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Exercise Training Effects on the Relationship of Physical Function and Health-Related Quality of Life Among Older Heart Failure Patients with Preserved Ejection Fraction

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Abstract

Purpose: Although exercise training (ET) has been shown to improve both physical function and health-related quality of life (HRQOL) in older patients with heart failure and preserved ejection fraction (HFpEF), the relationship between changes in these important patient-centered outcome measures has not been adequately investigated.

Methods: Patients (n=116) with HFpEF (from two previous randomized controlled trials) were assigned to either 16-wk of endurance exercise training (ET) or attention-control (CON). The ET in both trials consisted of up to 60 min of moderate-intensity endurance ET 3 times/wk. Peak exercise oxygen uptake ($\text{VO}_{2\text{peak}}$), and other exercise capacity measures were obtained from a cardiopulmonary exercise test on an electronically-braked cycle ergometer and 6 min walk test (6MWT). HRQOL was assessed using the Minnesota Living with Heart Failure (MLHF) Questionnaire and the Short Form Health Survey (SF-36).

Results: Compared to CON, the ET group demonstrated significant improvement in measures of physical function ($\text{VO}_{2\text{peak}}$ and 6MWT) at 16 wk of follow-up. There were no significant differences observed between the groups for MLHF scores, but the ET group showed significant improvements on the SF-36. There were no significant correlations between change in any of the physical function and HRQOL measures in the ET group.

Conclusions: While endurance ET improved both physical function and some domains of HRQOL, the lack of significant correlations between changes in these measures suggests the effects of ET on physical function and HRQOL are largely independent of one another. Since these measures assess important and unique patient-centered outcomes in HFpEF patients, both physical function and HRQOL should be assessed in exercise-based programs and clinical trials.

Condensed Abstract

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Conflicts of Interest: None

Endurance exercise training improved both physical function measures and some domains of health-related quality of life (HRQOL) in older heart failure and preserved ejection fraction (HFpEF) patients, but the lack of significant correlations between the change in these measures in the ET group suggests they assess different patient-centered outcomes. Thus, both physical and HRQOL should be evaluated in HFpEF exercise-based programs and clinical trials.

Keywords

HFpEF; exercise capacity; cardiac rehabilitation; psychosocial

Approximately 6.5 million American adults are estimated to have chronic heart failure (HF) and the prevalence of this condition is projected to increase 46% by 2030.^{1,2} At least 50% of these patients have HF with preserved ejection fraction (HFpEF) and this phenotype is more common in older individuals, women, and those with a history of hypertension, obesity and anemia.^{3,4} In addition to preventing hospitalization and maximizing survival in patients with HF, an important goal is to improve the health status of these patients, particularly physical function and health related quality-of-life (HRQOL).^{5,6} Assessing these patient-centered outcomes is especially important in patients with HFpEF as the older age and increased non-cardiovascular comorbid burden of these patients appear to reduce efficacy of pharmacotherapies.⁷⁻⁹

Exercise intolerance, manifested as severe exertional dyspnea and fatigue, is a hallmark of chronic HFpEF.¹⁰⁻¹² While most pharmacotherapies have been ineffective at improving clinical endpoints,¹³⁻¹⁵ endurance exercise training (ET) has been shown to improve measures of physical function, including peak exercise oxygen uptake ($\text{VO}_{2\text{peak}}$) and six minute walk test (6MWT) distance in HFpEF patients.¹⁶⁻²¹ Due to the presence of chronic symptoms and physical impairments, HFpEF patients also commonly report reduced HRQOL compared to healthy individuals.²²⁻²⁴ Endurance ET typically results in improved HRQOL in HFpEF patients, yet conflicting findings have been reported,²⁵ possibly due to the variability in instruments used to assess this patient reported outcome. Although not well validated in patients with HFpEF, the disease-specific Minnesota Living with Heart Failure (MLHF) and Kansas City Cardiomyopathy Questionnaire (MCCQ), as well as the more general 36-item Short Form Health Survey (SF-36), are commonly used to assess HRQOL in this population.^{26,27} Regardless of the instrument used, it's widely believed that an increase in physical function will result in improvement in HRQOL in patients with chronic disease conditions such as HFpEF. While several cross-sectional studies have reported significant, albeit moderate strength, correlations ($r=0.30-0.58$), between physical function and HRQOL measures in HFpEF patients,²³⁻²⁵ the relationship of these important patient-centered outcomes in response to endurance ET has not been examined in this unique and important patient population.

