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Exercise Training in Older Patients with Heart Failure and Preserved Ejection Fraction: A Randomized, Controlled, Single-Blind Trial

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Abstract

Background—HF with preserved left ventricular ejection fraction (HFPEF) is the most common form of HF in the older population. Exercise intolerance is the primary chronic symptom in HFPEF patients and is a strong determinant of their reduced quality of life (QOL). Exercise training (ET) improves exercise intolerance and QOL in HF patients with reduced ejection fraction. However, the effect of ET in HFPEF has not been examined in a randomized, controlled trial.

Methods and Results—This was a randomized, attention-controlled, single blind study of 16 weeks of medically supervised ET (3 days per week) on exercise intolerance and QOL in 53 elderly (mean age 70±6 yrs; range 60–82; 46 women, 7 men) patients with isolated HFPEF (EF ≥ 50%, and no significant coronary, valvular, or pulmonary disease). Attention controls received biweekly follow-up telephone calls. Forty-six patients completed the study (24 ET, 22 controls). Attendance at exercise sessions in the ET group was excellent (88%; range 64–100%). There were no trial-related adverse events. Peak exercise oxygen uptake, the primary outcome, increased significantly in the ET group compared to the control group (13.8±2.5 to 16.1±2.6 ml/kg/min, change 2.3±2.2 ml/kg/min vs. 12.8±2.6 to 12.5±3.4, change −0.3±2.1 ml/kg/min) (p=0.0002). There were significant improvements in peak power output, exercise time, 6 minute walk distance, and ventilatory anaerobic threshold (all p<0.002). There was improvement in the physical QOL score (p=0.03) but not the total score (p=0.11).

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Conclusions—ET improves peak and submaximal exercise capacity in older patients with HFPEF.

Keywords

heart failure; aging; exercise intolerance; exercise training

Introduction

Heart failure (HF) afflicts over 3 million Americans annually (1) and is the only major cardiovascular disorder that is increasing.(2) HF is primarily a disorder of the elderly; more than three-fourths of diagnosed patients are ≥ age 65. Among older HF patients, a majority have a preserved left ventricular (LV) ejection fraction (HFPEF).(3–7) HFPEF prevalence is growing faster than HF with severely reduced EF (HFREF) and results in substantial morbidity, mortality, and health care costs.(6;8)

Exercise intolerance, manifested by dyspnea and fatigue during exertion, is the primary chronic symptom in HF patients, is a major determinant of their reduced quality of life (QOL), and is an independent predictor of mortality.(6;9;10) It can be quantified objectively by measurement of peak exercise oxygen uptake (VO_2), is valid and reproducible even in older HF patients,(11) is potentially modifiable, and is recognized as a valid therapeutic target. We have previously reported that peak exercise VO_2 is severely reduced in older patients with HFPEF compared to age-matched healthy volunteers, to a similar degree as patients with HF with severely reduced EF (HFREF), and is accompanied by diminished QOL.(9) However, the pathophysiology of exercise intolerance in HFPEF is not well understood and data regarding strategies to improve it are needed.

Several studies have examined ET in HFREF and most have shown significant improvements in exercise intolerance and QOL and some have suggested reduced mortality.(12–18) However, to our knowledge, there has been no published study of ET in patients with established HFPEF. In 18 patients with dyspnea and Doppler evidence of diastolic dysfunction, Smart et al reported that ET significantly improved peak VO_2 and QOL and to a similar extent as those with systolic dysfunction.(19) However, and there was no randomization, control group, or blinding of the observers assessing the exercise and QOL outcomes.

Therefore, the purpose of the present study was to test the hypothesis that supervised ET in older patients with HFPEF would improve the primary outcome of peak exercise VO_2 and the secondary outcome of disease-specific QOL.

