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Response to Endurance Exercise Training in Older Heart Failure Patients with Preserved Versus Reduced Ejection Fraction

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Abstract

Background—The CMS recently approved coverage for cardiac rehabilitation for stable outpatients with HF with reduced ejection fraction (HFrEF), but denied coverage for patients with HF with preserved EF (HFpEF). However, the relative magnitude and predictors of responses to exercise training have not been systematically examined among older patients with these two main HF subtypes.

Methods—The study included individual-level data from the exercise training arms of a randomized controlled trial that evaluated the effect of 16-weeks of supervised moderate intensity endurance exercise training in older patients with chronic, stable HFpEF and HFrEF. The changes

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in peak oxygen uptake (VO_{2peak}) in response to supervised training were compared among HFpEF vs. HFrEF patients. The significant clinical predictors of changes in VO_{2peak} with exercise training were assessed using univariate and multivariate regression models.

Results—Subjects were 48 HF patients (24 HFrEF and 24 HFpEF) who underwent supervised exercise training. Training related improvement in VO_{2peak} was higher in HFpEF vs. HFrEF patients (% change: 18.7 ± 17.6 vs. -0.3 ± 15.4 ; p-value: <0.001). In univariate analysis, echocardiographic abnormalities in LV structure and function and lower BMI were associated with blunted response in VO_{2peak} with exercise training. In multivariate regression analysis using stepwise selection, submaximal exercise systolic blood pressure and resting early deceleration time were independent predictors of change in peak VO_2 .

Conclusions—The change in VO_{2peak} in response to endurance exercise training in older patients with HF differs significantly by HF subtype, with greater VO_{2peak} improvement in HFpEF vs. HFrEF patients. These results suggest that the current CMS policy excluding HFpEF patients from reimbursement from cardiac rehabilitation may need to be revisited.

Introduction

Heart failure (HF) is associated with high morbidity and mortality, poor quality of life, and high cost of care. (1,2) It is particularly common in the older population, in whom its prevalence is growing and is the leading cause of hospitalization. (3,4) Exercise intolerance, measured objectively as decreased peak exercise oxygen uptake (VO_{2peak}), is the primary manifestation of chronic HF, and is a strong determinant of prognosis. (5–8) Multiple studies have shown that exercise training can improve VO_{2peak} in HF patients. However, there are fewer data regarding the effect of exercise training specifically in older patients, and particularly in patients with HF with preserved ejection fraction (HFpEF), the most common form of HF in older persons, compared with HFrEF.

Previous studies have demonstrated considerable heterogeneity in the response to exercise training in healthy individuals and in patients with risk factors for HF. (9–12) However, there are relatively few data in this regard in older patients with established HF. Further, to our knowledge, the patterns and clinical predictors of response in VO_{2peak} to training have not been examined among older patients with HFpEF versus HFrEF. This is particularly relevant considering the high burden of exercise intolerance and cardiac structural and functional abnormalities in this patient population, as well as the increasing role of exercise training for management of chronic HF.

Therefore, in this study, we sought to characterize the variability in VO_{2peak} response to supervised endurance exercise training among older patients with HFpEF and HFrEF. We also determined the significant predictors of VO_{2peak} change in response to endurance exercise training among patients with HFpEF and HFrEF.

Methods

Study population

We examined individual-level data from a prospective, randomized, blinded, attention controlled trial of facility-based, supervised endurance exercise training in patients aged 65 years and older in which randomization was stratified by HFpEF vs. HFrEF.(13–15) Detailed descriptions of the screening, recruitment, inclusion and exclusion criteria, and methods of the trial, and the main outcomes of each of the two stratification arms (HFpEF, HFrEF) have been reported previously.(13,15) Briefly, chronic, well-compensated HF patients on a stable medication regimen for 6 weeks or more were recruited from review of inpatient and outpatient records. HF was defined using clinical criteria from NHANES-1 and the criteria described by Rich, et al.(16,17) HFpEF was defined based on presence of clinical HF with preserved ejection fraction (EF >50%) and no evidence of a significant medical condition that could mimic HF symptoms.(13,14) HFrEF was defined based on presence of clinical HF and reduced ejection fraction (EF <45%).(15) Patients with significant valvular disease, recent stroke or myocardial infarction, uncontrolled diabetes or hypertension, known cancer diagnosis, significant renal impairment, dementia, non-compliance or any chronic condition that limited participation in exercise training were excluded. For the present analysis, which examined training response and its determinants, the two randomized strata (HFpEF and HFrEF) were combined, with each containing two treatment groups: an attention control group and an exercise group. We found a highly significant interaction between treatment group and HF category ($p=0.006$), therefore, all analyses were completed using participants randomized to the exercise groups only. The Wake Forest institutional review board approved the study protocol, and written informed consent was obtained from all the study participants.