Therefore, the purpose of this study was to determine the effect of endurance ET on the relationship between physical function and HRQOL among patients with HFpEF. If the common assumption is valid, endurance ET induced changes in physical function will be significantly associated with changes in HRQOL measures in these patients.

METHODS

The study protocol was approved by the Wake Forest School of Medicine Institutional Review Board. During a screening visit, written informed consent was obtained and participants were familiarized with the testing environment and procedures. Baseline patient-centered outcome measures of physical function and HRQOL were obtained in a single subsequent visit by an individual blinded to group assignment and other clinical information. Participants were then randomized using Statistical Analysis Software v.94 (SAS Institute) into either 16 wk of ET or attention-control (CON). All outcome measures were reassessed in a similar fashion following the 16-wk intervention.

PARTICIPANTS

Participants in this investigation were from two National Institutes of Health-funded trials of ET in older patients with chronic, stable HFpEF for which the primary outcomes have been previously reported.^{16,17} As previously described in these studies, all prospective participants for these investigations were interviewed and examined by a board-certified cardiologist and met the following inclusion criteria: 60 yr of age; signs and symptoms of HF, as defined by National Health and Nutrition Examination Survey score of 3,²⁸ the criteria of Rich et al.,²⁹ or both; left ventricular (LV) EF 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. Participant characteristics are provided in Table 1.

PHYSICAL FUNCTION

Cardiopulmonary exercise testing with expired gas analysis was performed on an electronically braked cycle ergometer, with appropriate electrocardiogram (ECG) and blood pressure monitoring. Subjects started at an initial workload of 12.5 Watts (W) for 2 min, followed by incremental stages beginning at 25W and increasing thereafter by 25W every 3 min until the subject reached severe fatigue, exhaustion, or dyspnea. Upon test completion, subjects assumed a supine position in order to obtain immediate recovery data.

Breath-by-breath expired gas analysis was performed using the MedGraphics CPX/D system (Minneapolis, MN). $\text{VO}_{2\text{peak}}$ and ventilatory anaerobic threshold (VAT) were determined by an individual blinded to group assignment. VAT was determined using the V-Slope method as previously reported.³⁰ $\text{VO}_{2\text{peak}}$ was determined by averaging breath-by-breath data (expressed in 15 sec intervals) over the last 60 sec of exercise.

A 6MWT was performed as described by Guyatt.³¹ Patients were instructed to walk at their own pace around an indoor track or hospital corridor with the intent of covering as much ground as possible in 6 min. Patients were allowed to slow or stop and rest during the walk, but were instructed to resume walking when recovered. No encouragement was given during the test. Distance-walked was measured to the nearest meter.

HEALTH-RELATED QUALITY OF LIFE

The disease-specific MLHF was used to assess the effect of HF on a subject's well-being. This measure includes 21 questions and produces a total score, as well as emotional and physical subscale scores. Scores range from 0 – 100, with lower scores indicating better HRQOL, or less limitation due to HF (33).

The standardized SF-36 was used as a generic index of HRQOL (33). The SF-36 produces two broad composite scale: physical health and mental health. Physical health includes subscales for physical functioning, role-physical, bodily pain, and general health, whereas mental health has subscales for vitality, social functioning, role-emotional, and emotional health. Scores range from 0–100, with higher scores indicating higher levels of HRQOL.

ENDURANCE EXERCISE TRAINING

As previously described subjects randomly assigned to endurance ET participated in three 1-hr exercise sessions/week for 16 wk.^{16,17} These participants were strongly encouraged to complete all 48 ET sessions and make-up sessions were offered. Each training session consisted of a 5 min warm-up, a 40 min stimulus phase, and a 10 min cool-down with stretching. The stimulus phase included walking on an indoor track and Schwinn Airdyne cycle ergometry for up to 20 min each. During the first 2 wk, patients exercised at 40–50% of heart rate reserve (HRR) while gradually increasing exercise time on each of the two modes from 5–10 min to 10–15 min. Over the following 2 wk, most subjects increased intensity to 60% HRR and exercise duration to 15–20 min for each training mode.

