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Effect of Endurance Exercise Training on Endothelial Function and Arterial Stiffness in Older Patients With Heart Failure and Preserved Ejection Fraction

A Randomized, Controlled, Single-Blind Trial

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Objectives The study sought to evaluate the effects of endurance exercise training (ET) on endothelial-dependent flow-mediated arterial dilation (FMD) and carotid artery stiffness, and their potential contributions to the training-related increase in peak exercise oxygen consumption (Vo_2) in older patients with heart failure with preserved ejection fraction (HFPEF).

Background Elderly HFPEF patients have severely reduced peak Vo_2, which improves with ET, however, the mechanisms of this improvement are unclear. FMD and arterial distensibility are critical components of the exercise response and are reduced with aging. However, it is unknown whether these improve with ET in elderly HFPEF or contribute to the training-related improvement in peak Vo_2.

Methods A total of 63 HFPEF patients (age 70 ± 7 years) were randomized to 16 weeks of ET (walking, arm and leg ergometry, n = 32) or attention control (CT) (n = 31). Peak Vo_2, brachial artery FMD in response to cuff ischemia, carotid artery distensibility by high-resolution ultrasound, left ventricular function, and quality of life were measured at baseline and follow-up.

Results ET increased peak Vo_2 (ET: 15.8 ± 3.3 ml/kg/min vs. CT: 13.8 ± 3.1 ml/kg/min, p = 0.0001) and quality of life. However, brachial artery FMD (ET: 3.8 ± 3.0% vs. CT: 4.3 ± 3.5%, p = 0.88), and carotid arterial distensibility (ET: 0.97 ± 0.56 vs. CT: 1.07 ± 0.34 × 10^{-3} mm·mm Hg^{-2}; p = 0.65) were unchanged. Resting left ventricular systolic and diastolic function were unchanged by ET.

Conclusions In elderly HFPEF patients, 16 weeks of ET improved peak Vo_2 without altering endothelial function or arterial stiffness. This suggests that other mechanisms, such as enhanced skeletal muscle perfusion and/or oxygen utilization, may be responsible for the ET-mediated increase in peak Vo_2 in older HFPEF patients. (Prospective Aerobic Reconditioning Intervention Study [PARIS]; NCT01113840) (J Am Coll Cardiol 2013;62:584–92)

Approximately 50% of older heart failure (HF) patients have preserved left ventricular ejection fraction (HFPEF) (1,2), and their primary symptom is severe exercise intolerance, measured objectively as reduced peak exercise oxygen uptake (Vo_2peak) (3–9). Reduced peak and reserve arteriovenous oxygen difference (A-Vo_2Diff) are important contributors to the reduced Vo_2peak in HFPEF (5,8). Furthermore,

See page 593

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improved A-Vo_2Diff accounts for most of the increase in Vo_2peak following endurance exercise training (ET) (10). This suggests roles for impaired arterial and/or skeletal muscle function in the severe exercise intolerance in HFPEF and its improvement with ET (11).

In HFPEF, arterial stiffness is increased and endothelial function may be decreased, and both may contribute to exercise intolerance (6,7,12–15). In HF with reduced ejection fraction (HFREF), ET improves endothelial function and arterial compliance (16–22), and the former is correlated with the ET-related improvement in Vo_2peak (18,23). Therefore, we performed a randomized, controlled, single-blind trial to test the hypothesis that ET would enhance endothelial function and arterial distensibility in HFPEF and that these would be important contributors to the improvement in Vo_2peak.

Methods

Study protocol. The study was approved by the Wake Forest School of Medicine Institutional Review Board for Protection of Human Subjects and registered (NCT01113840). During the screening visit, informed consent was obtained, and participants were familiarized with the testing environment and procedures. During a single subsequent visit, all outcome measures were obtained. Subjects were then randomized to 16 weeks of ET or attention control (CT). Exercise performance, echocardiography, and quality of life (QOL) were assessed at baseline and following the 16-week intervention. Brachial artery flow-mediated arterial dilation (FMD) and carotid arterial distensibility were measured at baseline, 8, and 16 weeks. Testing was performed and results were analyzed by individuals blinded to patient group. Baseline characteristics have been reported (15,24).

Subjects. HFPEF patients were identified from fortified search lists (4,5,10,15,25,26) and had symptoms and signs of HF defined by NHANES (National Health and Nutrition Examination Survey) HF score ≥3 and the criteria of Rich et al. (27), left ventricular (LV) ejection fraction ≥50%, no segmental wall motion abnormalities, and no significant ischemic or valvular heart disease, pulmonary disease, anemia, or other disorder that could explain the patients' symptoms (4,5,26). Because of the profound impact of atherosclerosis on arterial function (28), patients with hyperlipidemia, cigarette smoking, or coronary, cerebrovascular, or peripheral arterial disease were excluded by history, examination, exercise echocardiography, and vascular ultrasound (15,24).

