Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
The International Journal of Biochemistry & Cell Biology 37 (2005) 1938–1947
IJBCB
www.elsevier.com/locate/biocel

Short communication

Muscle wasting in cardiac cachexia

Sabine Strassburg [a], Jochen Springer [a], Stefan D. Anker [a,b,*]

[a] *Division of Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany*
[b] *Imperial College, NHLI, Department of Clinical Cardiology, London, UK*

Received 8 October 2004; received in revised form 1 March 2005; accepted 22 March 2005

Abstract

Cardiac cachexia is a serious complication of chronic heart failure which is characterized by complex changes that overall lead to a catabolic/anabolic imbalance resulting in body wasting and a poor prognosis. The wasting process affects all body components, but particularly the skeletal musculature, causing extreme fatigue and weakness, especially in cachectic heart failure patients. Available evidence suggests that several pathophysiologic pathways play a role in the muscle wasting process. Metabolic, neurohormonal, and immune abnormalities lead to an altered regulation of proliferation, differentiation, apoptosis, and metabolism in skeletal muscle, finally resulting in deterioration of the underlying cause with symptomatic exercise intolerance. Possible treatment strategies against muscle wasting and cachexia in chronic heart failure are also described here. As there is no validated therapy for cardiac cachexia yet, further research is necessary to find more therapeutic options for the wasting process.

Keywords: Muscle; Cachexia; Wasting; Chronic heart failure

1. Introduction

Cardiac cachexia is a serious complication of chronic heart failure (CHF) with a prevalence of 10–16% (Anker, Ponikowski, et al., 1997; Sharma & Anker, 1999). It can be defined as documented weight loss of >6.0% of the previous normal weight which is observed over a period of >6 months without signs of other primary cachectic states (e.g. cancer) (Anker, Negassa, et al., 2003). The dominant feature of cardiac cachexia is significant body wasting, mainly with the loss of lean tissue (muscle mass, Fig. 1) (for review see: Anker & Sharma, 2002; Davos et al., 2003). Muscle wasting in chronic heart failure is probably not due to a single factor, but is rather influenced by many factors which interact in a complex system with metabolic, immune, and neurohormonal alterations. Other issues that are important in the pathophysiology are an impaired skeletal muscle blood flow, muscle structure alterations, intestinal malabsorption, and physical inactivity. Furthermore, tissue ischemia and

Abbreviations: TNF-α, tumor necrose factor alpha; NYHA, New York Heart Association; NO, nitric oxide; (i)NOS, (inducible) nitric oxide synthase; GH, growth hormone; IGF-1, insulin-like growth factor 1

* Corresponding author. Tel.: +49 30 450 553463; fax: +49 30 450 553951.
E-mail address: s.anker@imperial.ac.uk (S.D. Anker).

1357-2725/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2005.03.013

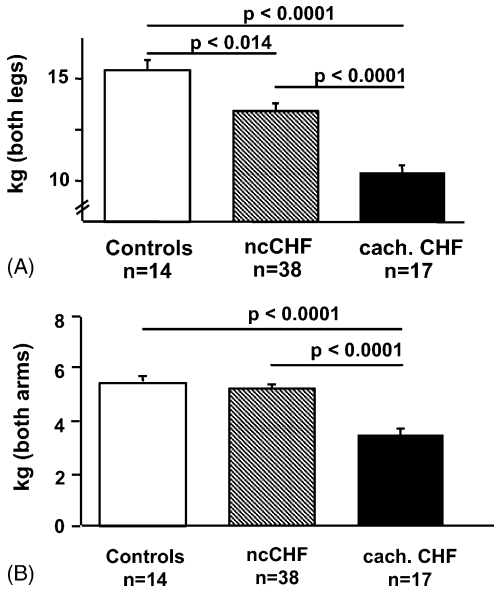

Fig. 1. Body composition analysis of skeletal muscle mass of (A) legs and (B) arms in non-cachectic (ncCHF), cachectic (cach) CHF patients and controls. Body composition measurements determined by dual X-ray absorptiometry. All results in mean ± S.E.M. (Data adapted from Anker et al., 1999.)

hypoxia are the result of a lower cardiac output which is caused by cardiac dysfunction. Through activation of muscular 'metabo-ergoreceptors' shortness of breath increases during exercise. When present over a longer period of time these abnormalities induce significant changes in skeletal muscle via endothelial dysfunction, impaired vascular perfusion, development of insulin resistance, cell death, and muscle wasting. Altogether, these changes deteriorate the heart failure and the prognosis of patients and create a vicious cycle (Fig. 2).

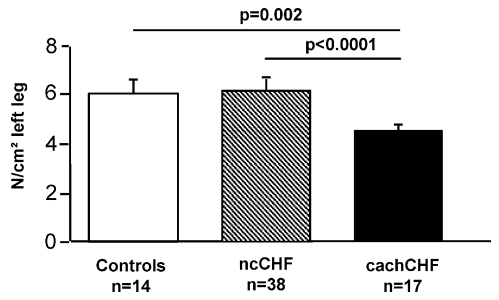

Fig. 2. Muscle weakness in heart failure. The muscle strength per unit of muscle quadrizeps area were lower in the cachectic CHF patients as shown in the example of the left leg. (Data adapted from Anker & Coats, 1999.)

This article focuses on the available knowledge concerning the pathogenesis of the muscle wasting in chronic heart failure including new developments and therapeutic approaches.

2. Pathogenesis

Available evidence suggests that in many patients increased skeletal muscle chemoreflexes are related to changes in ventilation that cannot be explained by cardiac or lung dysfunction. The muscle hypothesis describes the possible pathophysiologic link between skeletal muscle abnormalities, fatigue, dyspnoea, hyperpnoea, and the sympathoexcitation characteristics of patients with CHF (Coats, Clark, Piepoli, Volterrani, & Poole-Wilson, 1994; Piepoli et al., 1996): A reduction in left ventricular function causes several metabolic events that ultimately lead to wasting of skeletal muscle and consequent abnormalities of muscular metabolism and function. The metabolic state of skeletal muscle is centrally monitored via the activation status of 'ergoceptors' by unknown triggers. Through nerve fibers in the lateral spinothalamic tract an increase in ventilation and sympathetic outflow follows. Vasoconstriction in distant non-exercising vascular beds impacts the blood pressure and closes the link in a vicious cycle to reduce exercise tolerance and shortness of breath along with weakness, asthenia and exhaustion (Fig. 3). Muscle ergoceptors seem to play a significant role in the link between muscle wasting and exercise intolerance (Scott et al., 2000).