Methods

Study Design

This was a prospective, randomized, attention-controlled, single-blind trial of 16 weeks of supervised aerobic exercise training. The protocol was approved by the Wake Forest University Institutional Review Board. Patient recruitment and selection, testing methods, and results of measurements at baseline in this cohort have been previously described.(9) During a screening visit, subjects were familiarized with the testing environment and procedures and written informed consent was obtained. During a subsequent baseline visit, the outcome measures of exercise performance, QOL, LV morphology and function, and blood samples for neuroendocrine function were obtained. All tests were performed in the morning after participants had had no oral intake including medications except for water since midnight. Patients were randomized to receive either 16 weeks of aerobic exercise

training or attention control with biweekly telephone follow-up. Measures were repeated after 16 weeks of ET. All testing was performed by and results were analyzed by individuals blinded to patient group. Recruitment began in 1994 and trial follow-up was completed in 1999.

Patients

HF patients were recruited from review of hospital and clinic records as previously described in detail.(9;20–24) They were well-compensated, ambulatory outpatients who had been stable with no medication changes for > 6 weeks. As previously described, isolated HFPEF was defined as history, symptoms, and signs of HF, a preserved LV ejection fraction (≥ 50%), and no evidence of significant coronary, valvular, or pulmonary disease, or any other medical condition that could mimic HF symptoms (anemia, thyroid dysfunction).(9;11;20;20–22;24) HF diagnosis was verified by a board certified cardiologist upon completion of a history, physical examination, detailed review of all available medical records, electrocardiogram, rest and exercise echocardiogram, and spirometry. The diagnosis was based on clinical criteria as previously described that included a heart failure clinical score from the National Health and Nutrition Examination Survey-I of ≥3, and those used by Rich et al, that included a history of acute pulmonary edema, or the occurrence of at least 2 of the following with no other identifiable cause: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, bilateral lower extremity edema or exertional fatigue.(9;11;20–22;24–26) Patients were excluded if they had a contraindication to exercise testing or training, were unable to perform a valid baseline exercise test, were currently regularly exercising, had known cancer, significant renal dysfunction (creatinine > 2.5 mg/dl), substance abuse, uncontrolled diabetes, dementia, history of non-compliance, or any other disorder that would preclude participation in the intervention and follow-up.

Exercise Capacity

Exercise testing was performed as previously described in the upright position on an electronically braked bicycle using a staged protocol starting at 12.5 watts for 2 minutes, increasing to 25 watts for 3 minutes, and with 25 watt/3 minute increments thereafter to exhaustion.(9;11;14;21;22;24;27–29) Expired gas analysis was conducted using a commercially available system (CPX-2000, MedGraphics, Minneapolis, Minnesota) that was calibrated before each test with a standard gas of known concentration and volume. Breath-by-breath gas exchange data were measured continuously during exercise, averaged every 15 seconds, and peak values were averaged from the last 2 15-second intervals during peak exercise.(9;11;14;21;22;24;29) Ventilatory anaerobic threshold (VAT) was assessed by a blinded, experienced observer (PHB) as previously described.(9;11;14;24) A six minute walk test was performed as described by Guyatt et al.(9;14;24;30)

Quality of Life

The Minnesota Living with Heart Failure Questionnaire (MLHF), a condition-specific measure, was administered to assess the impact of the intervention on QOL.(9;31) The Medical Outcomes Study Short-Form 36 Item Health Survey (SF-36), a general health measure, and the Center for Epidemiological Studies Depression survey (CES-D), were administered.

Echocardiography

Doppler-echocardiogram exams were performed as previously described under resting conditions at baseline and 16-week follow-up using a Sonos 5500 ultrasound system (Philips Ultrasound, Andover, Mass.) with a multiple frequency transducer.(9;14;20;24;32) Standard 2-Dimensional images were obtained in the parasternal long and short axes and the apical 4

and 2 chamber views. Optimized pulsed-wave Doppler tracings of mitral valve inflow were recorded from the apical 4-chamber view. LV volumes and Doppler were analyzed using a digital workstation by blinded personnel as previously described.(9;14;23;32–34)

Neurohormones

As previously described, after 15 minutes of quiet, supine rest, venous blood samples were drawn into prepared, chilled EDTA vacutainers on ice, centrifuged and plasma separated and stored at −70° C.(9;24;35) Commercially available radioimmunoassays (Phoenix Pharmaceuticals, Inc, Mountain View, CA) were used for brain natriuretic peptide-32 (BNP).(9;24) Norepinephrine was analyzed by high pressure liquid chromatography with electrochemical detection.(9;24;35)

