

Rehabilitation in Heart Failure: Update and New Horizons

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Abstract

Purpose of the review Heart failure is very prevalent and exercise intolerance is one of its main symptoms. Various studies and meta-analysis have provided scientific evidence regarding the improvement of functional capacity and quality of life in patients with heart failure who undertake a cardiac rehabilitation program. This paper reviews the evidence published in recent years regarding the efficacy and safety of physical exercise, as well as the different exercise modalities that should be a part of the treatment of heart failure patients.

Recent findings Exercise training in heart failure is safe and effective. High-intensity interval training, especially when associated with strength exercises and inspiratory muscle training, offers the most benefits compared with the traditional continuous training of moderate intensity. It is also better tolerated in heart failure patients and this increases adherence. However, we are in need of a big randomized study in patients with heart failure in order to fully establish the best exercise modality in these patients.

Summary Patients with heart failure should be referred to a multidisciplinary Cardiac Rehabilitation program and receive an individual exercise prescription based on risk

stratification, exercise capacity, and patient's preference. There is no single exercise training program that covers all the individual patients' needs. Therefore, in most cases, a combination of exercise programs, such as aerobic interval or continuous training, strength exercise, and inspiratory muscle training, is needed.

Keywords Exercise training · Heart failure · Inspiratory muscle training · Intermittent exercise · Cardiac rehabilitation

Introduction

The guidelines of the European Society of Cardiology define heart failure (HF) as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures or only at the expense of increased filling pressures. Regular aerobic exercise increases the ability of the body to use that oxygen [1].

Up to 2 % of the adult population in Europe and the United States (U.S.) has HF. It is the first cause of hospital admission in people above 65 years old, contributing to an increasing use of medical resources [2]. During 2012, there were more than 1 million hospitalizations in the U.S. with estimated direct and indirect costs of 40 billion dollars [3]. Identifying the etiology of HF is fundamental in order to offer the most adequate treatment for the patient. Physical training is beneficial for HF patients with ischemic and nonischemic cardiomyopathies, although cardiac adaptation is best in HF patients with nonischemic etiology [4].

Until the nineties, rest and restraint in physical activity were recommended as a part of the treatment of HF.

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Currently, both the European and the American guidelines highlight the importance of regular aerobic physical activity in the treatment of HF patients, with a class IA level of recommendation to improve functional capacity and reduce morbidity and mortality [5••].

Exercise Training in Heart Failure

Intolerance to physical exercise is one of the main symptoms in patients with HF, either with reduced or preserved left ventricular ejection fraction (LVEF). This exercise intolerance is strongly correlated with prognosis and a reduced quality of life [6•, 7]; however, it does not correlate with LVEF [8•]. Exercise intolerance can be quantified as a reduction in peak oxygen consumption (VO_2) of about 40 % during maximal exercise compared with controls of similar age and sex. This reduction of peak VO_2 can be due to cardiac abnormalities such as diminished cardiac output (CO) and chronotropic incompetence but also to abnormalities in peripheral vessels and muscles [7].

As exercise intolerance is multifactorial, we will briefly review the physiopathology behind the central and peripheral mechanisms in patients with HF:

- (1) *Cardiac alterations* lead to systolic or diastolic dysfunction, which in turn lead to diminished systolic volume, increase in filling pressures, mitral regurgitation, and right ventricular dysfunction. In patients with reduced LVEF, the diminished CO at submaximal and peak exercise is the result of reduced systolic volume, together with the reduction in heart rate reserve. Ventricular filling during exercise is also altered secondary to diastolic dysfunction and this increase filling pressures, which are responsible for the increase in pulmonary capillary pressure and dyspnea. Diastolic dysfunction of the left ventricle is an independent predictor of reduced exercise capacity in patients with preserved LVEF [9].
- (2) Patients with HF have *vascular abnormalities* such as endothelial dysfunction secondary to diminished Nitric Oxide availability and an increase of reactive oxygen species that lead to vasoconstriction and a reduced vasodilatory capacity during exercise [7].
- (3) Patients with HF have *changes in the skeletal muscles* that include a reduction in muscle mass, changes of the muscle fibers from type I to type IIb, and a reduction of type IIa muscle fibers in comparison with type IIb fibers. There is also an altered metabolism of these skeletal muscles with a reduction in the oxidative capacity and generation of ATP (diminished function, density, size, and enzymes in the mitochondria that lead to a delay in the synthesis of high-energy components) [9]. Although it is clear that

there is an induced myopathy secondary to the state of HF and chronic hypoperfusion documented in some studies, it has been shown that the mitochondrial dysfunction could be the consequence of diminished use of the peripheral muscles and deconditioning [8•].

