

# Cardiac rehabilitation in chronic heart failure

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## Abstract

Chronic heart failure is a complex clinical syndrome characterized by multi-organ dysfunction and progressive functional deterioration. From the result of the literature, it is evident that the optimal care for heart failure is far from being reached, and exercise-based cardiac rehabilitation (Ex-CR) is a multidisciplinary therapeutic option with important clinical benefits. Longitudinal controlled studies and meta-analyses have demonstrated that Ex-CR improves functional capacity by 12-25%, and improves outcome by significantly decreasing hospital readmissions and cardiac mortality. These results have been obtained in patients with systolic dysfunction (HF-REF) with moderate aerobic endurance programs. More recently, greater improvements in functional capacity have been obtained even in older patients (>75 years) with high intensity interval training, but the number of patients is too small at present to reach definitive conclusion, and follow up is lacking. In diastolic heart failure (HF-PEF) improvements in functional capacity have been described in a total of 282 patients, with similar results as HF-REF but no evidence on outcome. Ex-CR programs are safe with a very low number of cardiac arrest (1/300,000 patient/hour) in different trials. Clinical benefits are the result of central and peripheral adaptations induced by exercise, which acts as a trigger of protein synthesis by specific genes activated by it. It is crucial to maintain a specific stimulus by repeating exercise bouts at least 2-3 times per week all life long, because after 2-3 weeks of inactivity functional adaptations disappear.

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Key words: Cardiac rehabilitation; chronic heart failure; diastolic heart failure.

Received for publication: 02 April 2016  
Accepted for publication: 29 June 2016

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Tipografia PI-ME Editrice, Italy  
Monaldi Archives for Chest Disease Cardiac Series 2016; 86:753  
doi: 10.4081/monaldi.2016.753

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## Introduction

Chronic heart failure (CHF) is a complex clinical syndrome characterized by multi-organ dysfunction and progressive functional deterioration. Every year, CHF has been diagnosed in 1 to 5/1000 subjects. Its prevalence and incidence increases with age, with a 5-year mortality rate of 45% [1-3]. The most frequent causes of CHF are coronary artery disease and hypertension, which account for 80% of all causes. Despite the progress of medical therapy over the last decades, which has been effective in reducing mortality rate in the hospital, the prognosis of CHF is unchanged, with 30-40% of patients dying within one year from diagnosis, while outpatient clinics increased the volume of activity and costs of care. From the result of the literature, it is evident that the optimal care for heart failure is far from being reached, and there is a need to find new methods of treatment in order to improve functional capacity, quality of life and clinical outcome [4-6].

Over the last three decades, exercise-based cardiac rehabilitation (ExCR) moved from a research tool to a clinical well-defined therapeutic option in patients with CHF. The European Society of Cardiology and the American Cardiology Societies (AHA/ACC) both recommend ExCR in stable CHF patients on the basis of previous longitudinal trials and more recent meta-analyses [7-9].

## Physiopathology

A reduced exercise tolerance is common in CHF as a consequence of a vicious cycle of cardiocirculatory failure and deconditioning. Heart failure stimulates adrenergic activity and renin-angiotensin system, and is a major determinant of skeletal muscle atrophy, which decreases aerobic enzymes activity favoring exercise intolerance [10]. This cascade of negative events is similar between diastolic heart failure (HF-PEF) and systolic heart failure (HF-REF), suggesting that ejection fraction is unrelated to peripheral abnormalities, which seem to play a major role in exercise deconditioning and clinical deterioration [11].

## Exercise training

Exercise training has been considered as the key point of cardiac rehabilitation programs since 1985. From the scientific evidence of the Duke group in the US and the Brompton's group in UK, other trials were performed in western countries over the next 2 decades, demonstrating the efficacy of exercise-based cardiac rehabilitation in HF-REF patients first, and HF-PEF later on [12-20].

## HF-REF

The ExTraMATCH meta-analysis summarized the results of the first group of trials on 801 HF-REF patients randomized into two groups:

exercise (n=395) and controls (n=406) [9]. Exercise training was performed on top of medical therapy at moderate intensity (60-80% of peak VO<sub>2</sub>), under supervision for 213(135) days with a mean follow up of 705(729) days. Functional capacity was improved, ranging 12-25%. Overall, there were 88 deaths in the exercise arm (median time to event, 618 days) and 105 in the control arm (421 days). Mortality was significantly lower in the exercise group (log rank X<sup>2</sup> = 5.9, p=0.015) and the hazard ratio for mortality was 0.65 (95% confidence interval 0.46 to 0.92). These results would imply 17 treated patients to prevent one death in two years.

