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# Heart failure and cachexia: insights offered from molecular biology

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## 1. ABSTRACT

Chronic heart failure (CHF) is an enormous medical and communal burden. The syndrome is common, carries a grim prognosis and severely impacts quality of life. Those patients who develop cardiac cachexia combat both important disability and a poor outlook. Muscle wasting is a critical component of cachexia. The pathophysiological determinants are numerous and some of them are common to other chronic severe illnesses. There is increasing awareness, however, that heart failure related myopathy is a distinct entity, characterized by specific functional, structural and morphologic changes and the involvement of several neurohormonal pathways, catabolic processes, a pro-inflammatory environment and increased oxidative stress. Although clear-cut evidence based solutions for the problem are not readily available, the modulating effects of regular exercise in CHF patients suggest that physical training should at least be incorporated in the essentially multi-disciplinary approach.

## 2. CHRONIC HEART FAILURE: BEYOND THE LIMITS OF THE HEART

Pathophysiological insights into the syndrome of chronic heart failure (CHF) have witnessed a paradigm shift. Until two decades ago, central haemodynamic disturbances seemed to perfectly fit the cardinal symptoms of CHF, with *fatigue* being the clinical translation of "forward failure" and *dyspnoea* reflecting the consequences of "backward failure". However, several observations have undermined the haemodynamic model of CHF. Left ventricular dysfunction, for instance, does not necessarily concur with compromised exercise capacity in patients with CHF (1). In addition, restoration of haemodynamics to near normal with inotropic drugs or after cardiac transplantation does not acutely improve physical capacity (2). Two important developments have dramatically changed heart failure research. First, there is the recognition that neurohormonal adaptation, providing initial haemostasis, eventually gives rise to a vicious circle, which encompasses

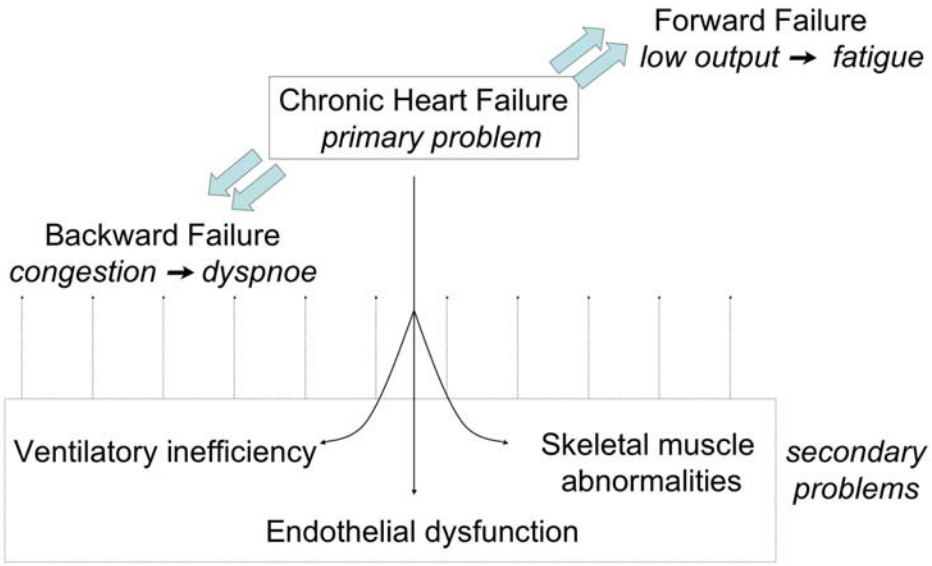


**Figure 1.** Chronic heart failure: a systemic disease. Primary cardiac dysfunction will lead to both symptoms of backward (dyspnoea) and forward failure (fatigue). With time, however, secondary maladaptations occur. Peripheral endothelial dysfunction, ventilatory inefficiency and skeletal muscle abnormalities have major impact on the symptoms and progression of the disease.