- (4) *Respiratory abnormalities* in HF patients are due to a mismatch in ventilation/perfusion, pulmonary edema, damage of the pulmonary vasculature, fibrosis, increase of the minute ventilation, and reduced diaphragmatic strength. As opposed to the changes seen in the skeletal muscle, in the diaphragm of patients with HF there is a change from type IIb to type I fibers, probably as an adaptation mechanism to the increase workload of the diaphragm [10•].
- (5) *The neurohormonal abnormalities* that occur during HF imply an increase in sympathetic activity and a decrease in vagal activity, activating the renin-angiotensin-aldosterone system that leads to tachycardia, chronotropic incompetence, vasoconstriction, increase in reactive oxygen species, and proinflammatory cytokines that lead to fibrosis and increased muscular catabolism [9].

It is important to note that the biggest contributors to the increase in peak VO_2 achieved by patients with HF after physical training are the peripheral factors above mentioned [7]. The biggest part of the oxygen consumption during the transition from rest to exercise occurs in the active skeletal muscles of the periphery. Therefore, an abnormality in the metabolism of these muscles has a deep impact in the exercise intolerance of patients with HF. In this transition, the increase of blood flow to the muscles is due to the activation of the sympathetic nervous system together with the metabolically mediated vasodilatation that occurs in the muscles that are being exercised. Changes in the central and peripheral arterial function in patients with HF result in an inefficient distribution of the CO to the active skeletal muscles and contribute to exercise intolerance. Although CO can be normal at rest in patients with HF, there is an insufficient capacity to increase CO during mild exercise, leading to an insufficient increase in perfusion of active muscles that could cause an early switch to anaerobic metabolism, with the consequent increase in lactate production, increase of inadequate muscle strength, and finally muscle fatigue. This is why lactate levels correlate well with peak exercise capacity [9].

It is well proven that physical exercise can improve physical capacity (an important prognostic marker in HF patients [11]), heart and vascular function [12], depression [13], and quality of life [14, 15••]. This increase in quality of life also may have a higher impact in patients below 60 years old [16•].

In systolic HF, aerobic training offers an improvement of systolic and diastolic function with beneficial effects in ventricular work. It improves arterial function, measured as a decrease in pulse wave velocity and an increase of the augmentation index [17•]. Aerobic exercise also improves prognostic markers such as the natriuretic peptides and the ventilatory equivalent of carbon dioxide (VE/VCO₂ slope) in patients with systolic HF [18].

Physical training with or without strength exercises is an effective treatment to improve exercise tolerance and quality of life in patients with stable HF and reduced LVEF (level of evidence B) [6•, 7]. It can improve peak VO₂ and hemodynamics, reduces chronotropic incompetence, and improves the function of the skeletal muscle and peripheral vasculature [9]. Peak VO₂ increased between 18 and 25 % and the duration of exercise between 18 and 34 % in the published studies [9]. Subjective symptoms, functional class, and quality of life all improved after exercise training [9].

Flow-mediated vasodilatation and arterial elasticity are reduced in patients with advanced age, and they are critical components in the response to exercise. Physical exercise in patients with HF increases peak VO₂ without influencing the flow-mediated arterial vasodilation or arterial elasticity; therefore, the adaptations at the level of the microcirculation and skeletal muscle that increase the transport and utilization of oxygen by the active muscles may be the mechanisms contributing to the increase in peak VO [19, 25].