Exercise Training

Patients randomized to ET exercised 3 times per week for 16 weeks for a total of 48 total sessions in a dedicated facility under medical supervision.(14;36) Each session lasted one hour and consisted of warm-up, stimulus, and cool-down phases. The stimulus phase consisted of walking on a track and lower extremity cycling on a Schwinn Airdyne. Data from the baseline exercise test were used to generate an individualized initial exercise prescription according to standard methods in HF patients.(14;36;37) Heart rate and rate of perceived exertion were assessed periodically during exercise sessions. For the first two weeks of training, patients exercised at 40–50% of heart rate reserve while the duration of exercise was gradually increased on each of the two modes of exercise. Over the next several weeks, exercise intensity was increased to 60–70 % of heart rate reserve and exercise duration increased to 15–20 minutes on each training mode. Exercise intensity and duration were adjusted as needed based on medical considerations and clinical responses.(36;37) Missed exercise sessions were made up so that each patient completed no less than 40 of the 48 (>80%) ET sessions.

Patients randomized to the attention control group received telephone calls every 2 weeks throughout the 16-week follow-up. This provided interaction with study staff of a similar nature to the ET group, but without exercise. The conversations focused on retention, reminders and encouragement to keep upcoming study visits, and any new medical events since the prior contact. The discussion intentionally did not address exercise behaviors.

Statistical Analysis

Two-sample t-tests and Fisher’s exact tests were used to assess for any potential differences in baseline characteristics between the two groups. Comparisons of outcome measures between intervention groups were made by analysis of covariance procedures. By prospective study design in order to reduce bias and increase precision, the analyses adjusted for pre-randomization values of the outcome measure being considered. Data are presented as raw, unadjusted mean +/− standard deviation at each visit for each group, along with the p-value corresponding to the adjusted least squares means from the analysis of covariance procedures accounting for all data at the follow-up visits. The neurohormone data were highly skewed and were log-transformed prior to analyses. Two-sided level of significance was set at $p<0.05$.

Results

Patient Characteristics

There were 53 patients enrolled; 26 were randomized to ET and 27 were randomized to attention control. The groups were well matched with no differences in a broad range of

characteristics (Table 1). At entry, all patients had NYHA class II-III HF symptoms. Medical therapy remained constant during the 16 weeks of ET.

There was one patient with atrial fibrillation in each arm of the trial. When these patients were excluded from the analysis, there was no difference in the primary results. Doppler data were not analyzed from these patients. There were no patients with an electronic pacemaker in the trial.

Exercise Training: Compliance, Adherence, and Events

Of the 53 patients randomized, 46 completed follow-up testing, 24 from the ET group, and 22 from the control group. Median time to completion of the program was 16 weeks. The reasons for not completing follow-up testing were non-HF illness (n=4; 2 in ET and 2 in control) and lost to follow-up (n=3, all in control). There were no adverse events related to the intervention or testing procedures. Six patients, 3 in each group, had a total of 11 adverse events that were unrelated to trial participation. The 5 adverse events in the ET group were: upper respiratory infection (2), bladder infection (1), and falls (2). The 6 adverse events in the control group were: pulmonary edema (1), upper respiratory infection (2), automobile accident (1), surgery for kidney mass (1), arrhythmia (1). There were 2 hospitalizations, both in the control group (pulmonary edema; surgery for kidney mass).

Patients randomized to ET attended an average of 43 ± 9 of the possible 48 sessions. ET patients attended 88% (range 64–100%) of the scheduled training sessions, and 98% attended ≥ 2 sessions per week.