ATTENTION CONTROL

Participants randomized to the attention CON were instructed not to modify their physical activity levels during the 16 wk study period received. Control participants did receive bi-monthly telephone calls during the intervention in order to enhance compliance with follow-up testing and track medical events.

STATISTICAL ANALYSIS

SPSS v25.0 statistical software (SAS Institute) was used for all analyses. Statistical significance was set at $P < .05$ with familywise adjustment for multiplicity. Thus, the physical function measures, the composite scales for the HRQOL measures, and the subscales of the HRQOL measures are treated as three separate groupings, adjusting the p -values within each family grouping with a Bonferroni adjustment to maintain a $P < .05$ within each group. Baseline comparisons were made using independent t -tests for continuous data, Fisher's exact tests for dichotomous data, and chi-square tests for categorical data.

Analysis of covariance (ANCOVA) was used for group comparisons on the variables of interest (physical function and HRQOL measures) in order to control for observed baseline differences, sex, and age. Pearson correlation coefficients were used to examine the relationship between changes in physical function and HRQOL measures in the ET group only.

RESULTS

There were no significant differences in participant characteristics between the two studies, thus the two studies were combined for statistical analyses examining differences by those randomly assigned to either an ET or CON treatment. In accord with the general HFpEF population, the study cohort was predominantly female (81%). The only significant difference at baseline between ET and CON groups was in body mass index (BMI), however this did not influence the outcome measures of physical function or HRQOL measures.

INTERVENTION SAFETY, COMPLIANCE, AND ADHERENCE

No serious adverse events occurred as a result of the ET intervention. Ninety-nine of 116 (85%) participants (48 ET, 51 CON) completed final testing. Reasons for not completing follow-up testing included non-HF illness (5 ET, 3 CON), unwillingness to return for testing (2 ET, 1 CON), lost to follow-up (3 CON), elective surgery (2 ET), and HF hospitalization (1 ET). Participants in the ET group completed 88% of the scheduled exercise training sessions.

PHYSICAL FUNCTION MEASURES

The unadjusted mean differences and least-squared means for physical function measures are shown by treatment condition in Figure 1 and Table 2, respectively. The ET group had significant increases in VO_{2peak} , VAT, 6 MWT and peak exercise test workload as compared to CON ($P < .001$), an effect that remained statistically significant after adjustment for multiplicity.

HEALTH-RELATED QUALITY OF LIFE

The unadjusted mean differences and least-squared means for HRQOL measures are shown by treatment condition in Figure 2 and Table 3, respectively. There were no significant differences, before or after adjustment for multiplicity, on MLHF scores between ET and CON, despite a clinically meaningful decrease of 8 points (reflecting improved HRQOL) on the MLHF total score. In contrast to CON, ET had significantly higher SF-36 physical composite ($P = .03$), role physical ($P = .006$), and vitality ($P = .001$) scores at follow-up, effects that remained statistically significant after adjustment for multiplicity. There were no differences between the groups on the SF-36 related to mental health sub-scores.

ASSOCIATION OF PHYSICAL FUNCTION AND HRQOL CHANGES

As shown in Table 4, all of the correlation coefficients between key physical functional and HRQOL changes in ET were small and indicated there were no significant associations between changes in VO_{2peak} and HRQOL after ET.

RESPONDERS ANALYSIS

We performed a final analysis of responders (increase in VO_{2peak} $\geq 10\%$ from baseline to follow-up, $n=26$) versus non-responders ($< 10\%$ increase VO_{2peak} from baseline to follow-up, $n=17$) in the ET group. As shown in Table 5, there are no significant differences in the

adjusted means for any of the HRQOL measures between the responder and non-responder groups.

