to avoid potential side effects of treatment, and to recover from a state of deterioration (Laviano et al., 2005).

1. Neuropeptide Y

Neuropeptide Y (NPY) is a neurotransmitter and -modulator in the central and peripheral nervous system, which was originally discovered in 1982 (Table 2, Figure 2) (Tatemoto et al., 1982, Krysiak et al., 1999). This 36-amino acid peptide with a molecular weight of 10.8 kDa is stored mainly in the hypothalamus, which is believed to be the central site of appetite regulation (Williams et al., 2004). NPY is a potent stimulator of food intake, i.e. it is orexigenic. It is presumed that NPY plays a central role in appetite regulation.
NPY excretion from the hypothalamus increases during fasting and exercise, two stimuli of the NPY-ergic arcuate-paraventricular nucleus. NPY secretion results in increased appetite, increased parasympathetic activity, and induction of corticotropin-releasing factor, which yields release of adrenocorticotropic hormone and cortisol. Sympathetic activity and energy expenditure, on the other hand, are being suppressed. Additionally, the NPY pathway is suppressed by insulin and the adipocyte-derived polypeptide leptin (see below) (Kokot & Ficek, 1999).

Circulating NPY originates predominantly from the sympatho-adrenomedullary nervous system, because only small amounts of the peptide cross the blood–brain barrier. NPY is co-released with norepinephrine, and it has a vasoconstrictive and mitogenic effect on blood vessels (Zukowska-Grojec et al., 1998). A study in 30 patients with CHF and 16 healthy controls demonstrated elevated plasma levels of NPY in the subset of patients with CHF (p<0.01) (Feng et al., 2000). Although vasoconstriction is an effect of endogenous NPY, intravenous infusion of the peptide had no haemodynamic effect in 7 healthy volunteers (Ullman et al., 2002).

2. Leptin

Leptin (Greek: leptos – lean) was the first adipocyte-derived hormone to be discovered (Houseknecht et al., 1998), and its identification surmounted the paradigm that fat tissue merely serves as an energy depot (Table 2, Figure 2). Leptin is a 16 kDa protein hormone, which is was identified only about a
decade ago. It is encoded by the ob (obese) gene. This gene is responsible for the development of obesity in the ob/ob mouse (Zhang et al., 1994). Leptin belongs to a subfamily encompassing growth hormone, leukemia inhibiting factors, erythropoietin, and interleukins (Gaucher et al., 2003). In the blood stream, it circulates either free or protein bound, it can cross the blood-brain barrier, and acts through the leptin receptor. One of five isoforms, the OBRb, is primarily expressed in the hypothalamus but it can be found in several peripheral tissues such as skeletal muscle, heart, lung, kidney, liver, pancreas, adrenal gland, and in adipocytes. Thus, in addition to its main action on food intake and energy homeostasis regulation through direct inhibition of NPY, it may have important peripheral actions as well (Tartaglia et al., 1995, Lee et al., 1996, Emilsson et al., 1996). These would include interaction with several metabolic and hormonal pathways, e.g. lipogenesis in adipose tissue, growth hormone signaling, and insulin sensitivity (Doehner et al., 2002b, Doehner et al., 2001). Together with another fat tissue hormone, adiponectin, it sensitizes peripheral tissues to insulin (Ronti et al., 2006).

Leptin release is directly proportional to the amount of body fat tissue and exerts an inhibitory effect on food intake whilst increasing energy expenditure by means of increased thermogenesis and physical activity. It is a key regulator of food intake and energy homeostasis. Considering body composition in men and women, it is not surprising that leptin serum levels are higher in the latter (Kennedy et al., 1997). Leptin levels decline during body fat deprivation, whilst the opposite applies during periods of increases in body weight. Indeed, it has been shown that a 10% reduction in body weight
led to a 53% reduction in serum leptin whereas a 10% body weight increase caused a 300% increase in serum leptin (Considine et al., 1996).

Leptin effects on body metabolism are mediated by multifactorial means. These include insulin, glucocorticoids, catecholamines, and in particular the melanocortin system. Indeed, leptin activates pro-opiolanocortin (POMC) cells, which triggers the release of α-melanocyte stimulating hormone. This, in turn, activates the type 4 melanocortin receptor. The activation of this receptor eventually leads to the suppression of food intake and increases in energy expenditure. On the other hand, leptin suppresses the arcuate nucleus NPY/agouti-related protein neurons. These would otherwise antagonize the α-melanocyte stimulating hormone actions (Horvath, 2005, Cone, 2005). Additionally, both systems are targeted by several peripheral metabolic signals including insulin, glucose, ghrelin, and peptide YY (Schwartz & Morton, 2002, Cowley et al., 2001).

The association between body fat content and serum leptin levels appears to be preserved in patients with CHF (Toth et al., 1997a). Indeed, several studies have reported lower serum leptin in cachectic patients with CHF who have lower body fat content than non-cachectic patients (Doehner et al., 2001, Filippatos et al., 2000). Yet, the interpretation might not be entirely straightforward as another study reported normal leptin levels in patients with CHF when compared to controls (Toth et al., 1997b). Scrutinizing the methodology and results of various leptin studies, it seems important to normalize leptin for body fat content, which primarily refers to sex differences
and the cachectic sub-population (Doehner & Anker, 2000). Once the results had been normalized for body fat content, both cachectic and non-cachectic patients with CHF had increased levels of serum leptin (Doehner et al., 2002b). Importantly, leptin levels are comparable in cachectic and non-cachectic patients with CHF when analyzed in this way. This argues against the important contributing role of reduced appetite and consequently insufficient food intake in the development of cardiac cachexia. Another important factor to be considered are several metabolic perturbations, which are present in patients with CHF. Of these, insulin resistance is well described and could lead to hyperleptinemia [Tsutamoto et al., 1998, Leyva et al., 1998]. Recently, a comparison of carvedilol- and bisoprolol-mediated effects on body weight, leptin and insulin, had been reported (Kovacic et al., 2008). Interestingly, it was noted that among 26 non-cachectic beta-blocker naïve patients with CHF who were randomized to carvedilol or bisoprolol treatment, plasma leptin concentration increased only in the group treated with carvedilol (mean change +4.2 ng/ml, p=0.019 vs. baseline). It seems that increases in leptin in non-cachectic patients with CHF are primarily driven by increases in body weight.

3. Melanocortins

Melanocortins are peptides, derived after cleavage of pro-opiomelanocortin. To date, 3 melanocortin stimulating hormones (α-, β-, and γ-MSH) have been described (Table 2). They primarily stimulate the melanogenesis and/or steroidogenesis in melanocytes and adrenal cortical cells, respectively. Due
to their specific structure, melanocortins can bind and activate 5 different melanocortin receptors (Coll, 2007). Food intake and energy expenditure are mainly regulated through melanocortin 4 receptors (MC4R), which are widely distributed within the central nervous system, including the hypothalamus, the thalamus, and the spinal cord (Mountjoy et al., 1994). The strongest ligand for MC4R is α-MSH, whilst β-MSH has been proposed as the most important ligand for control of food intake and energy expenditure homeostasis (Biebermann et al., 2006).

Loss of normal melanocortin signaling leads to obesity. In humans, this may be due to deficiency in POMC or MC4R. A report of 2 patients with congenital lack of the POMC gene dates back to 1998 (Krude et al., 1998). These patients developed severe early-onset obesity associated with hyperphagia. Two reports on heterozygous MC4R mutations, associated with dominantly inherited obesity were published in the same year (Yeo et al., 1998, Vaisse et al., 1998). The overactivity of this system, on the other hand, would lead to energy wasting (Sharma et al., 2005a). Evidence is mounting that an increased melanocortin activity plays a role in the pathogenesis of cachexia. This appears to be mainly due to an increased production of systemic pro-inflammatory cytokines (Inui, 1999). Thus, the melanocortin system may directly generate symptoms of cachexia, and treatment with antagonists of the system is a logical next step from a pathophysiological point of view. Indeed, several reports evaluated the effectiveness of MC4R antagonists in animal models of cachexia. In cancer or renal failure, these antagonists were shown to improve food intake and lean body mass. To date, no data on the human
application have been published but this approach seems feasible for cachexia in chronic disease (DeBoer, 2007).

4. Ghrelin

Ghrelin, originally identified in 1999 (Kojima et al., 1999) and structurally related to motilin, is a highly conserved 12.9 kDa peptide containing 28 amino acids (Table 2, Figure 2). Like its receptor, it has been localized to chromosome 3 (Smith et al., 1997). The promotor region contains binding sites for several transcription factors including NF-κB as well as oestrogen and glucocorticoid response elements (Kishimoto et al., 2003). Ghrelin is mainly produced in the fundus region of the stomach (Date et al., 2000), but it is also expressed in other organs, including the duodenum, jejunum, ileum, colon (with gradually decreasing expression), where it promotes gastric motility (Date et al., 2000). It is also found in the pancreas (Date et al., 2002), in the arcuate nucleus of the hypothalamus, in the kidneys (Mori et al., 2000), and the placenta (Gualillo et al., 2001).

The ghrelin peptide is present in two forms - the active, acylated form and the inactive form. Both are found in significant amounts in stomach and blood (Hosoda et al., 2000), where they are bound to high density lipoprotein (Beaumont et al., 2003). Active ghrelin binds to the growth hormone secretagogue receptor (GHS-R), a typical g-protein coupled receptor with 7 transmembrane domains (Howard et al., 1996, McKee et al., 1997). Physiologically, ghrelin induc

Physiologically, ghrelin induc
appetite, and has anti-inflammatory properties. Growth hormone is released in a dose-dependent manner from pituitary gland upon binding of ghrelin to the GHS-R (Kojima et al., 1999). In humans, high doses of ghrelin also increase the levels of adrenocorticotropic hormone, prolactin and cortisol (Arvat et al., 2001).

Ghrelin expressing neurons are found in the arcuate nucleus in the hypothalamus, a region that is involved in the regulation of appetite (see above) (Kojima et al., 1999). These neurons have direct contact to neurons containing NPY, agouti-related protein (AgRP), and POMC (Figure 2) (Cowley et al., 2003). Hence, ghrelin is likely to exert its effect on feeding by stimulating the release of NPY and AgRP (Chen et al., 2004), while reducing the release of POMC (Cowley et al., 2003). Interestingly, ghrelin injected into the periphery is able to stimulate the hypothalamus (Hewson & Dickson, 2000) and food intake (Wren et al., 2001), although peptides generally do not pass the blood brain barrier. However, the ghrelin signal may reach the hypothalamus via afferent nerve fibers of the vagus (Sakata et al., 2003), which among other target areas project to the stomach and bowel.

GHS-R mRNA has been found in numerous tissues including fat tissue, muscle, bowel, heart, pancreas, liver, kidney, spleen, lymph nodes, thyroid and human lymphocytes (Gnanapavan et al., 2002). Specifically, it is found in T and B cells, as well as monocytes (Hattori et al., 2001, Dixit et al., 2004). Ghrelin has been shown to inhibit the expression of pro-inflammatory cytokines in a time- and dose-dependent fashion (Dixit et al., 2004), and
reduced proliferation of murine anti-CD3 activated T cells has been described (Xia et al., 2004). Moreover, ghrelin was shown to inhibit pro-inflammatory responses in human endothelial cells (Li et al., 2004) and to down-regulate the circulating level of pro-inflammatory cytokines in a rat model of endotoxaemia (Chang et al., 2003). The mechanism of this anti-inflammatory action of ghrelin has not completely been defined, although activation of the vagus may be involved (Wu et al., 2007).

Ghrelin-levels have been shown to be elevated in the plasma of cachectic heart failure patients compared to non-cachectic CHF patients, where the ghrelin plasma levels correlated with plasma levels of growth hormone and TNF-α (Nagaya et al., 2001a). A small, uncontrolled study of intravenous infusion of ghrelin in 10 patients with CHF, predominantly cachectic patients in NYHA class III, showed promising cardiovascular results (Nagaya et al., 2004). Patients were treated with 2 µg/kg of body weight for 30 min twice daily for 3 weeks, which increased food intake and lean body mass, as well as LVEF (p<0.05). Interestingly, plasma levels of B-type natriuretic peptide decreased over the 3 week treatment period (Nagaya et al., 2004). Similar results regarding heart function, body weight and body composition have been described in animal models of heart failure (Nagaya et al., 2001b). Currently, several trials aim to reproduce these data in a double-blind, placebo-controlled fashion.

5. Growth hormone
Growth hormone (GH) is a 191 amino acid peptide hormone with anabolic effects that is also involved in the regulation of energy stores during various types of stress (Table 2). GH exerts pleitropic effects, which may be direct or mediated by insulin-like growth factor-1 (IGF-1) and somatomedins (Ho et al., 1996). It is the most abundant pituitary gland hormone, which continues to be produced after cessation of childhood growth. Thus, it affects body metabolism throughout the lifespan. Direct actions of GH include glucose, lipid, and sodium metabolism. GH causes hyperinsulinaemia with an impaired ability of insulin to suppress hepatic glucose production. Direct lipolytic effects are mediated through enhanced fat utilisation. In patients with acromegaly, increased lipolysis and fat oxidation are clinically evident as reduced fat mass. Sodium retention occurs partly through activation of the renin-angiotensin-aldosteron system. Thus, GH plays a significant role in the regulation of substrate metabolism and body composition in man.