Most of the studies regarding exercise training in HF have been performed in chronic patients with functional class II–III of the New York Heart Association (NYHA). The biggest study was the HF-ACTION [20••], a randomized and controlled trial that analyzed the effects of physical exercise in 2331 patients with HF in functional class II–III of the NYHA and a LVEF <35 %. One group was randomized to supervised physical exercise that consisted of 36 sessions of aerobic exercise at 60–70 % of the heart rate reserve during 15–35 min, followed by a home exercise program of 40 min, five times per week. The control group received usual care (recommendations to do regular exercise at moderate intensity but without structured sessions or supervision). The primary outcome was death or all-cause hospitalization, and there was a tendency to favor the exercise group but it was not statistically significant (HR 0.93; $p = 0.13$) after 30 months of follow-up. In a prespecified analysis, adjusting for variables that strongly predicted outcomes such as the cardiopulmonary exercise duration, LVEF, the Beck II depression score, and atrial fibrillation or flutter, exercise was associated with a significant reduction of the primary outcome of 11 % ($p = 0.03$). A significant improvement in the quality of life at 3 months was also seen in the exercise group [21••].

However, the benefits of exercise training in patients with systolic HF may have been underestimated due to the following factors: (1) At randomization, 55 % of patients assigned to the control group were not satisfied with the assigned treatment. (2) There was an important crossover rate, as 22–28 % of the control group performed exercise regularly. (3) Adherence in the exercise group diminished gradually from 95 min per week at 4–6 months to 74 min per week at 10–12 months after starting the program.

Many of the published studies, including HF-ACTION, excluded patients with decompensated HF or those who have been hospitalized in the previous 4–6 weeks [22], needing a stabilization period prior to starting a Cardiac Rehabilitation (CR) program. Although the indication for exercise training is more limited in patients with acute HF, the published studies showed a benefit of a protocolized exercise program initiated during the hospitalization. The majority of patients hospitalized for acute HF are older, with multiple comorbidities and deficits in mobility, strength, and balance that can worsen during hospitalization, and all this is associated with increased risk of adverse events such as rehospitalization and death [23]. Exercise training of certain muscles such as the knee extensor during 2 months can be very beneficial to improve diffusive O₂ transport in patients with HF and could be very useful in severely deconditioned patients with minimal reserves [24•].

Exercise Training Protocols in Heart Failure

The prescription of an exercise program must be individualized, and the type and intensity of the exercise must be tailored to each case in order to obtain the maximum benefit with the minimum risk. To do this, we must perform an individual clinical evaluation, be aware of the physical and social situation of our patient as well as their personal preferences in order to improve adherence to the therapeutic program. To stratify risk, we recommend risk models that include functional parameters such as the Heart Failure Survival Score or the Metabolic Exercise and Cardiac, and Kidney Indexes (MECKI) [25] that includes the peak VO₂ and the VE/VCO₂ slope, respectively. The VE/VCO₂ slope indexed for the VO₂ or the respiratory oscillation index has also been shown to have a role in risk stratification [26].

There are multiple training protocols: Aerobic continuous exercise, interval training alone or combined with strength, and/or respiratory exercises. All of them include a warming-up phase and a cooling-down phase. Also, these programs can be supervised or not and they can be done in hospitals, primary health care centers, sports facilities, or at home. Table 1 describes the training programs of most of the referenced studies, and we will briefly review the

different types of exercise protocols and the evidence behind them.

Intermittent Versus Continuous Aerobic Training

Some studies have shown intermittent or interval training (IT) exercise programs to be superior to continuous training (CT) in patients with chronic HF.

Smart et al. [27••] performed a meta-analysis of studies comparing IT with CT in patients with chronic HF, and they concluded that the optimal exercise protocol to improve peak VO_2 and VE/VCO_2 slope would be an IT of 4 min of work at 90–95 % of the peak heart rate followed by 3 min of recovery at 50–70 % of the peak heart rate during 38 min, three times per week. With the same energy consumption, adding strength exercises seemed to improve the changes in peak VO_2 , which are associated with good prognosis.

Haykivsky et al. [28] in another meta-analysis found a higher increase in peak VO_2 with IT in comparison with CT of moderate intensity in patients with stable chronic HF and reduced LVEF, although the duration and intensity of exercise in the different studies analyzed were different.

An increase in peak VO_2 and CO with IT versus CT was also found by Fleg et al. [6•] after 3 months of training. Fu et al. [29•] also found that IT was associated with a better physical condition, cardiovascular function, and quality of life compared with CT [30].