2.1. Limited exercise capacity

Patients with symptomatic heart failure by definition have limited exercise capacity. There are several ways to describe the degree of limitation in exercise capacity which is normally done by employing the functional New York Heart Association (NYHA) classification or by performing symptom-limited exercise testing. There are numerous reviews on how to assess exercise capacity in CHF patients (Cicoira et al., 2004; Ponikowski et al., 2001).

The precise reasons for the development of shortness of breath and premature fatigue during exercise in

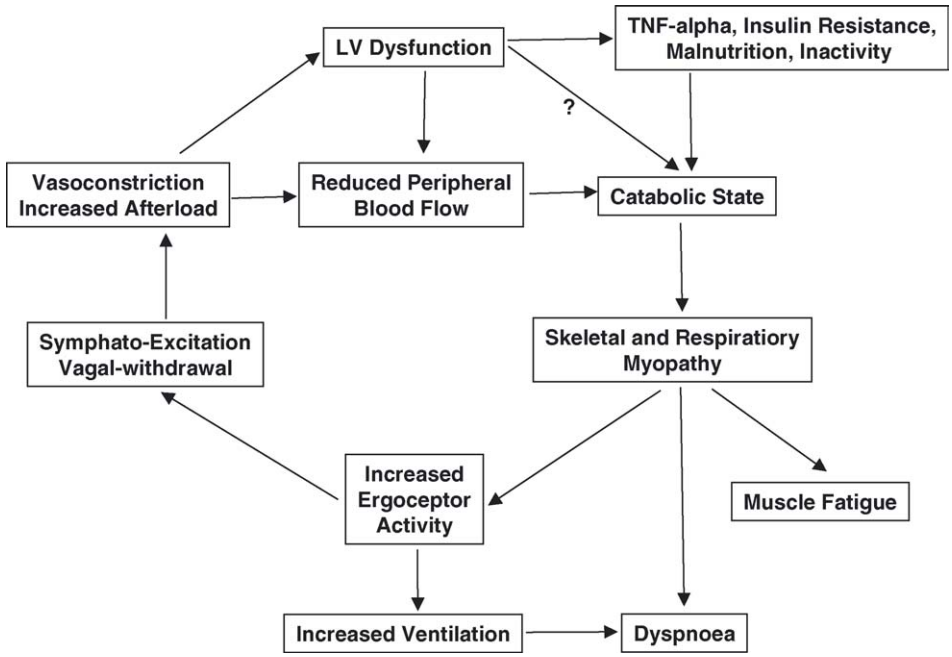

Fig. 3. The muscle hypothesis of CHF. A left ventricular (LV) dysfunction activates catabolic and reduces anabolic factors that cause skeletal myopathy. This, in turn, sensitizes muscle ergoceptors, which lead to exercise intolerance and sympatho-excitation. Through following vasoconstriction and increased afterload a further deterioration of LV dysfunction may occur. (Adapted from Piepoli et al., 1996.)

CHF patients have been researched for approximately 15 years (for review see e.g. Clark, Poole-Wilson, & Coats, 1996; Stassijns, Lysens, & Decramer, 1996). For the purpose of discussing wasting in cardiovascular illness, it is of importance to recognize that muscle wasting contributes to reduced exercise capacity in CHF. Additionally, alterations in cardiac and lung function, poor tissue perfusion due to lower cardiac output and endothelial dysfunction, as well as intrinsic muscle alterations, which lead to poor muscle performance and premature symptom generation, also contribute to impaired exercise capacity in CHF.

2.2. Structural muscle alterations

Up to 68% of CHF patients show muscle fiber atrophy, which contributes modestly to both, a reduced exercise capacity and an altered muscle metabolism (Lipkin, Jones, Round, & Poole-Wilson, 1988; Mancini et al., 1992). Accordingly, a reduced muscle cross-sectional area, a reduced maximal muscle strength, and lower electromyographic activity were found in the thigh of CHF patients, indicating an impaired muscular function in the advanced stage of heart failure (Schulze et al., 2004). A reduced capillary density and a reduced capillary-to-fiber ratio were found in muscles of CHF rats (Schieffer et al., 1995). Nevertheless, muscle capillary density reduction is apparently not the cause of exercise limitation in CHF patients (Williams et al., 2004).

In humans, an increased fibrosis was demonstrated in skeletal muscle biopsies in cardiac cachexia compared to non-cachectic CHF patients (Filippatos et al., 2003). However, apoptosis was not increased in these muscle biopsy samples. Morphological alterations, for example, loss of mitochondria and muscle fiber shift to slower fibers were found in the muscle itself and are thought to be a major cause of the exercise intolerance (Sullivan, Green, & Cobb, 1991) (Table 1).

2.3. Proteolysis and metabolism

Even a small decrease in the protein synthesis or an increase in the muscle degradation can cause a marked

Table 1
Skeletal muscle changes in heart failure

Functio leasa	Weakness
	Fatigability
Structural	Loss of muscle mass
	Atrophy, fibrosis, no ↑ apoptosis
	Fiber type switch Type I–Type IIb
	Loss of mitochondria
	Endothelial damage
Blood flow	Capillary density ↓?
	Vasodilatation
	Peak leg blood flow ↓
Metabolism	Proteolysis
	Oxidative metabolism ↓
	Acidosis
	Glycolysis ↑
Inflammation	Cytokine and oxidative markers
Neuroendocrine	GH, IGF-1, epinephrine, norepinephrine, cortisol
Inactivity	TNF-alpha ↑
Genetic factors	Myostatin, IGF

loss of body mass (Gomes-Marcondes & Tisdale, 2002; Mitch & Goldberg, 1996). The ubiquitin-proteasome pathway has been identified as the pathway for accelerated proteolysis in many, but not all, catabolic states (Combaret et al., 1996; Farges et al., 2002; Jagoe & Goldberg, 2001; Jagoe, Redfern, Roberts, Gibson, & Goodship, 2002). Recently it was found that IGF-1 and insulin suppress the expression of atrogin-1, a muscle-specific ubiquitin ligase which induces atrophy (Sandri et al., 2004). This ability of IGF-1 and Insulin constitute important new actions of these hormones that must contribute in a major way to their capacity to stimulate muscle growth.

