Exercise training in chronic heart failure: mechanisms and therapies

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Abstract Decreased exercise capacity negatively affects the individuals' ability to adequately perform activities required for normal daily life and, therefore, the independence and quality of life. Regular exercise training is associated with improved quality of life and survival in healthy individuals and in cardiovascular disease patients. Also in patients with stable heart failure, exercise training can relieve symptoms, improve exercise capacity and reduce disability, hospitalisation and probably mortality. Physical inactivity can thus be considered a major cardiovascular risk factor, and current treatment guidelines recommend exercise training in patients with heart failure in NYHA functional classes II and III. Exercise training is associated with numerous pulmonary, cardiovascular, and skeletal muscle metabolic adaptations that are beneficial to patients with heart failure. This review discusses current knowledge of mechanisms by which exercise training is beneficial in these patients.

Keywords Heart failure · Exercise training · Exercise capacity · Quality of life · Neurohumoral effects · Endothelial effects · Anti-inflammatory effects

Introduction

Progresses in the cardiovascular diagnosis and therapy have improved the prognosis of the patients [1]. As a result, the incidence and prevalence of heart failure (HF) are increasing. Patients with HF present with a range of symptoms that are often nonspecific, particularly in the elderly. The European task force proposed the definition of HF be based on

two criteria: symptoms of HF at rest or during exercise (typically breathlessness and fatigue), and objective evidence of cardiac dysfunction at rest [2].

As for many chronic diseases, however, the correlations between symptoms and the degree of cardiac impairment at rest, and between symptoms and disease prognosis, are poor in patients with HF [3]. Indeed, our understanding of the exact mechanisms of progressive intolerance to exercise is far from complete. Failure of inotropic and vasodilatory agents to improve exercise capacity implies that cardiac dysfunction is not the only factor contributing to progressive exercise intolerance [4]; impaired pulmonary and skeletal muscle function are also thought to have a role [5, 6].

Decreased exercise capacity negatively affects an individuals' ability to adequately perform activities required for normal daily life and, therefore, their independence and quality of life. Regular exercise training is associated with a reduced rate of coronary heart disease [7], as well as with improved survival in healthy individuals and in people with cardiovascular disease [8, 9]. In patients with stable HF, exercise training can relieve symptoms, improve exercise capacity and quality of life, and reduce disability, hospitalisation and mortality [10–12]. Physical inactivity can thus be considered a major cardiovascular risk factor [13], and current treatment guidelines recommend exercise training in patients with HF in NYHA functional classes II and III [11]. Exercise training is associated with numerous pulmonary, cardiovascular, and skeletal muscle metabolic adaptations that are beneficial to patients with HF. This review discusses current knowledge of mechanisms by which exercise training benefits these patients.

Neurohumoral effects of exercise

HF is associated with neurohumoral changes as the body attempts to reverse the effect of reduced cardiac output and organ perfusion. The sympathetic and renin–angiotensin–

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aldosterone systems are activated, by release of catecholamines, renin, vasopressin, and atrial natriuretic peptides in an attempt to increase myocardial contractility, heart rate and vasoconstriction, and expand extracellular fluid volume [14]. Persistent neurohumoral excitation, however, actually results in deterioration of myocardial function with inflammatory response, end-organ damage, and skeletal muscle derangement, which lead to worsened exercise capacity [15]. Patients with HF exhibit sympathetic hyperactivity with elevation of circulating catecholamines and reduced parasympathetic activity with decreased heart rate variability and baroreflex sensitivity [16]. Elevated levels of angiotensin II (Ang II), aldosterone, vasopressin, and natriuretic peptides are also present in these patients. The mechanisms of sympathetic excitation associated with HF are complex and not completely understood. Both inhibition of sympathoinhibitory reflexes (arterial and cardiopulmonary baroreflex) [17] and increased sympathoexcitatory reflexes (chemoreceptor, ergoreceptor, cardiac reflex) [18, 19] have been described in patients and animals with HF.

In the rostral ventrolateral medulla, elevated levels of the sympathoexcitatory peptide Ang II stimulate sympathetic activity by upregulating Ang II type 1 (AT1) receptors, NADPH expression and superoxide anion production [20]. Use of cultured rabbit neuronal cells has shown that oxidative stress can mediate the Ang II-induced upregulation of the AT1 receptor and activation of the transcription factor activator protein 1 [21]. Decreased synthesis of neuronal nitric oxide synthase (nNOS) and, therefore, reduced production of nitric oxide (NO) can also contribute to the increased sympathetic outflow found in patients with HF [22].

