Chronic heart failure and skeletal muscle catabolism: effects of exercise training

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Abstract

Although the clinical picture of cardiac cachexia is well-known in patients with advanced chronic heart failure (CHF) the factors that determine who is at risk for this progressive catabolic syndrome and who is not remain unclear. Different endocrine systems have been accused of being involved in this process: an imbalance between catabolic and anabolic steroids with an elevated cortisol/dihydroepiandrosterone ratio, an increased resting metabolic rate due to high levels of circulating catecholamines, various cytokines are activated in CHF (i.e. TNF-α, IL-6, IL-1β and others), and elevated levels of growth hormone (GH) with inappropriately normal or low serum levels of insulin-like growth factor-I (IGF-I) have been described in cardiac cachexia. These catabolic factors contribute to peripheral muscle atrophy, augment the expression of the inducible nitric oxide synthase (iNOS), which in turn inhibits the aerobic cellular metabolism. The present review examines whether the catabolic factors can be influenced by a classical anabolic intervention: regular physical exercise training. Long-term training programs increase skeletal muscle cytochrome c oxidase activity and are associated with reduced local expression of pro-inflammatory cytokines as well as iNOS, and augment local IGF-I production. In concert, these beneficial effects of exercise training may help to retard the catabolic process in CHF finally leading to cardiac cachexia and death.

Keywords: Cachexia; Skeletal muscle alterations; iNOS expression; Insulin-like growth factor

1. Introduction

The pivotal role of exercise intolerance and early fatigue as the clinical hallmark of chronic heart failure (CHF) has never been questioned since the New York Heart Association (NYHA) adopted this clinical feature for status determination in 1949 [1]. However, the debate whether to view skeletal muscle weakness and atrophy as cause or consequence of exercise intolerance has been continuing for decades: is it primary skeletal muscle atrophy as part of the heart failure syndrome that causes exercise intolerance in CHF patients or do cardiac exercise limita-

tions lead to muscle disuse and consecutive loss of muscle mass?

If skeletal muscle atrophy were just a matter of lack of exercise (i.e. disuse) it should be fully reversed by an increase in exercise to normal or above-normal levels. This is why systematic studies of exercise training (as an established anti-catabolic intervention) in CHF are so valuable for extending our pathophysiological concept of exercise intolerance.

2. Catabolic factors in chronic heart failure

Although the final clinical picture of cardiac cachexia is well-known in CHF patients with advanced heart failure, the factors that determine who is
at risk for this progressive catabolic syndrome and who is not remain unclear. Different endocrine systems have been accused of being involved in this process (Fig. 1).

1. An imbalance between catabolic and anabolic steroids with an elevated cortisol/dihydroepiandrosterone ratio has been observed in CHF patients [2].
2. An increased resting metabolic rate due to high levels of circulating catecholamines has been reported in CHF [3].
3. Various cytokines are activated in CHF (i.e. TNF-α, IL-6, IL-1β and others) that have been shown to contribute to loss of muscle bulk and cachexia in CHF [4–6].
4. As a key regulator of normal growth, hyper trophy, and atrophy of tissues, the GH/IGF-I axis has recently received more attention as a potential factor for muscle catabolism and wasting in CHF. Elevated levels of GH with inappropriately normal or decreased serum levels of IGF-I have been described in cardiac cachexia [2].

In addition to systemic and local abnormalities of various endocrine systems, investigations into the nutritional status of patients with CHF have shown alterations of gastrointestinal fat absorption [7] although intestinal protein loss does not seem important [8]. In addition, a central dysregulation of food intake has been proposed since experimental data suggest increased levels of neuropeptide Y in the brain consequently leading to anorexia in patients with CHF [9]. Unfortunately, no large-scale study has systematically assessed the nutritional status of patients with CHF.

2.1. Insulin-like growth factor I (IGF-I)

In animal models of catabolism the role of systemic IGF-I levels has been closely investigated: in rats with 30% body surface area burn injuries, continuous infusion of IGF-I over 24 h was effective in preventing the increased protein breakdown and reduced protein synthesis in extensor digitorum longus muscles [10]. This finding documents a potent antiacellular effect of systemic IGF-I.