Other studies published in recent years did not find this superiority of IT versus CT [31, 32, 33•]. The study by Nathalie et al. [34•] found that after 24 sessions of training, both the IT and CT group had significant improvements in physical condition, maximal work load, peak VO_2 , oxygen uptake at the anaerobic threshold, and peak O_2 pulse. There were no changes in cardiovascular structure or in quality of life (SF-36, Minnesota) in any of the groups. Aksoy et al. [35•] also found that both types of exercise protocols reduced serum markers of adhesion molecules associated with endothelial dysfunction (a noninvasive biomarker used to identify high-risk patients) [36].

Short-Duration Interval Training

The majority of studies on cardiac rehabilitation in patients with HF have been performed with CT of moderate intensity (50–70 % of peak VO_2), but more recently, high-intensity interval training (HIT) at 80–95 % of peak VO_2 during 2–5 min alternating with resting periods have been tested [37, 38]. A recent study by Chrysohoou et al. [17•] evaluated the effect of HIT combined with strength exercise on left ventricular function and aortic elastic properties in patients with chronic HF. Compared with control patients, there was a significant reduction in the pulse wave

velocity of 9 % and in the augmentation index of 29 %. They found an increase of peak oxygen uptake of 28 %, peak power of 25 %, peak heart rate of 25 %, and a decrease of the VE/VCO_2 slope. There was also an improvement in diastolic function with significant decreases in the E/A and E/E' ratios. All these changes were accompanied by improved quality of life of 66 %, as measured by the Minnesota living with heart failure questionnaire, improved depression score of 19 %, and an increase of the 6-min walking test (6MWT) of 13 % in the intervention group versus the control.

Interval Training at Different Intensities

Hashbullah et al. [38•] published a meta-analysis comparing the effect of different exercise intensities on peak VO_2 , adherence to treatment and adverse effects in patients with HF. They observed an improvement in peak VO_2 in the HIT group as the intensity of the exercise program increased from 4 to 52 weeks and from 45 to 200 min/week. The improvements that they found in the low intensity and control group were attributed to the pharmacological treatment. They did not find significant differences between vigorous exercise and controls regarding cardiac events or mortality, although rehospitalizations were 15 % lower in the vigorous exercise group. When they compared vigorous-intensity exercise with high-intensity exercise, there was a tendency to diminish mortality. Both exercise regimens were better tolerated if rest intervals were used, compared with CT. HIT programs can also increase adherence as the time and frequency of sessions are reduced.

Inspiratory Muscle Training

Inspiratory muscular training (IMT) improves functional capacity and quality of life, especially in patients with an increased weakness of these muscle groups and in association with aerobic exercise. Stamatis et al. [39••] obtained significant benefits in inspiratory muscle work capacity, quality of life, and dyspnea, and a reduction of C-reactive protein and natriuretic peptides in patients with HF that performed aerobic exercise associated with IMT in comparison with those that only did aerobic exercise. They found a significant increase in both groups in maximal inspiratory pressure, peak VO_2 , and LVEF after training.

Other authors also confirmed the benefit of IMT, showing that its performance during 4 weeks could improve aerobic capacity and peripheral changes [40•].

An exercise program that combines HIT with strength training and IMT showed benefits in the function of the skeletal and respiratory muscles, the cardiopulmonary