HF-ACTION was a multicenter, randomized controlled trial designed to measure the effects of exercise training in stable HF-REF patients (n=2331) on functional capacity, quality of life measures of outcome such as mortality and re-hospitalization [21]. Patients were randomized to 36 sessions of supervised aerobic endurance exercise at 60-70% heart rate reserve followed by home-based training or usual care. At a median follow-up of 30 months, there was a 7% reduction in the primary combined end point (p=0.13). However, after adjustment for pre-specified predictors of mortality, such as duration of exercise test, LVEF, BDI score and history of atrial fibrillation, there was a statistically significant reduction in mortality (HR 0.89, p=0.03). The improvement in peak VO<sub>2</sub> was only 4%, probably due to biases such as low adherence to training in the training group and regular home exercise in many control patients. In a subsequent analysis, patients who exercised as prescribed experienced a >30% reduction in mortality or hospitalization. For every 6% increase in VO<sub>2</sub> peak there was a 5% lower risk of the primary end point (p<0.001) and an associated 8% lower risk of combined cardiovascular mortality and hospitalizations (p<0.001).

In order to improve long-term outcome, adherence to exercise prescription is crucial. This concept has been demonstrated in a recent paper where 123 HF-REF patients followed a supervised program of exercise training at 60% of VO<sub>2</sub> peak twice a week for 10 years in a coronary club with periodic checks in the hospital [22]. The VO<sub>2</sub> peak was maintained at more than 60% throughout the 10 years [average: 65.3 (3%)], whereas it was less than 55% in untrained patients [52 (8%), p<0.01]. The training group had a better quality of life (p<0.05), fewer hospital readmissions (p<0.001), and a lower cardiac mortality (p<0.001) than the control group. Authors concluded that supervision seems to be a crucial factor to reduce dropouts and increase adherence to long-term exercise sessions. The coronary club may be an efficient model to apply in cardiac rehabilitation in future studies.

## HR-PEF

The results of 7 controlled trials on HF-PEF patients have demonstrated that exercise training improves aerobic capacity and quality of life at similar amounts of endurance training in HR-REF patients. A total of 282 patients were studied, 157 underwent endurance exercise training at moderate intensity, three times a week for 12-52 weeks [23-29]. In the only randomized multicenter study, the Ex-DHF pilot study (Exercise Training in Diastolic Heart Failure), VO<sub>2</sub> peak increased by 16% (p<0.001 vs controls) and was correlated with diastolic filling E/e' change (r= -0.37, P=0.002) and SF-36 physical functioning (r= -0.46, p<0.001). At present, there is not sufficient evidence that Ex-CR has positive effects on the clinical outcome of HF-PEF patients.

## Patient selection

The condition *sine qua non* to obtain benefits from exercise training in CHF is clinical stability. In all studies, patients enrolled did not have

severe ventricular arrhythmias, unstable angina and signs or symptoms of worsening heart failure over the last 3 months. Mean age was 59 years in a recent review (range 43-72 years) [14]. The majority of patients are men, NYHA class II and III, ischemic etiology. The dose of exercise training across studies ranged widely - average duration of 15 to 120 min/session, 2 to 7 sessions/week, at an intensity of 40% of maximum heart to 85% of maximum oxygen uptake (VO<sub>2</sub> max) and over a duration of 24 to 52 weeks.

## Methodology of exercise training

### Endurance aerobic training

It has been the most popular choice since the first application in CHF patients. Patients exercised in a supervised environment three to five times a week, at an intensity calculated at 50-70% VO<sub>2</sub> peak or heart rate reserve or heart rate at peak exercise. Each session started with calisthenics for 10-15 minutes, followed by aerobic exercise such as walking on a treadmill or cycling on a stationary cycle ergometer for a total of 40 min. Heart rate is monitored during each session, and blood pressure is measured electronically or manually at rest, during aerobic exercise and at the end of recovery. The duration of a training program averages 12 weeks, a duration sufficient to obtain improvements in functional capacity and quality of life. The results of the main trials using endurance protocols show increases in VO<sub>2</sub> peak by 12-31%.