Anabolic effects of GH are mediated through activation of the somatomedins and mainly through IGF-1. In states of GH deficiency, treatment with the hormone can reverse the reduction in lean body mass. This occurs chiefly through stimulation of protein synthesis and reduction in protein oxidation. Protein breakdown is apparently not affected. The main site of IGF-1 synthesis is the liver but peripheral tissues are also capable of its production (Underwood & Van Wyk, 1992). Interestingly, the concentration of IGF-1 increases after GH or testosterone challenge. This causes an increase in muscle protein synthesis (Tirapegui, 1999). Malnourishment and even an overnight fast cause a marked increase in circulating IGF-1 levels. However,
there is little evidence suggesting that refeeding restores IGF-1 to normal
values (Giovannucci et al., 2003).

Findings in patients with CHF suggest a state of acquired GH resistance (high
GH and low IGF-1 values), which is shared with a plethora of catabolic
diseases including surgery, trauma, sepsis, cancer, uraemia, chronic
obstructive pulmonary disease, and chronic liver disease (Cicoira et al.,
2003). A 3-fold increase in GH levels has been noted in cachectic patients
with CHF compared to non-cachectic patients with CHF and healthy subjects
(Morley et al., 2006). IGF-1 levels, on the other hand, are reduced, in
particular in patients with cachexia (Anker et al., 2001). Although treatment of
body wasting associated with CHF due to dilated cardiomyopathy seemed
plausible, the results of individual trials were disappointing (Osterziel et al.,
1998, Frustaci et al., 1996, Isgaard et al., 1998). This may be due to GH
resistance in general or due to a lack of response in individual patients. In
order to overcome GH resistance, several options have emerged. The most
simple one is to increase dosing regimens. Alternatively, the response to a
test dose may be warranted in individual patients or the combination of GH
with IGF-1 could be tried. Since no studies into the effects of GH treatment
are ongoing, we are currently left without such options in treating cachexia.

6. Insulin

Insulin is a peptide hormone composed of 51 amino acids with a molecular
weight of 5,808 Da (Table 2, Figure 2). It is produced within the Langerhans
Islets of in the pancreas and has several major functions in the organism. Its pivotal role in the regulation of body composition is often neglected as are its functions as a regulator of energy flux and substrate utilization and anabolism.

In the setting of CHF, disturbed metabolic pathways were reported more than a decade ago (Swan et al., 1994). Overt diabetes mellitus is a common co-morbidity, and the Euroheart Failure Surey reported an incidence as high as 27% (Cleland et al., 2003). As insulin and glucose metabolism are impaired long before the clinical presentation of diabetes mellitus, the true incidence may be much higher. Indeed, sub-clinical impairment of glucose metabolism has been reported for 43% of patients with CHF (Suskin et al., 2000). It is also well established that diabetes mellitus is an important risk factor for the development of CHF (Iribarren et al., 2001).

It is important to know that insulin resistance may also occur secondary to CHF, and it correlates with the severity of the condition (Swan et al., 1997). A study in 41 patients and 21 healthy control subjects assessed insulin sensitivity by intravenous glucose tolerance testing and total and regional body fat mass by DEXA scan (Doehner et al., 2002b). Interstingly, insulin sensitivity was reduced by 31% in patients with CHF compared to controls (p<0.01), and fasting insulin levels were higher in patients than in controls (p<0.01). Serum leptin levels were also higher in patients with CHF than in controls (p<0.01), even after correction for body fat content. There was an inverse correlation between insulin sensitivity and serum leptin (r=-0.65, p<0.0001 for pooled subjects). Serum leptin levels remained the only
independent predictor of insulin resistance (Doehner et al., 2002b). Moreover, a recent study identified insulin resistance as a prognosticator in patients with CHF independently of previously established prognosticators (Doehner et al., 2005). Mechanisms that cause insulin resistance in patients with CHF are not entirely understood. It seems that neurohormonal activation, overactivity of the immune system, metabolic disturbances, and hormonal imbalance all play a role. Eventually, all insulin actions are impaired, including its anabolic effects.

Pathophysiological mechanisms suggest insulin resistance as a potential treatment target, in particular when body wasting and cachexia are involved. Insulin sensitizers might be a plausible option. Selective agonists for the peroxisome proliferators activated receptor-\(\gamma\) or thiazolidinediones are another emerging option, which is already being tested in clinical settings. They modulate genes involved in glucose and lipid metabolism and improve insulin resistance. In a retrospective survey of 1,868 diabetics and 1,868 matched controls, pioglitazone treatment was associated with 50% less risk (hazard ratio 0.50, 95% confidence interval 0.33-0.76) to develop CHF (Rajagopalan et al., 2004). However, in patients with CHF there is an important caveat due to fluid retention and thiazolidinediones may not be ready for the prime time use (Macfarlane et al., 2006). In view of animal studies that suggest amiloride to counteract the weight gain effect (Guan et al., 2005) and reports of safety as well as prognostic benefit (Dargie et al., 2007, Masoudi et al., 2005) the current approach may change in the future.
V. MECHANISMS OF WASTING IN DIFFERENT BODY COMPARTMENTS

BRIEF SUMMARY
This section gives an overview of the wasting process seen in cardiac cachexia, which does not only involve lean tissue, i.e. skeletal muscle, but also fat tissue and bone. Skeletal muscle is lost due to an imbalance of protein synthesis and proteolysis. Typically pro-inflammatory cytokines induce the proteolytic systems, while simultaneously reducing the anabolic IGF-1 signaling. Lean body mass depletion is one of the major characteristics of cachexia. Indeed, up to 68% of patients with CHF have evidence of muscle atrophy (Mancini et al., 1992). Additionally myostatin, a negative regulator of muscle mass, is considered to be a key player, as it has been reported as up-regulated in HIV cachexia and sarcopenia. Later in the course of the disease, wasting of bone and fat mass is found. Fat wasting can be induced by numerous agents and the rate limiting step is the hormone sensitive lipase that can be activated by several receptors including β-adrenergic and natriuretic peptides receptors. The bone density in patients with cardiac cachexia is lower, and lower calcium and vitamin D levels have been reported, although no mechanisms have been identified so far. These alterations in body composition have their reasons in profound metabolic perturbations, which are initially meant to isolate and neutralize the insult that caused the heart to fail. However, at a later stage, they contribute to the development and the progression of cardiac cachexia.
1. Body composition

A study in 36 non-cachectic patients with stable CHF, 18 patients with cardiac cachexia, and 15 healthy controls found significant differences in body composition (Anker et al., 1999b). Non-cachectic CHF patients displayed reduced lean tissue in the legs as compared to healthy subjects (-9%, p<0.01). Cachectic patients had significantly reduced lean (-20% vs. non-cachectic CHF, -21% vs. control), fat (-37% vs. non-cachectic CHF, -33% vs. control), and bone tissue (-16% vs. non-cachectic CHF, -18% vs. control) as compared to both non-cachectic patients and controls (all p<0.0001) (Anker et al., 1999b). Genuine osteoporosis has also been observed in advanced stages of the diseases (Lee et al., 1994). However, the major site of protein loss has been observed in skeletal muscle (McMillan et al., 1994). Lundholm et al. studied muscle biopsies from 43 patients with newly diagnosed cancer and a history of weight loss. They found an increased rate of muscle protein degradation and a reduction in the rate of protein synthesis (Lundholm et al., 1976). Another study compared overall protein synthesis using a tracer infusion of leucine labelled with a stable isotope in five patients with cancer and a history of weight loss and seven healthy controls (Emery et al., 1984). Protein synthesis was significantly reduced in patients with cancer as compared to control subjects (p<0.01). Interestingly, the whole body rate of protein synthesis and degradation did not differ between the two groups (Emery et al., 1984). This might be due to an increase in non-skeletal muscle protein synthesis, for example hepatic release of acute phase reactants (Tisdale, 1997). Unfortunately, the cellular mechanisms are not well defined,
a fact that makes therapeutic interventions rather difficult.

2. Muscle

Mechanisms of Proteolysis

All tissues possess at least five different proteolytic pathways. These pathways are maintained by proteases, *i.e.* enzymes that catalyze the breakdown of proteins by hydrolysis of peptide bonds. At least 500-600 proteases have been identified in man. The main proteolytic pathways are the lysosomal (cathepsins) and the calcium-dependent (calpains) pathways, the caspase system, matrix metalloproteinases, and the adenosine triphosphate-dependent ubiquitin-proteasome system (Figure 3). The latter plays the predominant role in the breakdown of myofibrillar protein (Mitch & Goldberg, 1996), however, it is not able to degrade intact myofibrils. The other pathways have also been implicated in this process, but their impact appears to be less important. The beneficial effect of beta-adrenergic agonists in wasting, for example, appears to be mediated by impairment of muscle protein breakdown through the calpain system (Koohmaraie *et al.*, 1991, Sensky *et al.*, 1996). The significance of the ubiquitin-proteasome system in protein degradation, on the other hand, has been demonstrated *in vivo* in starvation (Wing & Goldberg, 1993), metabolic acidoses (Mitch *et al.*, 1994) and for cachexia in AIDS (Llovera *et al.*, 1998), sepsis (Tiao *et al.*, 1994, Garcia-Martinez *et al.*, 1994), cancer (Williams *et al.*, 1999), and renal failure (Bailey *et al.*, 1996).
The ubiquitin-proteasome system is activated by the NF-κB family of transcription factors in most, maybe even all catabolic states (Figure 3) (Cai et al., 2004, Jackman & Kandarian, 2004). In muscle, where all NF-κB family members are present (Hunter et al., 2002), chronic activation of the NF-κB dimer p50/p65 is associated with increased catabolism and subsequently skeletal muscle wasting as seen in cardiac cachexia (Bolger & Anker, 2000). In disuse atrophy, also present in heart failure, NF-κB again is a crucial factor for the breakdown of muscle fibers, but the NF-κB pathway that is activated seems to be distinct from that in cachexia. Using knock-out animals it was confirmed that p50 and Bcl-3 are required for atrophy (Hunter et al., 2006). The transcriptional active NF-κB dimers in atrophy are thought to consist of p50/c-Rel or a homodimer of p50 bound to Bcl-3 (Kandarian & Jackman, 2006).

The responsible activating factor for the NF-κB transcription factors are pro-inflammatory cytokines (Zamir et al., 1992, Zamir et al., 1993, Goodman, 1993) and reactive oxygen species (Ventadour & Attaix, 2006). Other factors that activate the ubiquitin-proteasome system include glucocorticoid hormones and myostatin. Insulin and insulin-like growth factor inhibit the system (Ventadour & Attaix, 2006). Ubiquitin serves as a cofactor that is covalently linked to proteins to be degraded in the 26S proteasome complex. Polyubiquitination requires a number of steps, which involve the action of three enzymes termed E1, E2, and E3. A small number of E2 and E3 enzymes were found to be overexpressed in several, but not all forms of
muscle wasting (Ventadour & Attaix, 2006). It is not fully understood how ubiquitin-binding to intracellular proteins is regulated, although Varshavsky reported that the half-life of a protein correlates with certain features of its N-terminal sequence (Varshavsky, 1997). The finding that protein degradation by the proteasome does not yield free amino acids but peptides, suggests that a number of other factors may also be important in the regulation of muscle protein breakdown (Hasselgren et al., 2002).

Myostatin

Another important consideration in wasting of muscle tissue is myostatin. Myostatin, also known as growth differentiation factor-8 (GDF-8) is a member of transforming growth factor-β superfamily, which was identified in 1997 (McPherron et al., 2001). Other members of the family have been identified as useful prognosticators in CHF (Kempf et al., 2007). In humans, myostatin is expressed almost exclusively in skeletal muscle and is essential for normal regulation of muscle mass. Normally, it inhibits myoblast proliferation and acts as a negative regulator of muscle bulk (Lee et al., 2001). Genetic myostatin deletions were reported to markedly increase muscle mass in animals and humans. Double muscled phenotype was initially reported in cattle (McPherron et al., 1997), followed by a fascinating case of extreme muscle hypertrophy in a child that was able to hold two 3 kg dumbbells at the age of 4 years (Schuelke et al., 2004).
Implications for a role of myostatin in the pathogenesis of cachexia are cumulating. In transgenic mice bearing the myostatin gene, cachexia features developed within 16 days (Zimmers et al., 2002). Treated animals had a 33% lower body weight and lost almost all of the white fat tissue when compared to control group. In humans, myostatin was determined in three different groups: healthy men and women aged 19-35 years, healthy men and women aged 60-75 years, and frail old women aged 76-92 years. A stepwise increase was reported, which was suggestive of sarcopenia (Yarasheski et al., 2002). Intriguing results were reported for human immunodeficiency virus (HIV) infected men with muscle wasting (Gonzalez-Cadavid et al., 1998). Again, the stepwise increase between healthy men vs. HIV-infected individuals without >10% weight loss vs. HIV-infected individuals with >10% weight loss had been documented. Additionally, skeletal muscle biopsies were performed that showed an increased intensity of 26 kDa myostatin related protein.

Cardiovascular studies with myostatin are generally lacking. However, two studies reported increased myostatin expression in the peri-infarct zone in sheep (Sharma et al., 1999) and in a rat model of volume overload (Shyu et al., 2006). Importantly, the expression remained increased after 4 weeks. To date, there are no studies that directly link myostatin to cardiac cachexia. Nonetheless, the evidence for association between myostatin and reduced skeletal mass is growing and a hypothesis on myostatin as a mediator of cardiac cachexia, insulin resistance, and osteoporosis in CHF was recently presented by Hoenig (Hoenig, 2008). Currently, clinical trials with the
myostatin modulator MYO-029 are ongoing and results on quality of life as well as prognosis are eagerly awaited.