Echocardiography. Doppler-echocardiograms were performed and analyzed as previously described (4,5,10,24,26). Doppler LV filling patterns were categorized using the ratio of early (E) to late (A) ventricular filling velocities, early deceleration time, and normal reference ranges for age (29,30).

Exercise testing. Exercise testing with expired gas analysis was performed, as previously described, in the upright position on an electronically braked bicycle using a staged protocol to exhaustion (4,5,10,15,24–26,31). Peak values were averaged from the last 2 15-s intervals during peak exercise (4,5,10,24–26,31). Ventilatory anaerobic threshold and ventilation per carbon dioxide slope were assessed as previously described (25,26,32). A 6-min walk test was performed by the method of Guyatt (25,26,32,33).

Brachial artery FMD. Brachial FMD was measured as previously described in our laboratory and in accordance with international standards (24,34–36). Participants were examined in the post-prandial state after 15 min of quiet, supine rest using a Biosound Phase II ultrasound system (Biosound Esaote, Indianapolis, Indiana) with a 9-mHz transducer to record images of the right brachial artery. A forearm cuff was then inflated 50 mm Hg above systolic pressure for 4 min. Images were recorded during the final 30 s before and 3 min following rapid cuff deflation (32,34).

Video frames were automatically digitized and analyzed using previously described techniques (24,34). The maximum diameter from the dilation phase was automatically determined, and the change in diameter and percent change were calculated as follows: absolute change = maximum minus baseline; percent change = 100 × absolute change/baseline. Brachial FMD by these techniques is highly reproducible in our laboratory (34).

Arterial stiffness. As previously described, 10-s images of the left common carotid artery were recorded using a Sequoia ultrasound instrument (Acuson, Inc., Mountain View, California) fitted with a 10-MHz linear probe (15,32,34) while optimizing the 4 boundaries defining the media–adventitia and blood–intima interfaces on the near and far walls. Later, these boundaries were traced from the digital images on a dedicated workstation to generate the mean, maximum, and minimum values of the arterial diameter, the lumen diameter, the far wall thickness, and the near wall thickness. Carotid stiffness indexes were calculated as previously described and according to accepted formulae (15,32,37,38). Overall systemic arterial stiffness was measured as pulse pressure/stroke volume.

QOL. As previously described (26,32), health-related QOL was assessed with the short-form 36 health survey (39) and the Minnesota Living With Heart Failure (40) questionnaire.

B-type natriuretic peptide-32 measurement. As previously described, a commercially available radioimmunoassay (Phoenix Pharmaceuticals Inc., Mountain View, California) was used for B-type natriuretic peptide (BNP) (4,26,32).

Abbreviations and Acronyms

- A-Vo_2Diff = arteriovenous oxygen difference
- BNP = B-type natriuretic peptide
- CT = attention control
- ET = exercise training
- FMD = flow-mediated arterial dilation
- HF = heart failure
- HFPEF = heart failure with preserved ejection fraction
- HFREF = heart failure with reduced ejection fraction
- LV = left ventricular
- QOL = quality of life
- RER = respiratory exchange ratio
- Vo_2 = oxygen consumption
- Vo_2peak = peak exercise oxygen uptake

JACC Vol. 62, No. 7, 2013
August 13, 2013:584–92

Endurance ET. The ET group exercised for 1 h 3 times per week for 16 weeks. Each session had 3 phases: 10-min warm-up, stimulus, and 10-min recovery. The stimulus phase consisted of walking on a track and cycle ergometry (Schwinn Airdyne, Boulder, Colorado). Isolated arm ergometry (operating the Airdyne with arms only) was performed ≥10 min each session in order to ensure upper extremity training. Patients exercised initially at 40% to 50% of heart rate reserve for 5 to 10 min each of walking and ergometry. The intensity increased gradually until 70% heart rate reserve was maintained for at least 20 min each of walking and ergometry.

Attention control. The CT group received telephone calls every 2 weeks for 16 weeks. These focused on retention, reminders and encouragement to keep study visits, and capture of medical events and did not address exercise behaviors.

Statistical analysis. The sample size was derived from a power analysis using data from a pilot study of 16 patients, indicating that a sample size of 44 evaluable patients (22 per group) would provide 80% power to detect a 2% absolute change in brachial FMD, the primary outcome. The secondary outcome was carotid distensibility. Vo_2peak (ml/kg/min) was the main exercise outcome.