Several metabolic abnormalities have been described in the skeletal muscle of CHF patients and biopsy studies have shown defects in oxidative and lipolytic enzymes, succinate dehydrogenase, citrate synthetase, and beta hydroxyacyl dehydrogenase (for an overview see Coats, 2002).

The reduced exercise capacity in CHF patients is to a large degree due to muscle wasting, we estimate a contribution of about 50% (Fig. 4) (Anker, Swan, et al., 1997; Volterrani et al., 1994). However, when patients are already cachectic, peripheral blood flow becomes a stronger predictor of exercise capacity than muscle mass (Anker, Swan, et al., 1997). Wilson, Martin, Schwartz, & Ferraro, 1984 suggested impaired

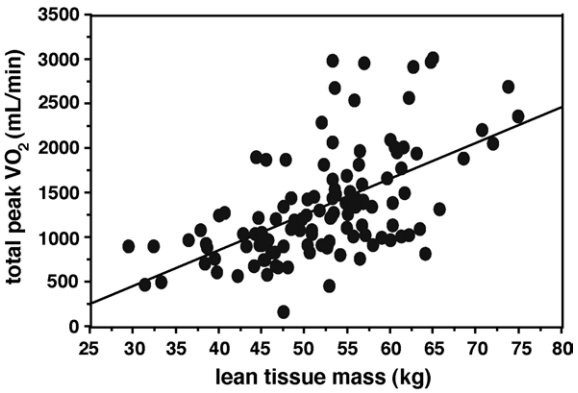

Fig. 4. Correlation of total peak oxygen uptake (VO2) vs. lean tissue in 117 CHF patients. ($r = 0.58$, $p < 0.0001$).

nutritional flow to the skeletal muscle as the reason for reduced maximal exercise capacity of CHF patients. Impaired skeletal muscle metabolism, seen in the lower and upper limbs during exercise in patients with CHF, was related to systemic exercise tolerance (Nagai et al., 2004). In contrast to this, there was no association between blood supply and muscle dysfunction in a study with CHF rats (Schiotz Thorud et al., 2004).

2.4. *Inflammatory activation*

Inflammatory activation, e.g. an increased TNF-α and other cytokines play a important role in the wasting condition (for review see: Anker & von Haehling, 2004). It was demonstrated that TNF-α directly induces skeletal muscle protein loss (Li, Schwartz, Waddell, Holloway, & Reid, 1998). There are several hypotheses regarding the cause of the TNF-α induction, as discussed elsewhere (Anker & von Haehling, 2004; von Haehling, Jankowska, & Anker, 2004). The endotoxin hypothesis suggests that endotoxin (lipopolysaccaride (LPS)) release from bowel wall edema is a strong inflammatory stimulus in CHF patients. This hypothesis is supported by two recent studies (Conraads et al., 2004; Krack et al., 2004).

There is also evidence for an increased inducible nitric oxide synthase (NOS) expression in skeletal muscle due to cytokine activation in severe CHF (Riede, Forstermann, Drexler, 1998). Increased NOS may cause muscle wasting in these patients (Coats et al., 1994).

2.5. Neuroendocrine abnormalities

Increased levels of the anabolic growth hormone (GH) are found together with low levels of its intermediary hormone insulin like growth factor-1 (IGF-1) in cachectic CHF patients. The increased GH-levels demonstrate a GH-resistance, which is of importance in the pathogenesis of the wasting process. Furthermore, increased catecholamines (norepinephrine and epinephrine) and elevated cortisol are significantly changed as described elsewhere (Anker et al., 2001; Niebauer et al., 1998).

2.6. Oxidative stress

The presence of elevated levels of markers of oxidative stress in heart failure patients correlates to functional class, reduced exercise tolerance, lower antioxidant levels and other indices of worse prognosis including cachexia (Belch, Bridges, Scott, & Chopra, 1991; Nishiyama, Ikeda, Haramaki, Yoshida, & Imaizumi, 1998). Catecholamines and cytokines stimulate the production of free radicals, which induce both, oxidative stress and expression of iNOS (Das, 2000; Hishikawa & Luscher, 1998). This activation may be via direct or indirect mechanisms involving endothelial dysfunction, tissue ischemia/hypoxia and alteration of the xanthine oxidase system (Doehner et al., 2001).

2.7. Inactivity

As mentioned before, patients with heart failure are limited in their ability to tolerate exercise and hence avoid exercise in many cases. However, in CHF there is increasing evidence that avoiding exercise can lead to changes in skeletal muscle and peripheral circulation that may impair exercise tolerance (Piepoli, Scott, Capucci, & Coats, 2001).

2.8. Genetic factors

The influence of genetic factors has not been investigated in reference to cardiovascular illness. We personally believe that a) there may be genetic factors like in cancer cachexia (Pajonk & McBride, 2001) that predispose patients to develop muscle wasting once they suffer from heart failure or chronic illness and b) that the myostatin (Bogdanovich et al., 2002), and IGF-1 (Barton-Davis, Shoturma, Musaro, Rosenthal, & Sweeney, 1998; Kuninger, Kuzmickas, Peng, Pintar, & Rotwein, 2004; Rosenthal & Musaro, 2002) systems are two important pathways in this context. Myostatin is a member of the transforming growth factor-beta family. It has been shown that blocking of the myostatin signalling pathway or genetic manipulation increase muscle mass in cattle, rodents (for review see Lee & McPherron, 1999), and humans (Schuelke et al., 2004). Therefore, manipulations of myostatin signalling may become useful for the treatment of muscle wasting. There is also evidence for the relevance of IGF-1 in cachexia. IGF-1 influences the differentiation of muscle cells (Adi, Bin-Abbas, Wu, & Rosenthal, 2002) and overexpression has been shown to block skeletal muscle wasting (Song, Li, Du, Mitch, Rosenthal, & Delafontaine, 2005). Studies on the genetics of wasting in CHF may lead to new therapeutic approaches in the future.