Cardiopulmonary Exercise Testing

Upright cycle ergometer exercise testing with expired gas-exchange analysis was performed at baseline and follow-up using previously reported protocols. Breath-by-breath gas exchange data were averaged for the last 30 seconds of the exercise test to determine the peak values. Ventilatory anaerobic threshold was determined using standardized protocol. A six-minute walk test was also performed at baseline and end of training period using a standard protocol.(5) As reported previously, the mean respiratory exchange ratio, a measure of exercise effort, was high (> 1.1) for both HFpEF and HFrEF groups during the baseline and follow-up exercise testing.(13,15)

Echocardiographic examination

Resting 2D and Doppler echocardiographic examination was performed during supine rest as reported previously to obtain standard 2-dimensional images in the parasternal long-axis and parasternal short-axis, the apical 2 chamber and apical 4 chamber views.(13,15) Left ventricular volumes were determined using a digital workstation by individuals blinded to the study group assignment.

Endurance Exercise Training

The training participants underwent supervised exercise training 3 times a week for 16 weeks as reported previously.(13–15) Each exercise training session was 1 hour long and consisted of warm-up, stimulus, and cool-down phases. The stimulus phase included walking on a track and lower extremity cycling, and the exercise intensity was gradually increased from 40 to 50% of heart rate reserve in the first 2 weeks to 60–70% over the next several weeks. The duration of exercise on each training mode was also increased gradually to achieve the target duration of 15 to 20 minutes each of walking and cycling. The training protocols used in the HFpEF and HFrEF exercise training groups were identical.(13,15) As reported previously, the adherence to exercise training among HFpEF and HFrEF patients was high. In the HFpEF group patients in the exercise training arm attended an average of 43 of the assigned 48 sessions.(13) Similarly, in the HFrEF group the exercise training patients attended an average of 45 sessions.(15)

Statistical Analysis

The primary outcome for assessing change in exercise capacity was the percent change in VO_{2peak} (ml/kg/min) from baseline to end of exercise training (16-week follow-up). Mean changes in VO_{2peak} , exercise time, six-minute walk distance, and ventilatory anaerobic threshold were compared among HFpEF vs. HFrEF groups using the t-test. The proportion of exercising HFpEF and HFrEF participants with 5% and 10% improvement in these measures was also compared using the chi-square test.

The significant clinical predictors of changes in VO_{2peak} with exercise training were assessed using data from both groups. Associations of changes in VO_{2peak} with dichotomous and categorical ordinal variables were tested by the t-test and trend test respectively with mean and standard error of each level given. Associations between changes in VO_{2peak} with continuous variables were summarized and tested for significance by the correlation coefficient. The test of associations was done for the overall study population and separately for HFpEF and HFrEF. A test for interaction between HF type and the clinical variables was also performed. A multivariate linear regression model was also constructed using stepwise selection considering all the variables that were significant in univariate analyses. All tests were made at the 5% two-sided level of significance.

Results

The study population included 48 HF patients (24 HFrEF and 24 HFpEF) who underwent 4-months of supervised exercise training. Table 1 provides the baseline characteristics of the combined study population as well as for each HF subtype. The groups were well matched for most variables, except for a higher frequency of women in the HFpEF group, as expected based on population demographics, and EF, by design. The proportion of participants with New York Heart Association (NYHA) class III symptoms was numerically higher in the HFrEF vs. HFpEF group. However, this difference was not statistically significant. Similarly, the baseline exercise capacity as assessed by multiple measures was not different between the two groups. Among echocardiographic characteristics, normal diastolic filling pattern was present in 23% of HFpEF participants. This observation is consistent with that

previously reported in other large randomized controlled trials with well-characterized HFpEF patients.(18–20)