In patients with CHF, Niebauer et al. observed an association between low serum IGF-I levels and loss of lean muscle mass as well as an increase in catecholamines [11]. This is consistent with the hypothesis that decreases in systemic levels of IGF-I occurs with advanced stages of heart failure. In a recent study of skeletal muscle biopsies in non-cachectic patients with CHF, the local IGF-I expression was substantially downregulated in the skeletal muscle, despite normal IGF-I serum concentrations [12].

This novel finding underlines that IGF-I can be produced locally by skeletal muscle fibres and may be regulated by factors independent from serum IGF-I levels. Local skeletal muscle IGF-I expression responds to stimuli from two different sources: (1) serum GH has the potential to augment local IGF-I expression. This mechanism is important for normal growth and development of the organism. It has been previously shown that a state of GH resistance may develop in cardiac cachexia. (2) Skeletal muscle IGF-I expression is modulated in response to alterations in muscle use: in animal experiments it has been shown that muscle unloading by zero gravity (spacflight for 16 days) resulted in growth retardation and decreased skeletal muscle IGF-I expression in neonatal rats [13]. While IGF-I overexpression alone was ineffective in preventing hindlimb suspension-induced muscle atrophy [14] a combination of GH/IGF-I supplementation and resistance exercise preserved skeletal muscle mass and was effective in preventing apoptosis in myonuclei and satellite cells.
during unloading. This finding is consistent with the hypothesis that both muscle loading/stretch and IGF-I are required to avert atrophy. Of note, the frequency with which apoptosis is seen in tissue samples of the skeletal muscle is also increased in CHF [15]. It is therefore conceivable, that the apoptotic process in the skeletal muscle might be accelerated in response to a decline in local IGF-I expression.

Important interactions between TNF-α and IGF-I have been discovered in animal models: TNF-α decreased the IGF-I content of the liver and the gastrocnemius muscle, whereas pretreatment with an anti-TNF-α antibody completely prevented the decrease in IGF-I in the muscle [16].

2.2. Cytokines, local inflammation, and iNOS expression

During the last decade immune activation and inflammation in CHF has received growing attention [4,17]. A number of proinflammatory factors have evolved as potential mediators of inflammatory processes in CHF: tumor necrosis factor α (TNF-α) [18,19], interleukin 1β (IL-1β), interleukin 6 (IL-6), and interferon γ (IFN-γ).

Cytokines may play a significant role for the progression of CHF in three different contexts: they are associated with poor prognosis and recurrent hospitalizations, they exert direct metabolic effects on the peripheral skeletal muscle, and they affect the muscular energy metabolism via the inducible nitric oxide synthase (iNOS) and intracellular accumulation of toxic levels of NO.

2.2.1. Prognostic implications

In a recent longitudinal study by Orús et al., 87 patients with advanced CHF (LV-EF 24±6%) serum cytokine levels and serum cytokine receptors were included in a univariate and a Cox analysis for prognostic markers for a combined cardiac event endpoint (death, new heart failure episodes, need for heart transplantation [20]). By Cox regression serum IL-6 was identified as independent predictor of prognosis (P<0.0005) together with NYHA functional class. By univariate analysis serum IL-1β, TNF-soluble receptor I and II also predicted a cardiac event. These findings are well in line with previous data describing increasing IL-6 values with the severity of CHF [21]. Serum IL-6 levels have been found to correlate with plasma norepinephrine concentrations [21]. It is thus conceivable that sympathetic vasoconstriction triggers local IL-6 activation at the endothelial or vascular smooth muscle level as a compensatory mechanism inducing NO-dependent vasodilation [22,23].