3. Therapeutic options

Currently, there is no validated specific therapy for muscle wasting in cardiac cachexia. The available therapeutic options cannot be discussed separately from the general treatment of advanced chronic heart failure.

The drug therapy of CHF is based on modulation of neurohormonal systems, particularly with ACE inhibitors, beta blockers and aldosterone antagonists. Anti-inflammatory and appetite stimulating drugs, and application of steroids or growth factors are possible future options, as well as inhibition of proteolysis and apoptosis. Further therapy options include nutritional support or mild exercise training. Guidelines, e.g. from the American Heart Association, the American College of Cardiology or the European Society of Cardiology, additionally suggest all treatments of advanced CHF, e.g. mechanical circulatory support, continuous positive inotropic infusions, cardiac transplantation, or hospice care in case of advanced CHF with cachexia (Hunt et al., 2001; Nieminen et al., 2005). Here we focus only on some of these issues and the new aspects of interest.

3.1. Anti-inflammatory approaches

Recent pathophysiological findings lead to the discussion that prevention of inflammatory immune acti-

vation might be a possible treatment option for body wasting. While IL-6 antibody therapy has been shown to prevent muscle atrophy and weight loss in animal models, anti-TNF-α therapy with etanercept and infliximab was not successful so far or is, like phosphodiesterase inhibitors, contradictorily discussed (Anker, Steinborn, & Strassburg, 2004). Several new cancer cachexia studies with opposing results exist about the anti-inflammatory effects of fish oil (*n*-3 polyunsaturated fatty acid), but there are no new studies in heart failure.

3.2. Neurohormonal modulators

ACE inhibitors belong to the state-of-the-art therapy in CHF and have beneficial modulating effects on neurohormones and endothelial function. This might prevent tissue damage and apoptosis in the muscle through improved nutritional status of tissues and reduction of ischemia and oxidative stress. The ACE inhibitor enalapril can reduce the frequency of future development of >6% weight loss, i.e. cachexia (Anker, Negassa, et al., 2003), likely associated with prevention of muscle wasting. However, detailed data on body composition in patients before and after treatment initiation with ACE inhibitors are not available.

Beta blockers are advantageous in cardiac cachexia to prevent and even partially reverse cachexia (Anker, Negassa, et al., 2003). In a recent study, patients with cachexia at baseline had a significantly greater weight gain compared to the non-cachectic CHF patients (mean 5.0 kg versus 0.8 kg, $p < 0.03$) after therapy with the beta blockers carvedilol or metoprolol (Hryniewicz, Androne, Hudaihed, & Katz, 2003).

3.3. Radical scavengers

The stimuli for free radical production, such as catecholamines and cytokine activation, are elevated in heart failure. Antioxidants and free radical scavengers like vitamin C and vitamin E can suppress or decompose the elevated production of free radicals in leucocytes (Herbaczynska-Cedro et al., 1995). This is further supported by a study showing that muscle wasting was prevented with an antioxidant in mice (Buck & Chojkier, 1996). Also, many micronutrients have the ability to scavenge free radicals; therefore they should be applied as food supplement.

Hyperuricemia is a hallmark of CHF and associated with poor prognosis (Anker, Doehner, et al., 2003). Lowering uric acid with the xanthine oxidase inhibitor allopurinol has been shown to have beneficial effects on endothelial function and to lower allantoin, a marker of free radical load (Bolger et al., 2002; Doehner et al., 2002; Farquharson, Butler, Hill, Belch, & Struthers, 2002). Another drug class are statins, which have been shown to counterbalance increased oxygen-free radicals in CHF and also possess anti-inflammatory characteristics (Node, Fujita, Kitakaze, Hori, & Liao, 2003; von Haehling, Anker, & Bassenge, 2003). Whether any of these therapies is useful in the context of muscle wasting in CHF patients remains – at this point in time – unclear.

3.4. Growth hormone

Increasing muscle mass in cardiac cachexia by the use of anabolic steroids may represent a further therapy option. A study in non-cachectic patients has shown promising effects (Pugh, Jones, West, Jones, & Channer, 2004), but data in cachectic patients is lacking. Important side effects, like kidney dysfunction and the potential to induce prostate hyperplasia may limit the potential of anabolic steroids particularly in patients with advanced CHF (Anker & Sharma, 2002). Growth hormone (GH) is another option for the treatment of cardiac cachexia, but high doses of GH may be necessary to overcome GH resistance in these patients (Anker et al., 2001). Alternatively, IGF-I or a combination of GH and IGF-I could be therapeutic options to overcome GH resistance (Anker, Doehner, et al., 2003; Cicoira, Kalra, & Anker, 2003).

3.5. Ghrelin

Ghrelin, a peptide hormone, causes a positive energy balance by stimulating food intake. In animal studies, ghrelin has been reported to increase body weight (Fig. 5) and to improve ventricular function (Nagaya, Kojima, et al., 2001). Elevated circulating levels of ghrelin were found in cachectic CHF patients. Plasma levels of ghrelin were found to correlate positively with TNF-α and negatively with the body mass index (Nagaya, Kojima, et al., 2001). Furthermore, there is evidence of beneficial hemodynamic effects of ghrelin: infusion of ghrelin decreased systemic

