

CARDIAC REHABILITATION IN HEART FAILURE. PART I, MECHANISM

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Abstract Diagnosis and treatment issues among heart failure (HF) patients are becoming one of the most important points in public health of developed countries, largely due to the aging of population and the fact that HF affects mainly the elderly. In this review we would like to focus on pathophysiology of exercise intolerance in patients with heart failure and potential benefits of cardiac rehabilitation (CR).

Analysis of articles in the EBSCO database using keywords: heart failure, cardiac rehabilitation, exercise training, pathophysiology. HF can be described as a composite syndrome which results from structural or functional impairment of ventricular filling or blood ejection. Patients have variety of symptoms which usually are nonspecific. The most frequently occurring symptoms of HF are dyspnea and fatigue, which may restrict exercise capacity, and fluid retention. There are many possible pathophysiological factors involved in the development of exercise intolerance. Based on the available literature pathological changes in central hemodynamic function, pulmonary system, skeletal muscles, endothelial function and neurohumoral system can be distinguished. They play a crucial role in the pathogenesis of HF symptoms and represent a potential curative object.

HF patients are characterized by diminished functional performance. Exercise training has many potential profits in patients with heart failure, including an increase in peak oxygen uptake, improvement in central hemodynamics, peripheral vascular and skeletal muscle function and has become part of evidence-based clinical therapy in these patients.

Key words heart failure, cardiac rehabilitation, exercise training, pathophysiology

Introduction

Diagnosis and treatment issues among heart failure (HF) patients are becoming one of the most important points in public health of developed countries, largely due to the aging of population and the fact that HF affects mainly the elderly. The rate of the heart failure (HF) occurrence is steadily increasing. Despite the progression in

the care of patients with heart failure, it did not improve outcomes among recently hospitalized patients, so it is important to modify strategies to minimize remissions of patients with heart failure (Chaudhry et al., 2010).

HF can be described as a composite syndrome which results from structural or functional impairment of ventricular filling or blood ejection. Patients have variety of symptoms which usually are nonspecific. The most frequently occurring symptoms of HF are dyspnea and fatigue, which may restrict exercise capacity, and fluid retention, which can cause pulmonary/splanchnic congestion and/or peripheral edema. A large number of possible symptoms, with even presentation of no signs of volume overload, makes diagnosis of HF difficult, especially that there is no single diagnostic test for heart failure (Yancy et al., 2013). The disease in question is major cause of morbidity, mortality, hospitalizations, impaired quality of life and disability (Taylor et al., 2014). HF patients experience a reduction in their overall physical activity. HF has poor prognosis: 50% of patients with diagnosed HF die within 5 years (Go et al., 2014).

The HF syndrome may result mostly from impaired left ventricular (LV) myocardial function, but every disorder of pericardium, myocardium, endocardium, heart valves, great vessels or metabolic abnormalities can cause described illness. According to large number of patients, HF may be associated with LV functional abnormalities, ranged from normal LV size and preserved ejection fraction (EF) to severe dilatation and/or reduced EF, which is used in general classification of HF patients. HF patients are divided into following subgroups: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) depending on EF values. This classification is important because of differing demographics, comorbid conditions, prognosis and responses to therapies (Yancy et al., 2013).

Other classifications of HF, which provide complementary information about severity of HF, are the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) stages and New York Heart Association (NYHA) classification. The ACCF/AHA stages emphasize the development and progression of disease, so it can be used on individuals and populations. On the other hand, the New York Heart Association (NYHA) classes focus on exercise capacity and symptoms of the disease (Yancy et al., 2013).

Material and methods

Articles in the EBSCO database have been analyzed using keywords: heart failure, cardiac rehabilitation, exercise training, pathophysiology. The available literature was subjectively selected due to its usefulness in showing the pathophysiology of heart failure and the effect of cardiac rehabilitation. Moreover, literature which reveals inconsistency in the results was shown as well.

Results

Cardiac rehabilitation

In patients with heart failure, exercise training in form of the cardiac rehabilitation (CR) has many potential profits, including increasing in peak oxygen uptake, improvement in central hemodynamics, peripheral vascular and skeletal muscle function (Lavie, Berra, Arena, 2013). Decrease in cardiac output were primarily hypothesized as being the only restricting factor to physical performance in HF. Furthermore, different changes in vascular function, skeletal muscle and pulmonary function also play significant roles in the pathogenesis of HF symptoms and represent a potential curative objects which author of the training protocol could aim at (Lavie et al., 2013).

Pathophysiological mechanisms of Exercise Intolerance in Heart Failure

There are many possible pathophysiologic factors involved in the development of exercise intolerance. Recent studies supply information about understanding of oxidative metabolism, molecular changes in skeletal and cardiac muscle, mechanisms of endothelial dysfunction, the role of sympathetic nervous system and inflammatory cytokines (Downing, Balady, 2011).