further deterioration of cardiac function and ventricular remodelling. Overstimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone pathway (RAAS), a low-grade inflammatory state and a profound anabolic-catabolic dysbalance are central elements of the disturbed neurohormonal network. Second, the concept of CHF as a mere cardiologic entity has been modified. The syndrome is now considered to be a multi-facetted systemic disease. CHF comprises an inciting cardiac event, which thereafter triggers the onset of several peripheral maladaptive processes (3). Three principal players in this field account for a significant part of heart failure symptoms. First, both at rest and during exercise, peripheral vasomotor tone is increased and vasodilatory responses are reduced. Mediated by the above-described neurohormonal disturbances, oxidative stress and deficient NO-mediated endothelial function play an essential role in this process. Secondly, excessive ventilation, particularly during exercise, causes a shift in the slope of the linear relationship between minute ventilation and $CO_2$ production. This ventilatory inefficiency is thought to origin from ventilation/ perfusion defects and more importantly, from an overactive muscle ergoreflex system. Lastly, and this is the main focus of this review, muscular alterations covering the entire range of macroscopic (i.e. loss of muscle bulk) (4) to histological (5) and ultrastructural changes (6, 7) , as well as functional abnormalities related to fibre shift (from slow oxidative type I to glycolytic type II fibres) (5-8) have been implicated. Figure 1 illustrates the intricate coupling of these different elements of the CHF-phenotype.

## 3. CARDIAC CACHEXIA: IS IT RELEVANT?

Within certain limits, a unifying pathogenesis, shared by several severe chronic diseases, ultimately leads to a general wasting syndrome. Although starvation can be relevant in patients with CHF, cancer, chronic obstructive pulmonary disease and AIDS, the fact that tissue loss in these patients is not limited to the fat compartment, suggests that other processes are at play. The occurrence of cachexia, irrespective of the underlying disease, infers poor prognosis and physical limitation. Anker and colleagues were the first to suggest a simple, objective criterion for the definition of cardiac cachexia. In the absence of other cachectic disease states, clinical cardiac cachexia can be diagnosed when non-intentional weight loss of > 7.5% of the previous normal and "dry" weight occurs over a period of at least 6 months. In a group of 171 patients with CHF, these investigators demonstrated that the cachectic state is an independent risk factor for poor outcome with a mortality rate after 18 months of 50% compared to 17% in non-cachectic patients (9). Later on, studying 1929 patients enrolled in the SOLVD trial, the poor outlook for weight-losing CHF patients was confirmed. At 8 months follow-up, all pre-defined cut points (i.e. 5, 7.5, 10 and 15%) for weight loss were significantly associated with impaired survival after adjustment for demographic characteristics, functional class, cardiac function and treatment allocation. Weight loss of 6% or more at any time was the strongest predictor of impaired survival (10) and its prevalence attained 12-15% of CHF patients in NYHA functional class II-IV. When judging a patient's condition, it is important to stress the fact that the *process* of weight loss cannot be interchanged with low body weight per se. Other confounding factors that complicate objective assessment result from fluctuating body weight related to congestion and diuretic treatment. Besides being a negative prognostic indicator, skeletal muscle wasting obviously affects global exercise performance and muscle strength, which are reflected in fatigue and low quality of life. Preservation of muscle mass is an independent determinant of peak oxygen

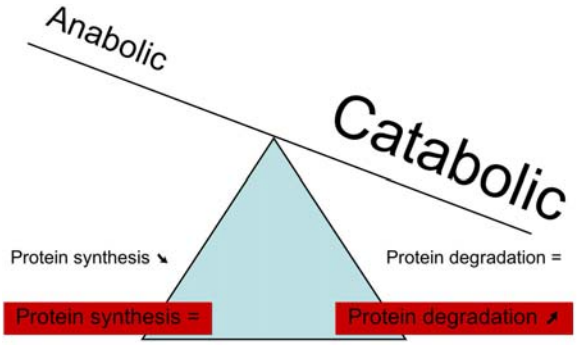


**Figure 2.** Cardiac cachexia: anabolic/catabolic imbalance. Despite the fact that both protein synthesis and degradation could be implied in muscular wasting, most of the evidence points into the direction of increased protein breakdown as a result of increased catabolism.

consumption ($VO_2$peak) in CHF patients (11). Harrington *et al.* (12) compared symptomatic with asymptomatic CHF patients ($VO_2$peak 14.6 + 1.3 versus 27.1 + 1.6 ml/kg/min), who were otherwise well matched for demographic characteristics and left ventricular function. Besides differences in peak leg blood flow, there was a significant reduction in cross sectional area (CSA) of the quadriceps muscle, which concurred with reduced muscle strength and increased fatigue in the symptomatic group. In addition, overactivation of the muscle ergoreflex, being a driving force for hyperventilation during exercise in CHF, appears strongly related to reduced muscle mass (13). Although the functional implications of skeletal muscle wasting catch the eye, tissue loss is not limited to the muscular compartment. Patients with cardiac cachexia suffer from a general loss of fat, lean, bone tissue and bone density (14).