3. Fat Tissue

Lipolysis is controlled mainly by the enzyme *hormone sensitive lipase*. It is chiefly activated by catecholamines via β-adrenoceptors (Holm, 2003). Fat cells are also sensitive to the effects of both atrial and B-type natriuretic peptides, which also activate lipolysis. Insulin is the main anti-lipolytic substance. Fat is stored in the form of triglycerides, which derive from circulating free fatty acids or from triglycerides in lipoproteins (Ryden & Arner, 2003). Loss of adipose tissue in patients with cachexia could be mediated by increased lipolysis or reduced lipogenesis (Ryden & Arner, 2003). Study data from patients with cancer cachexia point to the fact that the predominant mechanism is increased lipolysis. Indeed, fasting plasma glycerol levels, which reflect triglyceride breakdown, are higher in cancer patients with weight loss than in those without (Drott *et al.*, 1989, Zuijdgeest-van Leeuwen *et al.*, 2000). This has not been demonstrated in patients with cardiac cachexia or patients with CHF, however, it is tempting to speculate that increased levels of catecholamines and possibly natriuretic peptides may be responsible for the loss of adipose tissue that has been observed in such patients (Anker *et al.*, 1999b). TNFα, which is also over-expressed in both CHF (von Haehling *et al.*, 2004) and cardiac cachexia (Levine *et al.*, 1990), plays a major role in fat cell lipolysis and inhibiting insulin signalling. The latter is an important aspect in the development of insulin resistance.
4. Bone

Bone undergoes constant remodelling, i.e. a process of coordinated resorption and formation of skeletal tissue. The basic cellular components are osteoclasts and osteoblasts, the former being multinucleated bone-resorbing, the latter mononuclear bone-forming cells. Osteocytes are osteoblasts that have settled within the calcified bone matrix. They are responsible for identifying the sites of remodelling (Han et al., 2004). The assessment of markers of bone turnover can help in identifying patients at risk of fracture (Seibel, 2005). In osteoporosis, excess bone resorption is a consequence of an increase in osteoclast number or activity, or a decrease in osteoblast number or activity or a combination of the two (Canalis et al., 2007). Bone mineral density – expressed in grams per square centimeter – is an excellent predictor of fractures. Indeed, the relative risk of hip fracture is 2.6 for each 1 standard deviation decrease in bone mineral density at the hip (Marshall et al., 1996). In that context, osteopenia can be viewed as a pre-stage of osteoporosis, comparable to prehypertension, impaired fasting glucose, or borderline high cholesterol (Khosla & Melton, 2007).

Few studies have investigated alterations in bone mass in patients with CHF. Lee et al. studied 31 adult male cardiac transplant recipients and 14 adult men with CHF awaiting cardiac transplantation (Lee et al., 1994). Using DEXA scan they found that bone mineral density in the proximal femur was below normal in both groups compared to that in age-matched control
subjects. CHF patients had a trend toward elevations of parathyroid hormone, 1,25-dihydroxyvitamin D, and urinary calcium excretion compared to transplant patients. Eight of 31 transplant patients and 2 of 14 CHF patients presented with vertebral compression fractures ($p < 0.0006$) (Lee et al., 1994).

A study in 18 patients with cachectic CHF, 40 with non-cachectic CHF, and 16 control subjects demonstrated lower serum levels of calcium in both CHF groups compared to controls (Anker et al., 1999a). Bone mineral content and bone mineral density were lower in cachectic, but not non-cachectic patients than controls ($p<0.01$). No correlation between body composition and serum calcium, LVEF, peak oxygen consumption, or ventilatory response to exercise was found (Anker et al., 1994). An earlier study investigated markers of bone turnover in 101 patients with advanced CHF (NYHA class III-IV) (Shane et al., 1997). For this purpose, patients had parathyroid hormone, 1,25-dihydroxyvitamin D, serum osteocalcin, urinary hydroxyproline, and pyridinium crosslinks analysed. In addition, 91 of these patients were evaluated using DEXA scan. Osteoporosis was present in 7-19% (depending on the site of assessment), osteopenia in 42-47% of patients. Women were more severely affected ($p=0.007$). Low serum levels of 1,25-dihydroxyvitamin D ($\leq 15$ pg/ml) were found in 26% of patients, elevated serum levels of parathyroid hormone ($\geq 65$ pg/ml) in 30%. Low serum vitamin D metabolites were associated with biochemical evidence of increased bone turnover (Shane et al., 1997). Unfortunately, it is currently not possible to bring these findings together and to explain the mechanisms of bone wasting in cardiac cachexia. Future studies are warranted to investigate the findings in more detail.
VI. THERAPEUTIC APPROACHES TO CARDIAC CACHEXIA

BRIEF SUMMARY

There are currently no approved therapies to treat weight loss as such in cardiac cachexia. This section aims to give an overview of the different treatment strategies that might be pursued in preventing or treating loss of tissue. Some of these have been shown to provide benefit, as data from retrospective analyses show, some have even shown their efficacy in clinical studies. Others, however, may prove less effective although they have therapeutic appeal from a theoretical point of view. Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockers have both clinically shown their potential to delay and possibly prevent the onset of cardiac cachexia. Although feeding alone, the reversal of the clinically observed anorexia, does not reverse cachexia, nutrition itself still seems to be a major factor in treatment strategies. Often patients have deficiencies in micronutrients such as vitamins and a supplementation of branched-chain amino acids has shown to be beneficial. An overall induction of food intake to battle anorexia in these patients is considered supportive. Megestrol acetate has been shown to stop weight loss in hormone responsive cancer and has recently been approved for AIDS cachexia in the United States. The closely related compound, medroxyprogesterone acetate, has similar effects, but a trend towards peripheral oedema was observed. Cannabinoids are known inducers of food intake, but have clinically shown contradictory results. While positive effects
on appetite were seen in patients with AIDS and cancer, there was no concomitant weight gain. Also another study reported no improvement of appetite vs. placebo in a trial in patients with advanced cancer. The use of anabolic steroids in cachexia patients is limited to chronic obstructive pulmonary disease and AIDS, where positive effects on weight have been observed. In CHF, there was an improved cardiac function, but no effect on weight. Beta-adrenergic, especially $\beta_2$-adrenergic agonists are also known for their anabolic properties and have shown some beneficial effects in degenerative muscle diseases. Although short-lived, positive cardiac effects have been reported in CHF, but there was no improvement in the functional capacity of the patients. As cardiac cachexia represents a chronic inflammatory state, a lot of attention has been given to anti-inflammatory strategies. This includes (i) neutralizing antibodies like eternacept and infliximab, which showed a lack of efficiency in CHF, (ii) statins, which show beneficial pleiotropic effects like the reduction of pro-inflammatory cytokines in some settings and (iii) thalidomide, which potently reduces TNF\(\alpha\). The inhibition of the major proteolysis pathway, the ubiquitin-proteasome pathway is in its early stages and has so far only been tested in cancer, where weight gain has been reported. While pentoxifylline reduced the activity of muscle proteolytic systems in a rat model of cancer cachexia, it failed to improve weight in patients with cancer cachexia.

1. Prevention of Weight Loss
Angiotensin-Converting Enzyme Inhibitors

The development of angiotensin-converting enzyme (ACE) inhibitors started in the late 1960s with the finding that some peptides from the venom of the Brazilian snake Bothrops Jararaca inhibited the enzyme ACE. This led to the development of captopril, which was introduced into the market in 1979 (von Haehling et al., 2005d). This substance was initially approved for the treatment of hypertension but it soon emerged that ACE inhibitors exert cardioprotective effects that go far beyond simple blood pressure control (Figure 4). Indeed, these substances improve endothelial dysfunction and reduce or even normalize left ventricular hypertrophy. One longitudinal study found that ACE inhibitors induced a decrease of 40% in left ventricular mass during three years of follow-up (Franz et al., 1998). Additionally, ACE inhibitors have been implicated in the improvement of insulin resistance (Paolisso et al., 1995). A substudy of the randomized, placebo-controlled HOPE trial (Heart Outcomes Prevention Evaluation) has demonstrated that ramipril can delay new-onset of diabetes among high-risk patients with established vascular disease (Yusuf et al., 2001). Indeed, among those who received placebo (n=2883), a total of 155 patients (5.4%) developed new-onset diabetes during 4.5 years of follow-up as compared to 102 patients (3.6%, p<0.001) who received ramipril (n=2837).

A number of retrospective analyses have shown that ACE inhibitors may exert beneficial effects in that they prevent or delay the risk of weight loss in patients with CHF. A substudy from the SOLVD database showed that 817 of
1,929 patients had a weight loss of ≥5% during follow-up (Anker et al., 2003c). Treatment with enalapril at a dose of 20 mg once daily significantly reduced the risk of weight loss greater or equal to 6% compared to placebo (adjusted reduction 19%, p=0.0054). This is in line with results from animal models and in vitro studies. Indeed, exposure of murine myotubes to angiotensin I resulted in an increased proteasome activity (Sanders et al., 2005). Addition of the ACE inhibitor imidapril attenuated the effect confirming that it evolved only after conversion of angiotensin I to angiotensin II. However, these data indicate that angiotensin II may induce protein degradation by the proteasome (Sanders et al., 2005). Moreover, imidapril at a dose of 10 mg/kg of bodyweight three times daily attenuated the development of weight loss in mice bearing the MAC16 tumour compared to control animals (p<0.001) (Figure 5) (Sanders et al., 2005). The new, highly lipophilic ACE inhibitor imidapril is currently under investigation in a phase III, multicentre, randomized, placebo-controlled, double-blind study in patients with cachexia caused by gastrointestinal cancer (von Haehling et al., 2005d).

**Beta-Blockers**

The beta-blockers metoprolol, bisoprolol, and carvedilol have become part of CHF treatment guidelines now over a decade ago. The most recent addition is nebivolol, which was shown to have favourable effects in elderly patients with CHF (Flather et al., 2005). Indeed, the drug reduced the risk of death or cardiovascular hospitalization in these patients. In addition to their effects on survival, beta-blockers may exert beneficial effects on weight development.
This effect might be explained by the inhibition of catecholamine-induced lipolysis (Langin, 2006), by decreased resting energy expenditure, and decreased insulin sensitivity (Lamont et al., 2000). Additional effects have been reported in patients with severe burns, in whom beta-blockers have been shown to reverse excess protein catabolism. Indeed, Herndon et al. studied 25 children with burns >40% of total body surface area in a randomized trial (Herndon et al., 2001). Thirteen patients received propranolol for at least 2 weeks, and 12 children served as a control group. Propranolol treatment yielded a decrease in resting energy expenditure as compared with baseline (p=0.01) and as compared with the values in the control group (p=0.001). Whilst net muscle-protein balance increased by 82% over baseline values in the propranolol group (p=0.002), it decreased by 27% in the control group. The fat-free mass, as measured by whole-body potassium scanning, did not change substantially in the propranolol group, whereas it decreased by a mean of 9±2 percent in the control group (p=0.003) (Herndon et al., 2001). In addition to these effects, it has been observed in an animal model that beta-blockers may mediate an increase in skeletal muscle mass (Rehfeldt et al., 1994).

These data may explain the findings from retrospective analyses of large trials in CHF. A subanalysis of the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) database showed that carvedilol-treated patients showed a significant increase in weight compared to placebo-treated patients (Anker et al., 2002a). At four months of follow-up, mean changes in weight in the carvedilol vs. the placebo group were +0.5 kg vs. −0.1 kg.
(p=0.0002), at eight months +0.9 kg vs. –0.1 kg (p<0.0001), and at 12 months +1.1 kg vs. +0.2 kg (p<0.0001). These results were confirmed by data from the CIBIS II-study (Cardiac Insufficiency Bisoprolol Study). In this large-scale study, bisoprolol at a target dose of 10 mg once daily showed that it prevents or delays the risk of weight loss in patients with CHF (Anker et al., 2003b).

Like with carvedilol, patients on bisoprolol showed a significant increase in weight after 15 weeks (bisoprolol: +0.2 kg, placebo: -0.2 kg, p=0.0018), 12 months (bisoprolol: +0.8 kg, placebo: -0.04 kg, p<0.0001), and 24 months (bisoprolol: +1.2 kg, placebo: +0.03 kg, p=0.0041). This effect appears to be due to an increase in body fat mass. Indeed, a small prospective study found increases in body fat content with beta-blocker therapy (Lainscak et al., 2006). Total fat mass increased in 28 of 41 patients. At baseline, 16 of 41 patients were already on a beta-blocker; all other patients were started on such a drug during the study. After a follow-up of 263±106 days, there was a median increase in body fat mass of +0.89 kg. However, no significant change in body weight, body mass index, or body water was observed (Lainscak et al., 2006). The sample size might have been too small to detect such differences. Hryniewicz and colleagues studied 27 patients with CHF before and after 6 months of beta-blocker therapy, 13 of whom were termed cachectic (Hryniewicz et al., 2003). Interestingly, 6 months of beta-blocker therapy yielded a significantly greater weight gain in these patients than in the non-cachectic patients (+5.2±9.6 vs. +0.8±5.0 kg, p=0.027).

2. Nutrition
As noted earlier, it is a common misconception that reduced appetite triggers the development of a wasting process. However, patients with CHF are prone to reduced appetite and reduced food intake (Gibbs et al., 2000). The reasons are not well established but include changes in taste and smell, dietary advice on salt and calorie intake, social isolation, derangements in bowel perfusion, and an altered intestinal barrier (Sandek et al., 2007). These alterations are likely to cause both deficiencies in micronutrients and macronutrients. Such deficiencies fuel the wasting process once it is starting to become manifest. The above mentioned hormonal derangements likewise add insult to injury. Large-scale studies on appetite and food-intake in CHF are not available. Since both the intake of micronutrients and macronutrients may be affected in patients with CHF and those with cardiac cachexia, it may be necessary to optimize food intake of all components that are affected. This, however, is not always possible, and clinical guidelines on this issue for patients with CHF are missing. Some general rules, however, appear to apply for patients with CHF as for those with cardiac cachexia.