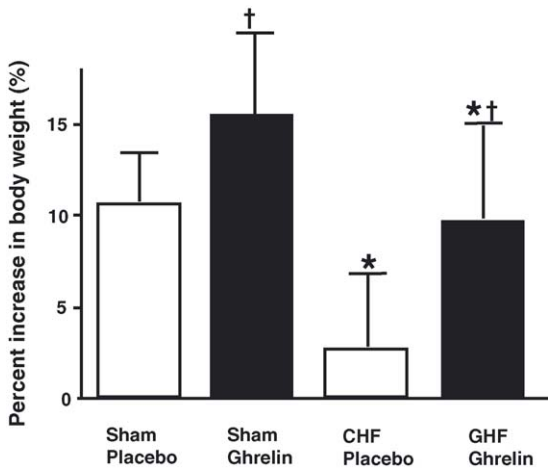

Fig. 5. Effects of ghrelin on relative changes in body weight in CHF and sham rats. Data are mean ± S.D. $^{*}p < 0.05$ vs. corresponding sham group; $^{\dagger}p < 0.05$ vs. corresponding placebo group. (Adapted from Nagaya, Uematsu, et al., 2001.)

vascular resistance and increases cardiac output in patients with heart failure (Nagaya, Kojima, et al., 2001). Although ghrelin is an endogenous ligand of the growth hormone secretagogue receptor and stimulates GH release, the vasodilatory effect of ghrelin acts trough a GH-independent mechanism (Nakagawa et al., 2002; Okumura et al., 2002). The exact mechanism of action is not clear yet, though it was already found that the pituitary, the adrenal, and thyroid glands play a role in the mechanism of action (Tschop, Flora, Mayer, & Heiman, 2002). Altogether, ghrelin or ghrelin-receptor agonists might become a therapy option in the future.

3.6. Exercise training

There is ample evidence that exercise rehabilitation reverses the muscular metabolic abnormalities and atrophy, as well as the impaired blood flow and the neurohormonal abnormalities (Adamopoulos et al., 1993; Coats, Adamopoulos, Meyer, Conway, & Sleight, 1990). Low intensity exercise training can minimize untoward cardiovascular events and increase the oxidative capacity of the skeletal musculature in patients with mild CHF, by changing oxygen uptake and mitochondrial density (Belardinelli, Georgiou, Scocco, Barstow, & Purcaro, 1995; Hambrecht et al., 1995). Exercise training has also the potential to reduce muscle cytokine expression and to increase anti-apoptotic factors like IGF-1 (Adams et al., 2002; Schulze, Gielen, Schuler, & Hambrecht, 2002). Furthermore, physical training corrected enzyme activities, like the citrate synthase activity, in rats with severe heart failure (Brunotte et al., 1995). Studies of exercise training in cachectic patients with CHF are lacking.

3.7. Gene therapy and stem cells

We are optimistic that gene therapy may become an option for treatment of cardiac cachexia in the future, but this is rather speculative at this stage. Beside the already mentioned two potential targets IGF and myostatin also stem cell therapy might become an option in the future, since the ability of muscle regeneration by bone-marrow derived progenitors could be already shown (Ferrari et al., 1998; Gussoni et al., 1999).

4. Conclusions

Cardiac cachexia is characterized by an imbalance of catabolic and anabolic body systems, which together cause the development of body wasting. There are a number of potentially important pathways that contribute to muscle wasting in CHF. At this stage it is very difficult to weigh the different pathomechanisms involved in the development of cachexia in heart failure. Altogether, neurohormonal, inflammatory and metabolic alterations as well as other factors, e.g. inactivity, and interrelations between these factors contribute to muscle wasting and cachexia in heart failure. Consequently, the possible treatment strategies are wide-ranging and we believe that in the future several pathways may need to be targeted to successfully prevent and reverse cachexia in CHF.

Acknowledgements

SS is supported by a grant from “Verein der Freunde und Förderer der Berliner Charité”, Berlin/Germany. SDA is supported with the Vandervell Fellowship (London, UK) and a donation from Dr. Hubert Bailey, London/UK. The Division of Applied Cachexia Research is supported with grant for from Charité Medical School, Berlin, Germany.

References

Adamopoulos, S., Coats, A. J., Brunotte, F., Arnolda, L., Meyer, T., Thompson, C. H., et al. (1993). Physical training improves skeletal muscle metabolism in patients with chronic heart failure. *J. Am. Coll. Cardiol.*, *21*(5), 1101–1106.

Adams, V., Nehrhoff, B., Spate, U., Linke, A., Schulze, P. C., Baur, A., et al. (2002). Induction of iNOS expression in skeletal muscle by IL-1beta and NFkappaB activation: An in vitro and in vivo study. *Cardiovasc. Res.*, *54*(1), 95–104.

Adi, S., Bin-Abbas, B., Wu, N. Y., & Rosenthal, S. M. (2002). Early stimulation and late inhibition of extracellular signal-regulated kinase 1/2 phosphorylation by IGF-I: A potential mechanism mediating the switch in IGF-I action on skeletal muscle cell differentiation. *Endocrinology*, *143*(2), 511–516.

Anker, S. D., & Coats, A. J. (1999). Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. *Chest*, *115*(3), 836–847.

Anker, S. D., Doehner, W., Rauchhaus, M., Sharma, R., Francis, D., Knosalla, C., et al. (2003). Uric acid and survival in chronic heart failure: Validation and application in metabolic, functional, and hemodynamic staging. *Circulation*, *107*(15), 1991–1997.

Anker, S. D., Negassa, A., Coats, A. J., Afzal, R., Poole-Wilson, P. A., Cohn, J. N., et al. (2003). Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: An observational study. *Lancet*, *361*(9363), 1077–1083.

Anker, S. D., Ponikowski, P. P., Clark, A. L., Leyva, F., Rauchhaus, M., Kemp, M., et al. (1999). Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur. Heart J.*, *20*(9), 683–693.

Anker, S. D., Ponikowski, P., Varney, S., Chua, T. P., Clark, A. L., Webb-Peploe, K. M., et al. (1997). Wasting as independent risk factor for mortality in chronic heart failure. *Lancet*, *349*(9058), 1050–1053.

Anker, S. D., & Sharma, R. (2002). The syndrome of cardiac cachexia. *Int. J. Cardiol.*, *85*(1), 51–66.

Anker, S. D., Steinborn, W., & Strassburg, S. (2004). Cardiac cachexia. *Ann. Med.*, *36*(7), 518–529.

Anker, S. D., Swan, J. W., Volterrani, M., Chua, T. P., Clark, A. L., Poole-Wilson, P. A., et al. (1997). The influence of muscle mass, strength, fatigability and blood flow on exercise capacity in cachectic and non-cachectic patients with chronic heart failure. *Eur. Heart J.*, *18*(2), 259–269.