Exercise Performance

Following the 16 week intervention, peak exercise VO_2, power output (watts), and exercise time (seconds) at follow-up were significantly increased in the ET compared to the control group (all <0.001; Table 2). Adjusting for the baseline value, the follow-up peak VO_2 was increased by 2.7 ml/kg/min in the ET compared to the control group (95% confidence intervals: 1.4–4.0 ml/kg/min). Individual responses of peak VO_2 are displayed in Figure 1. At follow-up, 19/24 (79%) of ET subjects had increased peak VO_2, and 11/22 (50%) of CON subjects had increased peak VO_2 (p=0.06). Traditionally, a ≥10% increase is used as a threshold for a clinically meaningful improvement in peak VO_2. This threshold was exceeded by 16 (67%) of ET subjects and 6 (27%) of CON subjects (p=0.01).

Peak respiratory exchange ratio (RER), an objective index of effort, was not different between the groups. Peak heart rate, heart rate reserve, and oxygen pulse (a coarse estimate of stroke volume assuming arteriovenous oxygen difference is held constant) were increased in ET compared to control. Ventilatory anaerobic threshold and six minute walk distance were significantly increased in ET compared to control, indicative of improved submaximal exercise performance. VE/VCO_2 slope, a measure of ventilatory efficiency, was not significantly different. Resting heart rate and diastolic and systolic blood pressure were unchanged.

Health Related Quality of Life

At baseline MLHF scores were moderately increased in both groups, suggesting significant impairments (Table 3). After 6 weeks of exercise training, the ET group had significantly lower (improved) physical score (p=0.03) but no change in mental score (p=0.35) resulting in a total score that was lower (improved) but did not reach statistical significance (p=0.11; Table 3). There were no differences in SF-36 component scores or in the CES-D score.

Left Ventricular Structure and Function

Doppler tracings were not analyzable in 4 patients due to atrial fibrillation (2; 1 in each group) and missing recordings (2; 1 in each group). At baseline, patients had normal LV ejection fraction, increased LV mass and increased mass/volume ratio indicative of typical hypertrophic concentric LV remodeling, and delayed relaxation (Table 4). After the 16 week intervention, no significant differences were observed in any resting echo-Doppler measures.

Neuroendocrine Function

After the 16 week intervention, there were no significant differences in BNP or norephinephrine (Table 4).

Discussion

Exercise intolerance is the primary symptom in chronic HF, a strong determinant of QOL, an independent predictor of survival, and a key therapeutic target. At baseline, the elderly HFPEF patients had severe exercise intolerance and moderately impaired QOL. Following the 16-week ET intervention, all 3 measures of exercise capacity, including peak exercise VO_2, power output, and exercise time were significantly increased in the patients randomized to ET but were unchanged or slightly reduced in the attention control group. Most (67%) of ET subjects had a ≥10% increase in peak VO_2, whereas this traditional threshold for a clinically meaningful improvement was observed in only 27% of CON subjects. Submaximal exercise performance, assessed by the ventilatory anaerobic threshold and the 6-minute walk test, were also significantly increased. These improvements in exercise tolerance were accompanied by improvement in the physical symptom score on the MLHF survey, but no change in mental score, resulting in a non-significant trend in total score. There were no changes in resting LV structure/function or neurohormone levels. The intervention was safe with no intervention or testing-related adverse events. These results confirm our primary hypothesis and suggest that formal exercise training may be a worthwhile consideration for improving exercise intolerance in chronic stable HFPEF patients.

There have been many reported studies of ET in patients with HFREF,(12–18) most of which have shown significant improvements in exercise performance, but similar studies in HFPEF have been relatively lacking. In general, the present results regarding exercise capacity and QOL mirror those observed in HFREF patients, as well as those of Smart et al in patients with dyspnea and Doppler diastolic dysfunction.(19) The present study significantly extends the previously available literature. It examined older HFPEF patients who were well characterized, had severe exercise intolerance similar to age-matched HFREF patients,(9) and who were closely representative of HFPEF patients reported in large, population-based observational studies with respect to age, gender, and other key characteristics.(3–7) The patients' mean age of 70 ± 5 years (range = 60–80 yrs) was 5 years greater than the patients studied by Smart et al(19) and was 10 years greater than reported in most studies of ET in HFREF.(13;15) The present study employed a randomized, controlled, single-blind design. Blinding is an important design feature given that exercise and QOL outcomes have a significant degree of subjectivity and susceptibility to observer bias. Notably, blinding has usually not been used in reported studies of ET.(13–15;18)

