Exercise Training in Older Patients With Heart Failure and Preserved Ejection Fraction

A Randomized, Controlled, Single-Blind Trial

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Background—Heart failure (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 patients with HFPEF and is a strong determinant of their reduced quality of life (QOL). Exercise training (ET) improves exercise intolerance and QOL in patients with HF with reduced ejection fraction (EF). However, the effect of ET in HFPEF has not been examined in a randomized controlled trial.

Methods and Results—This 16-week investigation was a randomized, attention-controlled, single-blind study of medically supervised ET (3 days per week) on exercise intolerance and QOL in 53 elderly patients (mean age, 70±6 years; range, 60 to 82 years; women, 46) 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% to 100%). There were no trial-related adverse events. The primary outcome of peak exercise oxygen uptake increased significantly in the ET group compared to the control group (13.8±2.5 to 16.1±2.6 mL/kg per minute [change, 2.3±2.2 mL/kg per minute] versus 12.8±2.6 to 12.5±3.4 mL/kg per minute [change, −0.3±2.1 mL/kg per minute]; $P=0.0002$). 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 in the total score ($P=0.11$).

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

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Key Words: heart failure ■ aging ■ exercise

Heart failure (HF) afflicts >3 million Americans annually[1] and is the only major cardiovascular disorder that is increasing in prevalence.[2] HF is primarily a disorder of elderly persons, with more than three fourths of patients aged ≥65 years. Among older patients with HF, the majority have HF with a preserved left ventricular ejection fraction (HFPEF).[3–7] HFPEF prevalence is growing faster than HF with severely reduced ejection fraction (HFREF) and results in substantial morbidity, mortality, and healthcare costs.[6,8]

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Exercise intolerance, manifested by dyspnea and fatigue during exertion, is the primary chronic symptom in patients with HF, 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 ($\dot{V}O_2$), is valid and reproducible even in older patients with HF,[11] is potentially modifiable, and is recognized as a valid therapeutic target. We have previously reported that peak exercise $\dot{V}O_2$ is severely reduced in older patients with HFPEF, compared to age-matched healthy volunteers, to a similar degree as patients with 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[19] reported that ET significantly

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improved peak $\dot{V}O_2$ and QOL and to a similar extent as those with systolic dysfunction, but 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 $\dot{V}O_2$ and the secondary outcome of disease-specific QOL.

Methods

Study Design

This 16-week study was a prospective, randomized, attention-controlled, single-blind trial 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, patients 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, left ventricular (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 randomly selected to receive either 16 weeks of aerobic ET or attention control with biweekly telephone follow-up. Measures were repeated after 16 weeks of ET. All testing was performed and results analyzed by individuals blinded to patient group. Recruitment began in 1994, and trial follow-up was completed in 1999.

Patients

Patients with HF were recruited from a 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 LVEF (≥50%); and no evidence of significant coronary, valvular, or pulmonary disease or any other medical condition that could mimic HF symptoms (anemia, thyroid dysfunction).[9,11,20–22,24] HF diagnosis was verified by a board-certified cardiologist on completion of a history, physical examination, detailed review of all available medical records, ECG, rest and exercise echocardiogram, and spirometry. The diagnosis was based on clinical criteria as previously described that included an HF clinical score from the National Health and Nutrition Examination Survey I of ≥3 and those used by Rich et al,[25] 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 exercising regularly; or had known cancer, significant renal dysfunction (creatinine >2.5 mg/dL), substance abuse, uncontrolled diabetes, dementia, history of noncompliance, 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 W for 2 minutes, increasing to 25 W for 3 minutes, and with 25 W per 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, Minn) 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 and 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 (P.H.B.) as previously described.[9,11,14,24] A 6-minute walk test was performed as previously published.[9,14,24,30]

QOL

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 (CES-D) survey were administered.