DISCUSSION

Endurance ET is known to result in improvements in physical function measures and generally, but not as consistently, HRQOL measures in patients with HFpEF.^{16–21} While it's often assumed that temporal changes in these patient-centered outcome measures are highly correlated, this has never been systematically examined in HFpEF patients. This is the first investigation to examine that the relationships between changes in physical function measures (i.e. VO_{2peak} and 6MWT) and HRQOL measures after endurance ET in patients with HFpEF. Contrary to our a priori assumption, our findings suggest that changes in physical function and HRQOL measures are relatively independent of each other during endurance ET and consequently represent unique, distinct patient-centered outcomes.

PHYSICAL FUNCTION OUTCOMES

Patients with HFpEF have severely reduced levels of physical function, commonly measured by VO_{2peak} and/or 6MWT, that is comparable to patients with HF with reduced EF (HFrEF) and ~ 50% lower than healthy-aged matched subjects (33). Endurance ET generally results in ~15–20% improvements in VO_{2peak} and 6MWT distance in older patients with HFpEF.^{16,17,19,20} The improvement in exercise capacity in HFpEF patients is the result of a multiple of physiological adaptations that translate into increased activities of daily living and reduced symptoms. The predominance of aforementioned studies has produced these physiologic adaptations in patients with HFpEF by using traditional ET interventions that includes moderate intensity-continuous endurance training (MICT). Of interest, one small pilot study has shown that high-intensity interval training (HIIT) can produce comparable, if not superior, benefits in HFpEF patients.³⁴ Assessing the safety and efficacy of HIIT versus MICT in older HFpEF warrants further investigation before recommending for clinical practice. Moreover, we have recently demonstrated the synergistic effect of endurance ET and prescribed weight loss through a caloric reduction, on physical function measures in older overweight HFpEF patients.³⁵

HEALTH-RELATED QUALITY OF LIFE OUTCOMES

The effects of endurance ET on HRQOL measures has been generally favorable in HFpEF, but less consistent, than physical function outcomes.^{36–38} Although the present study, with a moderate sized sample of patients, found a rather large and clinically meaningful difference (CMD) of 8 points in MLHF total score in the ET group, the difference between groups did not reach statistical significance. The ET group did however demonstrate greater improvements in the SF-36 physical function score. Although ET and CON did not differ after ET in the SF-36 mental health composite scale, the ET group did experience significantly greater improvement in vitality than CON, which is important given the role that fatigue plays in the lives of HFpEF patients.

While most ET studies in patients with HFpEF have shown significant improvement in some dimensions of the disease-specific MLHF measures, few studies have examined the effect of

ET with a general QOL instrument. To assess general QOL in the present investigation, we used the standard and widely accepted SF-36 instrument.³⁹ Unlike physiologic adaptations, the mechanisms mediating change in HRQOL, secondary to an ET intervention, are not well understood but warrant further investigation as maximizing improvement in these important patient-centered outcomes is imperative.

RELATIONSHIP BETWEEN PHYSICAL FUNCTION AND HRQOL OUTCOMES

Several studies have examined relationships between physical function and HRQOL at baseline and found significant albeit moderate strength ($r=0.30 - 0.58$), correlations between physical function and HRQOL measures in patients with HFpEF in cross sectional analyses.²⁴⁻²⁸ However, to our knowledge, none have examined the relationship between changes in physical function and QOL following ET. This is important since ET is, to date, the only intervention proven to improve the severely reduced exercise capacity and HRQOL (albeit less consistently) in HFpEF. Thus, it is important to understand these relationships in order to potentially develop other interventions to improve both of these two patient oriented outcomes. Even though variables may be correlated at baseline, doesn't ensure that changes subsequent to an ET intervention will be correlated. Thus, it was important to test the common assumption that improvements in physical function will lead to improvements in HRQOL. Chronic disease populations, including patients with HFpEF, it's commonly assumed that improvements in physical function will lead to improvements in HRQOL, particularly those representing the physical domains. However, in current study there were no meaningful relationships between change in the physical function and HRQOL measures suggesting these patient-center outcomes measures are independent. Potential mediators for changes in physical function and vitality include improvement in self-efficacy, satisfaction with physical function and enhancing in social functioning.⁴⁰⁻⁴² These findings highlight the need for multi-component interventions, including focal behavioral strategies that optimize both the physical and HRQOL related benefits of lifestyle related intervention, for patients with HFpEF.