Anker, S. D., Volterrani, M., Pflaum, C. D., Strasburger, C. J., Osterziel, K. J., Doehner, W., et al. (2001). Acquired growth hormone resistance in patients with chronic heart failure: Implications for therapy with growth hormone. *J. Am. Coll. Cardiol.*, *38*(2), 443–452.

Anker, S. D., & von Haehling, S. (2004). Inflammatory mediators in chronic heart failure: An overview. *Heart*, *90*(4), 464–470.

Barton-Davis, E. R., Shoturma, D. I., Musaro, A., Rosenthal, N., & Sweeney, H. L. (1998). Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function. *Proc. Natl. Acad. Sci. USA*, *95*(26), 15603–15607.

Belardinelli, R., Georgiou, D., Scocco, V., Barstow, T. J., & Purcaro, A. (1995). Low intensity exercise training in patients with chronic heart failure. *J. Am. Coll. Cardiol.*, *26*(4), 975–982.

Belch, J. J., Bridges, A. B., Scott, N., & Chopra, M. (1991). Oxygen free radicals and congestive heart failure. *Br. Heart. J.*, *65*(5), 245–248.

Bogdanovich, S., Krag, T. O., Barton, E. R., Morris, L. D., Whittemore, L. A., Ahima, R. S., et al. (2002). Functional improvement of dystrophic muscle by myostatin blockade. *Nature*, *420*(6914), 418–421.

Bolger, A. P., Sharma, R., von Haehling, S., Doehner, W., Oliver, B., Rauchhaus, M., et al. (2002). Effect of interleukin-10 on the production of tumor necrosis factor-alpha by peripheral blood mononuclear cells from patients with chronic heart failure. *Am. J. Cardiol.*, *90*(4), 384–389.

Brunotte, F., Thompson, C. H., Adamopoulos, S., Coats, A., Unitt, J., Lindsay, D., et al. (1995). Rat skeletal muscle metabolism in experimental heart failure: Effects of physical training. *Acta Physiol. Scand.*, *154*(4), 439–447.

Buck, M., & Chojkier, M. (1996). Muscle wasting and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants. *EMBO J.*, *15*(8), 1753–1765.

Cicoira, M., Davos, C. H., Francis, D. P., Doehner, W., Zanolla, L., Franceschini, L., et al. (2004). Prediction of mortality in chronic heart failure from peak oxygen consumption adjusted for either body weight or lean tissue. *J. Card. Fail.*, *10*(5), 421–426.

Cicoira, M., Kalra, P. R., & Anker, S. D. (2003). Growth hormone resistance in chronic heart failure and its therapeutic implications. *J. Card. Fail.*, *9*(3), 219–226.

Clark, A. L., Poole-Wilson, P. A., & Coats, A. J. (1996). Exercise limitation in chronic heart failure: Central role of the periphery. *J. Am. Coll. Cardiol.*, *28*(5), 1092–1102.

Coats, A. J. (2002). Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath. *Int. J. Cardiol.*, *85*(1), 133–139.

Coats, A. J., Adamopoulos, S., Meyer, T. E., Conway, J., & Sleight, P. (1990). Effects of physical training in chronic heart failure. *Lancet*, *335*(8681), 63–66.

Coats, A. J., Clark, A. L., Piepoli, M., Volterrani, M., & Poole-Wilson, P. A. (1994). Symptoms and quality of life in heart failure: The muscle hypothesis. *Br. Heart J.*, *72*(2 Suppl), 36–39.

Combaret, L., Taillandier, D., Voisin, L., Samuels, S. E., Boespflug-Tanguy, O., & Attaix, D. (1996). No alteration in gene expression of components of the ubiquitin-proteasome proteolytic pathway in dystrophin-deficient muscles. *FEBS Lett.*, *393*(2–3), 292–296.

Conraads, V. M., Jorens, P. G., De Clerck, L. S., Van Saene, H. K., Ieven, M. M., Bosmans, J. M., et al. (2004). Selective intestinal decontamination in advanced chronic heart failure: A pilot trial. *Eur. J. Heart Fail.*, *6*(4), 483–491.

Das, U. N. (2000). Free radicals, cytokines and nitric oxide in cardiac failure and myocardial infarction. *Mol. Cell Biochem.*, *215*(1–2), 145–152.

Davos, C. H., Doehner, W., Rauchhaus, M., Cicoira, M., Francis, D. P., Coats, A. J., et al. (2003). Body mass and survival in patients with chronic heart failure without cachexia: The importance of obesity. *J. Card. Fail.*, *9*(1), 29–35.

Doehner, W., Rauchhaus, M., Florea, V. G., Sharma, R., Bolger, A. P., Davos, C. H., et al. (2001). Uric acid in cachectic and noncachectic patients with chronic heart failure: Relationship to leg vascular resistance. *Am. Heart J.*, *141*(5), 792–799.

Doehner, W., Schoene, N., Rauchhaus, M., Leyva-Leon, F., Pavitt, D. V., Reaveley, D. A., et al. (2002). Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: Results from 2 placebo-controlled studies. *Circulation*, *105*(22), 2619–2624.

Farges, M. C., Balcerzak, D., Fisher, B. D., Attaix, D., Bechet, D., Ferrara, M., et al. (2002). Increased muscle proteolysis after local trauma mainly reflects macrophage-associated lysosomal proteolysis. *Am. J. Physiol. Endocrinol. Metab.*, *282*(2), 326–335.

Farquharson, C. A., Butler, R., Hill, A., Belch, J. J., & Struthers, A. D. (2002). Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation*, *106*(2), 221–226.

Ferrari, G., Cusella-De Angelis, G., Coletta, M., Paolucci, E., Stornaiuolo, A., Cossu, G., et al. (1998). Muscle regeneration by bone marrow-derived myogenic progenitors. *Science*, *279*(5356), 1528–1530.