Echocardiography

Doppler echocardiogram examinations 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 2D 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, Calif) were used for brain natriuretic peptide-32 (BNP).[9,24] Norepinephrine was analyzed by high-pressure liquid chromatography with electrochemical detection.[9,24,35]

ET

Patients randomly assigned to ET exercised 3 times per week for 16 weeks for a total of 48 sessions in a dedicated facility under medical supervision.[14,36] Each session lasted 1 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 (Schwinn Fitness; Louisville, Colo). Data from the baseline exercise test were used to generate an individualized initial exercise prescription according to standard methods in patients with HF.[14,36,37] Heart rate and rate of perceived exertion were assessed periodically during exercise sessions. For the first 2 weeks of training, patients exercised at 40% to 50% of heart rate reserve while the duration of exercise was gradually increased on each of the 2 modes of exercise. Over the next several weeks, exercise intensity was increased to 60% to 70% of heart rate reserve, and exercise duration increased to 15 to 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 fewer than 40 (>80%) of the 48 ET sessions.

Patients randomly assigned to the attention-control group received telephone calls every 2 weeks throughout the 16-week follow-up. This procedure 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 exact tests were used to assess for any potential differences in baseline characteristics between the 2 groups. Comparisons of outcome measures between intervention groups were made by ANCOVA procedures. By prospective study design in order to reduce bias and increase precision, the analyses were adjusted for prerandomization values of the outcome measure being

Table 1. Characteristics of the Study Population

Characteristic	Exercise (n=26)	Control (n=27)	*P*
Age, y	70±6	69±5	0.64
Female sex	20 (83)	20 (91)	0.46
White race	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
History of pulmonary edema	3 (14)	8 (36)	0.07
Diabetes mellitus	2 (8)	7 (32)	0.04
History of hypertension	20 (87)	16 (84)	0.81
Systolic BP, mm Hg	145±19	149±22	0.51
Diastolic BP, mm Hg	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
β-blockers	8 (35)	4 (19)	0.21
Calcium antagonists	9 (39)	10 (48)	0.78
Nitrates	3 (13)	2 (10)	0.57
Peak $\dot{V}o_2$, mL/kg per 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, W	51±18	45±15	0.31
Exercise time, min	6.8±2.3	6.2±1.9	0.75
6-minute walk, ft	1494±224	1412±437	0.50

Data are presented as mean±SD or no. (%). ACE indicates angiotensin-converting enzyme; BSA, body surface area; BMI, body mass index; BP, blood pressure; bpm, beats per minute; NYHA, New York Heart Association; RER, respiratory exchange rate.

considered. Data are presented as raw, unadjusted mean±SD at each visit for each group along with the *P* value corresponding to the adjusted least squares means from the ANCOVA procedures accounting for all data at the follow-up visits. The neurohormone data were highly skewed and were log-transformed before analyses. Two-sided level of significance was set at $P<0.05$.

Results

Patient Characteristics

There were 53 patients enrolled; 26 were randomly assigned to ET and 27 were randomly assigned to attention control. The groups were well matched, with no differences in a broad range of characteristics (Table 1). At entry, all patients had New York Heart Association class II to III HF symptoms. Medical therapy remained constant during the 16 weeks of ET.

There was 1 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 2 patients. There were no patients with an electronic pacemaker in the trial.

ET Compliance, Adherence, and Events

Of the 53 patients randomly selected, 46 completed follow-up testing (24 from the ET group, 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 from each group) and lost to follow-up (n=3, all from the control group). 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 2 upper-respiratory infections, 1 bladder infection, and 2 falls. The 6 adverse events in the control group were 1 instance of pulmonary edema, 2 upper-respiratory infections, 1 automobile accident, 1 surgery for kidney mass, and 1 instance of arrhythmia. There were 2 hospitalizations in the control group (1 for pulmonary edema, 1 for surgery for kidney mass).