Table 1 Training program description of the most significant studies

Study	Group	Training program intensity	Duration (min)	Frequency (days/week)	Length (weeks)
O'Connor et al. [20••]	CT	60–70 % of HR reserve	15–30	3	12
	Control	Usual practice			
Fu et al. [29•]	HIT	80 % of peak VO ₂ /recovery at 40 % of peak VO ₂	3/3 (30 in total)	3	12
	CT	60 % of peak VO ₂	30 min		
	Control	Usual practice			
Nathalie et al. [34•]	HIT	90 % maximal load in Watts (Börg 15–17)/30 % maximal load in Watts	1/2.5 (35 in total)	3	8
	CT	60–75 % maximal load in Watts (Börg 12–14)	30		
Aksoy et al. [35•]	IT	50–75 % Peak VO ₂ /30 Watts	1/0.5 (17 cycles)	3	10
	CT	50–75 % Peak VO ₂	35		
	Control	Usual practice			
Chrysohoou et al. [17•]	HIT	80–100 % of MW/rest + resistance 30–90 % of 1 MR	0.5/0.5 (45 in total)	3	12
Stamatis et al. [40•]	CT + IMT	70–80 % MHR + IMT at 60 % of MIP for 30 sec	45	3	12
	CT	70–80 % MHR + IMT at 10 % of MIP for 30 sec	45		
Siddhartha et al. [42]	HIT	Initially: 80–85 % MHR/50 % MHR Final: 85–90 % MHR/50 % MHR	2/2 (32 in total) 4/3 (28 in total)	3	4
	CT	60–70 % MHR	15–30		
Kitzman et al. [19•]	CT	Initially: 40–50 % peak VO ₂ ; Final: 60–70 % peak VO ₂	60	3	16
	Control	Usual practice			

CT continuous training, HR heart rate, HIT high-intensity interval training, IT interval training, VO₂ oxygen consumption, MHR maximal heart rate, MW maximal workload, MR maximal repetition, MIP maximal inspiratory pressure, IMT inspiratory muscle training

index, dyspnea, and quality of life compared with a traditional aerobic exercise training program [10].

Benefits of Aerobic Exercise Training in Patients with Preserved LVEF

Most of the studies of exercise training in patients with HF have been performed in those with reduced LVEF, and the effects of HIT in patients with HF and preserved LVEF are less well studied. Siddhartha et al. [41] studied patients with HF and preserved LVEF, and they found that patients that performed HIT had significant improvements in peak VO₂, parameters of diastolic dysfunction of the left ventricle, and a reduced diastolic arterial pressure compared with CT. However, there were no changes in endothelial function, maybe because they found no changes in the vasodilatory function among patients with preserved LVEF compared with those with reduced LVEF. Although it was a small study with very few women included, the intensity of HIT recommended (see Table 1) is in accordance with recent recommendations, and it may be an optimal exercise prescription for patients with HF and preserved LVEF.

Ambarish et al. [42] in a recent meta-analysis of patients with HF and a LVEF >45 % observed a significant improvement of cardiorespiratory function and quality of life in the exercise group versus the control, although they did not find significant changes in systolic or diastolic function. Therefore, the improvement in cardiorespiratory function may be mediated through mechanisms independent of the left ventricular function.

Kitzman et al. [19•] demonstrated an improvement in exercise tolerance, systolic and diastolic function, quality of life, and left ventricular dimensions in patients with HF and preserved LVEF after a supervised exercise training program. It was hypothesized that increased arterial stiffness and endothelial dysfunction could contribute to the exercise intolerance observed in patients with HF and preserved LVEF and that this could be improved by means of exercise training programs. However, in this study, they did not find an improvement in endothelial function and arterial stiffness. Other possible mechanisms for the improvement in exercise tolerance could be peripheral factors such as a better extraction of oxygen by the active skeletal muscles or physiological remodeling and associated improvement in stroke volume and cardiac output.

Benefits of Aerobic Exercise Training in Women

There is less evidence of the benefit of physical exercise in women with HF due to the lower number of these patients included in most studies. Piña et al. [43] observed increased benefit for the combined objectives of mortality and hospitalization for any cause in women compared with men. This improvement was primarily driven by a lower hospitalization rate with similar mortality rate. Adherence was similar between women and men and they found similar small increases in peak VO_2 with exercise training.

The contribution of hormones to exercise intolerance has not been shown in women with HF, but we do now that estrogen diminishes with age and this could be associated with diminished endothelial dysfunction. Further studies to evaluate this hypothesis are needed, and if this is the case, evaluation of hormonal intervention in older women and men could be beneficial in patients with HF.

