High intensity, interval exercise improves quality of life of patients with chronic heart failure: a randomized controlled trial

C. CHRYSOHOOU1, G. TSITSINAKIS1, I. VOGIATZIS2, E. CHEROUVEIM3, C. ANTONIOU1, A. TSIAINTILAS1, D. TSIACHRIS1, D. DIMOPOULOS4, D. B. PANAGIOTAKOS4, C. PITSAVOS1, N. G. KOULOURIS2 and C. STEFANADIS1

From the 1First Cardiology Clinic, Hippokration Hospital, School of Medicine, University of Athens, 2First Department of Respiratory Medicine, Pulmonary Rehabilitation Unit, Sotiria Hospital, National and Kapodistrian University of Athens, 3Department of Sports Medicine and Biology of Exercise, Faculty of Physical Education and Sport Science, University of Athens, 114 Vassilissis Sofias Ave, 11 528 Athens, Greece and 4Department of Nutrition and Dietetics, Harokopio University, 70 Eleftheriou Venizelou Ave, 176 71 Athens, Greece

Address correspondence to C. Chrysohoou, 46 Paleon Polemiston St., 166 74, Attica, Greece. email: chrysohoou@usa.net

Received 9 August 2013 and in revised form 12 September 2013

Summary

Background: The aim of this study was to evaluate the effect of high intensity, interval exercise on quality of life (QoL) and depression status, in chronic heart failure (CHF) patients.

Methods: A randomized controlled trial (phase III). Of the 100 consecutive CHF patients (NYHA classes II–IV, ejection fraction ≤ 50%) that were randomly allocated to exercise intervention (n = 50, high-intensity intermittent endurance training 30 s at 100% of max workload, 30 s at rest, for 45 min/day-by-12 weeks) or no exercise advice (n = 50), 72 (exercise group, n = 33, 63 ± 9 years, 88% men, 70% ischemic CHF and control group, n = 39, 56 ± 11 years, 82% men, 70% ischemic CHF) completed the study. QoL was assessed using the validated and translated Minnesota Living with Heart Failure questionnaire. Depressive symptomatology was evaluated using the validated and translated Zung Depression Rating Scale (ZDRS). Maximal oxygen uptake (VO2max) and carbon dioxide production (VCO2max) were also measured breath-by-breath.

Results: Data analysis demonstrated that in the intervention group MLHFQ score was reduced by 66% (P = 0.003); 6-min-walk distance increased by 13% (P < 0.05), VO2max level increased by 31% (P = 0.001), VCO2max level increased by 28% (P = 0.001) and peak power output increased by 25% (P = 0.001), as compared with the control group.

Conclusion: High intensity, systematic aerobic training, could be strongly encouraged in CHF patients, since it improves QoL, by favorably modifying their fitness level.
Introduction

Heart failure constitutes a serious health problem in modern societies. Beyond clinical implications of the disease, patients with heart failure suffer from low quality of life (QoL) because of their inability to perform daily activities, mainly due to excess dyspnoea and fatigue. Moreover, low QoL often leads to depression, initiating a downward spiral; which is related with worse outcomes when compared with those having preserved emotional health.

Regular exercise enhances muscular function and strength and promotes the body’s ability to consume and utilize oxygen; while it improves the capacity of blood vessels to dilate in response to exercise, left ventricular diastolic function and neurohormonal activation. Despite those facts, and the recent guidelines regarding the management of heart failure, the recommendation for exercise among heart failure patients has been poorly implemented in daily clinical practice. This has been attributed to the fact that several types of training protocols have been used in rehabilitation programs, with an ongoing debate regarding the intensity and type of exercise training that can provide optimal effects for chronic heart failure (CHF) patients. To our knowledge most studies of rehabilitation in heart failure patients were performed using moderate intensity continuous training (50–70% of \( \text{VO}_{2}\text{peak} \)) or repetitions of high-intensity intervals (80–95% of \( \text{VO}_{2}\text{peak} \)) of a relatively long duration (2–5 min), separated by moderately intense recovery periods.

The aim of this study was to evaluate the effect of high intensity, intermittent exercise of short duration in a 12-week training program on the QoL and depression status of CHF patients, due to coronary heart disease and dilated cardiomyopathy, under optimal pharmaceutical and invasive treatment.

Methods

Participants

Patients who were visiting the Heart Failure Unit of the clinic between September 2010 and September 2011, with CHF due to left ventricular systolic dysfunction (NYHA classes II–IV, ejection fraction \( \leq 50\% \)) were eligible for participation. Patients with heart stable stage of heart failure (I–III) due to ischemic or dilated heart failure, without several valve diseases were included in the study. Those patients that would have substantial changes in their medication, including neurohormonal drugs and invasive treatment, during the study period, would be also excluded from the final analysis.

