

## Impact of physical exercise on alterations in the skeletal muscle in patients with chronic heart failure

Volker Adams, Christian Doring, Gerhard Schuler

University Leipzig, Heart Center Leipzig, Leipzig, Germany

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Impact of exercise training on muscle fiber type distribution and muscle fiber size
4. Impact of exercise training on inflammatory cytokine expression
5. Impact of exercise training on anabolic / catabolic balance: Ubiquitin proteasome system, apoptosis versus IGF-1
  - 5.1. Ubiquitin Proteasome system
  - 5.2. Apoptosis
  - 5.3. Insulin-like growth factor-1
6. Impact of exercise training on oxidative stress
7. Impact of exercise training on metabolism and mitochondrial oxidative phosphorylation
8. Impact of exercise training on capillary density in skeletal muscle
9. Perspective
10. References

### 1. ABSTRACT

Chronic heart failure (CHF) is a condition characterized by exercise intolerance. The level of activity tolerated by an individual cannot be predicted by classical parameters of left ventricular performance. Therefore, considerable attention has been focused on the role of peripheral factors such as skeletal muscle, which are determinants of work capacity. In recent years, many alterations in the skeletal muscle have been described in patients with chronic heart failure. This knowledge has dramatically changed the treatment of patients with CHF. Previously, patients were asked to avoid excessive strain and physical exercise. Recently, however, patients are asked to participate in a supervised physical training program to increase their exercise capacity and to counteract the molecular changes occurring in the skeletal muscle. This review will focus on molecular and biochemical alterations especially in the skeletal muscle and how these alterations are influenced by exercise training finally contributing to better skeletal muscle performance.

### 2. INTRODUCTION

An estimated 5 million Americans have been diagnosed with heart failure (HF), a chronic condition associated with frequent hospitalization, widespread functional limitations, and a high mortality rate. Each year, approximately 550,000 new cases are detected and nearly 300,000 patients die of heart failure as a primary or contributory cause. Since HF is not a homogenous disease the management of these patients is extremely challenging. Primary goals of HF management include reduction in the frequency of HF as well as extending and improving quality of life. Additional goals are maximizing independence, and improving exercise capacity. To treat HF numerous pharmacological agents have been developed to improve central hemodynamics and myocardial contractility. Nevertheless, after initiation of such therapies patients still continue to experience activity-related symptoms like, shortness of breath, muscle fatigue and weakness. It is well known that measures of cardiac function like left ventricular ejection fraction correlate poorly with the clinical severity of heart failure (1,2).

Therefore, exercise has become an integral component of the management of patients with chronic heart failure. The main goal of exercise training is to improve physical activity and to counteract exercise intolerance, which is one of the hallmarks of the disease. Over the last ten years many different investigators could document the beneficial effect of exercise training in HF patients. In addition, molecular biology helped us to understand the molecular and biochemical basis for the observed effects.

### 3. IMPACT OF EXERCISE TRAINING ON MUSCLE FIBER TYPE DISTRIBUTION AND MUSCLE FIBER SIZE

Skeletal muscle abnormalities represent an inherent feature of patients with CHF. These include a shift in fiber type distribution with a transformation of slow-twitch type I to fast-type II fibers (for review see 3). Fast-twitch fibers (type II) have a low aerobic capacity and are easily fatigued. Beside the alterations in muscle fiber type distribution, the development of CHF is also associated with a decreased size (muscle cross-sectional area) in both type I and type II fibers.

Has any form of exercise training an influence on the fiber type distribution and muscle cross sectional area in patients with CHF? The analysis of data recently published revealed that the results are conflicting. Investigating the impact of 6 month ergometer training at 70% of maximal oxygen uptake ( $\text{VO}_2\text{max}$ ) in patients with CHF ( $n=18$ ), Hambrecht and colleagues reported for the first time a significant 8% increase in type I fibers, whereas type II fibers decreased significantly (4). During this time period a 6% decrease in the amount of type I fibers was observed in the control group. Fiber size was not investigated in this study. In a study published 3 years later, Kiilavuori and coworkers were not able to confirm the change in fiber type distribution after 6 month of moderate exercise training (5). In addition, no change in fiber size was documented. Looking specifically at female related skeletal muscle change, Tyni-Lenne showed that 8 weeks of intensive knee extensor endurance training increased the cross-sectional area of muscle fibers which after the exercise training was no longer distinguishable from healthy controls (6). What is the difference between the studies and why do we obtain so inhomogeneous results? So far the answer can only be speculative. All the studies differ in training intensity and time. At least, it seems that high intensity training is necessary to benefit from the training program with respect to fiber type distribution and muscle cross-sectional area.

What are possible molecular mechanisms responsible for the fiber type shift during the development of CHF and after exercise training? One molecular candidate influencing the fiber type composition of a skeletal muscle may be the peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1alpha). It is well known, that PGC-1alpha is down regulated in CHF (7,8), that it is involved in muscle fiber type switching during development (9) and that it is

induced in skeletal muscle after exercise training (10). The importance of PGC-1alpha as modulator for fiber type composition is furthermore supported by correlation analysis between the skeletal muscle fiber type and the PGC-1alpha expression (11) as well as by studies using transgenic animals (9).

### 4. IMPACT OF EXERCISE TRAINING ON INFLAMMATORY CYTOKINE EXPRESSION

Both systemic and local inflammation has been suggested to play an important role in the pathogenesis and progression of CHF (12). Cytokines may affect muscle metabolism and strength by direct effects, for example, by altering the expression of the sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase and phospholamban (13), or by induction of other pathological factors, most notably inducible nitric oxide synthase (iNOS) (14,15). A detailed analysis of the serum from asymptomatic patients enrolled into the SOLVD study (16), or patients with severe HF (17), revealed a stringent correlation between the serum concentration of tumor necrosis factor alpha (TNF-alpha) and the severity of the disease. Moreover, circulating levels of cytokines and cytokine receptors have acquired prognostic significance (18-20). Several studies have been performed in the recent years to investigate the impact of physical exercise training on the concentrations of circulating inflammatory cytokines. Depending on the disease severity of the enrolled patients and the training intensity the results differ significantly. For example, Adamopoulos and colleagues described that 12 weeks of exercise training (five days per week at 60-80% of maximum heart rate) of patients in New York Heart Association class II/III (NYHA II/III) reduced plasma levels of proinflammatory cytokines like TNF-alpha, its soluble receptors and interleukin-6 (21). In addition, a good correlation was found between a training-induced increase in  $\text{VO}_2\text{max}$  and the training-induced reduction in levels of TNF-alpha (21). On the other hand, several other studies applying comparable training modalities were not able to confirm these anti-inflammatory effects of exercise training (22-24).