## 4. MORPHOLOGIC, METABOLIC AND FUNCTIONAL CHANGES IN SKELETAL MUSCLE

Reduced quadriceps and total leg muscle CSA partly accounts for impaired maximal isometric strength and early fatigability in CHF patients. After correction for CSA, however, lower strength per unit muscle when compared to controls, implicates that muscle "quality" is also affected (12). Several histological and biochemical changes have been repeatedly reported in an attempt to explain the functional deficit of peripheral skeletal muscle in the setting of CHF. Increased collagen content (fibrosis) differentiated the skeletal musculature from cachectic versus non-cachectic CHF patients in a study by Filippatos *et al* (15). The correlation between endothelial cells/fibre and VO2peak in class II/III CHF patients suggests that reduced microvascular density of skeletal muscle might precede other muscle alterations (16). Ultrastructural abnormalities, such as lower mitochondrial volume (6), a decrease in the surface density of cytochrome c oxidase-positive mitochondria, of mitochondrial cristae and mitochondrial inner border membrane corroborate with the long known typical shift towards type IIx fibres (7). With the use of $^{31}$P nuclear magnetic resonance spectroscopy, a rapid depletion of phosphocreatine and a lower rate of resynthesis during exercise have been shown (17). Hambrecht and colleagues (18) demonstrated that reduced availability of mitochondrial creatine kinase (mi-CK), responsible for transfer of high-energy phosphates from the mitochondrion to myosin filaments, might account in part for compromised energetics. The simplified view of a muscle myopathy in CHF characterized by a shift from an oxidative to a more glycolytic phenotype is in contrast with the complex and incompletely understood alterations in skeletal muscle mitochondrial function (19). In a very elegant experiment, Mettauer *et al* (20) compared oxidative capacity of skeletal muscle of CHF patients with sedentary and active controls. Despite lower VO2peak, muscle oxidative capacity and regulation were comparable in the CHF and sedentary group, suggesting that disease-specific metabolic muscular changes in CHF patients take place upstream of mitochondria.

## 5. HOW DO CHF PATIENTS LOSE SKELETAL MUSCLE MASS?

### 5.1. Substrate utilization

Figure 2 illustrates a simplified view of what cardiac cachexia is all about; a profound imbalance between anabolic and catabolic factors, eventually culminating in loss of muscular mass. In theory, 2 possible scenarios exist. However, most of the gathered evidence to date, points towards the direction of protein degradation overpowering protein synthesis. The profound shift in substrate utilisation in CHF patients entails increased circulating levels and oxidation of free fatty acids (FFA), decreased skeletal muscle uptake and use of glucose and, importantly, increased protein turnover and breakdown (21). The interplay between the hyperadrenergic status, promoting lipolysis and thereby increasing FFA concentration, and the presence of insulin resistance (22), favours this less efficient metabolic divergence. Myofibrillar proteins are particularly important in the preservation of muscle mass and function. Myosin heavy chain (MHC) comprises about a quarter of cellular protein mass and is a key structural and functional component of myofibrils. Toth and colleagues (23) demonstrated that, in contrast to actin, MHC content in vastus lateralis biopsies from CHF patients was decreased in relation to disease severity. Since no changes in fractional MHC synthesis occurred, this finding suggests increased protein breakdown as a plausible mechanism. Differences in myofibrillar gene expression are suggested to explain the specific skeletal muscle myofibrillar protein phenotype (i.e.; shift from Type I to type Type IIx fibres) (24).

The relevance of nutrition adequacy, energy availability and basal metabolic rate is still debated. Poehlman *et al.* (25) , comparing CHF patients (mainly NYHA class III) and matched controls, showed a 18% higher resting metabolic rate, which was significantly correlated with reduced fat-free mass. Data obtained from non-obese and clinically stable CHF patients indicate that inadequate calorie and protein intake, together with reduced energy availability might trigger the development of muscle wasting (26). Higher resting energy expenditure has been attributed to sympathetic overactivity, whereas

stimulated thermogenesis might result from increased leptin levels. Whole-body protein metabolism in CHF patients appeared to be affected only if resting hypermetabolism coexisted (27). Of note, in this study, a pro-inflammatory status favoured protein breakdown. Overall, several components of the neuro-hormonal network, involved in the development of cachexia, affect food intake, energy expenditure and substrate utilization (see further).