The study’s flow diagram, according to the CONSORT guidelines is presented in Figure 1.

Based on an a priori statistical power calculation (using East 3, 2003, Cytel Software Corporation, USA), the number of studied patients \( (n=30 \text{ per group}) \) was adequate to evaluate standardized differences of the investigated QoL and ZDRS scores between the groups of the study, >0.5 two-tailed, since a power of 85% at significance level of 0.05 was achieved.

Randomization

Eligible patients who gave their consent were randomized to usual exercise or no exercise intervention. The Biostatistics Unit of the First Cardiology Department of our Institution performed the randomization of the participants using a block-randomization design (by age group, sex, NYHA class, years of known CHF, and ischemic CHF); each CHF patient was allocated to one or other group from a randomization list that was created for this purpose.

Intervention

The cardiopulmonary test consisted of an incremental exercise test on an electromagnetically braked cycle ergometer (Ergoline 800, SensorMedics, California, USA) to the limit of tolerance (WRpeak). After a 3-min of baseline measurement, followed by 3-min of unloaded pedaling, the work rate was increased every minute by 10 or 20 W to the limit of tolerance while subjects maintained a pedaling of 60 rpm. During the tests flow rate at the mouth and gas exchange variables were recorded breath-by-breath (Vmax 229, SensorMedics, California, USA). The same test was performed at the beginning and at the end of training. Criteria used to end the exercise test stress were: symptoms of fatigue, dyspnoea or leg fatigue/pain. The intervention group followed a high-intensity intermittent aerobic training. Patients were instructed to exercise at an intensity equivalent to 80% WRpeak and progressively to 100% of WRpeak for 30 s alternated with 30 s of rest for an accumulative period of 45 min/day, 3 days/week for 12 consecutive weeks. The period of 12 weeks has been considered adequate to improve cardio-respiratory fitness markers by other investigators in the past. Therefore, in this study it was hypothesized that improving cardio-respiratory fitness may lead to an improvement of patients’ QoL. Patients in the usual care group were managed as usual by the admitting physician
in the Heart Failure Unit, and no advice for any specific exercise protocol was given.

**End points**

The primary end point of this trial was the patients’ QoL, which was evaluated using the validated and translated into Greek language Minnesota Living with Heart Failure questionnaire (MLHFQ). The trial’s secondary end point was the depression status of the patients, which was evaluated using the validated short version (9 items) of the International Physical Activity Questionnaire (IPAQ), suitable for assessing population levels of self reported physical activity.

**Measurements**

Information regarding demographic characteristics, family status and education level was gathered for all patients at baseline. Moreover, overall quality of dietary habits was assessed using the MedDietScore smoking habits, hypercholesterolemia, diabetes mellitus, obesity and arterial hypertension were defined using standard procedures. The New York Heart Association (NYHA) functional classification system was used to categorize all CHF patients. In all statistical analyses continuous measurements of blood pressures and biochemistries were used.

The translated short version (9 items) of the validated International Physical Activity Questionnaire (IPAQ), suitable for assessing population levels of self reported physical activity was used in all patients at baseline examination. Furthermore, the distance that patients were able to walk over a total of 6 min on a hard, flat surface (6-min walking test, 6MWT); maximal oxygen uptake (VO\textsubscript{2max}) and carbon dioxide production (VCO\textsubscript{2max}), were also

![Figure 1. The flow diagram of the study.](image-url)
recorded continuously breath-by-breath via open-circuit spirometry (Vmax 229, SensorMedics, California, USA), at both examinations.

Bioethics

The Internal Reviewing Board (IRB) of our Institution approved the protocol of the study. All participants were informed about the aims, procedures, benefits and potential risks of the trial, and agreed to participate and signed an informed consent form.