Based on these observations, the question was raised, if the concentration of inflammatory cytokines measured in the plasma is not only a sign of a high local concentrations of the inflammatory factors. This notion is supported by the observation of Sagizadeh, who first described the expression of TNF-alpha in skeletal muscle myocytes (25). This could be confirmed several years later by our group (23). Instead of investigating changes in the plasma concentration of inflammatory cytokines, Gielen and coworkers analyzed for the first time the impact of physical exercise training on the local cytokine expression (23). Despite no changes observed in plasma concentration, a significant down-regulation of inflammatory cytokine expression in the myocytes was noted. This clearly demonstrates, that the local alteration in cytokine expression is influenced much earlier before changes are evident in the circulating system.

### 5. IMPACT OF EXERCISE TRAINING ON THE ANABOLIC CATABOLIC BALANCE: UBIQUITIN-PROTEASOME SYSTEM, APOPTOSIS VERSUS IGF-1

A general loss of skeletal muscle mass (muscle atrophy) is a characteristic, debilitating response to fasting, as well as many severe diseases, including advanced cancer, renal failure, sepsis, and chronic heart failure (26-29). In most types of muscle atrophy overall rates of protein synthesis are suppressed and rates of protein degradation are consistently elevated. This response accounts for the majority of the rapid loss of muscle protein. These processes are paralleled by the activation of apoptosis, the cell suicide program, which leads to a progressive loss of muscle myocyte nuclei, further contributing to the development of muscle atrophy.

#### 5.1. Ubiquitin Proteasome system

In a variety of animal models for different human diseases [e.g., fasting (30,31), diabetes (32), cancer cachexia (33-35), acidosis (36), sepsis (37), disuse atrophy (38), denervation (30), and glucocorticoid treatment (39)], most of the accelerated proteolysis in muscle appears to be due to an activation of the Ubiquitin-proteasome system (UPS) (40). The UPS is an ATP requiring multi-enzymatic process. Proteins degraded by the UPS are first conjugated to ubiquitin. This reaction requires the activation of ubiquitin by the ubiquitin-activating enzyme (E1), transfer to an ubiquitin conjugating enzyme (E2), and subsequent linkage to the lysine residue of proteins destined for degradation (E3) (41). Expression of the E3-ligases Murf-1 (for Muscle Ring Finger 1) and atrogin1/MAFbx (for Muscle Atrophy F-box) (42) is restricted to heart and skeletal muscle tissue. Murf-1 shows ubiquitin ligase activity (43), binds the sarcomeric protein titin (44), and degrades cardiac troponin I (43). MAFbx interacts with calcineurin A, alpha-actinin-2 (45), and degrades MyoD (46), respectively. At least in skeletal muscle cells TNF-alpha is able to stimulate the expression of MAFbx via the activation of p38MAPK (47). Do we have some evidence from the current literature, that exercise training influences the ubiquitin-proteasome-pathway? At least from animal experiments using healthy rats we know, that endurance exercise training over a period of 5 days significantly reduced the UPS activity (48). Concerning the impact of exercise training on the UPS in patients with heart failure the evidence is low. Preliminary data from our group demonstrated that 4 weeks aerobic training of patients with chronic heart failure was efficient in reducing the elevated Murf-1 expression (49).

#### 5.2. Apoptosis

Apoptosis is a highly regulated form of cell death that is characterized by specific morphological, biochemical, and molecular events (50). It is essential for the normal development of a multi-cellular organism (51) and apoptosis is involved in cell turnover in healthy adult tissues (52). Studies in humans as well as in several animal models over the last years showed, that the development of heart failure is associated with an increase in apoptotic myonuclei. Furthermore, the degree of apoptosis correlated

with the severity of the disease. This has been shown to be true in experimental models of CHF (53-55) and in humans with CHF (56,57). In rats treated with monocrotaline the degree of skeletal muscle apoptosis correlated directly with the degree of right-ventricle dilatation, while in humans apoptosis correlated inversely with peak oxygen consumption. Concerning the impact of an exercise training intervention on apoptosis no data are available so far from patients with chronic heart failure, as well as from CHF animal models.

#### 5.3. Insulin-like growth factor-1

Insulin-like growth factor 1 (IGF-1) is another important factor regulating skeletal muscle mass. A significant portion of IGF-1 is produced locally by skeletal muscle myocytes and acts as a paracrine regulator of skeletal muscle hypertrophy/atrophy. Several human and animal studies in the current literature demonstrated that chronic heart failure is associated with a reduced expression of IGF-1 in the skeletal muscle when compared to healthy controls (58,59). The plasma concentration was not altered under these conditions. The local IGF-1 expression correlated significantly with muscle cross sectional area, indicating that the local IGF-1 deficiency might contribute to loss of muscle bulk in CHF (58). Previous studies have shown that the local expression of IGF-1 in skeletal muscle is mainly regulated by two different mechanisms. (1) Growth hormone (GH) induces the local expression of IGF-1 through the activation of the GH-receptor (60) and (2) inflammatory cytokines like TNF-alpha decreases the IGF-1 expression (61,62) by interfering with the transcription factor CREB (cAMP responsive element binding protein), which regulates the transcription of IGF-1 (63). Based on the fact, that exercise training influences the expression of inflammatory cytokines (see above), it is reasonable to assume that exercise training has also an effect on the expression of IGF-1. In a study by Schulze and coworkers a more than two-fold increase in local IGF-1 expression after 6 months of exercise training in patients with stable CHF was observed (64). Two other studies also investigated in non-CHF populations the intramuscular changes of IGF-1 expression in response to exercise. One study documented a higher number of IGF-1 immunoreactive cells in skeletal muscle biopsies obtained after 1 week of terrain marching (65). A second study assessed the effect of a combined intervention - nutritional supplementation and resistance training - on muscular IGF-1 expression (66). The authors reported a six-fold increase in local IGF-1 expression after 10 weeks (66). Therefore, it seems that the local IGF-1 deficiency responded to long-term aerobic exercise indicating that the catabolic state in the skeletal muscle is at least partially reversible by adequate exercise training.

