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Cardiovascular effects of high-intensity interval aerobic training combined with strength exercise in patients with chronic heart failure. A randomized phase III clinical trial

Christina Chrysohoou [a,*], Athanasios Angelis [a], George Tsitsinakis [a], Stavroula Spetsioti [b], Ioannis Nasis [b], Dimitris Tsiachris [a], Panagiotis Rapakoulias [c], Christos Pitsavos [a], Nikolaos G. Koulouris [c], Ioannis Vogiatzis [b,c], Dimitris Tousoulis [a]

[a] First Cardiology Clinic, Hippokration Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[b] Physical Education and Sports Science, National and Kapodistrian University of Athens, Athens, Greece
[c] First Department of Respiratory Medicine, Pulmonary Rehabilitation Unit, Sotiria Hospital, National and Kapodistrian University of Athens, Greece

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ABSTRACT

Background: The aim of this work was to evaluate the effect of high-intensity interval exercise (i.e., 30 s at 100% of max workload, followed by 30 s at rest, 45 min 3 days/week working-out schedule for 12 weeks) on left ventricular function and aortic elastic properties among chronic heart failure (CHF) patients.
Methods: This study is a phase III clinical trial. Of the 100 consecutive CHF patients (NYHA classes II–IV, ejection fraction < 50%) that were randomly allocated, 72 completed the study (exercise training group, n = 33, 63 ± 9 years, 88% men, and control group, n = 39, 56 ± 11 years, 82% men). All patients underwent cardiopulmonary stress test, non-invasive high-fidelity tonometry of the radial artery, pulse wave velocity measurement using a SphygmoCor device and echocardiography before and after the completion of the training program.
Results: Both groups reported similar medical characteristics and physical activity status. General mixed effects models revealed that the intervention group reduced pulse wave velocity by 9% (p = 0.05); Emv/Vp by 14% (p = 0.06); E to A ratio by 24% (p = 0.004), E to Emv ratio by 8% (p = 0.05), MLHFQ score by 66% (p = 0.003) and the depression score by 19% (p = 0.5); increased augmentation index by 29%; VTI by 4% (p = 0.05), 6-minute-walk distance up to 13% (p = 0.05), peak oxygen uptake by 28% (p = 0.001) and peak power by 25% (p = 0.005). There were no significant changes in the control group.
Conclusion: Interval high-intensity aerobic training, combined with strength exercise, seems to benefit aortic dilatation capacity and augmented systolic pressure in parallel with improvement in left ventricular diastolic function and quality of life.

1. Introduction

Heart failure constitutes a complex health problem which involves both cardiac function and arterial circulation. This is due to the interactive functions of the left ventricle (LV) and peripheral arterial system (ie, ventricular/vascular coupling) [1]. Earlier studies, including the Systolic Hypertension in the Elderly (SHEP) and Survival and Ventricular Enlargement (SAVE) studies, have illustrated adverse outcomes in patients with LV dysfunction related with increased arterial stiffness, as assessed by a pulse pressure measurement [2–5]. Interestingly in those patients, arterial dysfunction was not related with augmented systolic pressure, as the observed decrease in late systolic augmented pressure may be due to the impaired LV systolic function [6,7].

Regular exercise enhances muscular function and exercise capacity and promotes the body's ability to utilize oxygen [8,9]. It also improves the capacity of the blood vessels to dilate in response to exercise, left ventricular diastolic function and neurohormonal activation [10–13]. Despite those facts, the recommendation for systematically performed exercise among heart failure patients has been poorly implemented in daily clinical practice; while there is lack of studies evaluating the role of exercise on aortic function in those patients. Furthermore, up to our knowledge, most studies of rehabilitation in heart failure patients have used moderate intensity continuous training (50%–70% of VO_{2max}) or repetitions of high-intensity intervals (80%–95% of VO_{2max}) of a relatively long duration (2–5 min) [14–16].

The aim of this study was to evaluate the effect of high intensity, intermittent and short duration exercise in a 12 week training program on

Abbreviations: LV, left ventricle; QoL, quality of life; CHF, chronic heart failure; VE, minute ventilation; VO_{2max}, oxygen uptake; VCO_2, carbon dioxide production; MLHFQ, Minnesota Living with Heart Failure Questionnaire; HR, heart rate; SVI, stroke volume index; ITT, Intention-to-Treat; ZDRS, Zung Depression Rate Scale.

* Corresponding author at: 46 Paleon Polemiston St., Glyfada, 166 74 Attica, Greece.
E-mail address: chrysohoou@usa.net (C. Chrysohoou).

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aortic elastic properties, left ventricular function and quality of life (QoL) in chronic heart failure (CHF) patients, due to coronary heart disease or dilated cardiomyopathy, under optimal therapy.

2. Methods

2.1. Participants

Chronic heart failure (CHF) patients due to left ventricular dysfunction (NYHA classes II–IV, ejection fraction ≤ 50%), that were visiting the Heart Failure Unit of our Hospital's Cardiology department, between September of 2010 and September of 2011 were eligible for participation. Among them, those on a stable heart failure stage (I to III) due to ischemic or dilated heart failure and without severe valve diseases were included in the study. Patients that would have substantial changes in their medication, including neurohormonal drugs and invasive treatment during the study period, were excluded from the final analysis.