2.2.2. Direct metabolic effects

Inflammatory cytokines may influence the expression of functionally relevant muscle proteins. IL-1β has been shown to downregulate the expression of sarcoplasmic reticulum Ca²⁺ ATPase (SERCA) and phospholamban at both mRNA and protein level in neonatal myocytes [24]. This causes a prolongation of the calcium transient—an effect also initiated by TNF-α [24,25]. Other factors like sphingosin have also been proposed as potential mediators of the negative inotropic actions of TNF-α on the myocardium. TNF-α transgenic animal models have revealed a number of additional pathways in the mouse myocardium, e.g. increased activity of metalloproteinases, activation of both pro- and antiapoptotic pathways, and a decrease in the α- and β-myosin heavy chain mRNA ratio [25]. All these molecular changes converge in a reduced contractility.

2.2.3. iNOS activation

As part of the inflammatory process initiated by cytokine production, TNF-α, IFN-γ, and IL-1β are potent activators of iNOS expression [26], which is known to be increased in the skeletal muscle of patients with CHF [27]. The intracellular accumulation of NO generated by iNOS may produce toxic levels of NO high enough to inhibit key enzymes of the oxidative phosphorylation. In vitro experiments documented that NO can thus attenuate the contractile performance of the skeletal muscle [28], a finding which puts cytokine production and iNOS expression in perspective for the development of exercise intolerance in patients with severe heart failure.

3. Functional, metabolic, and morphologic skeletal muscle alterations in CHF

Chronic heart failure has been found to be associ-
ated with profound functional [29], metabolic [30,31], and morphologic alterations in the skeletal muscles [32,33]. In the course of these scientific advances a new ‘muscle hypothesis of chronic heart failure’ [34] has been developed and peripheral changes have become a new therapeutic target.

3.1. Functional and metabolic alterations in CHF

While exercise intolerance is generally considered to be a clinical hallmark of CHF, systematic assessments of skeletal muscle function in CHF are relatively rare [11,29]. While maximal strength depends on the number of contractile filaments, fatigability is influenced by intracellular ATP-stores and ATP regeneration. We and others have previously shown that oxidative phosphorylation is attenuated in CHF patients, energy transfer by means of mitochondrial creatine kinase is impaired, and overall ATP levels are reduced [35,36]. These factors could explain why muscle fatigability develops earlier than reduction of maximal contractile force which is a consequence of muscle atrophy.

To evaluate the metabolic responses to local forearm or calf exercise in patients with chronic heart failure, $^{31}$P magnetic resonance spectroscopy was used. Despite normal limb blood flow during exercise, patients exhibited abnormal phosphocreatine depletion and acidosis during exercise [30,37].

In response to exercise, blood lactate levels increased earlier than expected in CHF patients. Reduced oxidative enzymes, reduced mitochondrial density, type I muscle fiber atrophy and an increase in the proportion of type II fibers have all been implicated as contributing factors for the increase of anaerobic energy production in CHF [30,31,38–40]. As previously mentioned, the impairment of oxidative phosphorylation may also be the consequence of toxic intracellular levels of NO produced by iNOS.

3.2. Skeletal muscle apoptosis

The ultimate result of catabolic processes in CHF is skeletal muscle atrophy. On the microscopic level atrophy is caused by an increased rate of programmed cell death or apoptosis. The frequency and significance of skeletal muscle apoptosis has been investigated in both animal models of CHF and in skeletal muscle biopsies [41]. In 47% of stable CHF patients, TUNEL-positive nuclei were detected and confirmed to lie in muscle fibres by counterstaining with anti-actin antibodies [15]. Evaluation of apoptosis positive muscle specimens revealed an apoptotic index of $0.7 \pm 0.4\%$. The apoptotic frequency correlated with a reduced exercise capacity ($VO_2$ max).

In an animal model of monocrotaline-induced right ventricular heart failure, Vescovo et al. demonstrated that the number of TUNEL positive myonuclei in the fast twitch muscle tibialis anterior increased significantly over time compared to control rats (after 27 days; $0.0025 \pm 0.005\%$ vs. $0.031 \pm 0.012\%$). The increase in apoptosis was accompanied by muscle atrophy evident by a drop in fiber cross-sectional area and muscle weight/body weight. Based on the available human and animal studies its seems that in CHF apoptosis occurs in skeletal muscle, and that it may have an influence on the muscle atrophy and contractility. The discussions on relevance and significance of apoptosis in skeletal muscle are further complicated by the fact that in each muscle fiber more than 100 nuclei are present, and that only a minority of myonuclei inside the myofiber display DNA fragmentation (nuclear death) [42]. Does the loss of a single or of several nuclei alter fiber morphology or even function? Based on the concept that one nucleus controls a specific territory (nuclear domain), one has to assume that the loss of a single nucleus is associated with the loss of the controlled cytoplasmic territory [43,44]. This hypothesis was confirmed by Hikida et al. [45]. They analyzed the myonuclear population in the soleus muscle of rats that had undergone atrophy due to 10 days spaceflight, and could demonstrate that the number of nuclei was reduced proportionally to the loss of fiber size.