A diet high in sodium is generally viewed as potentially harmful in CHF, as it may cause fluid overload and consequently acute decompensation. Rare cases of micronutrient deficiency as a cause of CHF have been reported for selenium and thiamine (vitamin B₁) (Witte et al., 2001). One study suggests that thiamine supplementation per se may improve cardiac function (Shimon et al., 1995). Low levels of selenium have been reported in patients with CHF. In a study in 21 patients with CHF (NYHA class II-III, mean LVEF 29±6%), baseline selenium levels were approximately 20% lower than those
in healthy control subjects (p=0.0004) (de Lorgeril et al., 2001). Lower levels of copper and zinc were also reported in this study (both p<0.05) (de Lorgeril et al., 2001).

Patients with CHF are usually receiving loop diuretics which increase urinary excretion of micronutrients. This affects, for example, magnesium and calcium (Witte et al., 2001). Witte et al. performed a placebo-controlled, randomized, double-blind study of multiple micronutrient supplementation in 30 patients with CHF (Witte et al., 2005). Patients received capsules containing thiamine (daily dose: 200 mg), vitamins C (500 mg) and E (400 mg), magnesium (150 mg), selenium (50 μg), zinc (15 mg), co-enzyme Q10 (150 mg), and various other substances. Interestingly, 9 months of treatment yielded an improvement in LVEF by 5.3±1.4% in the micronutrient group (p<0.05 vs. placebo). It is not clear how this effect had been mediated but it may be that a reduction in oxidative stress took place. Indeed, many micronutrients can scavenge free radicals (Witte et al., 2002). This may ensue through direct action as with vitamins C and E or through indirect action. In agreement with this, vitamin C has also been shown to improve endothelial dysfunction.

As discussed above, wasting takes place not only in muscle tissue but also in fat and bone. This has led Laviano et al. to state that cachexia implies that “all you can eat is yourself” (Laviano et al., 2005). Indeed, breakdown of the body’s own muscle protein is of paramount importance. The constituent amino acids are the only molecules capable of being transformed into all 3
macronutrients, *i.e.* protein, carbohydrate, and fat (Lennie, 2006). Therefore, amino acid supplementation has been studied in some clinical settings, and some models indicate that patients with CHF require a greater amount of protein than healthy adults of the same age (Lennie, 2006). Thus, the current dietary reference of 0.8 g protein per kg of body weight may be too low for patients with CHF and those with cardiac cachexia (Lennie, 2006).

Low plasma levels of glutamine were found in critically ill patients and patients with chronic illness associated with muscle wasting (Oudemans-van Straaten *et al.*, 2001, Schols *et al.*, 1993). After 4 weeks of treatment with glutamine, a non-essential amino acid that is involved in cellular integrity and immune function, patients with cancer cachexia gained 0.95±0.66 kg compared to control subjects who lost 0.26±0.78 kg (May *et al.*, 2002). This change was due to a significant increase in fat-free mass in the active treatment group (+1.12±0.68 kg vs -1.34±0.78 kg, p=0.02). Patients in the active treatment group received not only glutamine, but a mixture of β-hydroxy-β-methylbutyrate (3 g/day), L-arginine (14 g/day), and L-glutamine (14 g/day). Patients in the control group received a mixture of non-essential amino acids in double-blind fashion.

Branched-chain amino acids, namely leucine, isoleucine, and valine, have been suggested as a useful supplementation in the treatment of cachexia (Laviano *et al.*, 2005), as they may exert anabolic effects by promoting protein synthesis and by inhibiting proteolysis. This effect appears to be most potently exerted by leucine (Buse & Reid, 1975). Stein *et al.* investigated the effect of
amino acid supplementation during a 14-day period of bed-rest (Stein et al., 2003). Prolonged bed-rest is known to cause protein loss from weight-bearing muscle. Healthy volunteers received either a supplementation with the 3 branched-chain amino acids (30 mmol/day each) or a mixture of non-essential amino acids (glycine, serine, and alanine, 30 mmol/day each). The concentration of free amino acids in muscle biopsies was greater in patients who received branched-chain amino acid during bed rest as compared to the control group (p<0.05) (Stein et al., 2003). Nitrogen retention, which reflects the body’s protein pool, was greater in the branched-chain amino acid treated group (p<0.05) (Stein et al., 2003). Supplementation of any amino acid is certainly not beneficial. Homocysteine, for example, is known to possess negative inotropic properties (Kennedy et al., 2004). In patients with CHF, high levels of homocysteine were found in association with low levels of vitamins B₆, B₉ (folate), B₁₂, and magnesium. Indeed, a correlation has been shown between circulating homocysteine levels and certain vitamins, because homocysteine degradation is dependent on the presence of vitamins B₆, B₉, and B₁₂ (Herrmann et al., 2006). Gorelik et al. have shown that the intake of vitamin B₉ did not reach the recommended daily amount (400 µg) in 57 patients with CHF who were hospitalized and 40 healthy controls (Gorelik et al., 2003).

The use of n-3 polyunsaturated fatty acids derived from fish oil has been studied in a canine model of heart failure (Freeman et al., 1998). A total of 28 dogs, 15 of which were cachectic, were fed fish oil supplement or placebo for
eight weeks. Interestingly, active treatment decreased plasma levels of IL-1 (p=0.02) and improved cachexia (p=0.01) compared to the placebo group.

As an alternative to the supplementation of single substances, Rozentryt et al. studied the effects of enteral support in a small, randomized, placebo-controlled study in 29 patients with cardiac cachexia (Rozentryt et al., 2005). Patients were randomized in a 3:1 fashion to either enteral support (600 kcal daily in addition to their normal diet) or placebo for 6 weeks. After an additional 12 weeks of follow-up, weight increased from 63.4±10 kg at baseline to 66.0±11 kg (p=0.001). Moreover, there were increases in 6-minute walking distance (before: 366±108 m, after: 433±106 m, p=0.02) and total fat mass (before: 15.5±3 kg, after 17.2±4 kg, p=0.007).

**Nutritional Considerations**

Guidelines are divergent considering the sodium intake. However, the daily sodium intake should be restricted to 2 g in all patients with advanced CHF or cardiac cachexia (Gibbs et al., 2000). Thus, in these patients, all food rich in salt should be avoided. This is particularly true for cheese, sausages, crisps, tinned soup and vegetables, ham, bacon, tinned meat, and tinned or smoked fish (Gibbs et al., 2000). In the EuroHeart Failure survey, the recall of advice on reduction of salt intake and implementation by patients in everyday life was, however, rather disappointing as only 58% of patients reported to receive the advice and 36% of patients reported to follow the advice to decrease the salt Intake (Lainscak et al., 2007). Prolonged periods of fasting
are potentially harmful, and cachectic patients should be advised to eat small, frequent meals (Mustafa *et al.*, 2001). Regarding the fluid intake, we do not have the evidence from randomized controlled trials and the current guidance is rather anecdotal. Nevertheless, fluid intake should be restricted to 1.5-2.0 litres per day, especially in patients with severe symptoms or those requiring high doses of diuretics (Gibbs *et al.*, 2000). At least one study suggests that multiple micronutrient supplementation is potentially beneficial (Witte *et al.*, 2005). Such supplements should contain anti-oxidant supplements and B-group vitamins. Statin therapy should be initiated with caution, because retrospective data indicate that low levels of total cholesterol, LDL and triglycerides are associated with poor outcomes in CHF patients (Rauchhaus *et al.*, 2003, Horwich *et al.*, 2002). However, statin therapy is still associated with survival benefits in patients with CHF. Thus, statins may be beneficial in CHF patients not because but despite their cholesterol lowering effects (see below) (von Haehling & Anker, 2005b).

Another important consideration is to avoid food and lifestyle factors that trigger the acute phase response such as an excess of carbohydrates or saturated fats, alcohol, and smoking (Azhar & Wei, 2006). Food that counteracts inflammatory responses, on the other hand, can be recommended. This includes fish oil supplements, olives, walnuts, flaxseed oil, any fruits or vegetables, garlic, ginger, turmeric, sunflower seeds, eggs, herring, or nuts (Azhar & Wei, 2006). Enteral nutrition should always be given preference over parenteral nutrition, however, if the latter cannot be avoided, the general guidelines can be followed: 35 kcal per kg of body weight per day,
1.2 g of protein per kg per day, and a 70:30 glucose:lipid ratio for the non-protein energy (Wallace & Schwartz, 2002).

3. Pharmacotherapy of Cardiac Cachexia

3.1. Appetite Stimulants

Megestrol Acetate

Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone progesterone (Table 3). A large number of randomized controlled trials have shown its efficacy in stimulating appetite thus triggering weight gain in cachectic patients (Yavuzsen et al., 2005). The precise mechanism by which weight gain is mediated is presently unknown. One animal study suggests a role of neuropeptide Y, because its concentration increased by 90-140% in central areas of neuropeptide Y synthesis or action (McCarthy et al., 1994). Other studies suggest that megestrol acetate inhibits pro-inflammatory cytokines such as IL-1, IL-6, and TNFα whose plasma levels decreased after treatment with the drug (Mantovani et al., 2001). Finally, some animal data point to the fact that appetite enhancement might be due to the modulation of calcium channels in the ventromedial hypothalamus, and that the attenuation of firing of the associated neurons may lead to satiety (Costa et al., 1995). Clinical studies have mostly focused on patients with cancer cachexia and AIDS-associated wasting. No studies in patients with cardiac cachexia are available. Megestrol acetate is currently approved only for AIDS-associated
anorexia and cachexia (Table 3). Loprinzi et al. studied the effects of four different doses (160, 480, 800, and 1,280 mg/day) of megestrol acetate in a total of 342 patients with cancer-associated anorexia or cachexia (Loprinzi et al., 1994). Patients were randomly assigned to one of four treatment groups and followed-up for 18 weeks. Megestrol acetate was well tolerated. The authors reported a dose-related effect of megestrol acetate on appetite stimulation (p=0.02), however, the highest dose had no additional effect as compared to the 800 mg/d dose. Westman et al. studied 255 patients with advanced, progressive, hormone-insensitive cancer of different types (Westman et al., 1999). Patients were randomized to 160 mg of megestrol acetate twice daily or placebo and followed-up for 12 weeks. A beneficial effect of megestrol acetate on appetite loss was observed after four weeks (p<0.0001), a trend after eight weeks (p=0.058). Only patients in the placebo group experienced continuing weight loss (-1.3 kg after 12 weeks, p=0.0048), whereas no significant weight loss occurred in the megestrol acetate group (-0.5 kg, p=0.45).

Medroxyprogesterone Acetate

Medroxyprogesterone acetate is closely related to megestrol acetate. Indeed, both are synthetic orally active progestational agents (Table 3). Neri et al. treated 279 cancer patients undergoing either chemotherapy and/or radiotherapy treatment for different tumour types (Neri et al., 1997). Patients were randomly allocated to receive either medroxyprogesterone acetate (n=168) at a dose of 1000 mg per day for 12 weeks or no treatment (n=78).
Patients in the medroxyprogesterone acetate group experienced a significant increase in body weight of 3.2% after 12 weeks compared to baseline (p=0.001). Patients who were left without treatment experienced a decrease of 3.1% within the same time frame. Simons et al. performed a similar study in 134 patients with advanced-stage, incurable, non-hormone-sensitive cancer. Patients were treated with medroxyprogesterone acetate or placebo (Simons et al., 1996). After six weeks of treatment, there was a beneficial effect on appetite in the medroxyprogesterone acetate group (p=0.008). This result remained valid after 12 weeks of follow-up (p=0.01). Additionally, there was an increase in mean weight of 0.6±4.4 kg in the medroxyprogesterone acetate group as opposed to an ongoing weight loss of 1.4±4.6 kg in the placebo group (p=0.04). The side effects profile of medroxyprogesterone acetate was deemed favourable, but a trend towards an increase in peripheral oedema was observed. For this reason, it is recommended to avoid usage of megestrol acetate and medroxyprogesterone acetate in patients with heart failure (Nelson, 2000).

Cannabinoids

Cannabinoids can be administered via inhalation, intravenously, or orally. Most commonly, at least in North America and Europe, cannabis is ingested by smoking marijuana that is derived from the dried plant (Voth et al., 1997). The active ingredient of cannabis is delta-9-tetrahydrocannabinol. Dronabinol, nabilone, and levonantradol are synthetic cannabinoids for oral application. At present, there are only two approved indications for
administering delta-9-tetrahydrocannabinol: nausea and vomiting induced by cytotoxic chemotherapy and AIDS-associated anorexia and wasting (Table 3) (Voth et al., 1997). Acute effects of cannabinoids include tachycardia, hypotension, and decreased cardiac function (John, 2006). This is followed by an initial euphoria, which is later followed by drowsiness and relaxation.

Cannabinoids are known to stimulate appetite. Beal et al. studied the effects of dronabinol on appetite and weight in 139 patients with AIDS-related anorexia and ≥2.3 kg weight loss in a multi-institutional study (Beal et al., 1995). Patients were randomized to receive 2.5 mg dronabinol twice daily or placebo. Indeed, dronabinol administration was associated with increased appetite compared to baseline (38% vs. 8% for placebo, p=0.015), a trend towards an improvement in mood (p=0.06), and decreased nausea (20% vs. 7%; p=0.05). No significant difference in weight gain was noted between the 2 groups. Another study in 19 patients with advanced malignancies yielded similar results (Nelson et al., 1994). Indeed, delta-9-tetrahydrocannabinol 2.5 mg three times daily one hour after meals for four weeks led to an effective appetite stimulation.