Data analysis

Continuous variables are presented as mean values ± standard deviation, while categorical variables are presented as frequencies. A univariate analysis was initially applied in order to compare baseline characteristics of the patients between the two study groups. Associations between categorical variables were tested using contingency tables and the calculation of Pearson’s chi-squared test, while comparisons of normally distributed continuous variables were performed by the calculation of the independent samples Student’s t-test, after testing for equality of variances (homoscedacity), or the non-parametric Mann–Whitney test. For within group comparisons at baseline and at follow-up examinations, the paired samples t-test, the Wilcoxon test or the McNemar chi-square test, were applied. Correlations between normally distributed continuous variables were evaluated by the calculation of Pearson’s r-coefficient and correlations between skewed continuous or discrete variables were evaluated by the use of Spearman’s rho-coefficient. The Intention-to-Treat (ITT) procedure was applied in the current analysis of the data. The research hypothesis was evaluated using generalized estimating equations (GEE), with the linear as the link function. The explanatory variables entered in the model were: the group of study (i.e., intervention or control) and those variables that showed a significant association with the outcome, i.e., QoL and ZDRS, in the univariate analysis (at 0.15 significance level). Normality tests were applied using the Kolmogorov–Smirnov criterion. Assumptions of linearity for continuous independent variables and constant variance of the standardized residuals were assessed through plotting the residuals against the fitted values. All reported P-values are based on two-sided tests and compared to a significance level of 0.05. However, due to multiple significance tests we used the Bonferroni correction (since the number of comparisons was <10) in order to account for the increase in Type I error. SPSS 18.0 software (SPSS Inc. 2010, Chicago, IL, USA) was used for all statistical calculations.

Results

In Table 1 the baseline characteristics of the CHF patients are presented. As seen, patients in the intervention group were older; however, regarding other characteristics, in both groups were similar.

The MLHFQ score was 19±12 among patients in the control group and 21±7 in the intervention group (P=0.46) (Table 2). Exploratory analysis showed that worse QoL at baseline (i.e., higher MLHFQ score) was positively associated with age (rho = 0.268, P=0.03), higher likelihood of being divorced or widowed (P=0.03), higher NYHA classification (rho = 0.411, P=0.001), as well as higher likelihood of having a history of hypertension (P=0.04); no significant associations were noted between MLHFQ score and medical history (i.e., years of known CHF, P=0.18, history of diabetes, P=0.98, hypercholesterolemia, P=0.38), the BMI level (P=0.16), physical activity status (P=0.51) or education status (P=0.18).

All patients adopted the exercise intervention program well; more specifically, no serious adverse events, such as abnormal heart rhythm, hip fracture or hospitalization related to exercise, were observed, suggesting that exercise training was well tolerated and safe. Furthermore, no substantial changes were observed on their medications or need for invasive treatment during the study period in those who were finally analysed (Figure 1).

Results from the intervention trial are presented in Table 2. At the end of intervention the MLHFQ score was lower among CHF patients in the exercise group as compared with the control group; in particular, patients in the exercise intervention group sub-tripled their MLHFQ score after 12 weeks of intervention, whereas patients in the control group had similar scores (P for between groups comparisons <0.001). No between group differences were observed regarding depression status of patients (Table 2); however, it should be noted that ZDRS score was significantly lower after intervention in the exercise group (P=0.005), while it was similar in the control group (P=0.19). Following rehabilitation, there was a significant improvement for CHF patients in the intervention group in exercise tolerance as indicated by the greater distance walked during 6MWT (by 13%, P<0.05) and the higher VO2max (by 31%, P<0.001), V CO2max (by 28%, P<0.001) and WRpeak (by 25%, P<0.01), whereas CHF patients in the control group had no changes in the aforementioned indices. Analysis was subsequently focused on those CHF patients having an implantable cardioverter-defibrillator; patients in the exercise intervention group reduced by 1.5-times their MLHFQ score (P<0.001), whereas no
Similarly, exercise intervention CHF patients with implantable cardioverter-defibrillator improved the distance walked during the 6MWT, achieved higher $V_{O2max}$, $V_{CO2max}$ and WRpeak, as compared with the control group (all $P$'s < 0.05). Obesity status did not affect the aforementioned results, since patients in the exercise intervention group had lower MLHFQ score as compared with the control group, irrespective of their obesity status ($P_{obese}=0.02$ and $P_{non-obese}=0.04$). A significant age-by-group interaction was observed ($P=0.02$); thus, the analysis was stratified to patients below and above 60 years old. Patients below the age of 60 years, in the exercise intervention group sub-tripled the MLHFQ score following 12 weeks of rehabilitation, whereas patients in the control had similar score ($P$ for between groups comparisons <0.001); however, no significant change in MLHFQ score was observed between groups when only patients over 60 years were included in the analysis ($P=0.48$). No sex-by-intervention group interaction was observed ($P=0.83$), no NYHA class-by-group and no baseline physical activity status-by-group interactions on patients’ QoL were observed ($P=0.35$, $P=0.28$, respectively).