4. Effects of exercise training on skeletal muscle alterations

4.1. Effects of training on aerobic metabolism

In a morphometric study we analysed the effects of 6 months of aerobic in-hospital and home-based training on volume density of cytochrome c positive mitochondria in skeletal muscle biopsies [46,47].
Initially surface and total volume density of cytochrome c-oxidase-positive mitochondria was reduced by ~45% as compared to normal subjects, thereby compromising oxidative capacity of working skeletal muscle. Baseline volume density of cytochrome c oxidase-positive mitochondria was closely related to oxygen uptake at peak exercise. These changes in oxidative capacity are at least partially reversible by training therapy. The mean surface density of a single cytochrome c oxidase-positive mitochondrion increased by an average of 31% after exercise training, whereas the total number of cytochrome oxidase-positive mitochondria remained essentially unchanged. The significant increase in volume density of cytochrome oxidase-positive mitochondria was closely correlated with changes in oxygen uptake at the ventilatory threshold and at peak exercise (Fig. 2). Moreover, exercise training leads to a ‘re-shift’ from fast-twitch type II fibers to slow-twitch type I fibers in patients of the training group [47].

Using $^{31}$P nuclear magnetic resonance spectroscopy Adamopoulos et al. measured phosphocreatine depletion, muscle acidification and the increase in ADP during the first 4 min of plantar flexion exercise in the calf muscle of CHF patients, which were all increased ($P<0.04$) as compared with values in control subjects. After 8 weeks of training, phosphocreatine depletion and the increase in ADP during exercise were reduced significantly ($P<0.003$) and phosphocreatine recovery half-time was significantly ($P<0.05$) reduced. These findings indicate that a substantial correction of the impaired oxidative capacity of skeletal muscle in chronic heart failure can be achieved by exercise training [48].

4.2. Effects on cytokines, local inflammation, and iNOS expression

To date the effect of physical exercise on immune activation in patients with CHF has never been systematically addressed. Acute bouts of strenuous exercise in healthy volunteers have been described to induce an inflammatory response—especially under circumstances of eccentric high-intensity training with muscle trauma. Immediately after physical exertion an increase in serum TNF-$\alpha$ and IL-1$\beta$ has been described [49]—accompanied by a rise in several antiinflammatory mediators like IL-1ra, sTNF-r1, sTNF-r2, and IL-10. This inflammatory response to acute bouts of strenuous physical exercise has also been associated with influx of proinflammatory factors from the gut.

While acute physical exercise seems to mediate pro-inflammatory effects, long-term endurance exercise has been shown to act predominantly in an immunosuppressive way: in a rat model of endurance training Bagby et al. showed an attenuated TNF-$\alpha$ release in response to bacterial lipopolysaccharide in rats with prior exercise training [50]. In line with this animal experiment, Drenth et al. documented a decrease of LPS-stimulated production of IL-1$\beta$ and TNF-$\alpha$ after a 5-km run in 19 well-trained athletes [51]. Taken together, these results show that prolonged exercise in healthy subjects elicits a selective downregulation of the proinflammatory cytokine production.