Strasser et al., however, were not able to reproduce these results in a larger study population. They studied the effects of cannabis extract (n=95) and delta-9-tetrahydrocannabinol (n=100) in a randomized, placebo-controlled in patients with advanced incurable cancer (Strasser et al., 2006). All patients had a weight loss ≥5% within the preceding six months. Unfortunately, the intent-to-treat analysis showed no significant differences between the 3 arms
for appetite, quality of life, or cannabinoid-related toxicity. Increased appetite was reported by 73%, 58%, and 69% of patients receiving cannabis extract, delta-9-tetrahydrocannabinol, or placebo (n=48), respectively. Therefore, an independent data review board recommended early termination of the study (Strasser et al., 2006).

3.2. Anabolic Steroids

Anabolic steroids are chemically related to testosterone. Table 4 provides an overview of some anabolic steroids used in clinical practice. The effects of testosterone were first studied by the French neurologist and physiologist Charles Édouard Brown-Séquard (1817-1894) in 1889 (Cussons et al., 2002). Far from knowing the substance, he produced a bizarre elixir made from the testicles of guinea pigs and dogs and injected it via the subcutaneous route. In his publication in the Lancet, he claimed that the elixir increased his physical strength and intellectual prowess (Brown-Séquard, 1889), although this effect was likely to be a placebo effect (Cussons et al., 2002). However, by the end of 1889, more than 12,000 physicians were administering Brown-Séquard's fluid, and manufacturing chemists were making fortunes selling his “Elixir of Life” (Freeman et al., 2001). The hormone itself was identified more then 40 years later. In 1935, Károly Gyula David and Ernst Laqueur published their finding “On Crystalline Male Hormone from Testicles (Testosterone)” coining a name for the newly identified hormone (David et al., 1935).
Testosterone is rapidly degraded upon administration. Therefore modified analogues have been developed. Due to an extensive first-pass metabolism in the liver, the oral bioavailability of testosterone is poor. Intramuscular injections, implantable pellets, buccal, and transdermal systems are available for delivery. Other anabolic steroids such as methyltestosterone, danazol, oxandrolone, and others are available for oral administration (Table 4). These hormones exert their effects through binding to a cytosolic receptor (Sar et al., 1990). The common end-point is an increase in protein synthesis, which mainly yields an increase in muscle mass.

Few clinical studies made use of anabolic steroids in patients with cachexia. No study has been performed in patients with cardiac cachexia. One study was performed in patients with cachexia due to chronic obstructive pulmonary disease (n=82) (Yeh et al., 2002). These patients with a significant involuntary weight loss received oxandrolone 10 mg twice daily. After 2 months of treatment, 88% of patients had gained 6.0±4.36 lb (p<0.05). After 4 months, 84% (of the remaining 55 patients) had gained a mean of 6.0±5.83 lb (p < 0.05). At this time, bioelectric impedance analysis showed the weight to be primarily lean tissue, with a mean increase in body cell mass of 3±2.6 lb (p<0.05), and a mean increase in fat of 1.2±4.6 lb (p=0.38) (Yeh et al., 2002).

A study in 9 HIV-positive men with unexplained weight loss of >10% of their usual weight investigated the effects of megestrol acetate and nandrolone decanoate treatment over 16 weeks (Cuerda et al., 2005). Seven patients completed the study. There were significant increases in weight (11.9±9.1 kg, p<0.05), 4-site skinfold measurements (p0<.05), mid-arm circumference
(p<0.005), fat-free mass (5.1±4.1 kg, p<0.05), and muscle strength (p <0.005) (Cuerda et al., 2005).

Some studies have been performed in patients with CHF. In 12 patients with idiopathic dilated cardiomyopathy, the administration of oxymetholone 5-10 mg daily for 3 months, led to significant decreases in left ventricular end-diastolic (from 68±2 to 63±2 mm, p<0.001) and end-diastolic (from 53±3 to 46±3 mm, p<0.001) diameters (Tomoda, 1999). Left ventricular mass decreased from 381±37 g to 342±34 g (p<0.001). Interestingly, this trend stopped six months after drug discontinuation. There were significant improvements in LVEF (from 42±6% to 51±5%, p<0.005) and plasma B-type natriuretic peptide (from 96±9 to 46±7 pg/ml (p<0.001), but no changes in body weight (Tomoda, 1999). Another study tested the effects of testosterone in a double-blind, randomized, placebo-controlled cross-over trial (Pugh et al., 2003). The authors found that testosterone treatment yielded a relative increase in cardiac output 180 minutes after application (+10.6±4.6%, p=0.035 compared to baseline). At the same time, systemic vascular resistance was maximally reduced (-17.4±9.6%, p=0.085 compared to baseline) (Pugh et al., 2003).

3.3. Beta-Adrenergic Agonists

Beta-adrenergic drugs were originally developed to treat obstructive airway diseases (Table 5). Especially β2-adrenergic agonists are known to exert beneficial effects on muscle mass thus providing a potential means of
anabolic therapy. Molenaar et al. have suggested that for the purpose of reversing muscle loss, promoting muscle gain, strength and mobility the combination of a highly selective $\beta_2$-adrenoceptor agonist with a selective $\beta_1$-blocker could be most beneficial (Molenaar et al., 2006). In this context, it is particularly important to note that treatment of 20 patients with advanced CHF with oral salbutamol yielded ventricular tachycardia in 6 cases (Mettauer et al., 1985). A number of studies provided evidence that the impairment of the calpain system could be responsible for such beneficial effects (Harper et al., 1990, Koohmaraie et al., 1991). Additionally, beta-adrenergic agonists have been found to stimulate muscle protein synthesis with effects on $\alpha$-actin mRNA (Grant et al., 1993), $\alpha$-actin (Grant et al., 1993), Helferich et al., 1990), and myosin light chain (Smith et al., 1989). The mechanism is not clear, but an improvement in blood supply may help in understanding the concept. Indeed, clenbuterol was found to increase muscle blood flow in rats (Rothwell et al., 1987), which may aid in providing increased amounts of amino acids to the muscle.

Koohmaraie et al. studied 16 wether lambs that received 6 weeks of treatment with a novel beta-adrenergic agonist called L644,969 (Koohmaraie et al., 1991). Such treatment yielded a significant increase in biceps femoris and longissimus muscle area as compared to control fluid application (both $p<0.05$). This was apparently due to muscle hypertrophy. Moreover, beta-adrenergic agonist feeding altered the pattern of postmortem proteolysis. In treated lambs, postmortem storage had no effect on the myofibril fragmentation index and degradation of desmin and troponin-T. The authors
concluded that the ability of muscle to undergo postmortem proteolysis had been dramatically reduced. Thus, the occurrence of muscle hypertrophy is aided by a decrease in degradation with such treatment.

A large number of independent researchers have demonstrated beneficial effects on muscle strength mediated by beta-adrenergic agonists in patients with different muscular illnesses such as facioscapulohumeral muscular dystrophy (Kissel et al., 2001), Duchenne and Becker muscular dystrophy (Fowler et al., 2004), and spinal muscular atrophy (Kinali et al., 2002). A number of clinical studies have investigated the effects of beta-adrenergic agonists in patients with CHF. Timmis et al. studied the haemodynamic and metabolic short-term responses to pirbuterol and salbutamol in patients with CHF of ischaemic origin (Timmis et al., 1984). A total of 16 patients were randomly allocated to treatment with either pirbuterol 20 μg or salbutamol 6 mg. No differences were found between the two drugs, so that both were analysed together. After 90 minutes, there was a significant increase in cardiac index (p<0.001), a decrease in systemic vascular resistance (p<0.001), and an increment in left ventricular dp/dt_{max} (p<0.05). A modest reduction in left ventricular end-diastolic pressure was observed as well (p<0.01). Interestingly, there was an increase in arterial levels of free fatty acids (p<0.05), which resulted in the preferential utilization of these substrates as a myocardial energy source (Timmis et al., 1984). A double-blind, randomized, placebo-controlled study into the effects of pirbuterol (20 μg three times daily) showed significant increases in cardiac output and decreases in wedge pressure after 7 weeks of treatment with the drug (Weber
et al., 1982). However, these effects were short-lived after each application of the drug. No change in exercise tolerance, maximal oxygen uptake, or left ventricular echocardiographic dimensions was observed (Weber et al., 1982).

George et al. studied 7 patients who were started on oral clenbuterol 5-46 weeks after implantation of a left ventricular assist device (George et al., 2006). After 3 months of treatment, there was no change in LVEF, but a significant increase in end-diastolic dimension (from 4.73±0.67 to 5.24±0.66, p<0.01). Moreover, body weight (from 75.5±17.9 to 79.2±25.1 kg, p<0.05) and lean mass (from 21.1±8.9 to 23.6±9.7 kg, p<0.05) increased significantly (George et al., 2006).

3.4. Anti-Inflammatory Substances

A vast array of substances from different drug classes has shown to suppress inflammation, especially the production or the action of pro-inflammatory cytokines (von Haehling & Anker, 2005a). The cause of pro-inflammatory activation in CHF has been subject of debate in recent years (see above). Thus, inhibition of pro-inflammatory cytokines may have beneficial effects. This could be achieved by a number of different substances including TNFα antibodies like etanercept or infliximab. This concept, however, has yielded disappointing results, and it appears that inhibition of single mediators is not beneficial. Rather, broader approaches might be necessary. These include immunomodulatory therapies, statins, inhibition of inflammatory triggers, and potentially the immunoabsorption of inflammatory mediators, which has
recently shown promising results in patients with sepsis (Schefold et al., 2007). Some drugs are already in clinical use for their TNFα inhibitory potential. This is particularly so with thalidomide. Pentoxifylline has shown benefit in a number of studies in CHF but is not currently used in treating the disease. Some other substances have only been demonstrated to have anti-inflammatory potential in *in vitro* studies. Some of these are shown in Table 6.

**TNFα Inhibitory Antibodies**

Since TNFα was found to have a prominent role in CHF, it was tempting to speculate that its direct inhibition would elicit beneficial effects. One such approach is etanercept, which is a TNFα receptor 2 fusion protein. It binds to TNFα and functionally inactivates the cytokine. Etanercept is composed of two TNF receptor-2 receptors and an IgG1:Fc portion. A large trial programme to study the effects of 24 weeks of subcutaneous application of etanercept or placebo in CHF was terminated early a few years ago following a recommendation of its Independent Data Safety Monitoring Board (DSMB) (Mann et al., 2004). A North American (RENAISSANCE: Randomized Etanercept North American Strategy to Study ANtagonism of CytokinEs) and a European/Australian (RECOVER: Research into Etanercept: CytOkine Antagonism in VEntriculaR Dysfunction) arm were created, after a small pilot study in 18 patients with moderate CHF showed promising results (Deswal et al., 1999). The combined analysis was termed RENEWAL (Randomized EtaNErcept Worldwide evALuation). Analysis of the data of a total of 2,048
patients with CHF prompted the DSMB to recognize that “even by conservative bounds that adjusted for the interim nature of the analysis, the confidence interval for this estimate ruled out ... a 10% benefit from (etanercept), crossing the established boundary for lack of efficacy on the morbidity/mortality endpoint (Anker & Coats, 2002b).”. In fact, the number of patients classified "improved", "unchanged" or "worsened" was similar for patients on placebo or any dose of etanercept, and the primary endpoint of death or hospitalisation due to CHF was not different between the two groups (risk ratio 1.10, 95% confidence interval 0.91 to 1.33, p=0.33) (Anker & Coats, 2002b). The secondary endpoint (all-cause mortality) did not differ between the two groups (RR 1.13, 95% CI 0.86 to 1.50, p=0.39), and the survival curves overlapped throughout the first year of treatment.

The reasons behind these disappointing results are not entirely clear. Etanercept may act not only as an antagonist, but also as an agonist in some clinical settings (Klein & Brailly, 1995). Indeed, etanercept can serve as a carrier protein that stabilizes TNFα, which results in the accumulation of high concentrations of the immunoreactive cytokine in the bloodstream (Mann, 2002, Suffredini et al., 1995). Since complexed TNFα does not remain tightly bound but dissociates at an extremely fast off rate, the net effect might be an increase in the duration of TNFα bioactivity (Mann, 2002). This may not be a problem in rheumatoid arthritis in which plasma levels are relatively low, but in CHF this may produce worsening of the disease.
Infliximab is the other important antibody that was studied in a large-scale trial. It is clinically used with good effect in the treatment of Crohn’s disease (Table 6). Infliximab is a chimeric (mouse/human) IgG1 monoclonal antibody that binds both soluble and membrane-bound TNFα. The ATTACH (Anti-TNFα Therapy Against Chronic Heart failure) trial was a multicentre, randomized, double-blind, placebo-controlled study of infliximab in CHF (Chung et al., 2003). A total of 150 CHF patients were enrolled. Like the etanercept studies, ATTACH was stopped prematurely, because the higher dose of infliximab (i.e. 10 mg/kg body weight) was associated with an increased risk of death (RR 2.84, 95% CI 1.01 to 7.97, p<0.05). Interestingly, the lower dose of infliximab (i.e. 5 mg/kg body weight) was not associated with an adverse risk (RR 0.80, 95% CI 0.22 to 2.99), and LVEF in patients receiving this dose increased (p<0.05). Like with etanercept, it is not easy to explain the disappointing results. Infliximab was shown to be directly cytotoxic to cells expressing TNFα on their membranes. This effect is beneficial in eliminating activated T cells in Crohn’s disease, but it is deleterious in CHF, in which failing myocytes express TNFα on their surfaces (Torre-Amione et al., 1996).