The low frequency component of heart rate variability could be an indicator of the sympathetic influence on heart functioning (Malliani, Lombardi, Pagani, 1994). The mean low frequency powers in RR interval and resting muscle sympathetic nerve activity were lower in the 21 heart failure patients than in the 12 control subjects (Van De Borne, Montano, Pagani, Oren, Somers, 1997). Moreover, low-frequency power of heart rate variability was a significant predictor of a sudden, presumably arrhythmic death in a multivariate model testing in chronic HF patients (La Rovere et al., 2003).

Central Hemodynamic Function

Cardiac diseases belong to the main group of reasons impairment of exercise capacity. Unsatisfactory LV shortening with increases in end-systolic and end-diastolic volumes is the clue of response of the central circulation to exercise in the patient with systolic HF (Downing, Balady, 2011). Chronic elevated ventricular filling pressures can provide to secondary pulmonary hypertension and succeeding right ventricular dysfunction (Downing, Balady, 2011). Exorbitant increase in pulmonary capillary wedge pressure is the one of the main causes of exertional dyspnea (Kitzman, Higginbotham, Cobb, Sheikh, Sullivan, 1991).

Authors (Patwala, Woods, Sharp, Goldspink, Tan, Wright, 2009) demonstrated that cardiac resynchronization therapy increases the exercise capacity which might be caused by the improvement in systolic function during the treatment. However, several studies showed a poor correlation between left ventricular ejection fraction and exercise capacity (Franciosa, Park, Levine, 1981; Fleg et al., 1995).

HF with preserved ejection fraction concerns diastolic left ventricular (LV) dysfunction may be caused by for example hypertrophied hearts and with LV remodelling after small myocardial infarctions (Hanrath, Mathey, Siegert, Bleifeld, 1980). Increased resistance to ventricular filling describes diastolic dysfunction. Increased diastolic filling rate needed during physical activity is realized in the normal LV by an increase in chamber expansibility, which provides in an increase in LV diastolic volume without a pressure increase (Downing, Balady, 2011). This mechanism is impaired in patients with diastolic dysfunction which leads to a quick elevation in LV diastolic pressure and pulmonary capillary wedge pressure and can manifest as a dyspnea (Downing, Balady, 2011).

Pulmonary Function

The deteriorating LV is maintained by increased filling pressures, which next may result in pulmonary abnormalities (Clark, Poole-Wilson, Coats, 1996). The chronic pulmonary venous hypertension causes the pathologic changes in the lung, for example pulmonary vascular damage, fibrosis, pulmonary congestion or oedema (Clark et al., 1996; Ponikowski et al., 2001; Mancini, 1995). Patients with chronic heart failure demonstrate an increased ventilatory response during progressive exercise (Buller, Poole-Wilson, 1990). Studies (Buller, Poole-Wilson, 1990; Sullivan, Higginbotham, Cobb, 1988) showed that there is a linear correlation between minute ventilation and the rate of carbon dioxide production in HF patients during physical exercise.

Skeletal Muscle

Some evidences suggest that exercise capacity have potential peripheral determinants and muscle abnormalities are a part of the chronic HF and induce some symptoms of patients (Harrington et al., 1997). Changes in muscle function may be important contributors to exercise intolerance (Harrington et al., 1997). Study (Sullivan et al., 1990) based on muscle biopsy demonstrated histological abnormalities for example reduction in type I fibers and a shift toward type IIb fibers. Interestingly, researches showed evidence that biochemistry and histology of skeletal muscle can effect on the pathophysiology of exertional fatigue in patients with long-term heart failure (Sullivan et al., 1990). Biochemistry changes depend mainly on reducing mitochondrial-based enzymes, mitochondrial size and in the activity of oxidative enzymes (Clark et al., 1996; Sullivan et al., 1990). Moreover the abnormalities of lower limbs observed in HF can be caused by diminished muscle mass, which lead to increase in fatigue and a decrease in exercise tolerance (Clark et al., 1996). In consequence it leads to the reduction in leg blood flow and increased vascular resistance (Clark et al., 1996).

Endothelial function and neurohumoral system

Several researches showed evidences for abnormal endothelial function in patients with HF (Downing, Balady, 2011). Potential mechanisms of endothelial dysfunction are reduced nitric oxide, increased reactive oxygen species and reduced vasodilatory response to shear stress.