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

Exercise Performance

Following the 16-week intervention, peak exercise $\dot{V}O_2$, power output (Watts), and exercise time (seconds) at follow-up were significantly increased in the ET compared to the control group (all $P<0.001$) (Table 2). Adjusting for the baseline value, the follow-up peak $\dot{V}O_2$ was increased by 2.7 mL/kg per minute in the ET compared to the control group (95% CI, 1.4 to 4.0 mL/kg per minute). Individual responses of peak $\dot{V}O_2$ are shown in the Figure. At follow-up,19 (79%) of the 24 ET patients had increased peak $\dot{V}O_2$, and 11 (50%) of the 22 control patients had increased peak $\dot{V}O_2$ ($P=0.06$). Traditionally, a ≥10% increase is used as a threshold for a clinically meaningful improvement in peak $\dot{V}O_2$. This threshold was exceeded by 16 (67%) of ET patients and 6 (27%) of the control patients ($P=0.01$).

Peak respiratory exchange ratio, 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 patients compared to control patients. VAT and 6-minute walk distance were significantly increased in ET compared to control, indicating improved submaximal exercise performance. Ventilatory efficiency was not significantly different. Resting heart rate and diastolic and systolic blood pressure were unchanged.

Health-Related QOL

At baseline, MLHF scores were moderately increased in both groups, suggesting significant impairments (Table 3). After 6 weeks of ET, the ET group had a 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 2. Exercise Performance

	Exercise		Control		
	Baseline	Final	Baseline	Final	*P*
Peak exercise (bike)					
Indexed $\dot{V}O_2$, mL/kg per min	13.8±2.5	16.1±2.6	12.8±2.6	12.5±3.4	0.0001
$\dot{V}O_2$, 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, W	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, mm Hg	185±27	186±21	185±28	175±28	0.04
Diastolic BP, mm Hg	88±8	88±9	86±12	84±±11	0.31
Respiratory rate, breaths/min	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
$\dot{V}CO_2$, mL/min	1181±321	1414±354	1089±277	1036±345	0.0001
$\dot{V}E$, 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
$\dot{V}E/\dot{V}CO_2$ 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, ft	1494±224	1659±173	1412±382	1460±411	0.002

Data are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values. BP indicates blood pressure; bpm, beats per minute; RER, respiratory exchange ratio; $\dot{V}CO_2$, carbon dioxide production; $\dot{V}E$, minute ventilation.

(Table 3). There were no differences in SF-36 component scores or in the CES-D score.

LV Structure and Function

Doppler tracings were not analyzable in 4 patients due to atrial fibrillation (1 in each group) and missing recordings (1 in each group). At baseline, patients had normal LVEF, 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 Doppler echocardiography measures.

Neuroendocrine Function

After the 16-week intervention, there were no significant differences in BNP or norepinephrine (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 patients with HFPEF had severe exercise intolerance and moderately impaired QOL. Following the 16-week ET intervention, all 3 measures of exercise capacity (peak exercise $\dot{V}O_2$, power output, and exercise time) were significantly increased in the patients randomly assigned to ET but were unchanged or slightly reduced in the attention-control group. Most (67%) of the ET patients had a ≥10% increase in peak $\dot{V}O_2$, whereas this traditional threshold for a clinically meaningful improvement was observed in only 27% of the control patients. Submaximal exercise performance assessed by the VAT and the 6-minute walk test were also significantly increased. These improvements in