In experimental models of HF, exercise training reduces sympathetic activity and plasma Ang II levels, and normalises baroreflex [23], cardiopulmonary, ergoreflex and chemoreflex control. Exercise training also exerts beneficial effects in the central nervous system of animals with HF, including reduction of AT1 concentration, reduction of NADPH expression and upregulation of superoxide dismutase expression in the rostral ventrolateral medulla [24], and restoration of the expression of nNOS33 and the glutamergic system in the paraventricular nucleus. These findings demonstrate that exercise training can reduce sympathoexcitation through both peripheral and central effects.

Exercise training is associated with reversal of autonomic dysfunction in patients with HF, which produces an important shift from sympathetic to vagal activity [25]. Different protocols of exercise training are associated with reduction of sympathetic activity, as shown by reduced levels of plasma norepinephrine [26] and muscle sympathetic nerve activity. Physical training in patients with HF also results in an increase in parasympathetic tone, as demonstrated by an increase in heart rate variability and baroreflex sensitivity. Exercise training can also reduce the levels of circulating

neurohormones including Ang II, aldosterone, vasopressin and natriuretic peptides [27]. Exercise training thus counterbalances the long-term detrimental effects of neurohumoral activation in patients with HF, resulting in improved cardiac function, reduced vasoconstriction with better peripheral and skeletal blood delivery, and, ultimately, improved exercise tolerance.

Endothelial effects of exercise

Impaired endothelium-dependent vasodilatation in the microcirculation of patients with HF is thought to result from decreased endothelial production of NO and increased concentration of endothelin. In chronic HF, impaired NO production can be caused by reduced endothelial nitric oxide synthase (eNOS) expression or activity by asymmetric dimethyl arginine, NO scavenging by reactive oxygen species, and reduced availability of L-arginine and tetrahydrobiopterin. Oxidative stress has a major role in NO inactivation.

Regular exercise promotes NO release and, therefore, improves endothelium-dependent vasodilatation to slow vascular damage. Evidence suggests that improved endothelial function and neoangiogenesis could be related mechanisms by which exercise training can exert its beneficial effects in HF [28].

In experimental models, exercise training increases shear stress on the vascular endothelium, which promotes eNOS expression, decreases reactive oxygen species and prostanoïd production, and induces superoxide dismutase expression, which thereby reduces NO scavenging [29].

In patients with chronic HF, exercise training can produce antioxidative effects (through reduction of vascular expression of NADPH oxidase and AT1) that result in decreased generation of reactive oxygen species, which is associated with improved acetylcholine-mediated coronary vasodilatation and reduced Ang-II-induced vasoconstriction. Other effects are restoration of endothelial function and a contribution to the reduction of peripheral resistance with improved left ventricular ejection fraction. Aerobic interval training has been shown to be superior to moderate endurance training in increasing O₂ consumption (VO₂; 46 % versus 14 %). This improved peak VO₂ also correlated with brachial artery flow-mediated dilatation, which had a more marked improvement after interval training than after endurance training. Interval training was also associated with a 15 % increase in total antioxidant status, which was correlated with increased flow-mediated dilatation [30].

Dietary supplementation, with L-arginine, an NO precursor, and the antioxidant coenzyme Q10, in association with exercise, has an additive effect on improvement of the endothelial function.

Anti-inflammatory effects of exercise

Increased inflammatory response has been recognised as an important factor in the pathophysiology of HF. Levels of major proinflammatory cytokines, such as tumour necrosis factor (TNF) and interleukin (IL)-6, as well as chemotactic cytokines, such as macrophage chemo-attractant protein 1 and macrophage inflammatory protein 1, are elevated in patients with HF. Cytokine activation can negatively affect myocardial contractility by inducing activation of inducible nitric oxide synthase (iNOS), increasing oxidative stress, inhibiting sarcoplasmic reticulum Ca^{2+} release and phospholamban expression, and promoting myocyte apoptosis and cardiac remodelling [31].

Increased cytokine production can also lead to endothelial dysfunction, deleterious effect on skeletal muscle contractility and metabolism, by promoting oxidative stress and skeletal myocyte apoptosis, decreasing the expression of insulin-like growth factor 1, and inducing iNOS expression with impairment of aerobic metabolism by peroxynitrite and cytochrome c oxidase inhibition. Eventually, continually raised cytokine levels lead to muscle catabolism and wasting.

Regular exercise training can have an anti-inflammatory effect in patients with HF. In experimental models of HF, exercise training increases plasma levels of the anti-inflammatory cytokine IL-10, and can modulate the innate immune system, by influencing macrophage and lymphocyte function. In patients, intense exercise training can reduce plasma levels of inflammatory cytokines (TNF, soluble TNF, IL-6, IL-6 receptor, IL-1), platelet-related inflammatory mediators (CD40 ligand and P-selectin), and peripheral markers of endothelial dysfunction (granulocyte–macrophage colony-stimulating factor, macrophage chemoattractant protein 1, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1). Unsustained exercise training (less than 12 weeks) does not result in the same beneficial effects as exercise of longer duration [32]. Exercise training also reduces skeletal muscle expression of proinflammatory cytokines and iNOS, with enhancement of cytochrome c activity, to eventually improve muscular oxidative metabolism. Physical training can, therefore, be considered a valuable anti-inflammatory therapeutic strategy for patients with chronic HF.