### Interval training

It is a methodology of training where exercise is divided in bouts of high and low intensity, starting with a low intensity (*i.e.* cycling at 30% of VO<sub>2</sub> peak for 3 min) followed by high intensity (90% of VO<sub>2</sub> peak for 1 or 2 min) for a total of 30 min. This type of training has been recently emphasized by a group in Norway who exercised 27 patients (20 males, mean age 76 years) [11] with ischemic cardiomyopathy using high intensity interval training three times a week for 12 weeks as follows: 10 min warm up walking at 50-60% of VO<sub>2</sub> peak, followed by 4-min intervals at 90-95% of peak heart rate, each interval separated by 3-min active pauses, walking at 50-70% of peak heart rate [30]. The training session was terminated by a 3-min cool-down at 50-70% of peak heart rate, with a total exercise time of 38 min per session. They compared 9 patients in the interval-training group with 9 patients in the endurance moderate training group and 9 untrained controls. The results were favorable to the interval training group in terms of improvements in VO<sub>2</sub> peak (+46%) and ejection fraction (+35%). Major criticisms to this paper were the small number of subjects, the absence of follow up and the potential risk of arrhythmias due to the high intensity exercise.

Other studies followed with contrasting results. Of six studies comparing high intensity interval training with moderate intensity endurance training in stable HR-REF patients, 4 had similar improvements in VO<sub>2</sub> peak, while 2 had no improvement in VO<sub>2</sub> peak with endurance training, which is well below the average reported in the literature.

### Resistance training

Resistance training (RT) is an accepted component of ExCR programs in CHF patients, because it enhances muscular strength and contributes to improved functional capacity. Conventional RT typically consists of lifting heavier weights with longer rest periods, whereas circuit training consists of lifting lighter weights with shorter rest periods between exercise. Circuit training is the most popular RT among CHF patients, with a greater aerobic component to workout and less intensity. In older women with CHF randomized to 10 weeks of RT or

control, there was a 43% increase in muscle strength and a 49% increase in 6-min walk distance along with a 299% increase in submaximal endurance measured by the number of lifts at an intensity of 90% of baseline-1 repetition maximum. The beneficial effects of RT in CHF appear to be directed at improving skeletal muscle abnormalities and neuromuscular function, associated with an increased muscle mass, which correlates with  $VO_2$  peak [31]. Improvements in functional capacity has been mainly observed with RT in HF-REF patients, although RT has been included as an adjunctive modality to aerobic exercise training in the already cited Ex-DHF trial in patients with HF-PEF [32].

## Safety

There is evidence that ExCR is safe in general, with no difference between patients with HF-REF or HF-PEF. In our database, we recorded 2 ventricular fibrillations over 28 years, which were promptly resolved with full recovery [33]. In the HF-ACTION Trial, of 2331 patients with HF-REF, 37 patients in the training group had at least 1 hospitalization due to an event that occurred during or within 3 hours after exercise, while 22 control patients had an adverse event despite no formal exercise program [21]. Only 1 patient had ICD discharge during exercise. No serious adverse training-related events have been reported in 6 trials that studied training in HFPEF patients (approximately 250 patients), which generally included older patients than in systolic CHF trials and a larger percentage of women [34].

## Benefits and mechanisms

Ex-CR induces clear benefits to HF patients independent of age, sex and CHF type and etiology [35]. Benefits are related to improvement in functional capacity, which regresses in 2-3 weeks if patient stops exercising regularly. Recently, a 10-year supervised controlled endurance exercise program has been associated with a 32% relative risk reduction of cardiac mortality over 10 years, with a persistent maintenance of higher peak  $VO_2$  and lower resting heart rate and ventilator efficiency in the training group [22]. In the ExTraMATCH meta-analysis on 801 HF-REF patients, there was a 35% reduction in mortality and hospital readmissions in trained patients versus untrained controls over a 2-year follow up [9]. An analysis of >600,000 patients from the Medicare database addressed the effects of Ex-CR exercise training on mortality. Subgroup analyses of patients with CHF showed a 15% lower mortality in CHF patients who participated in Ex-CR compared with carefully matched CHF patients who did not participate [36].