Table 2 compares the changes in measures of exercise capacity. Overall in both groups combined, endurance training was associated with 9.2% increase in $\text{VO}_{2\text{peak}}$ (ml/kg/min) with substantial individual-level variability in the change in response to training (Figure 1). Among HF subtypes, the improvement in $\text{VO}_{2\text{peak}}$ in response to training was considerably higher in HFpEF vs. HFrEF patients (18.7 ± 17.6 vs. $-0.3 \pm 15.4\%$; $p < 0.001$, Table 2, Figure 2). A similar pattern was observed with absolute $\text{VO}_{2\text{peak}}$ (ml/min, Table 2, Figure 2). The proportion of patients with $> 5\%$ and $> 10\%$ improvement in $\text{VO}_{2\text{peak}}$ (ml/kg/min) was also significantly higher in HFpEF vs. HFrEF patients (75% vs. 33.3%, p -value 0.004 for $> 5\%$ improvement & 66.7% vs. 29.2%, p -value = 0.009 for $> 10\%$ improvement). Similar patterns of improvement were also observed in absolute $\text{VO}_{2\text{peak}}$ (ml/min) among HFpEF vs. HFrEF patients. Training-related increases in other measures of exercise capacity, including exercise time and ventilatory anaerobic threshold, were also greater in HFpEF vs. HFrEF patients, with trends towards statistical significance (Table 2, Figure 2). In contrast, the change in six-minute walk distance was not significantly different between the two groups (Table 2, Figure 2).

Results of the univariate analyses evaluating the clinical and demographic predictors of the change in $\text{VO}_{2\text{peak}}$ with exercise training in the overall HF as well as for HFpEF and HFrEF patients are shown in supplemental Tables S1,S2. For overall HF, higher body mass index was significantly associated with greater improvements in $\text{VO}_{2\text{peak}}$ in univariate analyses. Other baseline characteristics such as age, sex, ethnicity, and resting blood pressure were not associated with exercise training related changes in $\text{VO}_{2\text{peak}}$. Among resting echocardiographic characteristics, smaller left ventricular volumes, higher ejection fraction, lower baseline LV mass, and higher deceleration time were each associated with greater improvements in $\text{VO}_{2\text{peak}}$ (Supplemental Table S3). For HF subtypes, no significant interaction was observed between participant characteristics and HF type (HFpEF vs. HFrEF) for the change in $\text{VO}_{2\text{peak}}$. Thus, differential response in $\text{VO}_{2\text{peak}}$ to exercise training among HFpEF and HFrEF groups was not related to differences in baseline clinical characteristics. In the multivariate linear regression model using stepwise selection for variables shown to be significant in univariate analyses, submaximal systolic blood pressure ($p=0.008$) and deceleration time ($p=0.040$) were found to be independent predictors of change in $\text{VO}_{2\text{peak}}$. Similar results were also observed in sensitivity analysis evaluating the significant clinical predictors of changes in absolute $\text{VO}_{2\text{peak}}$ (ml/min).

Discussion

In this study we observed that training-related improvement in $\text{VO}_{2\text{peak}}$ varied substantially by HF type with considerably greater improvements in HFpEF vs. HFrEF patients. To our knowledge, the present study is the first to directly compare, in a single study and with randomized assignment and blinding of outcomes, the $\text{VO}_{2\text{peak}}$ response to training in older patients with HFpEF and HFrEF, and assess predictors of training response. These results are important because exercise intolerance is the primary symptom in chronic HF, the reduction in exercise capacity is particularly severe in older patients, and because exercise

training is one of the few interventions shown to improve this outcome in HFpEF, the most common form of HF in older patients.

We observed that patients with HFpEF had a greater average increase in $\text{VO}_{2\text{peak}}$ with a higher proportion of clinically meaningful improvement ($> 5\%$ and $> 10\%$) as compared with HFrEF. This observation was consistent across different cutoffs for meaningful $\text{VO}_{2\text{peak}}$ response despite use of identical exercise training regimens and high rates of adherence in the two groups. The relative lack of improvement in $\text{VO}_{2\text{peak}}$ with exercise training among older HFrEF patients in our study is supported by the results of the HF-ACTION trial, the largest randomized trial of exercise training in HFrEF, that demonstrated only a 4% increase in $\text{VO}_{2\text{peak}}$ after 3 months of supervised exercise training. Of note, this is below the 6–10% improvement in $\text{VO}_{2\text{peak}}$ that is generally accepted as clinically meaningful. This $\text{VO}_{2\text{peak}}$ outcome was not blinded in HF-ACTION and the cohort was considerably younger (mean age 59 years vs. 69 years in our study population).(21) In contrast to these findings in older HFrEF patients in our study and in the HFrEF patients in HF-ACTION, we observed a more robust and significant improvement in $\text{VO}_{2\text{peak}}$ with exercise training among older HFpEF patients.(22)

Patterns of improvement in other objective, independent measures of exercise capacity, including exercise time and ventilatory anaerobic threshold, were relatively similar to $\text{VO}_{2\text{peak}}$ among HFpEF vs. HFrEF patients, thereby supporting the internal validity of our study findings. Changes in six-minute walk distance were not significantly different between the two study groups. Notably, $\text{VO}_{2\text{peak}}$ is a reliable, ‘gold standard’ measure of maximal exercise capacity and has been demonstrated to have minimal learning effect. (23) In contrast, other measures such as six-minute walk distance may be influenced by learning effect from one test to the next. Furthermore, participants are not pushed to an exhaustive exercise endpoint in six-minute walk distance and the variability in speed may significantly influence the outcome.