While the present investigation is the first to investigate the relationship between changes in physical function and HRQOL in patients with HFpEF undergoing endurance ET, at least one study has evaluated this issue in HFrEF patients. Nilsson et al. found a significant, yet moderate, inverse correlation that was larger than the present investigation ($r = -0.49$ vs. 0.13) between change in MLHF total score (where a lower score reflects better HRQOL) and change in 6MWT in HFrEF.⁴³ There are several important difference between Nilsson et al. and the present investigation including; differences in HF phenotype (HFrEF vs. HFpEF), age, race, and sex of the participants (younger white men versus older black women), and the prescription of ET (HIIT versus MICT).

In a study that combined, but did not differentiate between HFrEF and HFpEF patients ($n=51$), Smart et al.²¹ reported that measures of HRQOL were not significantly correlated with the magnitude of change in VO_{2peak} . Nolte, et al.²⁷ reported a significant, yet weak ($r=0.29$) between change in VO_{2peak} and change in SF-36 general health perceptions in HFpEF patients but did not examine this relationship with a disease-specific HRQOL measure.

The current study has several strengths, including a relatively large (n=116), carefully screened, well-characterized group of older HFpEF patients who were studied under similar conditions and underwent randomized, single-blinded assessments. The current study also has several limitations. First, the ET training intervention was relatively short (16 wk) with no long-term follow-up. As shown by Belardinelli and colleagues⁴⁴ in HFrEF patients, it is possible that a longer ET intervention and a longer period of follow-up may influence the relationship between changes in physical function and HRQOL. Second, the training protocol involved moderate-intensity aerobic exercise, thus the results may have been different if higher intensity aerobic training (45) or resistance training (46) was utilized. Third, the structure of the ET intervention used in this investigation was the more traditional rehabilitation-based ET programs that, as noted earlier, did not include behavioral strategies that target social cognitive processes. Despite providing the randomly assigned CON group with bi-weekly phone calls, the ET group may have received more interaction and feedback from study personnel which may have influenced the HRQOL measures. Finally, it must be recognized that correlational analyses examine the association between two measures, but do not assess independence/dependence of these two measures.

CONCLUSIONS

This study showed that a 16-wk endurance ET intervention significantly improves physical function and select measures of HRQOL in older HFpEF patients. However, improvements in physical function and HRQOL measures after ET appear to be relatively independent of each other in this population. Since the mechanisms responsible for changes in HRQOL after ET remain unclear, future research should explore potential functional, physiological, psychological, social, and environmental factors that may mediate endurance ET induced improvements in HRQOL. Identification of possible mediators will allow for the design of optimal ET interventions to most effectively improve HRQOL in the HFpEF population.^{32,33,45}

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Figure 1.
Box plots (with 95% CI) of the Unadjusted Mean Changes in Physical Function Measures by Group.

Figure 2. Box plots (with 95% CI) of the Unadjusted Mean Changes in Health-related Quality of Life Measures (HRQOL) Measures by Group.

Table I.**Participant Demographics and Baseline Values by Treatment Group**

	Exercise (n=58)	Control (n=58)
Female	44 (76)	50 (86)
Caucasian	43 (74.1)	42 (72)
Age, yr	70.3±6.7	69.2±6.2
History of hypertension	52 (90)	46 (79)
Diabetes mellitus	11 (19)	13 (22)
Current medications		
ACE inhibitor	22 (38)	19 (33)
Beta-blocker	10 (17)	15 (26)
Calcium-channel blocker	26 (45)	17 (29)
Digoxin	8 (14)	5 (9)
Diuretic	32 (55)	33 (57)
Nitrates	6 (10)	6 (10)
BMI, kg/m ²	30.1±5.9 *	32.5±6.6 *
Resting SBP, mmHg	145.3±17.5	147.6±18.4
Resting DBP, mmHg	82.9±9.7	82.0±9.2
NYHA class		
II	32 (55.)	33 (57)
III	26 (45)	25 (43)
Ejection Fraction	60.5±0.1	59.5±0.1
VO _{2peak} , mL/kg/min	13.7±2.8	13.3±3.0
VAT, mL/min	721±161	703±184
6MWT, m	445±88	425±117
Peak workload, W	60±26	59±26

* $P < 0.05$ between groups

Data are presented as mean ± SD or n (%).