Baseline comparisons were made using 2-sample *t* tests for continuous data, Fisher exact tests for dichotomous data, or chi-square tests for categorical data. Comparisons of exercise testing, LV function, and QOL measures were made by analysis of covariance, with the baseline value of the measure as the covariate. Brachial FMD and carotid distensibility were analyzed using repeated measures analysis of covariance models fitted with the week 8 and 16 values as outcomes and the baseline value as the covariate. A 2-sample *t* test was used to compare baseline characteristics between participants who dropped out and those who completed the 16-week study. Logarithmic transformation was performed for highly skewed data. A 5% 2-sided significance level was used.

Results

Participants. Fortified search lists from hospital discharges, clinic visits, and echocardiogram reports were reviewed from Wake Forest Medical Center. From 827 records reviewed, 543 patients potentially met inclusion criteria; 156 responded to an invitation, passed telephone screening, and were scheduled for a screening visit. Most common reasons for exclusion were patient unwillingness or did not meet criteria.

Sixty-three HFPEF patients (age 70 ± 7 years) were enrolled; 32 were randomized to ET and 31 to CT (Table 1). All had New York Heart Association functional class II to III symptoms. There were no significant baseline intergroup differences in key characteristics except for more beta-blockers among CT patients.

ET safety, compliance, and adherence. One patient developed transient hypoglycemia during an exercise session; there were no other protocol-related events. Fifty-four patients (86%) completed final testing (24 ET, 30 CT). Reasons for not completing follow-up testing were: patient unwillingness (2 ET and 1 CT), elective surgery (2 ET), non-HF illness (3 ET), and HF hospitalization (1 ET). ET patients attended 88% of ET sessions. Among participants who completed follow-up testing, there were no significant intergroup differences in key baseline variables including Vo_2peak (14.2 ± 2.2 ml/kg/min vs. 14.0 ± 3.2 ml/kg/min, p = 0.54), brachial FMD (4.0 ± 2.2 vs. 4.7 ± 3.5, p = 0.18), and carotid distensibility (1.07 ± 0.50 vs. 0.89 ± 0.35, p = 0.19).

Table 1 Baseline Participant Characteristics

	ET (n = 32)	CT (n = 31)	p Value
Female, %	72	80	0.56
Caucasian, %	66	71	0.79
African American, %	28	23	0.77
Age, yrs	70 ± 7	70 ± 7	0.63
Body mass index, kg/m^2	32.2 ± 6.7	32.0 ± 6.6	0.92
Body surface area, m^2	1.95 ± 0.22	1.94 ± 0.25	0.84
History of hypertension, %	94	84	0.25
Diabetes mellitus, %	28	19	0.56
Systolic blood pressure, mm Hg	146 ± 17	147 ± 17	0.81
Diastolic blood pressure, mm Hg	82 ± 11	83 ± 10	0.83
Left ventricular mass, g	247 ± 95	266 ± 94	0.47
Posterior wall thickness, cm	1.3 ± 0.2	1.2 ± 0.2	0.41
Left atrial diameter, cm	3.6 ± 0.7	3.4 ± 0.7	0.27
Smoking history			
Never, %	41	61	
Former, %	50	35	
Current, %	9	3	0.26
New York Heart Association functional class			
II, %	47	55	0.62
III, %	53	45	
Diastolic filling			
Normal, %	0	0	1.0
Impaired relaxation, %	44	52	0.61
Pseudonormal, %	53	41	0.44
Restrictive, %	3	7	0.59
B-type natriuretic peptide, pg/ml	64.8 ± 74.5	72.2 ± 60.9	0.62
Medications			
Diuretic agents, %	66	55	0.45
Angiotensin-converting enzyme inhibitors, %	44	39	0.80
Beta-blockers, %	9	35	0.02
Calcium-channel blockers, %	44	19	0.06
Angiotensin receptor blockers, %	6	3	1.00
Estrogen (♀), %	34	36	0.92
Nitrates, %	13	10	1.00

Values are % or mean ± SD. For B-type natriuretic peptide, median (25th, 75th percentile) are 39.1 (18.8, 78.5) versus 55.4 (22.6, 109.7), and the p value shown is following logarithmic transformation of this highly skewed variable.

CT = attention control; ET = exercise training.