### 5.2. Processes involved in the loss of skeletal muscle protein

There is a very tight regulation of intracellular protein degradation, for which multiple proteolytic systems exist. Of particular interest in the setting of cardiac cachexia, is the ubiquitin-proteasome system (UPS) (28). In this system, proteins are first tagged for degradation by ubiquitin. The process of ubiquitination is repeated, until a chain of several ubiquitin molecules are linked to each other and to the protein substrate. This is an energy consuming process involving several enzymes and carrier proteins. Ubiquitin is activated by the E1 enzyme, resulting in the formation of ubiquitin-E1 thiol ester, which is then recognized by E2 enzymes, to which ubiquitin is transferred. E2 serves as an ubiquitin-carrier protein and delivers ubiquitin to the target protein with the aid of E3 (ubiquitin ligase), which is responsible for the target selection and specificity. After polyubiquitination, the modified protein is rapidly degraded by a very large cytosolic proteolytic complex, the 26S proteasome, again requiring ATP to function. It appears that multiple types of skeletal muscle atrophy involve a common program of UPS-related changes in gene expression. There appears to be an impressive upregulation of the E3 ligases atrogin 1/MAFbx and MuRF-1 in fasted mice, in rats with cancer cachexia, streptozotocin-induced diabetes, uraemia and after disuse (29, 30). Recently, the upregulation of these E3 ligases has been demonstrated in atrophic muscle (31), as well as in the myocardium in animal heart failure models (32) and in skeletal muscle biopsies of CHF patients.

Apoptosis or programmed cell death has also been put forward as a mechanism contributing to the reduction of muscle mass. Although the potential consequences of the loss of a single nucleus in a multi-nucleated muscle fibre seem limited at first glance, the nuclear domain theory supports the notion that each nucleus controls a specific cytoplasmatic territory. Data have been published on the presence of apoptotic nuclei in skeletal muscles of CHF patients. In a small selective patient group scheduled for surgical revascularisation, skeletal muscle contained a higher number of TUNEL positive nuclei compared to controls (33). Tissue concentrations of caspase 3 and ubiquitin were increased, whereas the anti-apoptotic protein bcl-2 was decreased. There was an inverse relationship between TUNEL positive nuclei and both fibre cross sectional area and $VO_2$peak. Adams *et al.* confirmed these findings (34). A larger group of CHF patients was divided according to the presence of apoptosis or not. Besides a significantly lower exercise capacity, the apoptosis-positive subgroup was characterized by increased iNOS and a lower bcl-2 expression. However, the lack of specificity of the TUNEL technique, which is often used to detect DNA fragmentation, might lead to overestimation of the relevance of apoptosis in this particular context. In our experience, skeletal muscle apoptosis in mild to moderate CHF patients could not be confirmed (35). Despite the presence of TUNEL positive nuclei in biopsies taken from the vastus lateralis muscle of CHF patients, confirmatory immunohistochemical analyses, using antibodies against cleaved caspase 3 and cleaved poly ADP-ribose polymerase (PARP) were negative. In addition, several TUNEL-positive nuclei also stained positive with SC35 splicing antibodies, indicating active gene transcription and thus precluding apoptosis.

Skeletal muscle satellite cells reside under the basement membrane, surrounding myofibres. Considered to guard muscular integrity, they awake from a quiescent state in case of muscle damage and re-enter the cell cycle. By fusing together or to existing myofibres, respectively, replacement or repair of injured tissue takes place. Although speculative, the limited proliferative capacity of residing satellite cells (≈ 50-60 doublings) might be overwhelmed by repeated skeletal muscle injury (i.e.; inflammation, oxidative stress, catecholamines). In addition, several neurohormonal maladaptations that characterise CHF might disorganise the satellite cell population. Recent studies have demonstrated the presence of another population of progenitor cells, identified as c-kit positive stem cells (36). Compared to healthy individuals, their number in skeletal muscle biopsies of CHF patients is significantly lower. If these cells actually contribute to skeletal muscle regeneration, the poor recruitment of circulating stem cells in CHF might be another limiting factor for skeletal muscle repair.