It is worth mentioning, that endothelium plays a crucial role in monitoring vascular tone as well as in preventing platelets and inflammatory cells from adhering to the vascular area (Dimmeler, Zeiher, 2003). It demonstrated disturbed balance between nitric oxide and oxidative stress which provide to local vasoconstriction. Nitric oxide restrains apoptosis of endothelial cell, inflammatory activation, and increases the function of free oxygen radical-scavenging enzymes (Dimmeler, Zeiher, 2003).

Numerous studies showed the role of inflammatory factors in the mechanism of skeletal muscle wasting and fatigue in patients with HF (Anke, Rauchhaus, 1999). Cachectic patients demonstrated elevated plasma levels of cortisol, catecholamines, and aldosterone. Moreover, cardiac cachexia is associated with increased plasma levels of tumor necrosis factor α (Anker, Rauchhaus, 1999; Vescovo et al., 2000). Inflammatory mediators can provide to muscle catabolism, loss of muscle protein, and apoptosis, which leads to a reduction in exercise capacity (Vescovo et al., 2000).

Effects of the physical exercise on HF patients

Physical exercises have beneficial effects on cardiovascular system. Study with animal models (Rinaldi et al., 2006; Kwak, Son, Lawler, 2006) showed that regular physical exercise provided to antioxidative protection in the myocardium and prevent to cardiomyocyte apoptosis. Moreover, cardiac changes associated with ageing process: decreased elasticity of wall, impaired early LV diastolic relaxation, increased end-systolic LV volume and reduced contractile reserve are inhibited by regular physical training (Arbab-Zadeh et al., 2004; Pugh, Wei, 2001). Studies demonstrated that aerobic training causes neurohormonal balance which concerns with reduction of norepinephrine secretion (Coats et al., 1992). Furthermore, 4-months training based on walking was related with reduction of angiotensin II, aldosterone, arginine vasopeptide, and atrial natriuretic peptide levels (Braith, Welsch, Feigenbaum, Kluess, Pepine, 1999).

Mobilization of endothelial progenitor cells causes vascular regeneration, for example physical exercise was related with increasing VEGF, which is a main factor of endothelial proliferation (Adams et al., 2004). Moreover, studies which used left common carotid artery recorded using an ultrasound instrument (Kitzman et al., 2013) showed no changes in arterial stiffness after CR implementation.

A positron emission tomography-based study (Legallois et al., 2016) have revealed that rest myocardial blood flow, endothelium-related change in myocardial blood flow from rest to cold pressor test as well as the percentage of myocardial blood flow increase during the cold pressor test, left ventricular ejection fraction, plasma levels of brain natriuretic peptide, VO₂max were significantly improved in HF patients due to dilated cardiomyopathy after the 12 weeks of the CR (Legallois et al., 2016).

Meta-analysis which included 801 patients (Collaborative, 2004) revealed positive effects of systematic, long-term (circa 700 days) CR. 88 deaths was noted in the exercise group, which constituted 22% of patients and 105 in the control group which stated for 26% of patients. A significant effect of exercise training in mortality and hospital admissions reduction was noted (Collaborative, 2004). Randomized-controlled trial (RCT) (Hambrecht et al., 2000) showed that after 6 months of CR, patients in the intervention group had statistically significant improvements in NYHA functional class, maximal ventilation, exercise time, and exercise capacity as well as diminished resting HR, LV end diastolic diameter and total peripheral resistance (TPR) during peak exercise and improved resting SV and LV ejection fraction.

3-months resistance exercise programme increased high-frequency and lowered low-frequency of heart rate variability in chronic HF patients (Selig et al., 2004). Moreover, such intervention significantly improved muscle endurance and strength (Selig et al., 2004). Moreover, another RCT study (Kitzman et al., 2013) showed that the 16-weeks systematic training protocol did not significantly improved the arterial stiffness, however increased the VO₂max and quality of life in HF patients. In contrary, brachial artery endothelial-dependent flow-mediated arterial dilation and carotid arterial distensibility, resting left ventricular systolic and diastolic function remained unchanged after the intervention (Kitzman et al., 2013). Additionally, a significant difference in left ventricular diameter and ejection fraction after 24 weeks exercise programme implementation was observed (Dehkordi, Far, 2015). In another RCT (Alves et al., 2012) subjects with moderate to severe systolic dysfunction and advanced diastolic dysfunction CR diminished the mean ratio of early to late mitral inflow velocities (E/A ratio) and improved the deceleration time (DT) compared to the control group (Alves et al., 2012).