The few large medication trials in HFPEF for mortality outcomes have had disappointing results.(38–41) A number of smaller medication studies have focused on exercise capacity in HFPEF or in patients with Doppler diastolic dysfunction and these have had varying results.(23;24;42–45) In our recently reported trial of enalapril in older HFPEF patients, we found

no improvement in exercise capacity.(24) In HFREF, gains in exercise capacity from medications have usually been relatively modest and on average less than with ET. In the large multi-center HF-ACTION trial of ET in HFREF, peak VO_2 increased by 4%.(15) In a trial that was conducted parallel to the present study and was similarly designed, we observed no significant effect of ET on peak VO_2 in older HFREF patients.(14) Against this background, the 17% increase in exercise capacity from ET in the present study is substantial and is similar to that reported in prior studies of middle-aged patients with HFREF.(13) The 2.3 ml/kg/min improvement in peak VO_2 substantially exceeded the 1.0 ml/kg/min threshold that is customarily considered clinically significant. This improvement is also clinically meaningful since peak VO_2 at baseline in patients randomized to ET was 13.8 ml/kg/min, below the threshold of 15.0 ml/kg/min usually associated with independence in the full range of activities in elderly persons, and after ET was 16.1 ml/kg/min, above this threshold.(46)

The present data do not allow definitive elucidation of the mechanism(s) responsible for the improved exercise performance. According to the Fick equation, an increase in VO_2 must be due to an increase in either cardiac output (the product of heart rate and stroke volume), arteriovenous oxygen difference, or both.(47) ET studies in HFREF have implicated a variety of mechanisms, including improved peak heart rate, LV function, peripheral vascular function, and skeletal muscle bulk and function.(17;48–50) In the present study following ET, peak heart rate, heart rate reserve, peak oxygen pulse, and VAT were significantly increased, implicating increased cardiac output and possibly arteriovenous oxygen difference.

We and others have previously shown that relative chronotropic incompetence is frequent among HFPEF patients and contributes to their reduced peak exercise VO_2.(29;51) Among the directly measured variables in the present study, the increase in peak heart rate and heart rate reserve due to ET appeared relatively similar in magnitude to the increase in peak VO_2. Several studies have reported that ET improves peak heart rate in patients with HF due to reduced EF.(12;52;53) In a meta-analysis of 35 studies, ET resulted in an average increase in peak heart rate of 4 beats per minute or 2.5% of the pre-training level.(53) Keteyian et al reported that peak HR increased by 7% (9 beats/min) and contributed 50% of the effect of the increase in peak VO_2 following ET.(52)

Although at baseline the patients had typical features of hypertrophic concentric LV remodeling, normal EF, and delayed relaxation, these were unchanged following ET. This is similar to the results of Smart et al(19) who found no ET-induced changes in Doppler diastolic function, including with tissue Doppler, which was not included in the present study.

The MLHF has been used as the primary disease-specific QOL instrument in other studies of HFPEF or diastolic dysfunction.(19;23;33;38;45;54) Smart et al also found no significant improvement in total QOL score by the MLHF and SF-36 surveys. In the HF-ACTION trial in HFREF, ET was associated with modest changes in QOL by the Kansas City Cardiomyopathy Questionnaire.(47)

We and others have previously shown that stable HFPEF patients have increased neurohormonal activity compared to healthy age-matched controls, but less than observed in HFREF.(9;55;56) In the present study, ET had no significant effect on BNP or norepinephrine. Although the BNP levels in these stable, ambulatory outpatients were lower than often seen in decompensated HF, they were on average approximately 5-fold increased compared to our previously published healthy age-matched controls using the same bioassay kit.(9) Furthermore, Borlaug et al and Penicka et al, recently reported that compensated,

stable patients with invasively diagnosed HFPEF have BNP levels similar to our patients. (56–58)

Limitations

The mechanism(s) of the improvements following ET are not elucidated by the present data and will require further study. Tissue Doppler was not included, limiting our ability to assess whether improved diastolic function contributed to the improvement in peak VO_2.