In a recent study we were able to show that local expression of IL-1$\beta$ and TNF-$\alpha$ in the quadriceps muscle is reduced after long-term endurance training of patients with CHF [52]. This novel finding confirms that the anti-inflammatory effects of chronic exercise previously described in healthy individuals are also pertinent to patients with CHF. Reduction of local cytokine expression was associated with a reduced iNOS expression which may in turn contribute to a disinhibition of aerobic enzymes by reduction of intracellular NO accumulation and protein nitrosylation.
4.3. Effects of training on effects of exercise training on skeletal muscle IGF-I expression

Of all non-humoral stimuli for IGF-I expression, muscular stretch ranks among the most potent: McKoy et al. recently confirmed that 4 days of muscle stretch induced a significant upregulation of IGF-mRNA [53] starting as early as 12 h after the stimulus [54].

Exercise training as a natural form of stretch exposure has similar effects on skeletal muscle IGF-I expression. In a model of treadmill exercise in young rats Eliakim et al. described a significant increase in skeletal muscle IGF-I protein levels after 6 days with no change in systemic IGF-I serum concentrations [55].

In a recent study we observed a more than twofold increase in local IGF-I expression after 6 months of exercise training in patients with stable CHF. Two other studies in non-CHF populations are available on intramuscular changes of IGF-I expression in response to exercise: one in military trainees documented a higher number of IGF-I immunoreactive cells in skeletal muscle biopsies obtained after 1 week of terrain marching [56]. A second assessed the effect of a combined intervention of nutritional supplementation and resistance training in 26 elderly patients and confirmed a sixfold increase in local IGF-I expression [57].

Our data are well in line with these previous studies. For the first time it has been confirmed that in CHF local IGF-I levels are reduced well before any systemic changes are apparent. The local IGF-I-deficient state associated with CHF responds to a long-term aerobic training intervention indicating that the catabolic state in the skeletal muscle is at least partially reversible by adequate rehabilitation [58].

4.4. Effects of training on skeletal muscle mass and function

Although increase in muscle mass is the most obvious result of training in healthy subjects only limited information is yet available about the effect of regular physical exercise on body composition or muscle bulk in patients with heart failure. In an observational study, Wilson et al. [59] investigated the effect of training on body composition using dual-energy X-ray absorptiometry (DEXA). In patients who increased their peak VO\(_2\) in response to exercise training, body lean mass remained essentially unchanged. The authors conclude that increases in the oxidative capacity of the skeletal muscle and not of muscle mass are responsible for the training effect.

Over the last decade, several prospective controlled studies have addressed the question whether exercise training improves the functional capacity of patients with CHF. In a recent meta-analysis of randomised controlled trials by the European Heart Failure Training Group exercise training improved peak VO\(_2\) up to 2 ml/kg min\(^{-1}\) [60]. The clinical benefit reported in terms of exercise tolerance is comparable to the most effective pharmaceutical treatments: ACE inhibitor therapy also increases peak VO\(_2\) up to 2 ml/kg min\(^{-1}\).

4.5. Training and skeletal muscle apoptosis

Despite the consensus that skeletal muscle apoptosis is present in biopsies of patients with CHF and in animal models of heart failure and may be relevant for the development of skeletal muscle atrophy and dysfunction, little is known about the effects of physical exercise on the apoptotic rate.

In animal experiments, acute bouts of strenuous physical exercise were associated with an increased rate of apoptotic myonuclei [61]. In healthy human volunteers, however, it has been demonstrated that cytosols from skeletal muscle biopsies lacked the ability to activate type-2 caspases by a cytochrome c-mediated pathway. This should represent a protective mechanism against mitochondrial-mediated proapoptotic stimuli.

Unfortunately, the effect of long-term exercise training has not been investigated so far neither in healthy volunteers nor in CHF patients. One would presume that the decrease of proapoptotic cytokines and NO and the concomitant increase in IGF-I would reduce the frequency of apoptosis. However, this has not been confirmed so far.

5. Conclusion

In conclusion, intrinsic alterations in skeletal mus-
Exercise training has the potential to reduce local muscle cytokine and iNOS expression, increases antiapoptotic factors like IGF-I, and improves cytochrome c oxidase activity (Fig. 3). These beneficial effects converge in an improved exercise capacity. Although exercise training offers no causal treatment of CHF it has great potential as an adjunct therapy directed to improving exercise tolerance and expanding the physical limits of CHF patients.

References