### 6. IMPACT OF EXERCISE TRAINING ON OXIDATIVE STRESS

In patients with CHF and animal models of HF excessive oxidative stress in skeletal muscle has been linked to peripheral hypo-perfusion as a consequence of low cardiac output and peripheral endothelial dysfunction (67-70). Various neurohormonal factors, including

catecholamines, angiotensin II, and cytokines, all known to be increased in heart failure, can activate the generation of reactive oxygen species (ROS) by activating ROS producing enzyme like xanthine oxidase or altering mitochondrial function (for review see 71). A cross-talk between oxidative stress and local inflammation has to be postulated. ROS are known to induce the expression of inflammatory cytokines (72), and it is also described that cytokines themselves promote the production of ROS (15,72). The concentration of ROS in the tissue has to be tightly controlled since it contributes to loss of muscle bulk. For this purpose the skeletal muscle, as all other tissues, is equipped with a variety of anti-oxidative enzymes like copper-zinc superoxide dismutase (CuZnSOD), manganese superoxide dismutase (MnSOD), glutathione peroxidase (GPX), and catalase (Cat) to protect the cells from ROS attacks (73).

Has exercise training any influence on the oxidant-antioxidant homeostasis in the skeletal muscle? To address this question we have to discriminate between single exercise bouts and an exercise program over a longer period of time. It is very well documented in the current literature that heavy exercise is associated with a dramatic increase in oxygen uptake particularly by the skeletal muscle. Using electron spin resonance spectroscopy (ESR), Davies *et al* (74) demonstrated that free radical signals were intensified in rat hind limb muscle after an acute bout of treadmill running to exhaustion. No data are available so far analyzing the impact of endurance training on ROS production by using ESR. Looking at the antioxidant system more data are available with regard to exercise training. At least four different studies, two animal studies (75,76) and two human studies (77,78), indicate that exercise training induces the expression of anti-oxidative enzymes in the skeletal muscle by 40 to 100%. This observation is not limited to CHF. Also in healthy animals, exercise training increases protective stress proteins in skeletal muscle including anti-oxidative enzymes and heat shock proteins (79,80).

The concept that exercise training in CHF patients exerts long-term anti-oxidative effects is further supported by the convincing normalization of lipid peroxidation and a reduction in nitrotyrosine formation, as measures of local oxidative stress, seen in the skeletal muscle of CHF patients after 6 months of exercise training (78). This attenuation in local oxidative stress was closely associated with a decrease in the rate of skeletal muscle apoptosis in CHF (78).

### 7. IMPACT OF EXERCISE TRAINING ON METABOLISM AND MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION

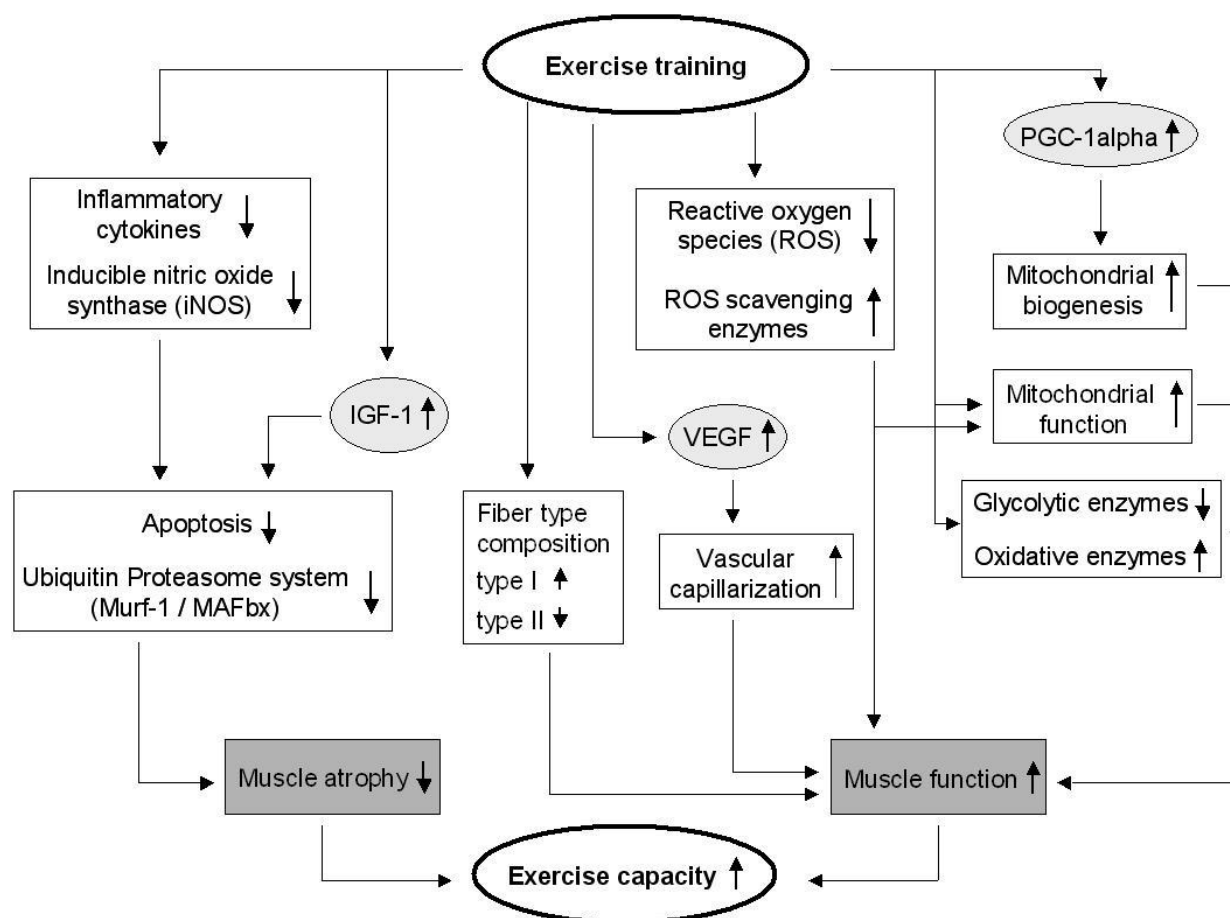
As a matter of fact, large metabolic defects are central features of the skeletal muscle from CHF patients and animal models of the syndrome. In several studies a rapid phosphocreatine (PCr) depletion, an increase in lactate production during exercise and a delayed PCr-recovery at the end of exercise could be documented (81,82). Skeletal muscles of CHF patients usually show an