Filippatos, G. S., Kanatselos, C., Manolatos, D. D., Vougas, B., Sideris, A., Kardara, D., et al. (2003). Studies on apoptosis and fibrosis in skeletal musculature: A comparison of heart failure patients with and without cardiac cachexia. *Int. J. Cardiol.*, *90*(1), 107–113.

Gomes-Marcondes, M. C., & Tisdale, M. J. (2002). Induction of protein catabolism and the ubiquitin-proteasome pathway by mild oxidative stress. *Cancer Lett.*, *180*(1), 69–74.

Gussoni, E., Soneoka, Y., Strickland, C. D., Buzney, E. A., Khan, M. K., Flint, A. F., et al. (1999). Dystrophin expression in the mdx mouse restored by stem cell transplantation. *Nature*, *401*(6751), 390–394.

Hambrecht, R., Adams, V., Gielen, S., Linke, A., Mobius-Winkler, S., Yu, J., et al. (1999). Exercise intolerance in patients with chronic heart failure and increased expression of inducible nitric oxide synthase in the skeletal muscle. *J. Am. Coll. Cardiol.*, *33*(1), 174–179.

Hambrecht, R., Niebauer, J., Fiehn, E., Kalberer, B., Offner, B., Hauer, K., et al. (1995). Physical training in patients with stable chronic heart failure: Effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J. Am. Coll. Cardiol.*, *25*(6), 1239–1249.

Herbaczynska-Cedro, K., Kosiewicz-Wasek, B., Cedro, K., Wasek, W., Panczenko-Kresowska, B., & Wartanowicz, M. (1995). Supplementation with vitamins C and E suppresses leukocyte oxygen free radical production in patients with myocardial infarction. *Eur. Heart J.*, *16*(8), 1044–1049.

Hishikawa, K., & Luscher, T. F. (1998). Felodipine inhibits free-radical production by cytokines and glucose in human smooth muscle cells. *Hypertension*, *32*(6), 1011–1015.

Hryniewicz, K., Androne, A. S., Hudaihed, A., & Katz, S. D. (2003). Partial reversal of cachexia by beta-adrenergic receptor blocker therapy in patients with chronic heart failure. *J. Card. Fail.*, *9*(6), 464–468.

Hunt, S. A., Baker, D. W., Chin, M. H., Cinquegrani, M. P., Feldman, A. M., Francis, G. S., et al. (2001). ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. *Circulation*, *104*(24), 2996–3007.

Jagoe, R. T., & Goldberg, A. L. (2001). What do we really know about the ubiquitin-proteasome pathway in muscle atrophy. *Curr. Opin. Clin. Nutr. Metab. Care*, *4*(3), 183–190.

Jagoe, R. T., Redfern, C. P., Roberts, R. G., Gibson, G. J., & Goodship, T. H. (2002). Skeletal muscle mRNA levels for cathepsin B, but not components of the ubiquitin-proteasome pathway, are increased in patients with lung cancer referred for thoracotomy. *Clin. Sci. (Lond.)*, *102*(3), 353–361.

Krack, A., Richartz, B. M., Gastmann, A., Greim, K., Lotze, U., Anker, S. D., et al. (2004). Studies on intragastric PCO2 at rest and during exercise as a marker of intestinal perfusion in patients with chronic heart failure. *Eur. J. Heart Fail.*, *6*(4), 403–407.

Kuninger, D., Kuzmickas, R., Peng, B., Pintar, J. E., & Rotwein, P. (2004). Gene discovery by microarray: Identification of novel genes induced during growth factor-mediated muscle cell survival and differentiation. *Genomics*, *84*(5), 876–889.

Lee, S. J., & McPherron, A. C. (1999). Myostatin and the control of skeletal muscle mass. *Curr. Opin. Genet. Dev.*, *9*(5), 604–607.

Li, Y. P., Schwartz, R. J., Waddell, I. D., Holloway, B. R., & Reid, M. B. (1998). Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. *FASEB J.*, *12*(10), 871–880.

Lipkin, D. P., Jones, D. A., Round, J. M., & Poole-Wilson, P. A. (1988). Abnormalities of skeletal muscle in patients with chronic heart failure. *Int. J. Cardiol.*, *18*(2), 187–195.

Mancini, D. M., Walter, G., Reichek, N., Lenkinski, R., McCully, K. K., Mullen, J. L., et al. (1992). Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation*, *85*(4), 1364–1373.

Mitch, W. E., & Goldberg, A. L. (1996). Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N. Engl. J. Med.*, *335*(25), 1897–1905.

Nagai, T., Okita, K., Yonezawa, K., Yamada, Y., Hanada, A., Ohtsubo, M., et al. (2004). Comparisons of the skeletal muscle metabolic abnormalities in the arm and leg muscles of patients with chronic heart failure. *Circ. J.*, *68*(6), 573–579.

Nagaya, N., Kojima, M., Uematsu, M., Yamagishi, M., Hosoda, H., Oya, H., et al. (2001). Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, *280*(5), 1483–1487.

Nagaya, N., Uematsu, M., Kojima, M., Ikeda, Y., Yoshihara, F., Shimizu, W., et al. (2001). Chronic administration of ghrelin improves left ventricular dysfunction and attenuates development of cardiac cachexia in rats with heart failure. *Circulation*, *104*(12), 1430–1435.

Nakagawa, E., Nagaya, N., Okumura, H., Enomoto, M., Oya, H., Ono, F., et al. (2002). Hyperglycaemia suppresses the secretion of ghrelin, a novel growth-hormone-releasing peptide: Responses

to the intravenous and oral administration of glucose. *Clin. Sci. (Lond.)*, *103*(3), 325–328.

Niebauer, J., Pflaum, C. D., Clark, A. L., Strasburger, C. J., Hooper, J., Poole-Wilson, P. A., et al. (1998). Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J. Am. Coll. Cardiol.*, *32*(2), 393–397.

Nieminen, M. S., Bohm, M., Cowie, M. R., Drexler, H., Filippatos, G. S., Jondeau, G., et al. (2005). Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur. Heart J.*, *26*(4), 384–416.

Nishiyama, Y., Ikeda, H., Haramaki, N., Yoshida, N., & Imaizumi, T. (1998). Oxidative stress is related to exercise intolerance in patients with heart failure. *Am. Heart J.*, *135*(1), 115–120.