Adherence to a Physical Exercise Training Programs

Adherence has been the Achilles heel of most of the Cardiac Rehabilitation programs; especially in the medium–long term. Home-based exercise programs were introduced to improve access and patient participation. A Cochrane review [15••] included 17 randomized controlled studies comparing home-based exercise with supervised exercise training in a center (hospital, gym, or sport center) in HF patients. After 12 months of follow-up, they did not observe any differences in mortality, cardiac events, exercise capacity, quality of life, costs or modifiable risk factors such as Total and LDL Cholesterol, systolic blood pressure, and smoking habits. There were small differences in favor of the center-supervised program regarding HDL Cholesterol, Triglycerides, and diastolic blood pressure. The home-based programs had better adherence and could be beneficial, depending on patient's preference, in low-risk patients after myocardial infarction, coronary revascularization, or in HF patients.

Lauren et al. [44••] described the association between social support and barriers to participate in an exercise program of 3 to 12 months duration, with adherence and clinical results. Higher exercise time correlated with a higher Perceived Social Support Score (PSSS) and a lower Barriers to Exercise Score (BTES) ($p < 0.005$). In the HF-ACTION study [20••], from 2331 patients that started the study, 2279 (1090 in the exercise group) completed it. A lower adherence was found in women with younger age, black race, higher body mass index, lower exercise

capacity, lower quality of life, and higher depression scores and who were single. There was no association between the baseline PSSS or BTES and peak VO_2 at 12 months. Social support was not associated with mortality or cardiovascular or all-cause hospitalization.

Although physical limitations and decreased social support can diminish the adherence to an exercise program, it is important to remember that there are studies that show that even low levels of exercise are better than none [45, 46]. To increase adherence to cardiac rehabilitation programs, life-style interventions can be useful, as well as psychosocial, socioeconomic, educational, and biological factors. There are a few studies on the predictors of behavior regarding physical exercise, including genetic markers [6•], although we need more studies regarding what interventions could improve the adherence to exercise programs in patients with chronic HF. The use of new technologies such as telemedicine using smartphones and internet could facilitate follow-up and adherence in some patient groups [47, 48].

New Horizons

In the future we need to perform more studies on the efficacy of exercise training programs in less-studied patient groups with heart failure such as older and frailer patients with increased comorbidities, women, patients with recently decompensated HF, and patients with HF and preserved LVEF.

HIT seems to be the best exercise training protocol in HF patients as it has been shown to be as safe as CT and more efficacious; however, physicians still hesitate to prescribe this type of exercise programs in HF patients as the existing studies have different exercise protocols with mostly soft outcomes. Therefore, a big randomized controlled trial of HIT combined with IMT and possibly strength exercises compared with CT and with a control group would seem appropriate in order to fully establish this therapy in HF patients.

Another great challenge is to increase the inclusion and adherence of patients with HF to Cardiac Rehabilitation programs. Home-based training programs can overcome geographical access and timetable incompatibilities with similar results to the center-based programs. Also, telemedicine can improve adherence, motivation, and long-term follow-up of the exercise training program by means of smartphone applications that record exercise activity, video conferences, audio tapes for relaxation, or chats. These new approaches to cardiac rehabilitation need to be evaluated in order to establish their safety and efficacy.

Conclusions

Exercise training in HF is safe and effective. HIT, especially when associated with strength exercises and IMT, offers the most benefits compared with the traditional CT of moderate intensity. It is also better tolerated in HF patients and this increases adherence. However, we are in need of a big randomized study in patients with HF in order to fully establish the best exercise modality in patients with HF.

We need multidisciplinary Cardiac Rehabilitation programs to make an individual exercise prescription based on risk stratification, exercise capacity, and patient's preference. There is no single exercise training program that covers all the individual patients' needs. Therefore, in most cases, a combination of exercise programs such as aerobic interval training or CT, strength exercise and IMT are needed.

And lastly, we must not forget that the Cardiac Rehabilitation Program in HF patients not only includes exercise training but must work side by side with the multidisciplinary heart failure units. Cardiovascular risk factor control, optimization of medical, surgical, and device treatment, psychosocial support, health and self-care education are important in the management of the patient and must be addressed adequately in order to improve the outcomes and quality of life of our HF patients.

Compliance with Ethical Guidelines

Conflict of Interest Marta Gómez-Cuba, Ana Perreau de Pinninck-Gaynés, Rosa Planas-Balagué, Nicolás Manito, and José González-Costello declare that they have no conflict of interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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