increased activity of glycolytic enzymes, whereas mitochondrial volume and enzymes of oxidative phosphorylation are significantly decreased (3,83). A fundamental enzyme system for energy production and transfer in the skeletal muscle is the PCr system. In a few studies it could be documented that the MM-isoform of creatine kinase (CK), as well as the mitochondrial isoform of the enzyme (mi-CK), is affected in the skeletal muscle of patients with CHF. These CK isoenzyme alterations could change the function of mitochondria including energy production as well as the sarcoplasmic reticulum. This will lead to a mismatch between energy production and utilization. Therefore, the decreased oxidative capacity of the skeletal muscle and the altered mitochondrial regulation and energy transfer may be a mechanistic link for the decreased oxygen utilization and exercise capacity, which are hallmarks in CHF.

Already in 1985, Howald and colleagues investigated the impact of endurance exercise on the ultrastructural morphology of skeletal muscle mitochondria (84). They could show, that endurance training promotes an increase in volume density of the mitochondria and an increase in mitochondrial protein expression. With the possibility to measure the function of the total mitochondrial population *in situ* using freshly saponin skinned muscle fibers it became evident that in an animal model exercise training over a period of 8 weeks (cages equipped with a running wheel) nearly fully restored metabolic parameters as well as oxidative capacity, mitochondrial enzymes and components of the phosphocreatine system (85). An explanation for the beneficial effect of exercise training on the CK system might be the anti-inflammatory effect of exercise training leading to a decreased expression of the inducible nitric oxide synthase (iNOS) (23), which demonstrates an inverse relationship with the mi-CK isoform (86). Beside nitric oxide, PGC-1 $\alpha$  is another factor that may influence muscle oxidative capacity. PGC-1 $\alpha$  plays a key role in regulating mitochondrial biogenesis in the skeletal muscle (for review see 87,88). The expression of PGC-1 $\alpha$  is downregulated in experimental HF (7) and patients with CHF (8). Concerning the impact of exercise training of humans on the expression of PGC-1 $\alpha$  only few data are available. Analyzing the impact of exercise training in healthy subjects Kuhl and colleagues detected after 12 weeks of a combined aerobic and strength training a significant increase in PGC-1 $\alpha$  protein expression (89). Performing a low-intensity concentric and eccentric endurance-type training program in patients with coronary artery disease over a period of 8 weeks no alterations in PGC-1 $\alpha$  were evident (90). The reason for this discrepancy in outcome is speculative at the moment, but one explanation may be exercise intensity. So far no results are available for patients with CHF enrolled into a training program.

### 8. IMPACT OF EXERCISE TRAINING ON CAPILLARY DENSITY IN SKELETAL MUSCLE

The vascular bed in skeletal muscle functions to supply oxygen and to remove waste products from skeletal



**Figure 1.** Schematic drawing of alterations in the skeletal muscle elicited by exercise training finally leading to an improvement of exercise capacity.

muscle fibers. Therefore, the relative capillary density of a muscle strongly correlates with the oxidative or endurance capacity of the muscle (91,92). In humans it is well established that exercise conditions result in an increase of capillaries per muscle fiber and an increase in capillaries per millimeter squared of muscle tissue (92). On the other hand immobilization results in a decrease in vascular density (93). Is this also the case in the situation of heart failure? Several studies, using either animal models (94) or investigating skeletal muscle biopsies obtained from patients with CHF (83,95,96), demonstrated that the capillary density per muscle fiber is significantly reduced. A possible explanation for the vascular rarefaction may be an increase in endothelial apoptosis (94) or the reduction in angiogenic growth factors like vascular endothelial growth factor (VEGF) (for review see 97). Upon an exercise training program an upregulation of VEGF (98) and subsequently an increase of vascular capillaries was noted (97,99).

## 9. PERSPECTIVE

During the last years the knowledge of molecular alterations occurring in the skeletal muscle of patients with CHF after an enrollment into an exercise program has dramatically increased. It is recognized that exercise

training has an influence on fiber type composition of the skeletal muscle and exerts an anti-inflammatory effect. Furthermore, it is anti-catabolic, via an increase in IGF-1 expression and a downregulation of the ubiquitin-proteasome system and an inhibition of apoptosis. On the energetic site exercise training favors the expression of oxidative enzymes and the energy transfer via mitochondrial creatine kinase. A schematic drawing of the effects of exercise training on the skeletal muscle is depicted in Figure 1. All these beneficial effects on the skeletal muscle in conjunction with alterations in endothelial function and central hemodynamics lead to a reduction in mortality (100) and an improvement in quality of life.

## 10. REFERENCES

1. A. J. Coats: Heart failure: What causes the symptoms of heart failure? *Heart*. 86(5):574-578 (2001)
2. J. A. Franciosa, M. Park and T. B. Levine: Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol*. 47, 33-39 (1981)
3. M. J. Sullivan and M. H. Hawthorne: Exercise intolerance in patients with chronic heart failure. *Prog Cardiovasc Dis*. 38, 1-22 (1995)