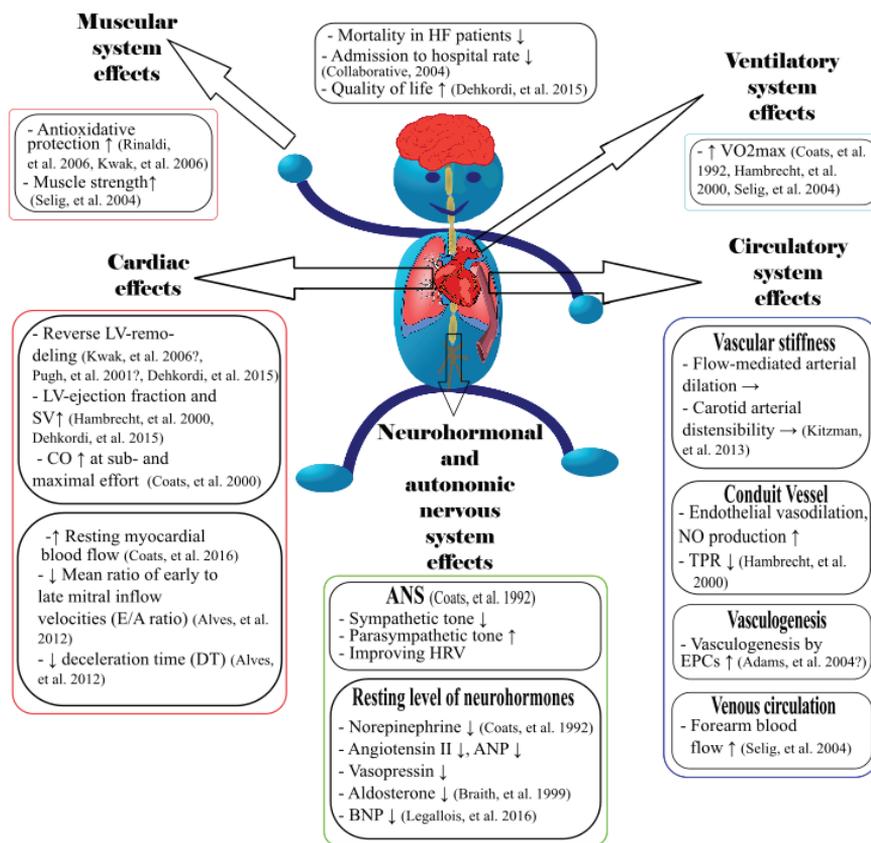


Figure 1. Selected effects of cardiac rehabilitation on physiological systems

The figure shows effects of CR on the main systems of the organism. “↑” denotes an improvement, “↓” refers to decline, “→” describes lack of effects and “?” denotes insufficient evidence on effects. List of abbreviations: HF – heart failure, VO_{2max} – maximal oxygen consumption, LV – left ventricle, NO – nitric oxide, CO – cardiac output, SV – systolic volume, ANP – atrial natriuretic peptide, BNP – brain natriuretic peptide, HRV – heart rate variability, ANS – autonomic nervous system, EPCs – endothelial progenitor cells, TPR – total peripheral resistance.

Discussion

In the above article we showed studies which demonstrated many potential benefits of CR including improvements in peak oxygen uptake (Kitzman et al., 2013), central hemodynamics (Arbab-Zadeh et al., 2004; Pugh, Wei, 2008; Hambrecht et al., 2000; Dehkordi, Far, 2015), peripheral vascular and skeletal muscle function (Selig et al., 2004), autonomic nervous system function and overall functional capacity. As it was mentioned earlier, exercise and functional capacity are clearly diminished in HF and provide to exertional fatigue and dyspnea and

in consequence reduce quality of life and increase depression (Downing, Balady, 2011). Many studies clarify physiological and biochemical mechanisms of exercise-induced cardiovascular therapeutic effects (Gielen, Schuler, Adams, 2010). It is worth to examine cardiac as well as pulmonary musculoskeletal and nervous system due to the variety of potential sites of CR effects. Moreover, combining few methods of evaluation altogether should be considered. Developing new techniques allows on examination of effects of CR on several levels simultaneously: examinations on molecular level (biochemical parameters) should be assisted by imaging studies (using PET and/or fMRI) and functional examination of cardiopulmonary, musculoskeletal and nervous systems. Studies on CR mechanism can translate to clinical benefit: revealing the most beneficial training protocol in terms of intensity and type of exercise adjusted by the initial health state of the patients would be a challenge for further researches.

Conclusions

1. There are several pathophysiological factors in HF patients which are considered to be responsible for the exercise intolerance. These multi-systemic factors are, inter alia: hemodynamic, ventilatory, and skeletal myopathic processes.
2. Exercise training has become part of evidence-based clinical therapy in patients with HF.
3. CR has positive effect on organism functioning and improvements in, inter alia, NYHA functional class, maximal ventilation and exercise capacity, due to improvement of systems functioning involving, inter alia, cardiopulmonary, musculoskeletal and nervous.

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