Node, K., Fujita, M., Kitakaze, M., Hori, M., & Liao, J. K. (2003). Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. *Circulation*, *108*(7), 839–843.

Okumura, H., Nagaya, N., Enomoto, M., Nakagawa, E., Oya, H., & Kangawa, K. (2002). Vasodilatory effect of ghrelin, an endogenous peptide from the stomach. *J. Cardiovasc. Pharmacol.*, *39*(6), 779–783.

Pajonk, F., & McBride, W. H. (2001). The proteasome in cancer biology and treatment. *Radiat. Res.*, *156*(5 Pt 1), 447–459.

Piepoli, M., Clark, A. L., Volterrani, M., Adamopoulos, S., Sleight, P., & Coats, A. J. (1996). Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: Effects of physical training. *Circulation*, *93*(5), 940–952.

Piepoli, M. F., Scott, A. C., Capucci, A., & Coats, A. J. (2001). Skeletal muscle training in chronic heart failure. *Acta Physiol. Scand.*, *171*(3), 295–303.

Ponikowski, P., Francis, D. P., Piepoli, M. F., Davies, L. C., Chua, T. P., Davos, C. H., et al. (2001). Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: Marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation*, *103*(7), 967–972.

Pugh, P. J., Jones, R. D., West, J. N., Jones, T. H., & Channer, K. S. (2004). Testosterone treatment for men with chronic heart failure. *Heart*, *90*(4), 446–447.

Riede, U. N., Forstermann, U., & Drexler, H. (1998). Inducible nitric oxide synthase in skeletal muscle of patients with chronic heart failure. *J. Am. Coll. Cardiol.*, *32*(4), 964–969.

Rosenthal, N., & Musaro, A. (2002). Gene therapy for cardiac cachexia? *Int. J. Cardiol.*, *85*(1), 185–191.

Sandri, M., Sandri, C., Gilbert, A., Skurk, C., Calabria, E., Picard, A., et al. (2004). Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell*, *117*(3), 399–412.

Schieffer, B., Wollert, K. C., Berchtold, M., Saal, K., Schieffer, E., Hornig, B., et al. (1995). Development and prevention of skeletal muscle structural alterations after experimental myocardial infarction. *Am. J. Physiol.*, *269*(5 Pt 2), 1507–1513.

Schiotz Thorud, H. M., Lunde, P. K., Nicolaysen, G., Nicolaysen, A., Helge, J. W., Nilsson, G. E., et al. (2004). Muscle dysfunction during exercise of a single skeletal muscle in rats with congestive heart failure is not associated with reduced muscle blood supply. *Acta Physiol. Scand.*, *181*(2), 173–181.

Schuelke, M., Wagner, K. R., Stolz, L. E., Hubner, C., Riebel, T., Komen, W., et al. (2004). Myostatin mutation associated with gross muscle hypertrophy in a child. *N. Engl. J. Med.*, *350*(26), 2682–2688.

Schulze, P. C., Gielen, S., Schuler, G., & Hambrecht, R. (2002). Chronic heart failure and skeletal muscle catabolism: Effects of exercise training. *Int. J. Cardiol.*, *85*(1), 141–149.

Schulze, P. C., Linke, A., Schoene, N., Winkler, S. M., Adams, V., Conradi, S., et al. (2004). Functional and morphological skeletal muscle abnormalities correlate with reduced electromyographic activity in chronic heart failure. *Eur. J. Cardiovasc. Prev. Rehabil.*, *11*(2), 155–161.

Scott, A. C., Francis, D. P., Davies, L. C., Ponikowski, P., Coats, A. J., & Piepoli, M. F. (2000). Contribution of skeletal muscle 'ergoreceptors' in the human leg to respiratory control in chronic heart failure. *J. Physiol.*, *529*(Pt 3), 863–870.

Sharma, R., & Anker, S. D. (1999). Cardiac cachexia is a world-wide problem. *Int. J. Cardiol.*, *71*(2), 113–114.

Song, Y. H., Li, Y., Du, J., Mitch, W. E., Rosenthal, N., & Delafontaine, P. (2005). Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. *J. Clin. Invest.*, *115*(2), 451–458.

Stassijns, G., Lysens, R., & Decramer, M. (1996). Peripheral and respiratory muscles in chronic heart failure. *Eur. Respir. J.*, *9*(10), 2161–2167.

Sullivan, M. J., Green, H. J., & Cobb, F. R. (1991). Altered skeletal muscle metabolic response to exercise in chronic heart failure. Relation to skeletal muscle aerobic enzyme activity. *Circulation*, *84*(4), 1597–1607.

Tschop, M., Flora, D. B., Mayer, J. P., & Heiman, M. L. (2002). Hypophysectomy prevents ghrelin-induced adiposity and increases gastric ghrelin secretion in rats. *Obes. Res.*, *10*(10), 991–999.

Volterrani, M., Clark, A. L., Ludman, P. F., Swan, J. W., Adamopoulos, S., Piepoli, M., et al. (1994). Predictors of exercise capacity in chronic heart failure. *Eur. Heart J.*, *15*(6), 801–809.

von Haehling, S., Anker, S. D., & Bassenge, E. (2003). Statins and the role of nitric oxide in chronic heart failure. *Heart Fail. Rev.*, *8*(1), 99–106.

von Haehling, S., Jankowska, E. A., & Anker, S. D. (2004). Tumour necrosis factor-alpha and the failing heart—pathophysiology and therapeutic implications. *Basic Res. Cardiol.*, *99*(1), 18–28.

Williams, A. D., Selig, S., Hare, D. L., Hayes, A., Krum, H., Patterson, J., et al. (2004). Reduced exercise tolerance in CHF may be related to factors other than impaired skeletal muscle oxidative capacity. *J. Card. Fail.*, *10*(2), 141–148.

Wilson, J. R., Martin, J. L., Schwartz, D., & Ferraro, N. (1984). Exercise intolerance in patients with chronic heart failure: Role of impaired nutritive flow to skeletal muscle. *Circulation*, *69*(6), 1079–1087.