Inhibition of Lipopolysaccharide Bioactivity

Since LPS is being discussed as a potential candidate that triggers inflammatory activation in CHF (see above), it appears that its inhibition may serve as a therapeutic aim. This can potentially be achieved by micell formation around LPS or by inhibition of its signaling cascade. Indeed, Toll-
like receptor 4, which is the principal transducer of LPS signals into the cell, has recently been discovered as a potential drug target in CHF (Foldes et al., 2006). The first step in LPS binding to the cell surface, however, is mediated by CD14, which initiates LPS binding to Toll-like receptor 4 (von Haehling & Anker 2005a, da Silva Correia et al., 2001). IC14, an antibody that blocks CD14, has been shown to down-regulate LPS-induced TNFα production in whole blood samples from patients with CHF (Genth-Zotz et al., 2006).

A rather curious finding was that patients with CHF and higher plasma cholesterol levels have better (not worse) survival than those with lower levels (Horwich et al., 2002, Rauchhaus et al., 2003). Higher total serum cholesterol was a predictor of improved survival among 114 patients with CHF (hazard ratio 0.64, 95% confidence interval 0.48 to 0.86), independent of CHF aetiology, age, LVEF, and exercise capacity (Rauchhaus et al., 2003). This study showed that ≤5.2 mmol/L (200.8 mg/dl) was the best cut-off value as a predictor of mortality at 12 months (sensitivity 80.0%, specificity 62.9%). Additional in vitro data showed a linear relationship between plasma cholesterol levels and LPS-stimulated TNFα production (Sharma et al., 2005). This suggests that LPS is inactivated by cholesterol, which lends support to the endotoxin-lipoprotein hypothesis (Rauchhaus et al., 2000). This hypothesis suggests that micell formation by cholesterol around LPS could be beneficial in CHF.

Statins
The first statin, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Coa) reductase inhibitor, was isolated by the Japanese biochemist Akira Endo and his colleagues in 1973 (Endo, 1992). They isolated 23 mg of a substance that was subsequently termed mevastatin from 600 litres of culture filtrate from the mold *Penicillium citrinum*. It proved highly effective in reducing plasma cholesterol levels (Yamamoto *et al.*, 1980). In 1980, an analogue was isolated from *Aspergillus terreus* that was later named lovastatin, which became the first statin to be approved for the treatment of hypercholesterolaemia in 1987 (Alberts *et al.*, 1980). Mevastatin, the very first HMG-CoA reductase inhibitor, never reached the market, and the reasons were never made entirely clear.

Statin application leads to two primary responses in the body. Since the cell compensates for the inhibition of HMG-CoA (the rate limiting enzyme in cholesterol biosynthesis) by increasing its total amount, the reduction in circulating cholesterol remains small. The second effect is more important. HMG-CoA inhibition leads to an upregulation in the number of low density lipoprotein receptors on hepatocytes (Page *et al.*, 1997). Thus, these particles are being scavenged by the cell, which leads to a dramatic decrease in plasma cholesterol levels. This effect leads to a significant reduction in cardiovascular risk (Shepherd *et al.*, 1995, (LIPID) Study Group, 1998). However, statins have shown a reduction in recurrent coronary events as early as 16 weeks after therapy initiation (Schwartz *et al.*, 2001), and this time frame is by far too short to ascribe the risk reduction to cholesterol reduction alone (Vaughan *et al.*, 2000). Moreover, statins seem to be able to ameliorate
morbidity and mortality in patients with coronary artery disease irrespective of plasma cholesterol values. Thus, statins appear to have effects beyond mere cholesterol reduction, so-called pleiotropic effects (von Haehling & Anker, 2005b). These effects have been subject to vigorous research over the last several years. Some of them might be particular helpful in the treatment of CHF and possibly cardiac or other forms of cachexia.

**Statin-Mediated Effects on Endothelial Function**

Statins have been found to improve endothelial function by a number of different mechanisms (von Haehling *et al.*, 2003). This is mediated by induction of endothelial nitric oxide synthase (eNOS) (Laufs *et al.*, 1998), an enzyme that produces the vasodilating substance nitric oxide. The attenuation of nitric oxide production is one of the most important features of endothelial dysfunction (Felmeden & Lip, 2005), commonly associated with CHF. Additionally, statin treatment yields an increase in nitric oxide release by indirect mechanisms (Feron *et al.*, 2001). An increase in xanthine oxidase activity is another frequent finding in patients with CHF (Landmesser *et al.*, 2002). This enzyme catalyzes the breakdown of uric acid. Overactivity of the enzyme, on the other hand, leads to an increased production of oxygen free radials, which contributes to the development of endothelial dysfunction (Belch *et al.*, 1991). Interestingly, statins have been proposed to reduce oxidative stress (Wassmann *et al.*, 2001), and atorvastatin, for example, has been shown to reduce vascular production of reactive oxygen species in spontaneously hypertensive rats (Wassmann *et al.*, 2001).
**Statin-Mediated Effects on Endothelial Progenitor Cells**

Statins are also able to mobilize bone-marrow-derived endothelial progenitor cells. Such cells have recently been demonstrated to be able to transdifferentiate into beating cardiomyocytes when co-cultured with neonatal rat cardiomyocytes or when injected into the post-ischaemic adult mouse heart (Condorelli *et al.*, 2001). Other than augmenting the mobilization of endothelial progenitor cells, atorvastatin also increased the survival of mice (n=75) during a four-week follow-up period after extensive myocardial infarction (atorvastatin: 80%, placebo: 46%, p<0.01) (Landmesser *et al.*, 2004). One prospective trial has been reported that recruited 15 patients with angiographically documented stable coronary artery disease. Treatment with atorvastatin 40 mg once daily for 4 weeks led to a significant increase in the number of endothelial progenitor cells in the bloodstream of these patients (Vasa *et al.*, 2001).

**Statin-Mediated on Inflammatory Markers and the Proteasome**

A number of studies have shown that statins possess anti-inflammatory properties. For example, lovastatin was shown to inhibit production of TNFα, IL-1, and IL-6 in certain rat cell lines (Pahan *et al.*, 1997). This may also translate into the clinical setting. Pravastatin at a dose of 40 mg once daily led to a reduction in TNFα plasma levels in patients with hypercholesterolaemia (n=40) after eight weeks of treatment (p=0.32 vs.
placebo) (Solheim et al., 2001). However, the clinical results are somewhat mixed. Indeed, in patients with CHF (n=86), six months of treatment with rosvastatin at an increasing dose (target: 40 mg once daily) in a randomized, double-blind, placebo-controlled study did not yield any improvement in the plasma levels of C-reactive protein, TNF$\alpha$, or IL-6 (Krum et al., 2007). However, other studies such as the PRINCE study (Pravastatin Inflammation/CRP Evaluation) did show significant reductions in serum levels of C-reactive protein. In PRINCE, pravastatin at a dose of 40 mg once daily reduced the levels of this inflammatory marker by 13% after 24 weeks compared to baseline (p<0.005) (Albert et al., 2001). The study enrolled a total of 1,182 patients with a history of myocardial infarction, stroke, or arterial revascularization procedure. In the PROVE IT-TIMI 22 study (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22), atorvastatin 80 mg once daily was more effective than pravastatin 40 mg once daily after a follow-up of one and four months at decreasing serum C-reactive protein levels among 3,745 patients with acute coronary syndromes (Ridker et al., 2005). The anti-inflammatory properties of statins may be particularly useful in cachectic patients. Additionally, it has been shown that lovastatin can inhibit proteasome activity in cell lysates of a human breast cancer cell line (Rao et al., 1999). Another study showed that mevastatin reduced viability of terminally differentiated murine neuroblastoma cells by inhibiting proteasome activity (Kumar et al., 2002). An important feature of these two studies is that the inhibiting effect on the proteasome was only seen if the respective statin was present in its closed-ring structure. Indeed, most statins possess a side-chain that is present either as an open-
ring (acid) or a closed-ring (lactone). It is commonly assumed that conversion to an open-ring structure is an important prerequisite for statin action. Thus, statins may exert their actions on the proteasome only if their “activation” – necessary for HMG-CoA reductase blockade – has not taken place. It remains a matter of speculation if this can be used clinically.

**Statin-Mediated Anti-Tumour Activities**

Statins have also been shown to possess anti-tumour activities. Indeed, lovastatin was demonstrated to inhibit the cell cycle of a murine fibroblast cell line (Vogt et al., 1996) and a human bladder carcinoma cell line (Jakóbisiak et al., 1991) in the G1 phase. In addition to this effect, the induction of apoptosis might be another important anti-tumour activity. This was shown, for example, in malignant mesothelioma cells, in which increasing doses of lovastatin reduced cell viability (Rubins et al., 1998). Apoptosis was also induced by lovastatin in a prostate cancer cell line (Marcelli et al., 1998). In clinical medicine, however, only dose escalating studies have taken place to date. Knox et al. studied the safety and maximum tolerated dose of lovastatin in 26 patients with squamous cell carcinomas of the head and neck and of the cervix (Knox et al., 2005). Patients received doses between 5 and 10 mg/kg of bodyweight per day over 2-3 weeks, divided into four doses. The authors concluded that the administration of 7.5 mg/kg per day for 21 consecutive days on a 28-day schedule is well tolerated in such patients, and that this dose should be used in a phase II-study (Knox et al., 2005). A similar study
by Holstein et al. tested the efficacy ofLovastatin every six hours for 96 hour-cycles every four weeks in patients (n=32) with advanced malignancies (Holstein et al., 2006). Doses ranged from 10 mg/m² to 415 mg/m², and a dose-limiting toxicity was not reached. However, an anti-tumour activity was also not observed.

Statins in Chronic Heart Failure

Only one large-scale clinical trial of a statin is available at the moment. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study enrolled 5,011 patients with ischaemic CHF and an impaired LVEF who were randomized to placebo or rosvastatin in a double-blind fashion (Kjekshus et al., 2007). Patients received 10 mg of rosuvastatin once daily for a median follow-up of 32.8 months. The primary end-point was defined as a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. A primary end-point was observed in 692 patients in the rosuvastatin and 732 patients in the placebo group (hazard ratio 0.92, 95% confidence interval 0.83-1.02, p=0.12). No significant difference between the 2 groups could be detected in terms of the primary outcome. The only beneficial effect that was noted in the rosuvastatin group was a reduction in the total number of hospitalizations for worsening heart failure (p=0.01). It is not easy to reconcile previous studies with the results from CORONA, especially because patients with CHF were deliberately excluded from most previous statin studies. It is possible that the pleiotropic effects are not a class effect, and indeed rosuvastatin may not possess effects that are
beneficial in CHF. On the other hand, CORONA made use of a dose that reduced low-density lipoprotein cholesterol levels significantly during follow-up (p<0.0001). Thus, the disadvantages from cholesterol reduction (see above) may outweigh the benefits from pleiotropic effects. Interestingly, rosvastatin did reduce levels of C-reactive protein during follow-up (p<0.0001), which, however, failed to translate into beneficial effects in the rosvastatin-treated patients. This calls the hypothesis of beneficial effects of C-reactive protein reduction per se into question, at least in patients with CHF (von Haehling & Anker, 2007a).

A similar study is still ongoing. The prospective, multicenter, randomized, double blind GISSI-HF trial (Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca) aims to investigate the impact of n-3 polyunsaturated fatty acids (PUFA) and rosvastatin in patients with chronic heart failure. Patients have been randomized in 2 steps to (i) n-3 PUFA (1 g once daily) or placebo and (ii) rosvastatin (10 mg once daily) or placebo. The GISSI-Prevenzione trial showed that 3-year treatment with low-dose n-3 PUFA was associated with a significant reduction of total mortality by 21% in patients who survived a recent myocardial infarction (GISSI-Prevenzione trial group, 1999).

**Thalidomide**

Thalidomide was part of one of the largest drug tragedies in the history of medicine. Kunz first synthesized it in 1954 (Kunz, 1956) in West Germany
where the drug was approved for clinical use as a sedative in 1956. Many other countries soon followed (Mellin & Katzenstein, 1962). Thalidomide was mostly sold on an over-the-counter basis, i.e. a prescription was not required. By 1961, its alleged lack of toxicity was called into question when reports were mounting of congenital abnormalities, most frequently phocomelia (Calabrese & Resztak, 1998). It has later been hypothesized that this effect is due to the inhibition of angiogenesis thus preventing blood vessel growth in the limb buds (D'Amato et al., 1994). Malformation of the unborn can be induced by a single dose of the substance taken during pregnancy (Eriksson et al., 2001). Therefore, the drug was banned from the German and British markets in 1961, soon to be followed by withdrawal in other countries.

In 1965, Jacob Sheskin, a dermatologist from Israel, opened a new chapter in the thalidomide story when he published a report that showed the drug to be effective in the treatment of acute inflammatory lesions associated with leprosy (Sheskin, 1965). Inhibition of angiogenesis, on the other hand, might be useful in the treatment of cancer, and indeed has thalidomide been successfully used in studies in patients with Karposi’s sarcoma, malignant melanoma, prostate cancer, and multiple myeloma [Bamias & Dimopoulos, 2005, Konstantinopoulos et al., 2007, Bringhen et al., 2006). In an in vitro model in LPS-stimulated human monocytes, thalidomide inhibited selectively the production of TNFα leaving other pro-inflammatory cytokines unaffected (Sampaio et al., 1991). Amino-substituted thalidomide analogues may have an even greater TNFα inhibitory potential (Muller et al., 1999). Thalidomide’s effect on TNFα production appears to be mediated by an enhanced
degradation of the cytokine’s mRNA (Moreira et al., 1993). This led to the suggestion of using thalidomide in the treatment of CHF (Davey et al., 2000) and cachexia (Gullestad et al., 2002).