Abbreviations: 6MWT, 6 min walk test; ACE, angiotensin converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; NYHA: New York Heart Association; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VO_{2peak}, peak oxygen uptake

Table 2.Post-Intervention Least Squared Means for Physical Function Measures by Group^a

Physical Function	Exercise (N=48)	Control (N=51)
VO _{2peak} , mL/kg/min	15.7 [15.2, 16.3] *	13.5 [13.0, 14.0]
VAT, mL/min	807.5 [768.8, 846.2] *	673.9 [636.5, 711.5]
6MWT, meters	489.3 [474.5, 504.1] *	448.6 [434.4, 462.9]
Peak workload, W	74.3 [70.6, 78.0] *	58.0 [54.4, 61.6]

^aControlling for baseline values and sex

Data presented as mean [95% CI]

Abbreviations: 6MWT, 6 min walk test; VAT, ventilatory anaerobic threshold.

* $P < .05$ level after adjustment for multiple comparisons; individual p values in text

Table 3.Post-Intervention Least Squared Means for HRQOL Measures by Group^a

MLWHFQ	Control (N=44)	Exercise (N=43)
Total	28.20 [23.61, 32.79]	23.13 [18.32, 27.95]
Physical	12.67 [10.37, 14.97]	10.59 [8.18, 13.00]
Emotional	3.96 [2.92, 5.01]	3.37 [2.27, 4.47]
SF-36		
Physical composite	38.42 [36.51, 40.32]	41.39 [39.47, 43.32] *
Physical Function	55.81 [51.10, 60.51]	60.69 [55.93, 65.45]
Role-Physical	32.19 [21.91, 42.48]	53.10 [42.70, 63.51] *
Bodily Pain	57.70 [52.18, 63.22]	60.96 [55.38, 66.54]
General Health	56.38 [52.15, 60.61]	55.75 [51.48, 60.03]
Mental composite	48.98 [46.58, 51.37]	50.61 [48.19, 53.04]
Vitality	41.86 [37.46, 46.27]	52.75 [48.29, 57.20] *
Social Functioning	73.09 [66.95, 79.22]	77.54 [71.33, 83.75]
Role Emotional	62.74 [52.30, 73.19]	71.46 [60.89, 82.03]
Emotional Health	74.63 [70.80, 68.67]	74.69 [70.71, 78.68]

^aControlling for baseline values and sex

Data presented as mean [95% CI]

* $P < .05$ level after adjustment for multiple comparisons; individual p values in text

Table 4.

Correlations between Change in Physical Function and Change in HRQOL in the Exercise Training Group

	MLHF Total	SF-36 PCS	SF-36 Role Physical	SF-36 Vitality
VO_{2peak}	-0.17	0.18	0.21	0.20
6MWT	0.13	0.06	-0.03	0.03

Comparisons made using residualized change scores.

Data are presented as Pearson's correlation coefficients.

None of the correlations were statistically significant after adjustment for multiple comparisons.

Abbreviations: 6MWT, 6 min walk test; VAT, ventilatory anaerobic threshold.

Table 5.**Least Squared Means for Health-Related Quality of Life by Exercise Response^{a,b}**

MLHF	Non-Responders (N=17)	Responders (N=26)
Total	24.3 [16.0, 32.5]	26.1 [19.4, 32.8]
SF-36		
Physical composite	41.1 [37.5, 44.8]	40.8 [37.9, 43.8]
Role-Physical	56.7 [37.0, 76.4]	42.7 [27.0, 58.5]
Vitality	52.2 [44.6, 59.8]	50.3 [44.2, 56.4]

^aControlling for baseline values and sex

Data presented as mean [95% CI]

^b Responders: Exercise training participants with an increase in VO_{2peak} ≥ 10%;

Non-Responders: Exercise training participants with an increase in VO_{2peak} < 10%

Abbreviations: MLHF, Minnesota Living with Heart Failure Questionnaire; SF-36, 36-item Short Form Health Survey