4. R. Hambrecht, E. Fiehn, J. Yu, J. Niebauer, C. Weigl, L. Hilbrich, V. Adams, U. Riede and G. Schuler: Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 29, 1067-1073 (1997)
5. K. Kiilavuori, H. Naveri, T. Salmi and M. Harkonen: The effect of physical training on skeletal muscle in patients with chronic heart failure. *Eur J Heart Fail.* 2(1), 53-63 (2000)
6. R. Tyni-Lenne, E. Jansson and C. Sylven: Female-related skeletal muscle phenotype in patients with moderate chronic heart failure before and after dynamic exercise training. *Cardiovasc Res.* 42(1), 99-103 (1999)
7. G. Vescovo, B. Ravara, V. Gobbo, A. Angelini and L. Dalla Libera: Skeletal muscle fibres synthesis in heart failure: role of PGC-1alpha, calcineurin and GH. *Int J Cardiol.* 104, 298-306 (2005)
8. A. Garnier, D. Fortin, J. Zoll, B. N'Guessan, B. Mettauer, E. Lampert, V. Veksler and R. Ventura-Clapier: Coordinated changes in mitochondrial function and biogenesis in healthy and diseased human skeletal muscle. *FASEB J.* 19, 43-52 (2005)
9. J. Lin, H. Wu, P. T. Tarr, C. Y. Zhang, Z. Wu, O. Boss, L. F. Michael, P. Puigserver, E. Isotani, E. N. Olson, B. B. Lowell, R. Bassel-Duby and B. M. Spiegelman: Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature.* 418, 797-801 (2002)
10. K. Baar, A. R. Wende, T. E. Jones, M. Marison, L. A. Nolte, M. Chen, D. P. Kelly and J. O. Holloszy: Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. *FASEB J.* 16, 1879-86 (2002)
11. D. K. Krämer, M. Ahlsen, J. Norrbom, E. Jansson, N. Hjeltne, T. Gustafsson and A. Krook: Human skeletal muscle fibre type variations correlate with PPAR alpha, PPAR delta and PGC-1 alpha mRNA. *Acta Physiol (Oxf)* 2006 188, 207-16 (2006)
12. A. M. Feldman, A. Combes, D. Wagner, T. Kadakomi, T. Kubota, Y. Y. Li and C. McTiernan: The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol.* 35(3), 537-544. (2000)
13. C. F. McTiernan, B. H. Lemster, C. Frye, S. Brooks, A. Combes and A. M. Feldman: Interleukin-1 beta inhibits phospholamban gene expression in cultured cardiomyocytes. *Circ Res.* 81, 493-503 (1997)
14. V. Adams, U. Spate, N. Krankel, P. C. Schulze, A. Linke, G. Schuler and R. Hambrecht: Nuclear factor-kappa B activation in skeletal muscle of patients with chronic heart failure: correlation with the expression of inducible nitric oxide synthase. *Eur J Cardiovasc Prev Rehabil.* 10, 273-277 (2003)
15. V. Adams, B. Nehrhoff, U. Späte, A. Linke, P. C. Schulze, A. Baur, S. Gielen, R. Hambrecht and G. Schuler: Induction of iNOS expression in skeletal muscle by IL-1beta and NFkappaB activation: an *in vitro* and *in vivo* study. *Cardiovasc Res.* 54, 95-104 (2002)
16. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 327(10), 685-691 (1992)
17. G. Torre-Amione, S. Kapadia, J. Lee, J. B. Durand, R. D. Bies, J. B. Young and D. L. Mann: Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. *Circulation.* 1996 93(4), 704-711 (1996)
18. R. Ferrari, T. Bachetti, R. Confortini, C. Opasich, O. Febo, A. Corti, G. Cassani and O. Visioli: Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation.* 92, 1479-1486 (1995)
19. M. Rauchhaus, W. Doehner, D. P. Francis, C. Davos, M. Kemp, C. Liebenthal, J. Niebauer, J. Hooper, H. D. Volk, A. J. Coats, S. D. Anker: Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation.* 102, 3060-3067 (2000)
20. A. Deswal, B. Bozkurt, Y. Seta, S. Pariltil-Eiswirth, F. A. Hayes, C. Bloesch, D. L. Mann: Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. *Circulation.* 99, 3224-3226 (1999)
21. S. Adamopoulos, J. Parissis, D. Karatzas, C. Kroupis, M. Georgiadis, G. Karavolias, J. Paraskevaidis, K. Koniavitou, A. J. Coats, D. T. Kremastinos: Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. *J Am Coll Cardiol.* 39, 653-663 (2002)
22. V. M. Conraads, P. Beckers, J. Bosmans, L. S. De Clerck, W. J. Stevens, C. J. Vrints and D. L. Brutsaert: Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J.* 23, 1854-1860 (2002)
23. S. Gielen, V. Adams, S. Möbius-Winkler, A. Linke, S. Erbs, J. Yu, W. Kempf, A. Schubert, G. Schuler and R. Hambrecht: Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 42, 861-868 (2003)
24. J. Niebauer, A. L. Clark, K. M. Webb-Peploe and A. J. Coats: Exercise training in chronic heart failure: effects on pro-inflammatory markers. *Eur J Heart Fail.* 7, 189-193 (2005)