The potential mechanisms underlying the differential $\text{VO}_{2\text{peak}}$ improvement among HFpEF vs. HFrEF patients are not well understood. Abnormal LV remodeling and higher LV mass are associated with blunted $\text{VO}_{2\text{peak}}$ response to training.(24) It is possible that HFrEF patients with higher burden of LV remodeling may not be able to adapt to exercise as well with favorable physiological changes in cardiac performance. In contrast, up to 40%–60% of HFpEF patients often have normal LV structure and cardiac function without LV hypertrophy or abnormal remodeling, which may make them more amenable to the physiological adaptations of exercise training. (20,25) Similarly, differential skeletal muscle response to exercise training may also explain some of the observed differences in $\text{VO}_{2\text{peak}}$ improvement in HFpEF vs. HFrEF.(26) Future mechanistic studies are needed to test these hypotheses.

In multivariate regression analysis, we identified submaximal systolic blood pressure and early LV deceleration time as significant independent predictors of $\text{VO}_{2\text{peak}}$ improvement with endurance exercise training, such that a higher systolic blood pressure and shorter early LV deceleration time were associated with blunted $\text{VO}_{2\text{peak}}$ response to training in HF

patients. Both of these factors may be associated with VO_2 response through their effect on stroke volume reserve.

Our study may have clinical implications. Several randomized controlled trials have failed to demonstrate an improvement in mortality among patients with HFpEF with use of available pharmacological interventions. (27–29) However, some studies have shown improved symptoms, hospitalizations, and/or quality of life.(27–30) Specifically, exercise training has been shown to improve quality of life, and potentially reduce hospitalizations among patients with HFrEF as well as HFpEF. (21,22,31) However, the Center for Medicare & Medicaid Services (CMS) recently approved expansion of coverage for cardiac rehabilitation in chronic, stable HFrEF but not HFpEF, thus effectively excluding the majority of older HF patients.(32) Our study findings provides strong evidence in favor of incorporating cardiac rehabilitation and exercise training as a therapeutic strategy for management of HFpEF, similar to HFrEF, and may help provide impetus for CMS to revise their reimbursement policy in the future.

Our study has several key advantages. It included only older patients, allowing examination of the relevant hypotheses specifically in this important and previously under-studied HF group. The HFpEF and HFrEF patients were enrolled in the trial at the same time, using identical method, personnel, equipment, and facilities for exercise testing and training, and the personnel assessing outcomes were blinded to randomization group thereby enhancing the validity of intergroup comparisons. The participants were well phenotyped with detailed clinical, echocardiographic, and cardiopulmonary exercise testing.

Our study also has several important limitations. First, the training protocol included only continuous, moderate-intensity exercise, and the $\text{VO}_{2\text{peak}}$ response may be different for other modes or intensity of exercise training. Second, we did not adjust for multiple comparisons in our study, so our findings may be viewed as hypothesis generating in need of confirmation in future studies. Finally, the percentage of beta-blocker usage was relatively low in the HFrEF group. This is likely due to the fact that the patients were elderly and had multiple co-morbidities. In addition, the study was conducted when beta-blockers were in the early phase of becoming standard therapy in patients with HFrEF. However, this enhances confidence in our findings of a training differential between HFpEF and HFrEF, since the medication profiles were fairly similar between groups.

In conclusion, $\text{VO}_{2\text{peak}}$ change in response to supervised moderate intensity endurance exercise training in older patients with HF varies by HF subtype, with greater peak VO_2 improvement in HFpEF vs. HFrEF patients. These results suggest that the current CMS policy excluding HFpEF patients from reimbursement from cardiac rehabilitation, in contrast to HFrEF, may need to be revisited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 2. Individual-level and mean changes in different measures of (A) exercise capacity (indexed and absolute peak exercise oxygen uptake) (B) exercise time and six-minute walk distance and (C) ventilatory anaerobic threshold with exercise training from baseline to follow-up among HFpEF and HFrEF patients.