## 6. DISRUPTION OF THE NEUROHORMONAL BALANCE: MEDIATORS OF SKELETAL MUSCLE WASTING

There is no doubt that numerous factors act upon the skeletal muscle in CHF, but the neurohormonal environment seems to be critical in this regard (Figure 3).

### 6.1.“Classical” neuroendocrine pathways: catecholamines and the RAAS

There is a significant upregulation of so-called stresshormones in cachectic versus non-cachectic CHF patients (37). It has long been known that catecholamines catalyze the vicious circle that characterizes the CHF syndrome. Besides the devastating consequences of their toxic myocardial and vascular effects, the peripheral musculature is also submitted to mainly beta-2 receptor mediated adrenergic effects. Both necrotic and apoptotic catecholamine-induced cell death, especially of slow-twitch fibres, have been described (38). Preliminary evidence suggests that weight gain, especially in cachectic CHF patients, can be obtained with the use of beta-blocker therapy (39, 40). Of note, there is important crosstalk between the peripheral skeletal muscle and the sympathetic nervous system. Indeed, increased ergoreflex sensitivity, which is related to reduced muscle mass in CHF patients, directly stimulates sympathetic drive, resulting in disruption of the autonomic nervous system (12).

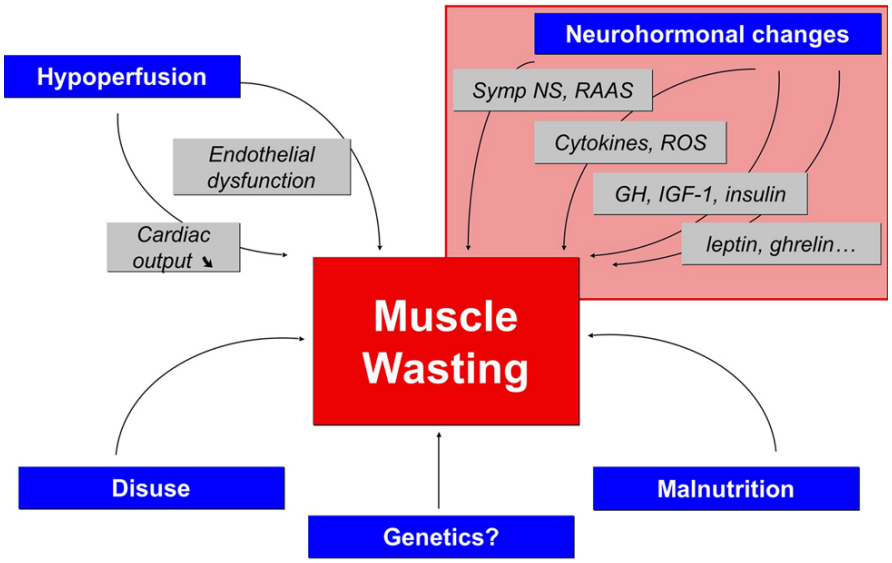


**Figure 3.** Determinants of muscle wasting in chronic heart failure. Several factors are responsible for the muscle changes observed in the setting of chronic heart failure. Despite the initial compensatory function, however, disturbance of the neurohormonal network is particularly relevant in the pathogenesis of muscular wasting.Symp NS: sympathetic nervous system, RAAS: renin-angiotensin-aldosterone system, ROS: reactive oxygen species, GH: growth hormone, IGF-1: insulin-like growth factor –1.

In animal experiments, angiotensin II induces pressor-independent weight loss, probably due to a significant anorexigenic effect. However, the observed concomitant increased protein breakdown and the reduction in circulating and local skeletal insulin-like growth factor 1 (IGF-1) levels also implicate metabolic consequences (41, 42). The muscular upregulation of Murf-1 and MAFbx mRNA implies an important role for the UPS. In transgenic mice with skeletal muscle specific IGF-1 expression, these changes were blocked (43). Skeletal muscles express angiotensin (AT)-1 receptors and the administration of angiotensin II in the rat results in myocyte apoptotic cell death (44). Dalla Libera *et al.* showed that in the monocrotaline induced CHF model, AT1 receptor blockade protected apoptosis-dependent skeletal muscle atrophy and CHF-related changes in the MHC pattern (45). Aldosterone injections induced skeletal muscle apoptosis in the soleus muscle of the rat, an effect that could be prevented by the prior administration of spironolactone (46). Similar to catecholamines, and probably mediated through the sympathetic nervous system, angiotensin II appears to induce lipolysis in subcutaneous and visceral fat (47).