### Table 1  Baseline characteristics of patients randomized to usual care or exercise intervention

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 39)</th>
<th>Intervention group (n = 33)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 11</td>
<td>63 ± 9</td>
<td>0.01</td>
</tr>
<tr>
<td>Men (%)</td>
<td>72</td>
<td>88</td>
<td>0.36</td>
</tr>
<tr>
<td>Years of school</td>
<td>11.5 ± 3.9</td>
<td>10.8 ± 4.0</td>
<td>0.49</td>
</tr>
<tr>
<td>Married (%)</td>
<td>51</td>
<td>82</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>31.3 ± 7</td>
<td>28.85 ± 4.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>49</td>
<td>42</td>
<td>0.60</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>105.2 ± 11.5</td>
<td>101.6 ± 9.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>104.8 ± 10.4</td>
<td>101.8 ± 6.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Smoking (ever) (%)</td>
<td>87</td>
<td>82</td>
<td>0.56</td>
</tr>
<tr>
<td>Physical activity status</td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Physically inactive (%)</td>
<td>31</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Minimally active (%)</td>
<td>41</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>HEPA (%)</td>
<td>28</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>MedDietScore (0–55)</td>
<td>35 ± 6</td>
<td>37 ± 7</td>
<td>0.03</td>
</tr>
<tr>
<td>Ischemic CHF (%)</td>
<td>70</td>
<td>70</td>
<td>0.99</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>32</td>
<td>31</td>
<td>0.91</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator (%)</td>
<td>33</td>
<td>35</td>
<td>0.85</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>24</td>
<td>28</td>
<td>0.71</td>
</tr>
<tr>
<td>Years of known CHF</td>
<td>3.9 ± 4.8</td>
<td>4.2 ± 4.6</td>
<td>0.78</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>I (%)</td>
<td>39</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>II (%)</td>
<td>51</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>III (%)</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>25</td>
<td>42</td>
<td>0.15</td>
</tr>
<tr>
<td>History of hypercholesterolemia (%)</td>
<td>61</td>
<td>63</td>
<td>0.83</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>36</td>
<td>33</td>
<td>0.45</td>
</tr>
<tr>
<td>B-Blockers (%)</td>
<td>89</td>
<td>100</td>
<td>0.22</td>
</tr>
<tr>
<td>A- and B-Blockers (%)</td>
<td>3</td>
<td>0</td>
<td>0.32</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors (%)</td>
<td>43</td>
<td>61</td>
<td>0.15</td>
</tr>
<tr>
<td>Angiotensin 1 Receptors inhibitors (%)</td>
<td>51</td>
<td>33</td>
<td>0.13</td>
</tr>
<tr>
<td>Aldosterone antagonists (%)</td>
<td>57</td>
<td>37</td>
<td>0.09</td>
</tr>
<tr>
<td>Loop Diuretics (%)</td>
<td>71</td>
<td>49</td>
<td>0.05</td>
</tr>
<tr>
<td>Coumadin anticoagulants (%)</td>
<td>17</td>
<td>21</td>
<td>0.67</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>74</td>
<td>82</td>
<td>0.46</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>11</td>
<td>6</td>
<td>0.44</td>
</tr>
<tr>
<td>Amiodarone (%)</td>
<td>3</td>
<td>12</td>
<td>0.16</td>
</tr>
<tr>
<td>Oral hypoglycemic (%)</td>
<td>20</td>
<td>21</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentages. $P$-values derived using independent samples Student’s $t$-test (age, BMI), Mann–Whitney test (waist, hip, MedDietScore, years of known CHF) and chi-square test (sex, marital status, medical history, NYHA class, physical activity).
Discussion

This is one randomized clinical trials that studied the effect of high-intensity intermittent exercise training among CHF patients. The influence of intensive exercise was beneficial on the QoL of heart failure patients, even among CHF patients having an implantable cardioverter-defibrillator or being in the worst NYHA class. However, beneficial effects were largely limited to patients <60 years old, a finding potentially alluding to the significance of biological (and its surrogate chronological) age in determining the response to exercise.

QoL among heart failure patients is crucial, as it is a powerful predictor of mortality and morbidity after hospital discharge. Several determinants of poor QoL have been described, including depression, younger age, higher body mass index, greater symptom burden, lower systolic blood, gender, race, blood pressure, sleep apnea, low perceived control, and uncertainty about prognosis, affecting functional capacity, vital status and mental health.