Table 2 Effect of Endurance Exercise Training on Exercise Performance

	ET		CT		
	Baseline (n = 24)	Final (n = 24)	Baseline (n = 30)	Final (n = 30)	p Value
Peak exercise (bike)					
Exercise time, min	9.5 ± 3.2	11.4 ± 3.1	9.6 ± 3.1	9.5 ± 3.3	<0.0001
Power output, watts	72 ± 31	89 ± 30	72 ± 26	67 ± 27	<0.0001
Vo_2, ml/kg/min	14.2 ± 2.8	15.8 ± 3.3	14.0 ± 3.2	13.8 ± 3.1	0.0001
Vo_2, ml/min	1,260 ± 329	1,388 ± 378	1,233 ± 398	1,217 ± 370	0.0004
Heart rate, beats/min	128 ± 18	132 ± 16	131 ± 21	127 ± 17	0.01
Systolic blood pressure, mm Hg	197 ± 19	199 ± 21	192 ± 27	192 ± 29	0.49
Diastolic blood pressure, mm Hg	91 ± 14	91 ± 11	91 ± 12	91 ± 14	0.99
Pulse pressure, mm Hg	106 ± 21	107 ± 21	102 ± 22	100 ± 27	0.47
Respiratory exchange ratio	1.13 ± 0.07	1.11 ± 0.08	1.11 ± 0.10	1.09 ± 0.08	0.68
6-min walk distance, m	447 ± 107	486 ± 89	438 ± 79	448 ± 70	0.009
Ventilatory anaerobic threshold, ml/min	699 ± 178	796 ± 163	734 ± 189	702 ± 186	0.01
Ve/Vco_2 slope	31.5 ± 4.4	32.2 ± 4.5	30.6 ± 3.6	30.2 ± 3.3	0.07

Values are mean ± SD; p value represents comparison of least square means at final visit following adjustment for baseline values.
Vco_2 = carbon dioxide production; Ve = minute ventilation; Vo_2 = oxygen consumption; other abbreviations as in Table 1.

Exercise testing. Following the 16-week intervention, Vo_2peak, exercise time, peak power output (all $p < 0.0001$), and ventilatory anerobic threshold ($p = 0.01$) were significantly greater in ET than CT (Table 2, Fig. 1). Although peak heart rate was mildly higher in ET than CT, there was no difference in respiratory exchange ratio (RER) ($p = 0.68$), suggesting similar, exhaustive levels of effort (Table 2). Further, 43 participants (80%) achieved RER ≥1.05 at the final visit. Of 11 participants with RER <1.05, 7 (23%) were CT and 4 (17%) were ET ($p = 0.74$), indicating similar effort. The 6-min walk distance was greater after 16 weeks in ET than CT ($p = 0.009$).

Following ET, there were no intergroup differences in resting or exercise systolic, diastolic, and pulse pressure (Table 2). At baseline, 17 (27%) patients met criteria for chronotropic incompetence. Despite the ET-related improvement in peak heart rate, ET did not reduce chronotropic incompetence significantly at follow-up ($p = 0.22$).

Brachial FMD. Brachial FMD (the primary study outcome) was not different between groups after 8 or 16 weeks (Table 3, Fig. 1). Within the ET group, FMD actually decreased slightly (4.0 ± 2.0% to 3.8 ± 3.0%). The estimated treatment effect size on absolute brachial FMD was only 0.2%; thus we can be 94% confident that the true effect is <1.0%, indicating that it is highly unlikely that the trial missed a clinically meaningful improvement in FMD.

Arterial stiffness. Carotid distensibility, the main arterial stiffness outcome, was not different after 8 or 16 weeks (Table 4). There was also no intergroup difference in any other measure of arterial stiffness (Table 4).

LV function. There were no significant differences after 16 weeks for resting LV volumes, ejection fraction, Doppler LV filling, or pulse pressure/stroke volume ratio (Table 5).

QOL. After the 16-week intervention, the emotional and physical short form–36 scores were higher in ET than CT, but the Minnesota Living With Heart Failure (40) questionnaire scores were not significantly different (Table 6).

Analysis based on medications and dropouts. Although beta-blockers were somewhat more prevalent in CT, the overall results were unchanged after adjusting for this. Baseline brachial FMD was not different between those who dropped out (4.4 ± 2.9%, n = 9) and those who completed the study (3.2 ± 2.0%, n = 54, p = 0.3). Baseline carotid distensibility was not different between those who dropped out ($0.67 \pm 0.59 \times 10^{-3}$ mm·mm Hg^{-1}, n = 5) compared with those who completed ($0.97 \pm 0.44 \times 10^{-3}$ mm·mm Hg^{-1}, n = 48, p = 0.29). Baseline Vo_2peak was lower in participants who dropped out versus completed (11.9 ± 2.8, n = 9; 14.1 ± 3.2, n = 54, respectively; p = 0.03).

Responders analyses. A responder was defined as having an absolute increase of 1.0% for brachial FMD and a 10% relative increase in carotid distensibility (36) at follow-up. There were 5 (21%) FMD responders in ET and 6 (21%) in CT ($p = 1.0$). There were 4 (17%) carotid distensibility responders in ET and 7 (35%) in CT ($p = 0.29$). Within ET, an additional analysis was performed to determine whether any key baseline variable differed between responders and nonresponders. For FMD, only E deceleration time was significantly different (174 ± 28 ms vs. 239 ± 43 ms, respectively; p = 0.004). For carotid distensibility, no variable was significantly different.