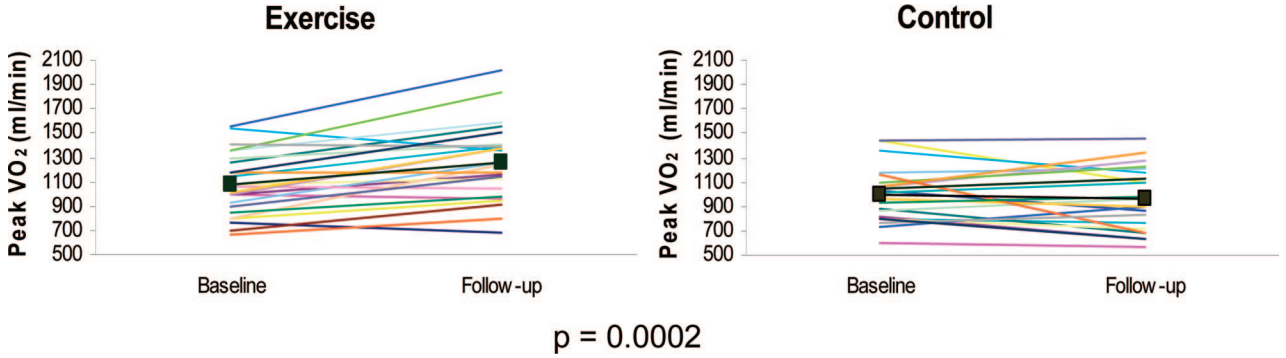

Figure. Individual and mean (■) responses of peak exercise $\dot{V}O_2$ following 16 weeks of supervised exercise training. Results are displayed in raw, nonindexed peak $\dot{V}O_2$, as this is uninfluenced by weight.

Table 3. QOL

	Exercise		Control		
	Baseline	Final	Baseline	Final	*P*
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 are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values.

exercise tolerance were accompanied by improvement in the physical symptom score on the MLHF survey but no change in mental score, resulting in a nonsignificant trend in total score. There were no changes in resting LV structure and 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 stable patients with chronic HFPEF.

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 patients with HFREF as well as those of Smart et al[19] in patients with dyspnea and Doppler diastolic dysfunction. The present study significantly extends the previously available literature. It examined older patients with HFPEF who were well characterized; had severe exercise intolerance similar to age-matched patients with HFREF[9]; and were closely representative of patients with HFPEF reported in large, population-based observational studies with respect to age, sex, and other key characteristics.[3–7] The mean age of the present study cohort of 70±5 years (range, 60 to 80 years) was 5 years greater than the patients studied by Smart et al and 10 years greater than that reported in most studies of ET in HFREF.[13,15] The present study used 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 usually has 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 patients with HFPEF, we found no improvement in exercise capacity.[24] In HFREF, gains in exercise capacity from medications usually have been relatively modest and on average less than with ET. In the large, multicenter Heart Failure: A Controlled Trial

Table 4. Doppler Echocardiography and Neurohormones

	Exercise		Control		
	Baseline	Final	Baseline	Final	*P*
Doppler echocardiography					
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
LVEF, %	61±5	57±8	60±10	55±8	0.12
LV mass, g	160±36	163±38	150±31	151±33	0.51
LV mass/volume ratio, g/mL	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 are presented as mean±SD. *P* represents comparison of least square means at final visit following adjustment for baseline values. Logarithmic transformation was used for the neurohormones, which were nonnormally distributed. IVRT indicates isovolumic relaxation time; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume.

Investigating Outcomes of Exercise Training (HF-ACTION) of ET in HFREF, peak $\dot{V}O_2$ 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 $\dot{V}O_2$ in older patients with HFREF.[14] Against this background, the 17% increase in exercise capacity from ET in the present study is substantial and similar to that reported in prior studies of middle-aged patients with HFREF.[13] The 2.3-mL/kg per minute improvement in peak $\dot{V}O_2$ substantially exceeded the 1.0 mL/kg per minute threshold that is customarily considered clinically significant. This improvement is also clinically meaningful because peak $\dot{V}O_2$ at baseline in patients randomly assigned to ET was 13.8 mL/kg per minute below the threshold of 15.0 mL/kg per minute usually associated with independence in the full range of activities in elderly persons, and after ET was 16.1 mL/kg per minute, above this threshold.[46]

The present data do not allow definitive elucidation of the mechanisms responsible for the improved exercise performance. According to the Fick equation, an increase in $\dot{V}O_2$ 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 patients with HFPEF and contributes to their reduced peak exercise $\dot{V}O_2$.[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 to be relatively similar in magnitude to the increase in peak $\dot{V}O_2$. Several studies have reported that ET improves peak heart rate in patients with HF due to reduced EF.[12,52,53] In a metaanalysis of 35 studies, ET resulted in an average increase in peak heart rate of 4 beats/minute or 2.5% of the pretraining level.[53] Keteyian et al[52] reported that peak heart rate increased by 7% (9 beats/minute) and contributed 50% of the effect of the increase in peak $\dot{V}O_2$ following ET.