By study design, participants were ambulatory outpatients who were stable, well compensated, had no recent acute hospitalization, and were physically able to participate in exhaustive exercise testing and a formal exercise training program. As a result, the mean BNP levels in the present study are relatively low, even though they are above those observed in a comparable group of healthy, age-matched normal subjects.(9) The BNP levels in our patients are similar to other studies of stable HFPEF patients that have included exercise testing.(24;57;59;60) These BNP levels are lower than in some mortality outcomes trials that have specifically targeted higher risk patients. Thus, our results may not apply to other patients who are sicker, poorly compensated, or less clinically stable.

The training protocol included only continuous, moderate intensity aerobic exercise; results may be different for other regimens, such as resistance training.(61) The ET sessions were medically supervised and the patients were well screened for contraindications to ET. Thus, while there were no adverse events attributable to the intervention, the present data do not address whether unsupervised or home-based ET would be as safe and effective in these elderly patients.

The study was conducted at a single center and the sample size may seem relatively modest, particularly compared to the recently reported multi-center HF-ACTION study in patients with HFREF.(15) However, our primary outcome was peak VO_2 rather than clinical events. (15) The sample size for this study was derived from a formal power analysis using previously published data in older persons(9;11;21;27;47) that indicated that 17 completed patients in each group would yield 80% power to detect a 15% difference in peak VO_2. The measured effect size in our 46 completed patients was greater than predicted, expressed as both percent (21%; 95% confidence intervals: 11–31%) and absolute values (2.7 ml/kg/min; confidence intervals: 1.4–4.0 ml/kg/min). Further, the lower 95% confidence intervals exclude the thresholds of 10% and 1.0 ml/kg/min which are often used as the minimal clinically relevant improvement.(11;62)

Some of the patients were on beta blocker medications which were held overnight prior to exercise testing. The relatively few data available in HF patients with reduced EF indicate that beta blockers have relatively modest effects on exercise test performance and exercise training.(63;64) The primary results were unchanged following adjustment for beta-blocker usage.

Designing a valid control regimen for an ET intervention is challenging. Although the randomly assigned attention control group participants received bi-weekly telephone calls, this was less interaction overall than the ET participants received and could have influenced results, despite blinding of the exercise tester and monitoring of objective measures during the exercise test. Finally, despite formal questioning, we cannot ensure that some control patients did not covertly undertake exercise on their own.

There were 5 dropouts in the CON group and 2 in the ET group, and we cannot be certain of their potential impact on the trial results. In order to conservatively explore the potential effect of the dropouts on peak VO_2, we performed a traditional sensitivity analysis for

continuous variables.(65) In this, the mean percent change in peak VO_2 observed in the ET group was imputed to all of the dropouts in the CON group, and the mean percent change in peak VO_2 observed in the CON group was imputed to all the dropouts in the ET group. This analysis indicated that the ET group had a significantly greater change in peak VO_2 than the CON group (p=0.002). We also did 2 additional analyses treating peak VO_2 as a binary outcome (≥ 10% increase). If all dropouts in both groups were imputed to have improved, then the ET group had a borderline significant treatment effect compared to CON (p=0.054). If instead, all dropouts in the ET group were imputed to have not improved and all dropouts in the CON group were imputed to have improved, then there was no significant treatment effect (p=0.56).

Although the trial was completed a number of years ago, these results remain applicable today because therapy of HFPEF is still empiric, there have been no proven, guidelines-based treatments, (66) and there has been no previously published randomized, controlled, blinded trial of exercise training in HFPEF.(57)

Conclusion

This randomized, controlled, single blind study showed that 16 weeks of ET was safe and significantly improved peak and submaximal exercise performance in older HFPEF patients. These results suggest that this non-pharmacological intervention may be a worthwhile consideration for patients with this common and increasing disorder.

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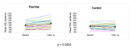

Figure 1.
Individual and mean (black boxes) responses of peak exercise VO2 following 16 weeks of supervised exercise training. Results are displayed in raw, non-indexed peak VO_2 as this is uninfluenced by weight.