Discussion

To our knowledge, this is the first report on the effect of ET on endothelial function and arterial stiffness in HFPEF. The effect size of ET on peak Vo_2 was 1.8 ml/kg/min (13%, 15.7 ± 0.3 ml/kg/min vs. 13.9 ± 0.3 ml/kg/min; least squares means from analysis of covariance). This supports findings from 3 previous trials (26,41,42), increasing the number of HFPEF patients reported in randomized ET trials nearly 50%. Despite the significant improvement in Vo_2peak, and in contrast to our hypothesis, ET did not improve brachial FMD (the primary outcome) or arterial stiffness. This indicates that improvements in large arterial

JACC Vol. 62, No. 7, 2013
August 13, 2013:584–92

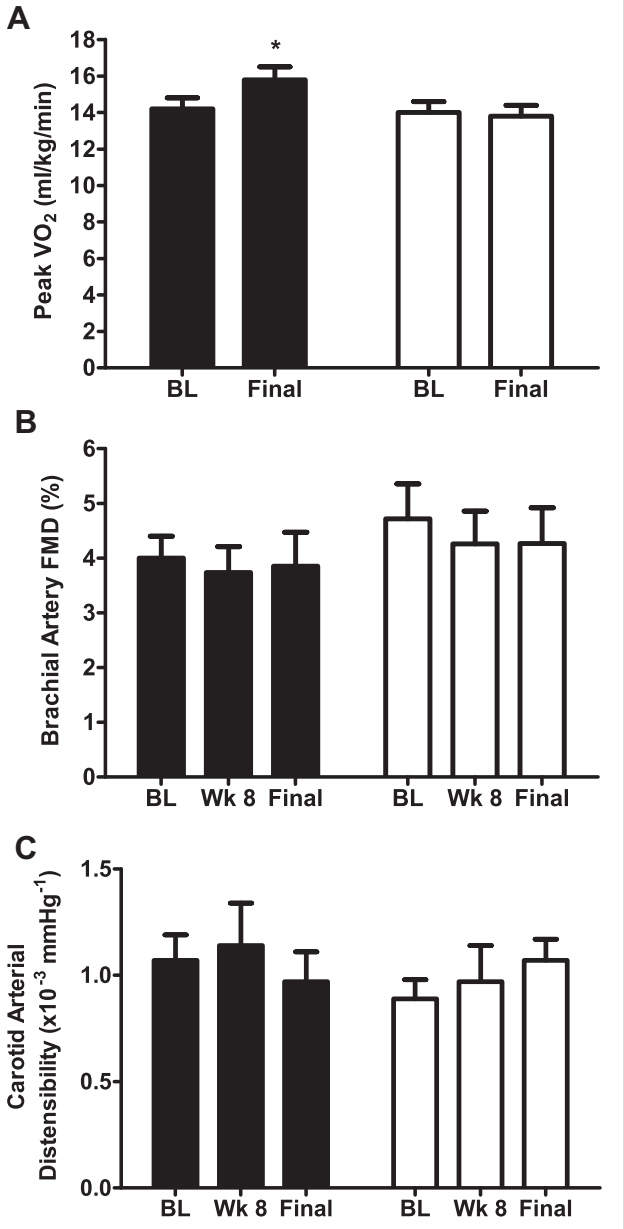

Figure 1 **Effects of Endurance Training**

(A) Peak oxygen consumption (V_{O_2}), **(B)** brachial artery flow-mediated dilation (FMD), and **(C)** carotid arterial distensibility in older heart failure with preserved ejection fraction (HFPEF) patients. **Solid bars** = exercise training; **open bars** = attention control. Values are raw mean ± SE at each time point. *$p < 0.05$ between groups. BL = baseline.

function were not responsible for the ET-related improvement in V_{O_2}peak. There were also no changes in resting LV function. Combined with our previously reported trial (10) and that recently reported by Fujimoto et al. (43), this suggests that the ET-related improvement in V_{O_2}peak in HFPEF may be related to microvascular and/or skeletal muscle adaptations that increase diffusive oxygen transport and/or utilization by the active muscles (19,44–47).

This study was driven by evidence suggesting that impaired arterial function (vasodilation and/or arterial stiffness) contributes to exercise intolerance in HFPEF. Borlaug et al. (6) showed that in HFPEF vasodilator reserve was reduced and correlated with reduced exercise capacity. Puntawangkoon et al. (48) found that submaximal exercise leg blood flow was reduced. Borlaug et al. (7) also reported reduced digital arterial function in HFPEF. However, the finding of abnormal vasodilation in HFPEF has not been universal, because Haykowsky et al. (24), using high-resolution brachial ultrasound, and Hundley et al. (13), using phase-contrast femoral magnetic resonance imaging, found FMD was not reduced in older HFPEF patients screened for atherosclerosis (13,24).