### 6.2. Anabolic/catabolic imbalance

Anabolic deficiency is related to abnormalities in 3 anabolic endocrine systems: the gonadal, adrenal and somatotropic axes. The cortisol/dehydroepiandrosterone (DHEAS) ratio in cachectic CHF patients is significantly increased and clearly related to lean tissue mass (14). In men with CHF, reduced testosterone, DHEAS and IGF-1 levels were independent markers of poor prognosis (48). Acquired growth-hormone (GH) resistance is a feature of severe catabolism. Its presence in other critical illnesses has stimulated interest in a possible role in the pathophysiology of cardiac cachexia. GH exerts catabolic actions via activation of somatomedins, of which IGF-1 is considered a main component. The classical pattern of GH resistance entails an increased GH level without a proportional rise in IGF-1. Niebauer *et al.* (49) divided CHF patients according to their IGF-1 level and showed a significant skeletal muscle functional and mass deficit in the legs of those with low levels. The ratio of IGF-1/GH appears significantly reduced in cachectic CHF patients (50). Interestingly, the most important predictor of this ratio was the level of GH-binding protein, which is identical to the GH receptor ectodomain and reflects the cellular GH receptor status. Anker and co-workers meticulously investigated the GH-IGF-1 axis and proposed that the increase in IGF-1 levels upon GH treatment in CHF patients depends on circulating concentrations of GH-binding protein. These observed changes in circulating levels could be just the tip of the iceberg, since Hambrecht and colleagues (51) demonstrated that even in non-cachectic CHF patients, local skeletal muscle IGF-1 production is decreased, whereas the IGF-1 receptor is upregulated. In this study, local IGF-1 expression was related to muscle CSA. Transgenic overexpression of locally acting IGF-1 inhibited UPS-mediated muscle atrophy in a CHF mice model (52). In addition, preliminary evidence supports the concept that local IGF-1 may act as a regenerative agent, increasing stem cell recruitment to sites of muscle injury and resulting in accelerated myogenic differentiation (53).

Chronic heart failure is to be considered an insulin-resistant state (22), which has an important effect on survival (54). Besides a shift in substrate utilisation, insulin resistance is inversely related to exercise capacity. This effect might be partly mediated by functional skeletal

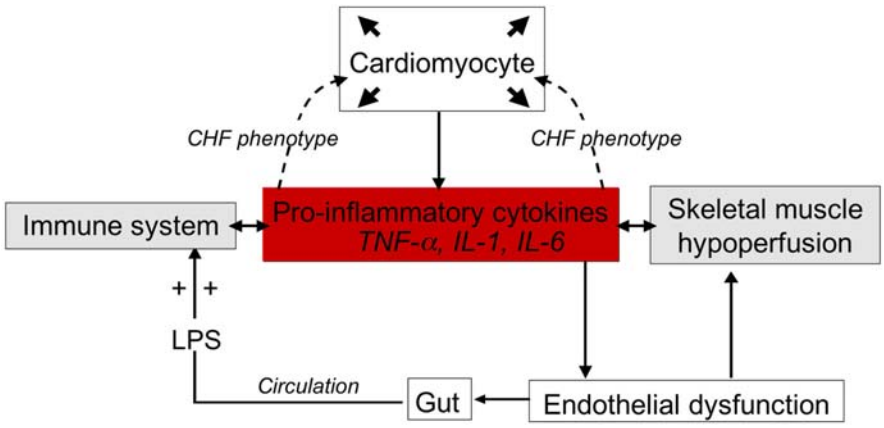


**Figure 4.** Pro-inflammatory adaptations in the setting of chronic heart failure. It is very likely that pro-inflammatory cytokines are produced in variable organs and tissues in the setting of chronic heart failure. Moreover, these cytokines not only contribute to the circulating pool, they also have para- and endocrine function, mostly with detrimental consequences. Whereas circulating pro-inflammatory cytokines are capable of inducing the heart failure phenotype, the local production by cardiomyocytes is probably the result of haemodynamic overload (arrows). Pro-inflammatory cytokines reduce endothelial vasodilatory capacity, which in turn leads to skeletal muscle and gut underperfusion. Skeletal muscles release pro-inflammatory cytokines secondary to hypoxia. The translocation of lipopolysaccharide (LPS) or endotoxin into the circulation could be an important trigger for immune activation.

muscle impairment, but muscle wasting as a result from activation of the UPS through suppression of PI3K/Akt signalling has also recently been described (55).