25. M. Saghizadeh, J. M. Ong, W. T. Garvey, R. R. Henry and P. A. Kern: The expression of TNF alpha by human muscle. Relationship to insulin resistance. *J Clin Invest.* 97(4), 1111-1116 (1996)
26. S. Acharyya, K. J. Ladner, L. L. Nelsen, J. Damrauer, P. J. Reiser, S. Swoap and D. C. Guttridge: Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *J Clin Invest.* 114, 370-378 (2004)
27. P. Costelli, R. D. Tullio, F. M. Baccino and E. Melloni: Activation of Ca(2+)-dependent proteolysis in skeletal muscle and heart in cancer cachexia. *Br J Cancer.* 84, 946-950 (2001)
28. M. D. Gomes, S. H. Lecker, R. T. Jagoe, A. Navon and A. L. Goldberg: Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. *Proc Natl Acad Sci U S A.* 98, 14440-14445 (2001)
29. G. Tiao, J. M. Fagan, N. Samuels, J. H. James, K. Hudson, M. Lieberman, J. E. Fischer and P. O. Hasselgren: Sepsis stimulates nonlysosomal, energy-dependent proteolysis and increases ubiquitin mRNA levels in rat skeletal muscle. *J Clin Invest.* 94, 2255-2264 (1994)
30. R. Medina, S. S. Wing and A. L. Goldberg: Increase in levels of polyubiquitin and proteasome mRNA in skeletal muscle during starvation and denervation atrophy. *Biochem. J.* 307, 631-637 (1995)
31. S. S. Wing and A. L. Goldberg: Glucocorticoids activate the ATP-ubiquitin-dependent proteolytic system in skeletal muscle during fasting. *Am. J. Physiol.* 264, E668-E676 (1993)
32. S. R. Price, J. L. Bailey, X. Wang, C. Jurkovitz, B. K. England, X. Ding, L. S. Phillips and W. E. Mitch: Muscle wasting in insulinopenic rats results from activation of the ATP-dependent, ubiquitin-proteasome proteolytic pathway by a mechanism including gene transcription. *J. Clin. Invest.* 98, 1703-1708 (1996)
33. V. E. Baracos, C. DeVivo, D. H. R. Hoyle and A. L. Goldberg: Activation of the ATP-ubiquitin-proteasome pathway in skeletal muscle of cachectic rats bearing a hepatoma. *Am. J. Physiol.* 268, E996-E1006 (1995)
34. M. Llovera, C. Garcia-Martinez, N. Agell, M. Marzabal, F. J. Lopez-Soriano and J. M. Argiles: Ubiquitin gene expression is increased in skeletal muscle of tumour-bearing rats. *FEBS Lett.* 338, 311-318 (1994)
35. S. Temparis, M. Asensi, D. Taillandier, E. Aurousseau, D. Larbaud, A. Obled, D. Bechet, M. Ferrara, J. M. Estrela and D. Attaix: Increased ATP-ubiquitin-dependent proteolysis in skeletal muscles of tumor-bearing rats. *Cancer Res.* 54, 5568-5573 (1994)
36. W. E. Mitch, R. Medina, S. Griebler, R. C. May, B. K. England, S. R. Price, J. L. Bailey and A. L. Goldberg: Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J. Clin. Invest.* 93, 2127-2133 (1994)
37. L. Voisin, D. Breuille, L. Combaret, C. Pouyet, D. Taillandier, E. Aurousseau, C. Obled and D. Attaix: Muscle wasting in a rat model of long-lasting sepsis results from the activation of lysosomal, Ca<sup>2+</sup>-activated, and ubiquitin-proteasome proteolytic pathways. *J. Clin. Invest.* 97, 1610-1617 (1996)
38. D. Taillandier, E. Aurousseau, D. Meynial-Denis, D. Bechet, M. Ferrara, P. Cottin, A. Ducastaing, X. Bigard, C. Y. Guezennec, H. P. Schmid, *et al.* Coordinate activation of lysosomal, Ca<sup>2+</sup>-activated and ATP-ubiquitin-dependent proteinases in the unweighted rat soleus muscle. *Biochem. J.* 316, 65-72 (1996)
39. D. Auclair, D. R. Garrel, A. Chaouki Zerouala and L. H. Ferland: Activation of the ubiquitin pathway in rat skeletal muscle by catabolic doses of glucocorticoids. *Am. J. Physiol.* 272, C1007-C1016 (1997)
40. R. T. Jagoe and A. L. Goldberg: What do we really know about the ubiquitin-proteasome pathway in muscle atrophy?. *Curr. Opin. Clin. Nutr. Metab. Care* 4, 183-190 (2001)
41. J. Herrmann, A. Ciechanover, L. O. Lerman and A. Lerman: The ubiquitin-proteasome system in cardiovascular diseases - a hypothesis extended. *Cardiovasc Res* 61, 11-21 (2004)
42. S. C. Bodine, E. Latres, S. Baumhueter, V. K. Lai, L. Nunez, B. A. Clarke, W. T. Poueymirou, F. J. Panaro, E. Na, K. Dharmarajan, Z. Q. Pan, D. M. Valenzuela, T. M. DeChiara, T. N. Stitt, G. D. Yancopoulos and Glass DJ: Identification of ubiquitin ligases required for skeletal muscle atrophy. *Science* 294: 1704-1708 (2001)
43. V. Kedar, H. McDonough, R. Arya, H. H. Li, H. A. Rockman and C. Patterson: Muscle-specific RING finger 1 is a bona fide ubiquitin ligase that degrades cardiac troponin I. *Proc Natl Acad Sci U S A* 101, 18135-18140 (2004)
44. T. Centner, J. Yano, E. Kimura, A. S. McElhinny, K. Pelin, C. C. Witt, M. L. Bang, K. Trombitas, H. Granzier, C. C. Gregorio, H. Sorimachi and S. Labeit: Identification of muscle specific ring finger proteins as potential regulators of the titin kinase domain. *J Mol Biol* 306, 717-726 (2001)
45. H. H. Li, V. Kedar, C. Zhang, H. McDonough, R. Arya, D. Z. Wang and C. Patterson: Atrogin-1/muscle atrophy F-box inhibits calcineurin-dependent cardiac hypertrophy by participating in an SCF ubiquitin ligase complex. *J Clin Invest* 114, 1058-1071 (2004)
46. L. A. Tintignac, J. Lagirand, S. Battonnet, V. Sirri, M. P. Leibovitch and S. A. Leibovitch: Degradation of MyoD mediated by the SCF (MAFbx) ubiquitin ligase. *J Biol Chem* 280, 2847-2856 (2005)