The results of thalidomide studies in patients with CHF are quite mixed. Indeed, the drug enhances CD8+ T cell activity and increases plasma levels of IL-12. This, together with its anti-angiogenic properties may limit its use in patients with CHF (Gullestad et al., 2005a). Gullestad et al. studied 9 patients with CHF who received thalidomide at a dose of 200 mg per day for 6 weeks (Gullestad et al., 2002). TNFα plasma levels decreased from 33.9±10.1 to 19.3±6.1 pg/ml (p<0.05), and LVEF increased from 26±9 to 34±10% (p<0.05). Another small open-label study in seven patients with advanced disease found that 12 weeks of maintenance therapy with the drug at doses ranging between 100 and 400 mg/day improved the 6-minute walking distance (p=0.035) but failed to improve LVEF (p=0.16) or quality of life (p=0.2) (Agoston et al., 2002). The same group of workers recently published results from a prospective, randomized, placebo-controlled study in 56 patients with CHF and an LVEF <40% (Gullestad et al., 2005b). Patients were treated with increasing doses of thalidomide (target dose: 200 mg/day) over 12 weeks. Thalidomide increased mean LVEF from 24±2 to 32±3% (p=0.006) and reduced left ventricular end-diastolic volume from 216±21 to 157±25 ml/m². The leukocyte count decreased as well (p<0.01) with thalidomide treatment, however, plasma levels of both TNFα (p<0.001) and soluble TNFR-1 (p<0.01) increased significantly upon this therapy. Moreover, the authors assumed a net matrix-stabilizing effect, because plasma levels of matrix
metalloproteinase-2 decreased with thalidomide treatment \((p<0.05)\) (Gullestad et al., 2005b). However, Orea-Tejeda et al. failed to find any differences in TNF\(\alpha\) plasma levels, LVEF or any other echocardiographic parameters after 6 months of treatment with thalidomide \((n=20)\) compared to control patients \((n=60)\) who did not receive a study drug (Orea-Tejeda et al., 2006).

### 3.5. Proteasome Inhibitors

Proteasome inhibitors are available since 1994. The first clinical phase I study was published in 2002. To date, four different classes of proteasome inhibitors have been described which are either reversible or irreversible inhibitors of specific activities of the proteasome (von Haehling et al., 2002). Bortezomid, for example, is a dipeptide boronic acid analogue that blocks proteasome activity via binding to its active sites. Bortezomib has been extensively studied in several trials of different types of cancer. In 2003 the drug was given approval by the US Food and Drug Administration for the treatment of multiple myeloma and mantle cell lymphoma in patients who had received at least one prior therapy. No studies are available that have specifically targeted patients with cachexia.

Richardson et al. conducted a multicentre, open-label, non-randomized phase II-trial in 202 patients with relapsed myeloma that was refractory to therapy so far (Richardson et al., 2003). Patients received 1.3 mg/m\(^2\) of bortezomid twice weekly for two weeks, followed by one week without treatment for up to eight cycles. Patients with suboptimal response received additionally oral
dexamethasone. The median duration of treatment was 3.8 months, and 60% of patients completed at least for cycles. A total of 67 patients (35%) had a complete, partial, or minimal response to bortezomib alone. Of these patients, 89% had an additional increase in haemoglobin of at least 1 g/dl (Richardson et al., 2003). A similar study compared the effects of bortezomib with high-dose dexamethasone in 669 patients with relapsed multiple myeloma (Richardson et al., 2005). The complete and partial response rates combined were 38% in the bortezomib and 18% in the dexamethasone group (p<0.001) (Richardson et al., 2005). Only very few studies have investigated the effects of bortezomib treatment on weight development. One retrospective analysis is available: Jatoi et al. performed a subanalysis of two anti-neoplastic trials in patients with adenocarcinoma of the pancreas (Jatoi et al., 2005). Of the 46 patients in this study who were treated with intravenous bortezomib-doses of 1.3 or 1.5 mg/m² during 21-day cycles, a total of nine (19.6%) gained weight during follow-up. The patients reported stable mean appetite scores during follow-up (Jatoi et al., 2005). Thus, prospective trials are necessary to evaluate whether bortezomib or possibly other proteasome inhibitors are able to reverse weight loss in cachectic patients.

3.6. Other Substances

Pentoxifylline

The US Food and Drug Administration first approved pentoxifylline in 1984. It was initially characterized as a haemorrheologic agent for the treatment of peripheral vascular disease and intermittent claudication (Windmeier &
Gressner, 1997). The clinical benefits seen after pentoxifylline treatment are mostly due to increased red blood cell flexibility and a reduction in blood viscosity, red blood cell aggregation, and fibrinogen levels (Windmeier & Gressner, 1997). These effects yield improved microcirculation and tissue oxygenation. However, pentoxifylline’s precise mode of action is still unknown. A study by Zabel et al. suggested that pentoxifylline may inhibit TNFα formation in vitro and in vivo (Zabel et al., 1991). Moreover, it can protect animals in models of septic shock (Zabel et al., 1993).

Meanwhile, a number of clinical studies have been performed in patients with CHF. In 1998, Sliwa et al. published the first of a series of studies into the effects of pentoxifylline in such patients (Sliwa et al., 1998). This study was a randomized, controlled trial performed in 28 patients with dilated cardiomyopathy. After six months of treatment with pentoxifylline, LVEF increased from 22±9 to 39±15% (p=0.04) and TNFα plasma levels fell from 6.5±3 to 2.1±1 pg/ml (p=0.0001). The difference in TNFα plasma levels was significant in the pentoxifylline group only, although the absolute change was almost identical in the placebo group, in which TNFα levels fell from 10.8±12 to 6.5±5 pg/ml (p=0.32). Another study from the same group of workers used a similar approach (Sliwa et al., 2004). Again, patients (n=38) received pentoxifylline at a dose of 400 mg three times daily for 6 months in a randomized, double-blind, placebo-controlled fashion. Pentoxifylline treatment was associated with an increase in LVEF from 28±7 at baseline to 37±14% by the end of follow-up (p<0.05). Furthermore, pentoxifylline produced a decrease in plasma levels of TNFα (from 7±3 to 5±1 pg/ml, p<0.05), Fas (a
marker of apoptosis), C-reactive protein (from 11±6 to 6±4 mg/l), and N-terminal-pro B-type natriuretic peptide (Sliwa et al., 2004). Another randomized, double-blind, placebo-controlled study in 39 patients with dilated cardiomyopathy found a significant increase in NYHA class (p=0.01 vs. placebo) after 6 months of treatment (Skudicky et al., 2001). Mean LVEF improved from 24±9 to 31±13% (p=0.03). Interestingly, TNFα plasma levels were not changed by pentoxifylline treatment in this study.

Unfortunately, it was not possible to confirm the aforementioned results by an independent group of workers as yet. Indeed, Bahrmann et al. studied 47 patients with CHF of ischaemic origin who were randomly assigned to pentoxifylline 600 mg twice daily or placebo for 6 months (Bahrmann et al., 2004). LVEF improved in the pentoxifylline and in the placebo group (p value between groups: not significant). Plasma levels of TNFα and IL-6 were not affected in both groups. Levels of B-type natriuretic peptide were reduced only in the placebo group (p=0.031), and there was a statistically significant increase in exercise capacity as assessed by peak resting whole-body oxygen consumption in both groups (both p<0.05). These disappointing results and the striking contrast between this study and the studies performed by Sliwa et al. have recently been discussed elsewhere (von Haehling & Anker, 2005a), but it seems that patient selection and the use of novel treatments may have had an effect. Indeed, beta-blockers were not part of standard CHF treatment regimens when the first studies with pentoxifylline were reported.

Some data point to the fact that pentoxifylline may have beneficial effects in
the treatment of cancer cachexia (Bossola et al., 2007). Indeed, its administration may prevent muscle atrophy and may suppress an increased protein breakdown by inhibition of the ubiquitin-proteasome pathway. At least one clinical study has been performed to assess pentoxiphylline’s clinical effects in the setting of cachexia. Goldberg et al. studied 70 patients with cachexia of malignant origin and a life expectancy of ≥3 months (Goldberg et al., 1995). Patients received pentoxifylline 400 mg three times daily or matching placebo in a double-blind fashion. Unfortunately, the drug failed to improve appetite, and no difference in weight gain was recorded in the pentoxifylline compared to the placebo group. Looking at the results, however, it should be kept in mind that the study population was a heterogeneous group of patients with cancers arising in a variety of primary sites and in various stages of advanced disease. Additionally, the follow-up was comparatively short around two months. Animal models, on the other hand, have yielded promising results. Indeed, male Wistar rats bearing the Yoshida AH-130 ascites hepatoma that received pentoxifylline at a dose of 10 mg/kg of bodyweight showed a significant reduction in the depletion of muscle mass at day four after tumour implantation (Costelli et al., 2002). Moreover, pentoxifylline reduced the activity of muscle proteolytic systems. Another study found that daily administration of pentoxifylline inhibited the activation of a non-lysosomal, calcium-independent proteolytic pathway in Yoshida sarcoma-bearing rats (Combaret et al., 1999). Pentoxifylline suppressed the enhanced expression of ubiquitin, the ubiquitin-conjugating enzyme E2, and a subunit of the 20S proteasome in muscle of the tumour-bearing rats. Future studies need to define the role of pentoxifylline in the setting of cachexia.
CONCLUSION

The pathophysiology of cardiac cachexia is exceedingly complex, and we still do not understand when and how CHF progresses into this syndrome. Pro-inflammatory cytokines and especially TNFα certainly play an important part. However, therapies that targeted specific single cytokines have largely failed, and it appears that broader approaches are required. One potential therapeutic aim is the inhibition of intracellular signalling pathways like NF-κB, which is also likely to inhibit TNFα-dependent proteasome activation. However, a complete inhibition of NF-κB activity may also have severe side effects, as NF-κB is involved immune function, adaptation to oxidative stress and anti-apoptotic effects. Furthermore, an activation of the NF-κB pathway during exercise has been described. Indeed, acute treadmill exercise increases the phosphorylation of IKKα/β and IκBα leading to an increased NF-κB-dependent transcription in rat skeletal muscle, which peaks just after the exercise (Ho et al., 2005).

We are currently not able to interfere with appetite regulation in a promising way, although initial steps have been undertaken, and both cannabinoids and progestational agents may prove beneficial. However, no studies are currently available that have specifically targeted cardiac cachexia using this approach. Nutritional recommendations for cardiac cachexia remain speculative, and no large-scale randomized, controlled trials have been
performed. Statins are another interesting approach, however the disappointing results of the CORONA study are a huge setback. Dose-finding studies or maybe even studies to find the right statin are urgently required. Further studies are warranted to specifically target wasting in patients cardiac cachexia. The aim of such therapies is clear at hand: to prolong life and to improve quality of life.
### Table 1. Cachexia in an adult patient: Diagnostic criteria (adapted from Evans et al., 2008).

<table>
<thead>
<tr>
<th>Underlying disease AND Weight loss of ≥5% in 12 months or less (or body mass index &lt;20)</th>
<th>PLUS ≥3 out of 5 criteria</th>
<th>Decreased muscle strength Fatigue Anorexia Low fat-free mass index Abnormal biochemistry Inflammation Anemia Low serum albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Regulatory mediators of appetite and feeding.

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Discovery</th>
<th>Molecular weight</th>
<th>Structure</th>
<th>Synthesis</th>
<th>Main functions</th>
<th>Effect on Appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropeptide Y</td>
<td>1982</td>
<td>10.8 kDa</td>
<td>36 amino acids</td>
<td>Hypothalamus</td>
<td>Regulation of energy balance, memory, learning</td>
<td>+</td>
</tr>
<tr>
<td>Leptin</td>
<td>1994</td>
<td>16 kDa</td>
<td>Protein hormone</td>
<td>Adipocytes</td>
<td>Appetite and metabolism regulator</td>
<td>-</td>
</tr>
<tr>
<td>α-melanocortin stimulating hormone</td>
<td>?</td>
<td>1.02 kDa</td>
<td>13 amino acids</td>
<td>Pituitary gland intermediate lobe</td>
<td>Skin pigmentation, immunomodulator, energy balance</td>
<td>-</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>1944</td>
<td>22 kDa</td>
<td>191 amino acids</td>
<td>Pituitary gland</td>
<td>Growth stimulation and cell reproduction</td>
<td>+</td>
</tr>
<tr>
<td>Insulin</td>
<td>1921</td>
<td>5.8 kDa</td>
<td>51 amino acids</td>
<td>Langerhans islets in the pancreas</td>
<td>Glucose homeostasis</td>
<td>+</td>
</tr>
</tbody>
</table>
### Table 3. Appetite stimulants in clinical use.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Chemical Formula</th>
<th>Drug Class</th>
<th>Original FDA Approval</th>
<th>Dosing Regimen</th>
<th>Available Doses</th>
<th>Route of Administration</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Megestrol acetate</td>
<td>C_{24}H_{32}O_{4}</td>
<td>Progesterone derivative</td>
<td>1971</td>
<td>Tablets: 40-320 mg per day</td>
<td>Tablets: 20, 40, 160 mg</td>
<td>oral</td>
<td>Tablets: recurrent, inoperable, or metastatic carcinoma of the breast or the endometrium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral suspension: 625-800 mg per day</td>
<td>Oral suspension: 40, 125 mg/ml</td>
<td></td>
<td>Oral suspension: AIDS-associated anorexia and cachexia</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>C_{24}H_{34}O_{4}</td>
<td>Progesterone derivative</td>
<td>1959</td>
<td>Tablets: 300-1000 mg per day</td>
<td>Tablets: 250, 500 mg</td>
<td>oral intramuscular</td>
<td>Advanced carcinoma of the breast, the endometrium, or the kidneys; low injectable dose used in contraception</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injection: Initially 400-1000 mg per week</td>
<td>Syringe: 150, 400 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>C_{21}H_{21}N</td>
<td>Serotonin and</td>
<td>1961</td>
<td>approximately 4-20 mg per day, but very</td>
<td>Tablets: 4 mg</td>
<td>oral</td>
<td>Allergic rhinitis and conjunctivitis, mild allergic skin manifestations</td>
</tr>
</tbody>
</table>
Table 4. Selected anabolic steroids.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Chemical Formula</th>
<th>Original FDA Approval</th>
<th>Elimination Half-Life</th>
<th>Dosing Regimen</th>
<th>Available Doses</th>
<th>Route of Administration</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol</td>
<td>C_{22}H_{27}NO_{2}</td>
<td>1976</td>
<td>4.5-29 hours</td>
<td>200-800 mg per day divided in 2-4 doses</td>
<td>100, 200 mg</td>
<td>oral</td>
<td>Endometriosis, menorrhagia, hereditary angioedema, fibrocystic breast disease</td>
</tr>
<tr>
<td>Fluoxymesterone</td>
<td>C_{20}H_{28}FO_{3}</td>
<td>1956</td>
<td>9.5 hours</td>
<td>5-20 mg per day</td>
<td>2, 5, 10 mg</td>
<td>oral</td>
<td>Androgen hormone replacement in men, breast cancer, delayed sexual development in boys</td>
</tr>
<tr>
<td>Methandrostenolone</td>
<td>C_{20}H_{28}O_{2}</td>
<td>1956</td>
<td>4.5-6 hours</td>
<td>50-100 mg per day</td>
<td></td>
<td>oral</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