### 6.3. Inflammation and oxidative stress

The seminal work of Levine and colleagues, published in 1990, opened a whole new area of heart failure related research (56). These authors documented elevated levels of the pro-inflammatory cytokine tumour necrosis factor (TNF)-α in cachectic CHF patients. Since then, it has become clear that pro-inflammatory cytokines and their receptors are produced in multiple organs and tissues in the setting of CHF (Figure 4) (57-59). The independent prognostic role of pro-inflammatory cytokines and their receptors has been demonstrated in large cohorts of CHF patients (60). The presumed catabolic role of TNF-α is reflected in its former quotation, 'cachectin'. Besides its anorexigenic effect, skeletal muscle atrophy and weakness are elicited by this cytokine through a variety of mechanisms. First, TNF-α and interleukin (IL)-1 impair myogenesis through the activation of the transcription factor nuclear factor-κB, which may lead to the inability of satellite cells to differentiate into functional fibres after damage *in vivo* (61). Secondly, the pro-apoptotic effect of TNF-α at the level of the skeletal muscle could be relevant (62). Finally, TNF-related muscle atrophy is mediated by p38 MAPK signalled expression of MAFbx, resulting in activation of the UPS (63). Reactive oxygen species (ROS) are likely to function as a second messenger after TNF-receptor binding. Cytokines and circulating soluble TNF receptor levels correlate with exercise performance of CHF patients (64). The local mRNA expression of IL-1, IL-6, TNF-α and iNOS illustrates the para- and autocrine function of these cytokines (65). In a rat model, Janssens *et al.* (66) demonstrated that even short-term exposure to IL-6 significantly reduces the cross-section of both type I and type II muscle fibres. The intricate link between local inflammation and oxidative stress is reflected by the concomitant increased expression of pro-inflammatory cytokines and the downregulation of radical scavenger enzymes, resulting in increased rates of apoptosis when compared to sedentary controls (67).

### 6.4. Leptin

Recently, several new candidates for lean and fat body mass regulation in CHF have been studied. Leptin is the adipocyte product of the ob gene, with a direct inhibitory effect on neuropeptide Y, which is located mainly in the hypothalamus (68). Leptin induces saturation, it reduces lipid synthesis and increases energy expenditure and thermogenesis. The adipocyte origin of leptin explains its relationship and regulation by body weight and the amount of fat tissue. This negative feedback mechanism appears to be disturbed, since fat-corrected leptin levels in CHF patients are higher than normal. However, no difference between cachectic and non-cachectic CHF patients has been reported (69). The close relationship of leptin levels with the previously mentioned GH-BP suggests that leptin might play a role in GH resistance.

### 6.5. Ghrelin

Ghrelin is a GH releasing peptide derived from the stomach that stimulates food intake resulting in a positive energy balance. It also has anti-inflammatory, anti-apoptotic and vasodilatory effects and it reduces the activation of the central nervous system. Nagaya and colleagues (70) nicely demonstrated that cachectic CHF patients show significantly increased levels of circulating ghrelin, which tended to increase with the severity of the disease and were related to plasma levels of GH and TNF-α. These researchers proposed that ghrelin levels are elevated in CHF as a sort of compensatory mechanism. Intravenous infusion of ghrelin in 10 CHF patients apparently augmented food intake without an impressive

rise in body weight, but with a significant increase in lean body mass (71). In addition, left ventricular function and exercise capacity significantly improved.

## 7. HEART FAILURE RELATED MYOPATHY; WHERE DOES EXERCISE TRAINING COME IN?

Scepticism surrounding the mere existence of a specific myopathy related to CHF has fuelled the comparison with other chronic illnesses that involve skeletal muscle wasting, with age-related sarcopenia and with sedentary normal subjects.