Effects of exercise on skeletal muscle

Chronic HF is associated with skeletal muscle myopathy that contributes to fatigue and dyspnoea. In skeletal muscle of patients with HF, increased NO production contributes to myocardial dysfunction, remodelling and muscle wasting. There is compelling evidence that skeletal muscle dysfunction has an important role in exercise intolerance in HF. A skeletal myopathy of HF has been described histologically and metabolically, and contributes significantly to exercise

limitation during HF. The skeletal myopathy of HF is ubiquitous, involving the large muscles of locomotion, small muscles of the arms, and even the muscles of respiration. This condition begins very early after the primary cardiac injury, even before the symptoms of HF manifest. Muscles are often atrophied, with evidence of apoptosis of the myocytes. Apoptosis is not normally present in skeletal muscle, but has been reported to be present in approximately 50 % of patients with HF [33].

Other observed modifications are decreased capillary density, a shift from high aerobic capacity to low aerobic capacity (with fatigue-resistant type I fibres being converted to easily fatigue-prone type IIB fibres), and a reduction in mitochondrial density and structure with decreased cytochrome oxidase activity and oxidative enzymes. These changes lead to increased muscle fatigability, decreased oxidative metabolism, increased oxidative stress, and ineffective high energy phosphate use (as shown by increased inorganic phosphate and phosphocreatine levels), to result in early accumulation of lactate during exercise. Reduced perfusion, neurohumoral changes, endothelial dysfunction and inflammatory activation can all participate in skeletal muscle abnormalities.

Some studies have pointed towards the existence of a reflex network that becomes hyperactive secondary to skeletal muscle alterations and might contribute to exercise intolerance. The overactivation of signals that originate from skeletal muscle receptors (mechano-metaboreceptors) is an intriguing hypothesis proposed to explain the origin of symptoms and the beneficial effect of exercise training in patients with HF. The ‘muscle hypothesis’ speculates that one possible explanation for sympathetic overdrive is an exaggerated metaboreflex activity that takes place in response to chronic underperfusion and metabolic changes occurring in the contracting muscle. This reflex overactivity leads to increased vasoconstriction and blood pressure increments in response to exercise, which contribute to the exercise intolerance observed in patients with HF. This mechanism, known as exercise pressor reflex, is a circulatory reflex that originates from skeletal muscle and contributes substantially to generation of the exaggerated cardiovascular response. Exercise-induced signals in the afferent arm of the exercise pressor reflex are generated by activation of mechanically (muscle mechanoreflex) and metabolically (muscle metaboreflex) sensitive skeletal muscle receptors. Activation of these receptors and related fibres increases blood pressure and heart rate during physical activity. The muscle hypothesis proposes that HF is a vicious cycle in which damage to the heart and disturbance to central haemodynamics trigger compensatory mechanisms—including neurohumoral and sympathetic activation which, in the long term, cause persistent vasoconstriction, vascular and endothelial response, inflammation, and necrosis [19]. These changes alter the function of all organs, including the kidneys, lungs, and skeletal muscle.

The beneficial effect of exercise training on reducing skeletal muscle alterations in these patients demonstrates that this process is reversible.

Indeed, physical training can have beneficial effects on skeletal muscle abnormalities and oxidative metabolism. In experimental models of HF, exercise training increases muscle oxidative capacity, normalises skeletal muscle metabolism, and reduces oxidative stress. In patients with HF, exercise training improves oxygen use and oxidative capacity through increased activity of oxidative enzymes and an increase in mitochondrial content [34]. These changes lead to an improvement in peak VO₂ and lactate threshold, and delayed onset of anaerobic metabolism, as shown by only a small increase of inorganic phosphate and phosphocreatine levels after training. Clinical studies have shown contrasting effects of exercise training on muscle fibre type distribution and capillary densities, which probably reflects differences in training level and duration. Exercise training also has anti-inflammatory effects, as described above, and can increase local expression of the anabolic peptide insulin-like growth factor 1. Additionally, reduced sympathetic hyperactivation and improved endothelial dysfunction with exercise training contribute to improved muscle blood flow and clinical performance.