Arterial stiffness has been uniformly reported to be increased in HFPEF. We and others have shown that aortic and carotid distensibility are significantly reduced in elderly HFPEF and are independent predictors of reduced V_{O_2}peak (13,15,49,50). Borlaug et al. reported that arterial stiffness increases during exercise and is inversely related to exercise performance (7,14).

This study was also driven by several reports that ET in HFREF patients enhances arterial function (16,17,19–21,23,51). Hornig et al. (16) and others (17,21) showed that ET-mediated improvements in endothelial arterial function may be region-specific (to the locally active muscles), whereas Hambrecht et al. (21,23) found that effects of ET extended beyond regional effects because lower-limb ET increased upper-limb FMD. Moreover, Parnell et al. (22) demonstrated that ET improves arterial stiffness in HFREF.

In our study, 16 weeks of ET did not change endothelial function or arterial stiffness. This suggests that the vascular adaptations to ET may differ between HFREF and HFPEF patients (52). If so, that may be partly explained by the fact that the effects of ET on vascular function appear to be sex and age dependent. This is relevant because the majority of the HFPEF patients in our study were older women, as in the general population (1), whereas most HFREF patients are men. Specifically, Pierce et al. (53) recently found that brachial FMD was not different between older women undergoing high-frequency, long-term ET (≥5 years) versus age-matched healthy sedentary controls, whereas it was 49% greater in older men with long-term ET compared with controls. Also, 2 months of ET improved brachial FMD in previously sedentary healthy middle-aged men, but not in older post-menopausal women (53). Of note, the HFREF patients in prior studies of the effect of ET on endothelial function were predominantly men (1). Furthermore, among master ET athletes, carotid artery compliance is lower in older women compared with men (54). Thus, sex- and age-dependent effects may explain, at least partly, differences in the effect of ET on arterial function in HFPEF patients in the present study compared with previous studies of HFREF.

Another potential explanation for differing results of ET on arterial function in HFPEF compared with HFREF is

Table 3 Effect of Endurance Exercise Training on Brachial Artery Diameter in Response to Cuff Ischemia (FMD)

	ET			CT			
	Baseline	8 Week	Final	Baseline	8 Week	Final	p Value
n	25	23	24	30	22	29	
Baseline diameter, mm	4.17 ± 0.91	4.41 ± 0.89	4.30 ± 0.83	4.13 ± 0.87	4.11 ± 1.02	4.23 ± 0.98	0.78
Maximum diameter, mm	4.33 ± 0.89	4.56 ± 0.88	4.45 ± 0.79	4.31 ± 0.85	4.28 ± 1.01	4.40 ± 0.95	0.41
Absolute change, mm	0.16 ± 0.07	0.16 ± 0.08	0.15 ± 0.09	0.18 ± 0.12	0.16 ± 0.09	0.16 ± 0.10	0.94*
Brachial artery FMD, %	4.0 ± 2.0	3.7 ± 2.2	3.8 ± 3.0	4.7 ± 3.5	4.3 ± 2.8	4.3 ± 3.5	0.88*

Values are mean ± SD; p value represents comparison of least square means of the main effect across the follow-up visits following adjustment for baseline values. *p value is shown following logarithmic transformation of this highly skewed variable.

FMD = flow-mediated dilation; other abbreviations as in Table 1.

the profound effect of atherosclerosis on vascular function (28). A strength of the present study is that patients were screened to exclude those with coronary, cerebrovascular, and peripheral vascular disease to avoid the strong, confounding influence of atherosclerosis (28,55). However, this has not been accounted for in most prior studies of FMD and arterial stiffness, and atherosclerosis is more common in HFREF than HFPEF (1). However, studies using animal models of HFREF and carefully selected HFREF patient groups indicate that abnormal endothelial function is present in HFREF even in the absence of atherosclerosis (56,57). Our finding that ET did not improve brachial FMD and that FMD did not contribute to the ET-related improvement in V_{O_2}peak, taken together with our 2 prior reports that found no significant difference in brachial or femoral FMD at baseline in older patients with HFPEF versus controls (13,24), suggests that in contrast to HFREF, abnormal FMD may not be a fundamental component of the pathophysiology of exercise intolerance in older HFPEF patients.