Although at baseline the patients had typical features of hypertrophic concentric LV remodeling, normal EF, and delayed relaxation, these were unchanged following ET. This finding 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[19] 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 patients with HFPEF have increased neurohormonal activity compared to healthy age-matched controls but less than that 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,[56]From and Borlaug,[57] and Penicka et al[58] recently reported that compensated, stable patients with HFPEF that was invasively diagnosed had BNP levels similar to our patients.

Limitations

The mechanisms 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 $\dot{V}O_2$.

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 patients with HFPEF 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, although 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 with the recently reported multicenter HF-ACTION study in patients with HFREF.[15] However, our primary outcome was peak $\dot{V}O_2$ 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 $\dot{V}O_2$. The measured effect size in our 46 completed patients was greater than predicted, expressed as both percent (21%; 95% CI, 11% to 31%) and absolute values (2.7 mL/kg per minute; 95% CI, 1.4 to 4.0 mL/kg per minute). Further, the lower 95% CIs exclude the thresholds of 10% and 1.0 mL/kg per minute, which often are used as the minimal clinically relevant improvement.[11,62]

Some of the patients were on β-blocker medications, which were held overnight before exercise testing. The relatively few data available in patients with HFREF indicate that

β-blockers have relatively modest effects on exercise test performance and ET.[63,64] The primary results were unchanged following adjustment for β-blocker use.

Designing a valid control regimen for an ET intervention is challenging. Although the randomly assigned attention-control group patients received biweekly 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 control group and 2 in the ET group, and we cannot be certain of their potential impact on the trial results. To conservatively explore the potential effect of the dropouts on peak $\dot{V}O_2$, we performed a traditional sensitivity analysis for continuous variables.[65] In this analysis, the mean percent change in peak $\dot{V}O_2$ observed in the ET group was imputed to all the dropouts in the control group, and the mean percent change in peak $\dot{V}O_2$ observed in the control 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 $\dot{V}O_2$ than the control group ($P=0.002$). We also did 2 additional analyses, treating peak $\dot{V}O_2$ 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 the control group ($P=0.054$). If instead all dropouts in the ET group were imputed to have not improved and all dropouts in the control 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 empirical; there have been no proven, guidelines-based treatments[66]; and there has been no previously published randomized, controlled, blinded trial of ET 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 patients with HFPEF. These results suggest that this nonpharmacological intervention may be a worthwhile consideration for patients with this common and increasingly prevalent disorder.

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CLINICAL PERSPECTIVE

Heart failure (HF) with preserved left ventricular ejection fraction (HFPEF) is the most common form of HF in the older population, and exercise intolerance is its primary chronic symptom and a strong determinant of reduced quality of life (QOL). In patients with HF with reduced ejection fraction, exercise training (ET) improves exercise intolerance and QOL; however, little is known regarding the effect of ET in HFPEF. In this randomized, attention-controlled, single-blind study of elderly patients with isolated HFPEF, 16 weeks of medically supervised ET (3 days per week) was found to be safe and resulted in a 21% improvement in exercise capacity (peak exercise oxygen uptake) in the ET group compared to the control group ($P=0.0002$). There were also significant improvements in 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 in the total score ($P=0.11$). Although the present results do not allow elucidation of the mechanism of improvement in exercise capacity, there were no changes in resting left ventricular structure and function or neurohormone levels. These results indicate that ET is safe and can improve both peak and submaximal exercise performance in older patients with HFPEF. This finding is particularly relevant because large pharmacological intervention trials in HFPEF have thus far had neutral results and because exercise intolerance is an important determinant of QOL in these patients. Therefore, this nonpharmacological intervention may be a worthwhile consideration for patients with this common and increasingly prevalent disorder.

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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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