In a recent Cochrane review on 3647 patients, heart failure specific hospitalizations were reduced with exercise heart failure specific admissions (fixed effects RR 0.72, 95% CI: 0.52 to 0.99;  $p=0.04$ ). Across the five studies that reported disease specific health-related quality of life using the Minnesota living with heart failure (MLWHF) questionnaire, there was a significant improvement in health-related quality of life (HRQoL) with exercise (random effects mean difference: -10.3, 95% CI: -15.9 to -4.8,  $p=0.0003$ ). (37) Pooling across all studies reporting HRQoL regardless of outcome measure, there was also evidence of a significant improvement with exercise (random effects standardized mean difference: -0.56, 95% CI: -0.82 to -0.30,  $p<0.0001$ ). No significant predictors of all-cause mortality or quality of life treatment response were found.

In HF-ACTION, exercise training-induced increases in  $VO_2$  peak were closely correlated with a better prognosis. Exercise training at 3 to 5 metabolic equivalent (MET) h/week was associated with 37% and 64% reductions in adjusted risks for death/hospitalization ( $p=0.03$ ) and cardiovascular death/heart failure hospitalization ( $p=0.001$ ).

These results are in agreement with those showing that 1 MET increase in functional capacity is associated with a 12.4% lower mortality risk per year [38]. Moreover, for exercise to improve long-term outcomes, adherence to the exercise prescription is necessary [39].

The clinical benefits of exercise training in CHF can be expected to be long lasting. The effects of exercise training on prognosis may relate to its effects on autonomic function [40,41]. Neuro-humoral excitation and increased sympathetic nerve activity, both characteristic of CHF, are associated with long-term mortality, and exercise training reduces these abnormalities. The improvement in functional capacity is the results of central and peripheral adaptations induced by exercise training. Exercise training improves skeletal muscle aerobic capacity, as demonstrated by increased expression of oxidative enzymes such as citrate synthase and succinate dehydrogenase, an increased distribution of oxidative type I fibers and capillary to fiber, and an increased volume density of mitochondria which correlated with pre-post training  $VO_2$  peak [42,43]. The decreased sympathetic tone and the improved endothelial function are associated with enhanced vasodilatory capacity depending on greater nitric oxide biological activity and improved smooth muscle fibers relaxation. The improved endothelium-dependent relaxation is also related to decreased oxidative stress, as demonstrated by reduced skeletal muscle expression of NADPH oxidase and increased expression of ec-SOD dismutase [44-47]. Central adaptations have been described and may play a role to improve cardiocirculatory function. An anti-remodeling effect is associated with lower cardiac volumes and higher cardiac efficiency [48]. Diastolic relaxation is also improved after endurance training and translates into higher systolic efficiency [49]. Coronary adaptations have been also described, as greater vasodilatory capacity and improved collateral circulation, which correlates with improved myocardial perfusion and function [50,51].

## Heart transplantation

Exercise training is recommended after heart transplantation (HTx) because of positive effects on exercise performance and quality of life [52]. The majority of trials have used endurance aerobic exercise at moderate intensity. The American College of Sports Medicine and American Heart Association recommend exercising with intensity between 50% and 90% of maximum  $VO_2$ , which refers to approximately 60%-95% of the maximum heart rate [53,54]. Accumulating evidence suggests that chronotropic incompetence is not a factor limiting exercise capacity in the majority of HTx recipients and that interval training is a feasible, safe and effective way to improve exercise capacity and general health in stable, long term HTx recipients. This type of exercise should be introduced and used more frequently among a broader audience. However, the transplanted heart seems to respond differently to this type of exercise, resulting mainly in peripheral improvements rather than improved cardiac function. The optimal timing to start a Ex-CR program is still a matter of debate. At present, there is not sufficient evidence to conclude that interval training is superior to endurance moderate exercise in HTx recipients.

## Conclusions

In summary, Ex-CR is a therapeutic intervention able to induce clinical benefits related to improved functional capacity. The most important benefits are improved quality of life, reduced hospital readmissions and cardiac mortality. Exercise is an important component of CR, but patient's care is more complex requiring patient and family

education, psychological support, diet counseling and drug optimization. The main objective of this multidisciplinary intervention is to correctly motivate patients to follow the CR program, which should be personalized according to individual clinical picture. The crucial point is the adherence to training, which is highly dependent on patient's motivation induced by cardiac rehabilitation team.

It seems that exercise is a trigger to stimulate protein synthesis by specific genes, which induce molecular adaptations able to maintain a higher aerobic capacity for months or years depending on the number of exercise sessions. It is crucial to maintain a specific stimulus by repeating exercise bouts at least 2-3 times per week all life long, since after 2-3 weeks of inactivity functional adaptations disappear.

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