Table 1

Characteristics of the Study Population

Characteristic	Exercise (N=26)	Control (N=27)	P-Value
Age (years	70 ± 6	69 ± 5	0.64
Women	20 (83)	20 (91)	0.46
Caucasian	21 (88)	16 (73)	0.31
Body Weight (kg)	79 ± 16	79 ± 17	0.98
BSA (m^2)	1.84 ± 0.21	1.81 ± 0.19	0.75
BMI (kg/m^2)	30 ± 6	31 ± 7	0.54
NYHA class			
II	15 (79)	12 (63)	0.82
III	4 (21)	7 (37)	0.74
Diastolic Function			
Normal	5 (21)	3 (12)	0.46
Abnormal relaxation	17 (71)	17 (68)	0.98
Pseudonormal	2 (8)	5 (20)	0.42
Hx pulmonary edema	3 (14)	8 (36)	0.07
Diabetes mellitus	2 (8)	7 (32)	0.04
Hx hypertension	20 (87)	16 (84)	0.81
Systolic BP (mmHg)	145 ± 19	149 ± 22	0.51
Diastolic BP (mmHg)	83 ± 7	81 ± 9	0.38
Heart rate (bpm)	68 ± 13	70 ± 13	0.57
Current medication			
ACE-inhibitors	7 (30)	5 (24)	0.44
Digoxin	4 (17)	3 (14)	0.53
Diuretics	14 (61)	13 (62)	0.39
Beta-blockers	8 (35)	4 (19)	0.21
Calcium Antagonists	9 (39)	10 (48)	0.78
Nitrates	3 (13)	2 (10)	0.57
Peak VO_2 (ml/kg/min)	13.8 ± 2.5	12.8 ± 2.6	0.20
Peak RER	1.12 ± 0.09	1.12 ± 0.10	0.86
Peak workload (watts)	51 ± 18	45 ± 15	0.31
Exercise time (min)	6.8 ± 2.3	6.2 ± 1.9	0.75
6 minute walk (feet)	1494 ± 224	1412 ± 437	0.50

mean ± sd, or count (%) Abbreviations: BSA: body surface area; BMI: body mass index; NYHA: New York Heart Association; BP: Blood pressure; peak VO_2: peak exercise oxygen consumption; RER: respiratory exchange rate

Table 2

Exercise Performance

	Exercise		Control		P-Value
	Baseline	**Final**	**Baseline**	**Final**	
Peak Exercise (Bike)					
Indexed VO_2 (ml/kg/min)	13.8 ± 2.5	16.1 ± 2.6	12.8 ± 2.6	12.5 ± 3.4	0.0001
VO_2 (ml/min)	1073 ± 255	1259 ± 316	991 ± 225	958 ± 259	0.0002
Time (min)	6.8 ± 2.3	8.2 ± 2.2	6.2 ± 1.9	5.6 ± 2.1	0.0001
Workload (Watts)	51 ± 18	61 ± 18	45 ± 15	44 ± 15	0.0007
Heart rate (bpm)	133 ± 20	137 ± 16	136 ± 18	129 ± 20	0.02
Heart rate reserve (bpm)	64 ± 24	68 ± 17	64 ± 17	57 ± 17	0.004
Systolic BP (mmHg)	185 ± 27	186 ± 21	185 ± 28	175 ± 28	0.04
Diastolic BP (mmHg)	88 ± 8	88 ± 9	86 ± 12	84 ± 11	0.31
Respiratory rate (bpm)	33 ± 7	37 ± 6	36 ± 7	37 ± 7	0.005
Oxygen pulse (ml/beat)	8.1 ± 1.7	9.2 ± 2.0	7.2 ± 1.6	7.4 ± 1.8	0.02
VCO_2 (ml/min)	1181 ± 321	1414 ± 354	1089 ± 277	1036 ± 345	0.0001
VE (l/min)	45 ± 13	53 ± 14	42 ± 12	39 ± 13	0.0001
RER	1.12 ± 0.09	1.15 ± 0.09	1.12 ± 0.10	1.10 ± 0.11	0.07
VE/VCO_2 slope	34 ± 6	35 ± 8	33 ± 5	34 ± 5	0.44
VAT (ml/min)	746 ± 149	822 ± 180	660 ± 174	618 ± 126	0.001
6 Minute walk (feet)	1494 ± 224	1659 ± 173	1412 ± 382	1460 ± 411	0.002