Table 1

Baseline Characteristics of the study participants

Variable	All (n=48)	HFpEF (n=24)	HFReEF (n=24)	p-value
Demographics				
Age, years	69.6 ± 5.5	70.0 ± 6.4	69.3 ± 4.5	0.68
Women	28 (58%)	20 (83%)	8 (33%)	0.001
White	39 (81%)	21 (88%)	18 (75%)	0.46
Height, in.	65.8 ± 4.1	64.0 ± 3.5	67.6 ± 3.9	0.002
Weight, lbs.	173.5 ± 34.0	174.3 ± 36.1	172.8 ± 32.5	0.88
BMI, kg/m ²	28.3 ± 5.6	29.9 ± 5.9	26.7 ± 4.9	0.047
Cardiovascular Measures, Comorbidities, and Medications				
NYHA Class				
II	26 (54%)	15 (62%)	11 (46%)	0.39
III	22 (46%)	9 (38%)	13 (54%)	
Ejection Fraction, %	46 ± 17	60 ± 5	31 ± 10	<0.001
LV mass, g	196.5 ± 64.5	160.6 ± 34.3	244.3 ± 65.0	<0.001
LV Mass, g/m ² *	105.6 ± 33.4	87.0 ± 16.6	130.4 ± 34.3	<0.001
Diastolic Filling Pattern				
Normal	5 (13%)	5 (23%)	0 (0%)	0.016
Impaired Relaxation	25 (64%)	15 (68%)	10 (59%)	
Pseudonormal	9 (23%)	2 (9%)	7 (41%)	
B-type natriuretic peptide, pg/ml	121.0 ± 174.9	43.7 ± 55.7	209.2 ± 220.0	0.003
History of diabetes mellitus	7 (26%)	2 (13%)	5 (45%)	0.084
History of hypertension	33 (80%)	20 (87%)	13 (72%)	0.27
Resting Blood Pressure				
Systolic, mmHg	143 ± 22	148 ± 20	138 ± 23	0.11
Diastolic, mmHg	80 ± 9	82 ± 7	78 ± 11	0.11
Current Medications	43 (91%)	20 (83%)	23 (100%)	0.11
Diuretics	30 (65%)	10 (42%)	20 (91%)	<0.001
ACE Inhibitors	26 (55%)	8 (33%)	18 (78%)	0.003
Beta Blockers	9 (20%)	7 (29%)	2 (9%)	0.14
Calcium Channel Blockers	14 (30%)	11 (46%)	3 (13%)	0.024
Exercise Capacity				
Peak VO ₂ , ml/min	1085.2 ± 289.0	1073.1 ± 255.0	1097.3 ± 324.6	0.77
Peak VO ₂ , ml/kg/min	13.8 ± 2.8	13.8 ± 2.5	13.9 ± 3.0	0.87
Peak RER	1.13 ± 0.11	1.12 ± 0.09	1.14 ± 0.12	0.43
Ventilatory anaerobic threshold	727.7 ± 152.9	741.7 ± 147.3	713.1 ± 160.9	0.55
Exercise Time, minutes	6.64 ± 2.51	6.80 ± 2.25	6.46 ± 2.81	0.65
6-Minute Walk Distance, feet	1486 ± 272	1506 ± 226	1466 ± 314	0.62

Data are presented as Mean $\pm$ SD, or number (%).

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; BMI, body mass index; NYHA, New York Heart Association; LV, left ventricle; ACE, angiotensin-converting enzyme; RER, respiratory exchange ratio.

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Table 2

Changes in measures of exercise capacity with training

Variable	All (n = 48)	HFpEF (n = 24)	HFrEF (n = 24)	P-value HFpEF vs. HFrEF
Peak VO ₂ (ml/kg/min)				
Absolute change	1.2 ± 2.4	2.3 ± 2.2	0.1 ± 2.0	<0.001
% Change	9.2 ± 19.0	18.7 ± 17.6	-0.3 ± 15.4	<0.001
Peak VO ₂ (ml/min)				
Absolute change	97.5 ± 187.7	186.2 ± 182.9	8.9 ± 148.9	<0.001
% Change	9.1 ± 18.6	18.2 ± 17.3	-0.0 ± 15.3	<0.001
Exercise Time (min)				
Absolute change	1.2 ± 1.4	1.4 ± 1.6	0.9 ± 1.1	0.20
% Change	21.8 ± 32.9	29.3 ± 42.0	13.6 ± 16.0	0.10
Six-minute Walk Distance (feet)				
Absolute change	150.2 ± 206.3	170.2 ± 237.3	130.2 ± 173.3	0.53
% Change	11.4 ± 16.7	13.5 ± 20.8	9.3 ± 11.4	0.41
Ventilatory Anaerobic Threshold				
Absolute change	65.2 ± 115.1	93.8 ± 108.2	35.2 ± 117.1	0.096
% Change	9.3 ± 17.0	13.6 ± 15.5	4.8 ± 17.7	0.091

Data are presented as Mean ± SD.