Cardiovascular effects of exercise

Physical training can also have beneficial effects on cardiac performance in patients with chronic HF. Experimental data show that exercise training can improve heart function by restoring cardiomyocyte contractility and calcium sensitivity. Exercise training re-establishes calcium cycling by normalising the activity of Ca²⁺-regulating proteins, such as sarcoplasmic reticulum Ca²⁺ ATPase, phospholamban, the ryanodine receptor and the Na²⁺ and Ca²⁺ exchanger, which increases myofilament Ca²⁺ sensitivity and, thus, myocyte contractility [35].

Two meta-analyses of randomised, controlled trials show that exercise training can improve cardiac performance in patients with HF, with significant improvements in left ventricular ejection fraction, end-diastolic and systolic volumes, and maximal heart rate, systolic blood pressure and cardiac output.

Ageing is associated with diminished endogenous myocardial protective mechanisms, and increases susceptibility to injury. Brief episodes of ischaemia can have a negative effect on the heart (stunning), but can also result in ‘ischaemic preconditioning’—a powerful endogenous protective mechanism against myocardial ischaemia. The protective effect of preinfarction angina is preserved in elderly patients who have a high level of physical activity. Rat studies have suggested that exercise training might restore the protective preconditioning effect in an ageing heart by increasing norepinephrine release in response to preconditioning stimulus.

Exercise training restores the ability of the senescent heart to release norepinephrine during global ischaemia and reperfusion, which might restore preconditioning and its protective effect to the heart. Elderly patients who have a high level of physical activity appear to demonstrate benefits of preinfarction angina, including less cardiogenic shock, more non-Q-wave myocardial infarction, a lower creatine kinase-MB isoenzyme peak and less ventricular arrhythmia [36]. In the critical balance of the ageing process, exercise training might minimise the stunning effects and maximise the preconditioning effects of brief ischaemic episodes.

Type of exercise training

Most of the evidence of the benefits of exercise training in patients with HF is from patients with stable HF in NYHA functional classes II or III. No trial evidence of beneficial effects of exercise training in patients with unstable HF or those with NYHA functional class IV exists to date [2].

In studies of patients with stable HF, the exercise intervention varied in mode, intensity and duration. Indeed, the type and intensity of exercise training might determine the level of benefit: endurance and strength training and moderate continuous training seem to be less effective than high-intensity interval training. Current guidelines for exercise training in patients with HF acknowledge the benefits of aerobic training; however, the precise protocol is yet to be established and should be individually tailored to the patient’s clinical and functional status.

A recent statement reviews the modality of implementation of exercise training in clinical practice in HF [37].

Although most studies of exercise training have been conducted predominantly in young patients, exercise-based cardiac rehabilitation has also proven to be beneficial in elderly (65 years) patients, even in those with poor left ventricular function (ejection fraction <40 %). The intensity of exercise training that exerts maximum beneficial effects in these patients is still debated. The cardiovascular effect of aerobic interval training (95 % peak heart rate) was found to be superior to that of moderate continuous training (70 % peak heart rate) in elderly patients who exercised three times per week for 12 weeks in a randomised study; peak VO₂ increased more with aerobic interval training and was associated with reverse left ventricular remodelling, a 35 % increase in left ventricular ejection fraction, and a 40 % decrease in the levels of pro-brain natriuretic peptide. Long-term studies are needed to determine whether the effects of different training regimens endure, particularly in elderly patients.

The potential benefits of resistance training have received very little attention, and this type of exercise is not generally used in patients with HF. A growing body of literature suggests that resistance training prevents the decline in

skeletal muscle mass and function that is associated with ageing, and regular and vigorous resistance training results in a shift from fatigue-prone type II fibres to fatigue-resistant type I fibres in patients with cardiovascular disease who suffer from skeletal muscle myopathy. Some studies also demonstrate a 10–18 % increase in peak VO₂ in patients with HF during resistance training, compared with a 20 % increase observed during aerobic training. Circuit training (i.e. training that involves both resistance and aerobic exercise) is a well-tolerated form of exercise training for patients with HF, which is associated with similar oxygen and haemodynamic demand to aerobic exercise alone.

Conclusions

Progressive exercise training should be considered a valuable therapeutic choice in patients with HF. Adherence by patients to the exercise training regimen is essential to obtain beneficial results. Physical training can have beneficial effects on neurohumoral, inflammatory, metabolic and central haemodynamic responses, as well as on endothelial, skeletal muscle and cardiovascular function, leading to improvement in functional capacity and quality of life. All these training-induced changes can effectively counteract the progression of deleterious compensatory mechanisms of HF.

The efficacy of exercise training on functional capacity and quality of life is clear in the short term, but long-term effects are as yet unknown. Large, long-term, pragmatic trials of exercise training in patients with HF are needed to determine the effectiveness of exercise training on morbidity, quality of life, and mortality. The value of continued exercise training for maintenance of benefit also requires evaluation.

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