Mechanisms through which exercise training in patients with heart failure may improve QoL are not well understood and appreciated. Tabet et al. have shown that a lack of increase in exercise capacity with training in patients with CHF has strong prognostic value for cardiac events, since patients with a <6% of improvement in $\text{VO}_{2\text{peak}}$ were eight times more likely to have a cardiac event over the next 16 months. Additionally, the improvement in exercise tolerance can lead to improvements in neurohormonal activation, peripheral vascular reactivity (as assessed by flow-mediated dilatation), ventilatory function and diastolic function (as demonstrated by reduced brain natriuretic peptide levels). Furthermore, it protects from arrhythmia genesis, and increases muscle aerobic capacity, myofibril cross-sectional area and mitochondrial density.

Exercise type has also been shown to exhibit different effects on muscular capacity, with the combination of moderate and high-intensity resistance training in the exercise program improving muscular strength and endurance by 25–100%. The most well-known large-scale exercise intervention study is the HF-ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of exercise TraiNing) study which evaluated the benefits from exercise training among 2331 patients with heart failure. Half of the participants received usual care plus 36 sessions of group based, supervised aerobic exercise training of up to 35 min three times per week, and were asked to transition to home-based training at the same intensity five times per week. Compared with the usual care group, the exercise training group had an 11% lower risk of all-cause death or hospitalization and a 15% lower risk of cardiovascular-related mortality and morbidity, and scored significantly better on a quality-of-life questionnaire. In the present trial, the exercise program was more intense than the one used in the HF-ACTION trial, suggesting that heart failure patients are able to adopt a more intensive program appearing to be highly effective in terms of improving their QoL; although this intensive program showed more beneficial effects on middle-aged patients. A recent meta-analysis suggested that combined (strength and intermittent) exercise training elicits larger benefits in peak VO\textsubscript{2} than intermittent exercise training alone, although intermittent exercise training elicits larger benefits in peak VO\textsubscript{2} and VE/VCO\textsubscript{2} than continuous exercise training in patients with moderate to severe heart failure. This more intense exercise program may be also responsible for the age interaction that was noticed in this study compared to other studies, as in more

### Table 2 QoL, depression status and clinical characteristics, of patients randomized to usual care or exercise intervention

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=39)</th>
<th>Intervention group (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12-week after</td>
<td></td>
</tr>
<tr>
<td>MLHFQ score (0–105)</td>
<td>19±12</td>
<td>21±13</td>
<td>0.003</td>
</tr>
<tr>
<td>ZDRS score (0–80)</td>
<td>37±8</td>
<td>41±10</td>
<td>0.54</td>
</tr>
<tr>
<td>ZDRS score &gt; 50 (%)</td>
<td>18</td>
<td>5*</td>
<td>0.51</td>
</tr>
<tr>
<td>6-min-walk (m)</td>
<td>406±64</td>
<td>423±65</td>
<td>0.05</td>
</tr>
<tr>
<td>$\text{VO}_{2\text{max}}$ (ml/kg/min)</td>
<td>17±6</td>
<td>18±4</td>
<td>0.001</td>
</tr>
<tr>
<td>$\text{VCO}_{2\text{max}}$ (L/min)</td>
<td>1.57±0.6</td>
<td>1.59±0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>WRpeak (Watt)</td>
<td>88±42</td>
<td>85±29</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentages. Between groups P-values derived using GEE, after adjusting for age, sex, BMI and MedDietScore. *P<0.05, for the within groups comparisons.
advanced aged patients the beneficial effect was limited. This beneficial effect of intermittent exercise may be due to a greater generation of large shear stress forces within the endothelium leading to improvements in endothelial function, and promotion of an increase in muscle mass, hence improving oxygen metabolism. Other studies had conflicting findings, ranging from absence of effect to significant effect or to adverse effect. However, QoL is a complex parameter; several other factors may also play a role, such as the existence of comorbidities (chronic obstructive pulmonary disease, sleep apnea, diabetes mellitus, ischemic disease). Those comorbidities may be responsible for the conflicting findings of rehabilitation programs on QoL in several studies.

Strengths and limitations

Measurement of QoL is a very difficult task, especially among heart failure patients. Due to the wide heterogeneity in clinical characteristics and origin of heart failure, only patients suffering from ischemic or dilated cardiomyopathy were enrolled (even with implanted defibrillator or cardiac resynchronization system); while few patients with severe chronic obstructive pulmonary disease, sleep apnea were included.

Conclusions and public health implications

Application of a combined high-intensity interval exercise program in patients with systolic heart failure of ischemic or idiopathic origin seems to offer substantial beneficial effects on several hemodynamic and clinical factors and especially on markers of QoL, improving the ability to perform daily activities, even in terminally ill patients, although the beneficial impact was limited in advanced aged patients.

Conflict of interest: None declared.

References


5. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14:803–9.