Data represent means ± SD; p-value represents comparison of least square means at final visit following adjustment for baseline values. Abbreviations: VO_2: oxygen consumption; VCO_2: VE: minute ventilation; carbon dioxide production; RER: respiratory exchange ratio; VAT: ventilatory anaerobic threshold; BP: blood pressure

Table 3

Quality of Life

	Exercise		Control		P-Value
	Baseline	**Final**	**Baseline**	**Final**	
MLHF					
Emotional	5 ± 4	3 ± 5	3 ± 5	4 ± 5	0.35
Physical	16 ± 10	11 ± 11	12 ± 11	12 ± 9	0.03
Total	32 ± 20	25 ± 24	25 ± 22	27 ± 19	0.11
SF-36					
Physical	50 ± 20	54 ± 19	48 ± 23	46 ± 21	0.53
General Health	42 ± 16	41 ± 14	46 ± 17	51 ± 14	0.47
Social Role	40 ± 14	41 ± 13	44 ± 14	43 ± 14	0.74
Role-Physical	35 ± 34	52 ± 35	38 ± 34	47 ± 35	0.30
Role-Emotional	60 ± 38	67 ± 40	55 ± 39	63 ± 42	0.95
Pain	46 ± 18	51 ± 19	40 ± 19	42 ± 21	0.50
Mental	58 ± 10	57 ± 10	55 ± 12	53 ± 10	0.76
Vitality	42 ± 12	48 ± 12	45 ± 14	40 ± 13	0.20
CES-D Short Form					
Total	2.5 ± 2.2	1.2 ± 1.5	2.2 ± 2.0	1.4 ± 1.5	0.30

Data represent means ± SD; p-value represents comparison of least square means at final visit following adjustment for baseline values. Abbreviation: MLHF: Minnesota Living With Heart Failure; SF-36: Medical Outcomes Study Short-Form 36 Item Health Survey; CES-D: Center for Epidemiological Studies Depression survey (CES-D)

Table 4

Echo-Doppler and Neurohormones

	Exercise		Control		P-Value
	Baseline	**Final**	**Baseline**	**Final**	
Echo-Doppler					
LVEDV (ml)	79 ± 24	79 ± 20	77 ± 19	79 ± 20	0.71
LVESV (ml)	31 ± 11	31 ± 10	32 ± 14	33 ± 13	0.30
LVSV (ml)	48 ± 13	48 ± 11	46 ± 11	46 ± 10	0.23
LV ejection fraction (%)	61 ± 5	57 ± 8	60 ± 10	55 ± 8	0.12
LV mass	160 ± 36	163 ± 38	150 ± 31	151 ± 33	0.51
LV mass/volume ratio	2.12 ± 0.62	2.13 ± 0.64	2.02 ± 0.46	1.90 ± 0.42	0.64
E wave velocity (cm/s)	79 ± 19	82 ± 19	85 ± 23	88 ± 21	0.61
A wave velocity(cm/s)	93 ± 29	86 ± 29	87 ± 18	84 ± 22	0.61
E deceleration time (ms)	220 ± 55	230 ± 40	227 ± 52	221 ± 52	0.44
E/A ratio	0.90 ± 0.24	1.02 ± 0.28	1.02 ± 0.38	1.12 ± 0.36	0.81
IVRT (ms)	100 ± 20	96 ± 20	92 ± 24	89 ± 18	0.66
Neurohormones					
Norepinephrine	307 ± 221	321 ± 290	276 ± 120	360 ± 529	0.71
BNP	45 ± 56	72 ± 115	72 ± 122	55 ± 118	0.06

Data represent means ± SD; p-value represents comparison of least square means at final visit following adjustment for baseline values. Logarithmic transformation was used for the neurohormones, which were non-normally distributed.

Abbreviations: LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVSV: left ventricular stroke volume; IVRT: isovolumic relaxation time; BNP: brain natriuretic peptide