Histamine antagonist: Individual dosing regimens, not to exceed 0.5 mg/kg of bodyweight per day. Dronabinol (C_{21}H_{30}O_{2} Cannabinoid 1985): 2.5-20 mg per day. Oral. Doses: 2.5, 5, 10 mg. AIDS-associated weight loss; nausea and vomiting associated with cancer chemotherapy.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Formula</th>
<th>Year</th>
<th>Half-life</th>
<th>Dosage</th>
<th>Route</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyltestosterone</td>
<td>C_{20}H_{30}O_{2}</td>
<td>1940</td>
<td>2.5-3.5 hours</td>
<td>10-50 mg per day (higher doses in breast cancer)</td>
<td>Oral</td>
<td>Androgen hormone replacement in men, breast cancer, delayed sexual development in boys</td>
</tr>
<tr>
<td>Nandrolone decanoate</td>
<td>C_{28}H_{44}O_{3}</td>
<td>1962</td>
<td>7-12 days</td>
<td>women: 50-100 mg every 1-4 weeks; men: 50-200 mg every 1-4 weeks</td>
<td>Intramuscular</td>
<td>Anemia associated with renal insufficiency</td>
</tr>
<tr>
<td>Nandrolone phenpropionate</td>
<td>C_{27}H_{34}O_{3}</td>
<td>1959</td>
<td>2-3 days</td>
<td>25-100 mg once a week</td>
<td>Intramuscular</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>Oxandrolone</td>
<td>C_{19}H_{30}O_{3}</td>
<td>1964</td>
<td>9 hours</td>
<td>2.5 mg to 20 mg given divided in 2-4 doses</td>
<td>Oral</td>
<td>Adjunctive therapy to offset protein catabolism during prolonged corticosteroid therapy; bone pain in osteoporosis</td>
</tr>
<tr>
<td>Oxymetholone</td>
<td>C_{21}H_{32}O_{3}</td>
<td>1972</td>
<td>8-9 hours</td>
<td>1-5 mg/kg of body weight per day</td>
<td>Oral</td>
<td>Anemias caused by deficient red cell production.</td>
</tr>
<tr>
<td>Stanozolol</td>
<td>C_{21}H_{32}N_{2}O</td>
<td>1962</td>
<td>9 hours</td>
<td>2-6 mg per day divided in 1-3 doses</td>
<td>Oral</td>
<td>Hereditary angioedema</td>
</tr>
</tbody>
</table>
Table 5. Selected beta-adrenergic agonists.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Chemical Formula</th>
<th>Drug Class</th>
<th>Original FDA Approval</th>
<th>Dosing Regimen</th>
<th>Available Doses</th>
<th>Route of Administration</th>
<th>Clinical Use</th>
<th>Anabolic activity on skeletal muscle in vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bambuterol</td>
<td>C_{18}H_{29}N_{3}O_{5}</td>
<td>Long acting selective β2-agonist</td>
<td>Not approved††</td>
<td>10 mg once daily (can be increased to 20 mg once daily)</td>
<td>10 mg</td>
<td>Oral</td>
<td>Obstructive airway diseases</td>
<td>No data</td>
</tr>
<tr>
<td>Clenbuterol</td>
<td>C_{12}H_{18}Cl_{2}N_{2}O</td>
<td>Long acting selective β2-agonist†</td>
<td>Not approved††</td>
<td>Tablets: 0.02-0.1 mg per day, divided in 2 doses Syrup: 30-80 ml per day, divided in 2 doses</td>
<td>Tablets: 0.01, 0.02 mg Syrup: 0.005 mg/5 ml</td>
<td>Oral</td>
<td>Obstructive airway diseases</td>
<td>Animal studies: Spurlock et al., 2006, Burniston et al., 2007, Ryall et al., 2002, Moore et al., 1994 Human studies: George et al., 2006, Maltin et al., 1993</td>
</tr>
<tr>
<td>Formoterol (Eformoterol)*</td>
<td>C_{18}H_{22}N_{2}O_{4}</td>
<td>Long acting selective β2-agonist†</td>
<td>2001</td>
<td>Inhalation or nebulization every 12 hours</td>
<td>Various preparations</td>
<td>Inhalation</td>
<td>Obstructive airway diseases</td>
<td>Animal studies: Harcourt et al., 2007, Ryall et al., 2006, Ryall et al., 2002</td>
</tr>
<tr>
<td><strong>Pirbuterol</strong></td>
<td>C₁₂H₂₀N₂O₃</td>
<td>Short acting selective β₂-agonist</td>
<td>1986</td>
<td>Two inhalations (400 μg) repeatedly every 4-6 hours</td>
<td>200 μg per inhalation</td>
<td>Inhalation</td>
<td>Obstructive airway diseases</td>
<td>No data</td>
</tr>
<tr>
<td><strong>Salbutamol (Albuterol)</strong></td>
<td>C₁₃H₂₁NO₃</td>
<td>Short acting selective β₂-agonist</td>
<td>1981</td>
<td>Inhalation or nebulization repeatedly every 4 to 6 hours Tablets: 2 or 4 mg three or four times per day</td>
<td>Tablets: 2, 4 mg Inhalation: various preparations</td>
<td>Oral Inhalation</td>
<td>Obstructive airway diseases</td>
<td>Animal studies: Soic-Vranic et al., 2005, Cepero et al., 2000 Human studies: Kissel et al., 2001, Fowler et al., 2004, Kinali et al., 2002, Uc et al., 2003</td>
</tr>
<tr>
<td><strong>Salmeterol</strong></td>
<td>C₂₅H₃₇NO₄</td>
<td>Long acting selective β₂-agonist†</td>
<td>1994</td>
<td>Two inhalations (42 μg) twice daily</td>
<td>0.021, 0.046 mg per inhalation</td>
<td>Inhalation</td>
<td>Obstructive airway diseases</td>
<td>Animal studies: Moore et al., 1994, Ryall et al., 2006</td>
</tr>
<tr>
<td><strong>Terbutaline</strong></td>
<td>C₁₂H₁₉NO₃</td>
<td>Short acting selective β₂-agonist</td>
<td>1974</td>
<td>Tablets: 5-15 mg per day, divided in 2-3 doses Injection: 0.25 mg</td>
<td>Tablets: 2.5, 5, 7.5 mg Injection: 1 mg/ml</td>
<td>Oral Subcutaneous</td>
<td>Obstructive airway diseases</td>
<td>Animal studies: Ito et al., 2006</td>
</tr>
</tbody>
</table>

*Eformoterol is the former British Approved Name of formoterol.

**The World Health Organization recommends to use the International Nonproprietary Name salmeterol instead of the United States Adopted Name albuterol.
†Long-acting (i.e. 12 hours or more) selective \( \beta_2 \)-agonists are not recommended for the sole therapy of chronic airway diseases.

††Bambuterol and clenbuterol are approved in some European countries, but not in the United States.
Table 6. Substances with TNF\(\alpha\) inhibitory potential.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Original FDA Approval</th>
<th>Clinical Use</th>
<th>Mechanism by which TNF(\alpha) is affected</th>
<th>Effects on TNF(\alpha) production in vitro</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Antiarrhythmic agent</td>
<td>1989</td>
<td>Paroxysmal supraventricular tachycardia</td>
<td>Unknown, possibly mediated by adenosine receptor A(_2) and transduced through a G protein-adenylyl cyclase pathway</td>
<td>Decreases TNF(\alpha) in a dose-dependent manner in LPS-stimulated neonatal rat myocytes</td>
<td>Wagner et al., 1998</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Antiarrhythmic agent</td>
<td>1985</td>
<td>Ventricular arrhythmias, supraventricular arrhythmias</td>
<td>No data</td>
<td>Concentration-dependent decrease in LPS-stimulated human PBMC</td>
<td>Matsumori et al., 1997b</td>
</tr>
<tr>
<td>Etanercept</td>
<td>TNF(\alpha) inhibitor</td>
<td>1998</td>
<td>Rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, active arthritis, psoriatic arthritis, active ankylosing spondylitis</td>
<td>TNFR-2 fusion protein (extracellular domain of TNFR-2 is fused to Fc region of human IgG(_1), which binds and inactivates TNF(\alpha))</td>
<td>No data.</td>
<td>Deswal et al., 1999, Anker &amp; Coats, 2002b</td>
</tr>
<tr>
<td>IC14</td>
<td>LPS receptor blocker</td>
<td>Not approved</td>
<td>Not approved</td>
<td>Chimeric (mouse/human) monoclonal antibody, which blocks the monocylic LPS-</td>
<td>Dose-dependent reduction of TNF(\alpha)</td>
<td>Genth-Zotz et al., 2006</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Year</td>
<td>Description</td>
<td>Mechanism</td>
<td>Effect</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>Infliximab</td>
<td>TNFα inhibitor</td>
<td>1998</td>
<td>Crohn’s disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis</td>
<td>Chimeric (mouse/human) IgG1 monoclonal antibody, which binds and neutralises soluble and membrane-bound TNFα</td>
<td>Decreased serum levels of TNFα immediately after infusion, but significantly elevated at all other time points</td>
<td>Chung et al., 2003</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Adrenergic receptor agonist (β₁, β₂)</td>
<td>1956</td>
<td>Mild or transient episodes of heart block, serious episodes of heart block and Adams-Stokes attacks, bronchospasm occurring during anaesthesia, bronchospasm associated with acute and chronic asthma</td>
<td>No data</td>
<td>Dose-dependent reduction of TNFα release from human whole blood</td>
<td>von Haehling et al., 2005c</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Adrenergic receptor agonist (α₁, α₂, β₁)</td>
<td>1950</td>
<td>Blood pressure control in certain acute hypotensive states</td>
<td>No data</td>
<td>Dose-dependent reduction of TNFα release from human whole blood</td>
<td>von Haehling et al., 2005c</td>
</tr>
<tr>
<td>Ouabain</td>
<td>Positive inotropic drug</td>
<td>Not approved</td>
<td>Not approved</td>
<td>Inhibits TNFα transcription in LPS-stimulated human PBMC (possibly Na⁺/K⁺-ATPase dependent)</td>
<td>Concentration-dependent decrease in LPS-stimulated human PBMC; inhibits LPS-dependent</td>
<td>Matsumori et al., 1997a</td>
</tr>
<tr>
<td>Drug</td>
<td>Category</td>
<td>Year</td>
<td>Disease/Condition</td>
<td>Mechanism</td>
<td>Effect</td>
<td>References</td>
</tr>
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</tr>
<tr>
<td>Pentoxifylline</td>
<td>Orphan drug</td>
<td>1984</td>
<td>Chronic peripheral artery disease</td>
<td>Inhibition of TNFα gene transcription</td>
<td>Increase of TNFα plasma level in mice</td>
<td>Sliwa et al., 1998, Sliwa et al., 2004, Skudicky et al., 2001</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory agent</td>
<td>Re-apprved 1998</td>
<td>Erythema nodosum leprosum, newly diagnosed multiple myeloma</td>
<td>Enhances TNFα mRNA degradation</td>
<td>Selective decrease in human monocyte TNFα production</td>
<td>Sampaio et al., 1991, Moreira et al., 1993</td>
</tr>
<tr>
<td>Vesnarinone</td>
<td>Positive inotropic drug</td>
<td>Not approved</td>
<td>Not approved</td>
<td>Inhibits TNFα transcription in LPS-stimulated human mononuclear phagocytes (possibly K⁺-channel dependent)</td>
<td>Concentration-dependent decrease in LPS-stimulated human mononuclear phagocytes and whole blood</td>
<td>Kambayashi et al., 1996, Matsumori et al., 1994</td>
</tr>
</tbody>
</table>
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LEGENDS

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