The study's flow diagram, according to the CONSORT guidelines [17] has been presented elsewhere [18].

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

2.2. Randomization

Eligible patients after giving their consent were randomized to exercise and no exercise-control groups. 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.

2.3. Peak exercise tolerance

The cardiopulmonary stress test consisted of an incremental exercise protocol on an electromagnetically braked cycle ergometer (Ergoline 800, SensorMedics, California, USA) to the limit of tolerance (WRpeak). After a 3-min baseline measurement, followed by a 3-min 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 revolutions per minutes. During the test, gas exchange and flow rate variables were recorded breath-by-breath (Vmax 229, SensorMedics, California, USA). The same test was performed at the beginning and the end of the training-intervention period. Criteria used to end the stress-test were: symptoms of fatigue/exhaustion, dyspnea, or leg fatigue/pain.

2.4. Training intervention

The intervention group followed a high-intensity intermittent aerobic training. Patients were instructed to exercise on electromagnetically braked cycle ergometers (Cateye Ergociser, ECl600; Cat Eye; Osaka, Japan) at an intensity equivalent to 80% WRpeak with a pedaling rate of 50 to 60 rpm and progressively to 100% of WRpeak for 30 s, alternated with 30 s of rest for a accumulative period of 45 min/day, 3 days/week for 12 consecutive weeks. Resistance training was performed with a fitness equipment. Each session was consisting of 4 exercises i.e. knee extension, seated chest press, peck deck and lateral pull-down. Training was initiated at an intensity of 30% of the one repetition maximum (1RM, performed at baseline) with a training amount of 3 sets of 8–10 repetitions for the first 2 weeks, followed by 3 weeks of training at an intensity of 50% of the baseline 1RM. For the remaining 7 weeks the intensity was set up at an intensity of 90% of the 1RM. Patients in the control group were managed as usual by the admitting physician in the Heart Failure Unit, and no advice for any specific exercise protocol was given.

2.5. End points

The primary end points of this trial were quality of life (QoL), left ventricular diastolic function, and aortic elastic properties. Other secondary end point was the depression status of the patients, and physical activity status.

2.6. Measurements

Information regarding demographic characteristics, family status and education level was gathered for all patients at baseline. Moreover, overall lifestyle habits were defined using standard procedures. Body-surface area was calculated [BSA = $(\text{height})^{0.725} * (\text{weight})^{0.425} * 0.007184$] and the New York Heart Association (NYHA) functional classification system was used to categorize all CHF patients [19]. In all statistical analysis, continuous measurements were used for blood pressure and biochemical parameters. 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 [20]. Furthermore, the distance that patients were able to walk over a total of 6 min on a hard, flat surface (six-minute walking test, 6MWT) was recorded, whereas peak values for oxygen uptake (VO_{2max}), minute ventilation (VE) and carbon dioxide production (VCO_{2max}) were also recorded breath-by-breath via open-circuit spirometry (Vmax 229, SensorMedics, California, USA), at both examinations. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) [21] and Zung's Depression Rating Scale (ZDRS) translated into Greek were used to evaluate Patient's quality of life (QoL) and depression status respectively [22]. Detailed echocardiography assessment was performed in all patients, using a Hewlett Packard 5500 Sonos with a multifrequency transducer (2.5–4 MHz), equipped with tissue Doppler imaging (TDI) technology. Images were acquired with patients in left lateral decubitus position and subjects with left ventricular ejection fraction < 50% defined by the Simpson's method were enrolled. From the apical four-chamber view, a 10 mm^3 sample volume was placed at the lateral mitral and tricuspid annuli, and spectral TDI was recorded, with the motion of annuli parallel to the TDI cursor. Pulse wave TDI was characterized by the systolic wave (Smv and Stv) and two diastolic waves (Emv and Amv and Etv and Atv, respectively). Furthermore, using pulse wave Doppler at the tips of mitral leaflets, early and late velocity waves (E and A) were recorded. Heart rate (HR) was defined as beats per minute. Left atrial volumes were measured at end-diastole and systole and left atrial ejection fraction was calculated. Left ventricular outflow area was calculated from the left parasternal long axis view, while stroke volume index (SVI) was calculated by the formula $\pi/4 \times (\text{LVOT})^2 \times \text{VTI}_{\text{LVOT}}$ / BSA, where VTI_{LVOT} is the time-velocity integral of the left ventricular outflow tract, as detected by pulse wave Doppler, from the apical four chamber view. All measurements were averaged on three to five measurements obtained during end-expiration. Furthermore, using the color M-mode by placing the M-mode cursor aligned parallel to the left ventricular inflow extending from the apex to the tips of the mitral valve, we measured the propagation velocity (Vp) [23]. Additionally, arterial elastance (Ea) was calculated from the formula $0.9 \times \text{SBP} / \text{SV}$ [24]. Furthermore, a 24-hour Holter monitoring of heart rate was applied in all patients before and after intervention.

2.7. 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.

2.8. 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 was 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 a 0.05 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 less than ten) 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.

3. Results

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

Exploratory analysis showed that evidence of a worse quality of life 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