There appears to be a very specific process of age-related loss of muscle mass, termed "age-related motor-unit remodelling", which encompasses the transition towards a slower phenotype (more type I fibres) and more pronounced atrophy of type II fibres. This shift appears to be related to denervation and subsequent reinnervation of type II fibres, although part of the denervated fibres is lost (72). Without going into detail, it is obvious from the well-known phenotypic changes observed in CHF patients, which involve exactly the opposite processes (i.e. shift from type I to type IIx fibres), that CHF related myopathy is distinct. Elderly CHF patients, however, might exhibit a "mixed" pattern, resulting in an even greater vulnerability to the disabling consequences of skeletal muscle adaptations (73).

Although the "chicken and egg" discussion will not be easily resolved, the previously described neurohormonal and molecular abnormalities that go hand in hand with the development of muscle wasting strongly suggest that this clinical entity cannot be simply attributed to muscle disuse. The implementation of exercise training in the CHF population, however, offers an effective non-pharmacological opportunity to improve exercise capacity and quality of life and also provides survival benefit (74). The fact that muscle hypertrophy, increased muscle strength, reduced muscle fatigability and enhanced aerobic capacity co-occur with the reversal of several pathways that are considered characteristic of cachexia, underscores the existence of a specific CHF related myopathy.

In a series of randomized exercise-based studies, Hambrecht *et al.* (7, 75) showed that endurance training in CHF patients induces a re-shift in fibre phenotype, together with a partial restoration of metabolic abnormalities at the level of the skeletal muscle. Improved aerobic metabolism is illustrated by the observed increase in volume density of mitochondria and of cytochrome c oxidase-positive mitochondria in biopsies taken from the vastus lateralis muscle (75). There is now ample evidence that exercise training has anti-inflammatory effects, both at the level of the skeletal muscle itself (65), and in the peripheral circulation (76, 77). Interestingly, besides the significantly down-regulated expression of TNF-$\alpha$, IL-1$\beta$ and IL-6 in the skeletal muscle of CHF patients after a 6-month program of endurance training, Gielen *et al.* (65) also found a 50% lower expression of iNOS. Later studies confirmed the anti-oxidative capacity of regular physical exercise by demonstrating the augmented activity of radical scavenger enzymes (i.e. catalase and glutathione peroxidase activity), together with decreased nitrotyrosine production (67). Exercise training reduces the level of circulating neurohormones (64, 78) and muscle sympathetic nerve activity (MSNA) (79). In line with the well-known stimulatory effect of muscular stretch on IGF-1 expression in animal studies, exercise training led to a strong increase in local skeletal muscle IGF-1 expression, despite the lack of changes in circulating levels of both GH and IGF-1 (80).

An important issue that has been insufficiently addressed until now, is the choice of training modalities for this specific population. Although it is tempting to speculate that resistance training will preferentially tackle and reverse muscle atrophy, a direct comparison of endurance and resistance training is urgently needed. There is evidence to support the notion that resistance training in these patients is safe and effective (81). In addition, many of the observed effects of endurance training have been duplicated with the use of resistance training in CHF patients. This is true for changes in the autonomic nervous system (82) and restoration of peripheral endothelial function (82, 83). Comprehensive training programs, combining dynamic resistive exercise with regular endurance training are gradually gaining popularity in severely debilitated CHF patients. Neuromodulation (64) as well as anti-inflammatory properties (76) have been ascribed to combined resistance-endurance exercise training.

## 8. CONCLUSIONS

It has taken the medical community a long time to fully recognize the detrimental consequences of muscular wasting and this is particularly true for cardiologists. The term cachexia already appears in ancient literature. Although Hippocrates associated "melting of the thighs" with poor prognosis, basic scientists have only recently begun to explore this fascinating field. Cachexia characterizes the end stage of numerous chronic illnesses. Therefore, important breakthroughs in deciphering this complex disease state are expected to surface from various domains in medicine. Pathophysiological insight is a requisite for the development of therapeutic strategies designed to reverse or halt muscular wasting. Although post hoc analyses of large randomized drug trials provide substantial support for the idea that optimal evidence based CHF treatment is beneficial, a specific anabolic approach for cardiac patients with cachexia is still lacking. The complexity of this disorder will necessitate a multi-facetted and multi-disciplinary approach. Although detailed information is beyond the scope of this review, efforts to evaluate the effects of exercise training, nutritional optimization, neurohormonal modulation, anti-inflammatory approaches, GH and ghrelin infusions are being actively pursued.

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