47. Y. P. Li, Y. Chen, J. John, J. Moylan, Jin B, Mann DL, Ried MB. TNF-alpha acts via p38 MAPK to stimulate expression of the ubiquitin ligase atrogin1/MAFbx in skeletal muscle. *The FASEB Journal* 19, 362-370 (2005)
48. A. J. Kee, A. J. Taylor, A. R. Carlsson, A. Sevette, R. C. Smith and M. W. Thompson MW: IGF-I has no effect on postexercise suppression of the ubiquitin-proteasome system in rat skeletal muscle. *J Appl Physiol.* 92,2277-2284 (2002)
49. S. Gielen, V. Adams, N. Schneider, P.Lurz, S. Erbs, A. Linke, G. Schuler and R. Hambrecht: Anti catabolic effects of a 4-week endurance training program in patients with stable chronic heart failure and healthy subjects. Reduced RNF28 expression in skeletal muscle biopsies of trained subjects. *Circulation* 114, II-850 (2006)
50. H. Steller: Mechanisms and genes of cellular suicide. *Science.* 267, 1445-1449 (1995)
51. R. C. Duke, D. M. Ojcius and J. D. Young: Cell suicide in health and disease. *Sci Am.* 275, 80-87 (1996)
52. U. Carraro and C. Franceschi: Apoptosis of skeletal and cardiac muscles and physical exercise. *Aging Clin Exp Res* 9, 19-34 (1997)
53. L. Dalla Libera, R. Sabbadini, C. Renken, B. Ravara, M. Sandri, R. Betto, A. Angelini and G. Vescovo: Apoptosis in the skeletal muscle of rats with heart failure is associated with increased serum levels of TNF-alpha and sphingosine. *J Mol Cell Cardiol.* 33, 1871-1878 (2001)
54. R. Persinger, Y. Janssen-Heininger, S. S. Wing, D. E. Matthews, M. M. LeWinter and M. J. Toth: Effect of heart failure on the regulation of skeletal muscle protein synthesis, breakdown, and apoptosis. *Am J Physiol Endocrinol Metab.* 284, E1001-1008 (2003)
55. G. Vescovo and L. Dalla Libera: Skeletal muscle apoptosis in experimental heart failure: the only link between inflammation and skeletal muscle wastage? *Curr Opin Clin Nutr Metab Care.* 9, 416-422 (2006)
56. V. Adams, H. Jiang, J. Yu, S. Mobius-Winkler, E. Fiehn, A. Linke, C. Weigl, G. Schuler and R. Hambrecht Apoptosis in skeletal myocytes of patients with chronic heart failure is associated with exercise intolerance. *J Am Coll Cardiol.* 33, 959-965 (1999)
57. V. Adams, S. Gielen, R. Hambrecht and G. Schuler: Apoptosis in skeletal muscle. *Front Biosci.* 6, D1-D11 (2001)
58. R. Hambrecht, P. C. Schulze, S. Gielen, A. Linke, S. Mobius-Winkler, J. Yu, J. J. Kratzsch, G. Baldauf, M. W. Busse, A. Schubert, V. Adams and G. Schuler: Reduction of insulin-like growth factor-I expression in the skeletal muscle of noncachectic patients with chronic heart failure. *J Am Coll Cardiol.* 39, 1175-1181 (2002)
59. P. C. Schulze, S. Gielen, V. Adams, A. Linke, S. Mobius-Winkler, S. Erbs, J. Kratzsch, R. Hambrecht and G. Schuler: Muscular levels of proinflammatory cytokines correlate with a reduced expression of insulin like growth factor-I in chronic heart failure. *Basic Res Cardiol.* 98, 267-274 (2003)
60. P. T. Loughna, P. Mason, and P. C. Bates: Regulation of insulin-like growth factor 1 gene expression in skeletal muscle. *Symp Soc Exp Biol.* 46, 319-330 (1992)
61. S. R. Broussard, R. H. McCusker, J. E. Novakofski, K. Strle, W. H. Shen, R. W. Johnson, G. G. Freund, R. Dantzer and K. W. Kelley: Cytokine-hormone interactions: tumor necrosis factor alpha impairs biologic activity and downstream activation signals of the insulin-like growth factor I receptor in myoblasts. *Endocrinology* 144, 2988-2996 (2003)
62. J. P. Thissen and J. Verniers: Inhibition by interleukin-1 beta and tumor necrosis factor-alpha of the insulin-like growth factor I messenger ribonucleic acid response to growth hormone in rat hepatocyte primary culture. *Endocrinology.* 138, 1078-1084 (1997)
63. M. J. Thomas, Y. Umayahara, H. Shu, M. Centrella, P. Rotwein and T. L. McCarthy: Identification of the cAMP response element that controls transcriptional activation of the insulin-like growth factor-I gene by prostaglandin E2 in osteoblasts. *J Biol Chem.* 271, 21835-21841 (1996)
64. P. C. Schulze, S. Gielen, G. Schuler and R. Hambrecht: Chronic heart failure and skeletal muscle catabolism: effects of exercise training. *Int J Cardiol.* 85, 141-149 (2002)
65. Y. Hellsten, H. A. Hansson, L. Johnson, U. Frandsen and B. Sjodin. Increased expression of xanthine oxidase and insulin-like growth factor I (IGF-I) immunoreactivity in skeletal muscle after strenuous exercise in humans. *Acta Physiol Scand.* 157,191-197 (1996)
66. M. A. Singh, W. Ding, T. J. Manfredi, G. S. Solares, E. F. O'Neill, K. M. Clements, N. D. Ryan, J. J. Kehayias, R. A. Fielding and W. J. Evans: Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. *Am J Physiol.* 277, E135-143 (1999)
67. R. Hambrecht, E. Fiehn, C. Weigl, S. Gielen, C. Hamann, R. Kaiser, J. Yu, V. Adams, J. Niebauer and G. Schuler: Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation.* 98, 2709-2715 (1998)
68. R. Hambrecht, S. Gielen, A. Linke, E. Fiehn, J. Yu, C. Walther, N. Schoene and G. Schuler: Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA.* 283, 3095-3101 (2000)
69. G. D. Thomas, W.Zhang and R. G. Victor: Impaired modulation of sympathetic vasoconstriction in contracting