If neither increased exercise cardiac output (10) nor improved large arterial function primarily accounts for the improved V_{O_2}peak following ET in older HFPEF, this suggests a potential role for skeletal muscle adaptations, such as either increased diffusive oxygen transport of O_2 from red blood cells to muscle mitochondria and/or improved O_2 utilization by the active muscles, primarily via mitochondrial function. Some independent data support this possibility. Bhella et al. (8) recently showed that skeletal muscle oxidative metabolism was abnormal in a small number of older patients with HFPEF and appeared related to their severely reduced V_{O_2}peak. Furthermore, several studies have shown that abnormal skeletal muscle perfusion and metabolism contribute significantly to exercise intolerance in HFREF and to improvements in V_{O_2}peak following ET (44,58–61).

Our study also confirmed prior reports that ET improves peak heart rate response, QOL, and 6-min walk distance in HFPEF (10,26,41).

Study limitations. Although our study duration was long enough to produce a significant improvement in V_{O_2}peak and included upper as well as lower extremity training, we cannot exclude that training that was longer and more intense could produce detectable improvements in vascular or

Table 4 Carotid Arterial Stiffness Measurements

	ET			CT			
	Baseline	8 Weeks	Final	Baseline	8 Weeks	Final	p Value
n	24	20	23	24	21	20	
Main measure							
AD ($\times 10^{-3}$ mm·mm Hg^{-1})	1.07 ± 0.50	1.14 ± 0.70	0.97 ± 0.56	0.89 ± 0.35	0.97 ± 0.51	1.07 ± 0.34	0.65
Other measures							
AC ($\times 10^{-3}$ mm·mm Hg^{-1})	65.1 ± 20.9	76.8 ± 64.7	58.8 ± 32.8	51.6 ± 23.4	51.3 ± 17.4	61.7 ± 21.1	0.64*
PEM, kPa	232 ± 150	223 ± 181	224 ± 198	242 ± 109	235 ± 147	242 ± 111	0.41*
YEM, kPa	1,504 ± 1,160	1,302 ± 1,089	1,427 ± 1,385	1,209 ± 642	1,195 ± 864	1,128 ± 648	0.82*
Beta index	16.11 ± 9.36	16.45 ± 12.46	15.77 ± 12.66	16.91 ± 7.61	16.82 ± 10.46	16.58 ± 7.16	0.50*
Pulse pressure, mm Hg	70 ± 16	65 ± 12	62 ± 13	73 ± 17	67 ± 12	68 ± 12	0.24
Arterial dimensions							
IMT, mm	0.74 ± 0.08	0.75 ± 0.09	0.76 ± 0.11	0.84 ± 0.14	0.82 ± 0.10	0.84 ± 0.10	0.30
SAD, mm	8.33 ± 1.12	8.31 ± 1.18	8.45 ± 1.20	8.26 ± 0.92	8.11 ± 0.89	8.35 ± 0.97	0.47
DAD, mm	7.93 ± 1.15	7.90 ± 1.17	8.01 ± 1.19	7.89 ± 0.90	7.72 ± 0.89	8.00 ± 0.96	0.52
SLD, mm	6.98 ± 1.19	7.02 ± 1.29	6.83 ± 1.02	6.63 ± 1.02	6.46 ± 0.88	6.53 ± 0.87	0.90
DLD, mm	6.53 ± 1.22	6.57 ± 1.17	6.43 ± 1.02	6.21 ± 0.94	6.08 ± 0.91	6.09 ± 0.80	0.72
ADC, mm	0.40 ± 0.17	0.41 ± 0.20	0.44 ± 0.24	0.38 ± 0.16	0.39 ± 0.27	0.35 ± 0.14	0.49*

Values are mean ± SD; p value represents comparison of least squares means of the main effect across the follow-up visits following adjustment for baseline values. *p value is shown following logarithmic transformation of this highly skewed variable.

AC = arterial compliance; AD = arterial distensibility; ADC = arterial diameter change during cardiac cycle; DAD = diastolic arterial diameter; DLD = diastolic lumen diameter; IMT = mean wall intimal medial thickness; PEM = Peterson's elastic modulus; PP = pulse pressure; SAD = systolic arterial diameter; SLD = systolic lumen diameter; YEM = Young's elastic modulus; other abbreviations as in Table 1.

Table 5 Effect of Endurance Exercise Training on Resting Left Ventricular Volumes and Doppler Filling

	ET		CT		
	Baseline	Final	Baseline	Final	p Value
n	24	24	28	28	
End-diastolic volume, ml	103 ± 32	101 ± 34	88 ± 26	85 ± 22	0.41
End-systolic volume, ml	43 ± 13	43 ± 16	39 ± 12	38 ± 11	0.64
Stroke volume, ml	60 ± 22	59 ± 21	50 ± 15	47 ± 12	0.29
Pulse pressure/stroke volume, mm Hg/ml	1.42 ± 0.47	1.31 ± 0.51	1.52 ± 0.44	1.38 ± 0.31	0.98
Ejection fraction, %	58 ± 6	58 ± 6	56 ± 5	56 ± 5	0.58
Early filling velocity, cm/s	77 ± 21	75 ± 19	72 ± 23	68 ± 15	0.24
Atrial filling velocity, cm/s	87 ± 25	85 ± 24	78 ± 24	78 ± 21	0.95
Early/atrial filling velocity ratio	1.03 ± 0.94	0.99 ± 0.59	1.07 ± 0.87	0.99 ± 0.64	0.81*
Early deceleration time, ms	225 ± 48	219 ± 51	216 ± 63	233 ± 57	0.24
Isovolumic relaxation time, ms	80 ± 24	80 ± 23	81 ± 22	81 ± 24	0.95

Values are mean ± SD; p value represents comparison of least square means at final visit following adjustment for baseline values. *p value is shown following logarithmic transformation of this highly skewed variable.
Abbreviations as in Table 1.

ventricular function. Molmen-Hansen et al. (62) compared high-intensity aerobic interval exercise with moderate intensity continuous ET and usual care in patients with essential hypertension. They reported that change in V_{O_2}peak after high-intensity interval training was 3- and 5-fold greater than moderate continuous training or usual care groups, respectively. LV systolic and diastolic function and brachial FMD improved significantly after high-intensity training but were unchanged with moderate continuous training or usual care (62). Wisloff et al. (20) showed that high-intensity aerobic interval training was superior to continuous moderate intensity ET for improving V_{O_2}peak, resting ejection fraction, and brachial FMD in older (75 years of age) men with HFREF.

We did not measure FMD or arterial stiffness (other than pulse pressure, which was unchanged; Table 2) during peak exercise, which would provide the most definitive evidence of relation to changes in V_{O_2}peak, but would be challenging. However, in studies of ET in HFPEF patients where hemodynamics were assessed at peak exercise, neither 16 weeks nor 1 year of ET produced a change in peak exercise or reserve pulse pressure/stroke volume ratio, a measure of arterial stiffness (10,43).

There were more dropouts in the ET than the CT group; however, the number of evaluable patients at the end of the study was within our sample size estimates. Furthermore, among those who completed the study, key baseline variables were similar in ET and CT participants. Also, brachial FMD and carotid distensibility were not different at baseline between those who completed compared to dropouts.

Tissue Doppler was not measured. Thus, there may have been improvements in resting LV diastolic function following ET that were not detected.

By design, participants were stable, well-compensated outpatients who were able to participate in exhaustive exercise testing and ET. As a result, the mean BNP level was less than in patients with acute, decompensated HF. BNP levels are also known to be lower in HFPEF than in HFREF, likely due to smaller LV cavity size (63). The BNP levels are similar to other studies of stable HFPEF patients able to undergo maximal exercise testing (7,12,32,64) and are several-fold increased compared with healthy, age-matched, normal subjects (4). However, our results may not apply to patients who are sicker, poorly compensated, or less clinically stable. Further, we enrolled HFPEF patients without

Table 6 Effect of Endurance Exercise Training on Health-Related Quality of Life

	ET		CT		
	Baseline	Final	Baseline	Final	p Value
n	20	20	27	27	
SF-36					
Physical	48 ± 18	63 ± 20	50 ± 25	53 ± 27	0.03
Emotional	63 ± 30	83 ± 31	66 ± 37	62 ± 35	0.04
MLHFQ					
Physical	17 ± 8	12 ± 8	13 ± 11	11 ± 10	0.50
Emotional	6 ± 5	5 ± 4	4 ± 5	3 ± 4	0.19*
Total	36 ± 19	26 ± 19	28 ± 23	25 ± 22	0.50

Values are mean ± SD; p value represents comparison of least square means at final visit following adjustment for baseline values. *p value is shown following logarithmic transformation of this highly skewed variable.
MLHFQ = Minnesota Living With Heart Failure Questionnaire; SF = short form 36; other abbreviations as in Table 1.

known or suspected coronary, cerebrovascular, and peripheral arterial disease. Thus, we cannot exclude the possibility that ET improves arterial stiffness or endothelial function in a broader population of HFPEF patients with these comorbidities.

Conclusions

ET significantly improves V_{O_2}peak without altering brachial FMD or carotid arterial stiffness in older HFPEF patients. Combined with our previous finding that improved peripheral function (A-V_{O_2}Diff) is an important contributor to the ET-related increase in V_{O_2}peak (10), this suggests that microvascular and/or skeletal muscle adaptations may contribute to the ET-related increase in V_{O_2}peak in older HFPEF patients.

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