- skeletal muscle of rats with chronic myocardial infarctions: role of oxidative stress. *Circ Res.* 88, 816-823 (2001)
70. H. Tsutsui, T. Ide, S. Hayashidani, N. Suematsu, T. Shiomi, J. Wen, Ki. Nakamura, K. Ichikawa, H. Utsumi and A. Takeshita: Enhanced generation of reactive oxygen species in the limb skeletal muscles from a murine infarct model of heart failure. *Circulation.* 104, 134-136 (2001)
71. D. Sorescu and K. K. Griendling: Reactive oxygen species, mitochondria, and NAD(P)H oxidases in the development and progression of heart failure. *Congest Heart Fail.* 8, 132-40 (2002)
72. D. L. Mann and M. B. Reid: Exercise training and skeletal muscle inflammation in chronic heart failure: feeling better about fatigue. *J Am Coll Cardiol.* 42, 869-872 (2003)
73. S. K. Powers, L. L. Ji and C. Leeuwenburgh: Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. *Med Sci Sports Exerc.* 31, 987-997 (1999)
74. K. J. Davies, A. T. Quintanilha, G. A. Brooks and L. Packer: Free radicals and tissue damage produced by exercise. *Biochem Biophys Res Commun.* 107, 1198-1205 (1982)
75. H. Lew and A. Quintanilha: Effects of endurance training and exercise on tissue antioxidative capacity and acetaminophen detoxification. *Eur J Drug Metab Pharmacokinet.* 16, 59-68 (1991)
76. J. M. Lawler, H.B. Kwak, W. Song and J. L. Parker: Exercise training reverses downregulation of HSP70 and antioxidant enzymes in porcine skeletal muscle after chronic coronary artery occlusion. *Am J Physiol Regul Integr Comp Physiol.* 291, R1756-1763 (2006)
77. P. V. Ennezat, S. L. Malendowicz, M. Testa, P. C. Colombo, A. Cohen-Solal, T. Evans and T. H. LeJemtel: Physical training in patients with chronic heart failure enhances the expression of genes encoding antioxidative enzymes. *J Am Coll Cardiol.* 38, 194-198 (2001)
78. A. Linke, V. Adams, P. C. Schulze, S. Erbs, S. Gielen, E. Fiehn, S. Mobius-Winkler, A. Schubert, G. Schuler and R. Hambrecht: Antioxidative effects of exercise training in patients with chronic heart failure: increase in radical scavenger enzyme activity in skeletal muscle. *Circulation* 111, 1763-1770 (2005)
79. J. Hammeren, S. Powers, J. Lawler, D. Criswell, D. Martin, D. Lowenthal and M. Pollock: Exercise training-induced alterations in skeletal muscle oxidative and antioxidant enzyme activity in senescent rats. *Int J Sports Med.* 13, 412-416 (1992)
80. J. W. Starnes, A. M. Choilawala, R. P. Taylor, M. J. Nelson and M. D. Delp: Myocardial heat shock protein 70 expression in young and old rats after identical exercise programs. *J Gerontol A Biol Sci Med Sci.* 60, 963-969 (2005)
81. B. Massie, M. Conway, R. Yonge, S. Frostick, J. Ledingham, P. Sleight, G. Radda and B. Rajagopalan: Skeletal muscle metabolism in patients with congestive heart failure: relation to clinical severity and blood flow. *Circulation.* 76, 1009-1019 (1987)
82. D. M. Mancini, E. Coyle, A. Coggan, J. Beltz, N. Ferraro, S. Montain and J. R. Wilson: Contribution of intrinsic skeletal muscle changes to <sup>31</sup>P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation.* 80, 1338-1346 (1989)
83. M. Schaufelberger, B. O. Eriksson, G. Grimby, P. Held and K. Swedberg: Skeletal muscle alterations in patients with chronic heart failure. *Eur Heart J.* 18, 971-980 (1997)
84. H. Howald, H. Hoppeler, H. Claassen, O. Mathieu and R. Straub: Influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans. *Pflügers Arch.* 403, 369-376 (1985)
85. E. De Sousa, P. Lechene, D. Fortin, B. N'Guessan, S. Belmadani, X. Bigard, V. Veksler and R. Ventura-Clapier: Cardiac and skeletal muscle energy metabolism in heart failure: beneficial effects of voluntary activity. *Cardiovasc Res.* 56, 260-268 (2002)
86. R. Hambrecht, V. Adams, S. Gielen, A. Linke, S. Mobius-Winkler, J. Yu, J. Niebauer, H. Jiang, E. Fiehn and G. Schuler: 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, 174-179 (1999)
87. H. Liang and W. F. Ward: PGC-1 $\alpha$ : a key regulator of energy metabolism. *Adv Physiol Educ.* 230, 145-151 (2006)
88. C. D. Moyes: Controlling muscle mitochondrial content. *J Exp Biol.* 206, 4385-4391 (2003)
89. J. E. Kuhl, N. B. Ruderman, N. Musi, L. J. Goodyear, M. E. Patti, S. Crunkhorn, D. Dronamraju, A. Thorell, J. Nygren, O. Ljungkvist, M. Degerblad, A. Stahle, T. B. Brismar, K. L. Andersen, A. K. Saha, S. Efendic and P. N. Bavenholm: Exercise training decreases the concentration of malonyl-CoA and increases the expression and activity of malonyl-CoA decarboxylase in human muscle. *Am J Physiol Endocrinol Metab.* 290, E1296-1303 (2006)
90. L. Zoll, R. Steiner, K. Meyer, M. Vogt, H. Hoppeler and M. Fluck: Gene expression in skeletal muscle of coronary artery disease patients after concentric and eccentric endurance training. *Eur J Appl Physiol.* 96, 413-422 (2006)
91. O. Hudlicka: Growth of capillaries in skeletal and cardiac muscle. *Circ Res.* 50, 451-461 (1982)

92. F. Ingjer: Effects of endurance training on muscle fibre ATP-ase activity, capillary supply and mitochondrial content in man. *J Physiol.* 294,419-432 (1979)
93. P. Kannus, L. Jozsa, M. Kvist, M. Lehto and M. Jarvinen: The effect of immobilization on myotendinous junction: an ultrastructural, histochemical and immunohistochemical study. *Acta Physiol Scand.* 144, 387-394 (1992)
94. D. J. Nusz, D. C. White, Q. Dai, A. M. Pippen, M. A. Thompson, G. B. Walton, C. J. Parsa, W. J. Koch and B. H. Annex: Vascular rarefaction in peripheral skeletal muscle after experimental heart failure. *Am J Physiol Heart Circ Physiol.* 285, H1554-1562 (2003)
95. M. Schaufelberger, B. O. Eriksson, G. Grimby, P. Held and K. Swedberg: Skeletal muscle fiber composition and capillarization in patients with chronic heart failure: relation to exercise capacity and central hemodynamics. *J Card Fail.* 1, 267-272 (1995)
96. B. D. Duscha, W. E. Kraus, S. J. Keteyian, M. J. Sullivan, H. J. Green, F. H. Schachat, A. M. Pippen, C. A. Brawner, J. M. Blank and B. H. Annex: Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. *J Am Coll Cardiol.* 33, 1956-1963 (1999)
97. T. Gustafsson and W. E. Kraus: Exercise-induced angiogenesis-related growth and transcription factors in skeletal muscle, and their modification in muscle pathology. *Front Biosci.* 6, D75-89 (2001a)
98. T. Gustafsson, K. Bodin, C. Sylven, A. Gordon, R. Tyni-Lenne and E. Jansson: Increased expression of VEGF following exercise training in patients with heart failure. *Eur J Clin Invest.* 31, 362-366 (2001)
99. M. Scarpelli, R. Belardinelli, D. Tulli and L. Provinciali: Quantitative analysis of changes occurring in muscle vastus lateralis in patients with heart failure after low-intensity training. *Anal Quant Cytol Histol.* 21, 374-380 (1999)
100. M. F. Piepoli, C. Davos, D. P. Francis and A. J. Coats: ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH) *BMJ.* 328, 189-195 (2004)

**Key Words:** Chronic Heart Failure, Skeletal Muscle, Gene Expression, Exercise Training, Review

**Send correspondence to:** Volker Adams, PhD, University Leipzig, Heart Center Leipzig, Strumpellstrasse 39, 04289 Leipzig, Tel: 49341865-1671, Fax: 49341865-1461, E-mail: adav@medizin.uni-leipzig.de

<http://www.bioscience.org/current/vol13.htm>