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Sex Differences in Exercise Capacity and Quality of Life in Heart Failure with Preserved Ejection Fraction: A Secondary Analysis of the RELAX and NEAT-HFpEF Trials

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Abstract

Background: Few studies have compared clinical characteristics, echocardiographic parameters, exercise capacity, and quality of life between women and men with heart failure with preserved ejection fraction (HFpEF).

Methods and Results: Subjects in the NIH-sponsored RELAX (N = 216) and NEAT (N = 107) trials completed baseline echocardiography, the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and 6-minute walk test (6MWT). In exploratory analysis, multivariable linear regression models were used to associate clinical and imaging characteristics with baseline 6MWT distance and MLHFQ score in women and men. Our cohort included 158 (49%) men and 165 (51%) women. Men had higher prevalence of atrial arrhythmias, ischemic heart disease, diabetes, anemia, and left ventricular (LV) hypertrophy. 6MWT and MLHFQ score did not differ between sexes. In multivariable analysis, ischemic heart disease, diastolic dysfunction, and exercise capacity predicted MLHFQ score for men, while only age and BMI predicted MLHFQ score for women.

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In multivariable models for six-minute walk test distance, $R^2 = 0.307$ for men, and $R^2 = 0.383$ for women. In multivariable models for Minnesota Living with Heart Failure Questionnaire score, $R^2 = 0.38$ for men, and $R^2 = 0.178$ for women.

Conclusions: Men with HFpEF had more co-morbidities and LV hypertrophy than women with HFpEF. In men, quality of life was associated with diastolic dysfunction, ischemic heart disease, and exercise capacity. Further research is needed to identify determinants of quality of life in women with HFpEF.

Keywords

heart failure with preserved ejection fraction; sex differences; women's health; quality of life

Introduction

Heart failure with preserved ejection fraction (HFpEF) poses a large and growing public health problem.¹ Women constitute the majority of HFpEF patients, and women with heart failure are more likely to have HFpEF than HF with reduced ejection fraction (HFrEF).² Reasons for this disparity may stem from differences in cardiac structure, vascular function, and baseline comorbidities.³ Prior work suggests that, compared to men, women have greater arterial stiffness, more concentric left ventricular (LV) hypertrophy, smaller LV cavities, and worse diastolic function.⁴ Additionally, recent data suggested sex differences in response to HF therapies, further demonstrating sex differences in HFpEF.^{5,6} Despite having more favorable clinical outcomes,^{2,7,8} women with HFpEF may have worse functional status and quality of life.⁹

Exercise intolerance is a hallmark feature of HFpEF.³ Because no targeted therapies for HFpEF exist, standard treatment goals include improving exercise capacity and quality of life. Despite the female preponderance of HFpEF, women have historically been underrepresented in HF trials, and few studies have examined sex-specific differences in functional and patient-reported outcomes. Here, we combined two HFpEF cohorts to compare clinical characteristics, exercise capacity, and quality of life in men and women with HFpEF. In exploratory analysis, we compared predictors of exercise capacity and quality of life between sexes.

Materials and methods

We pooled subjects in the RELAX (N = 216)¹⁰ and NEAT-HFpEF (N = 107)¹¹ trials, two randomized controlled trials conducted by the Heart Failure Clinical Research Network. Three individuals were enrolled in both trials; they were only included in the dataset once using data from RELAX because it was conducted first. Data collection, management, and analysis were performed at the network's data coordinating center at the Duke Clinical Research Institute. All subjects provided written informed consent.

RELAX evaluated the effect of sildenafil on peak oxygen consumption with cardiopulmonary exercise testing. NEAT-HFpEF assessed the effect of isosorbide mononitrate on exercise capacity as measured by patient-worn accelerometers. Inclusion and exclusion criteria have been published previously and were similar between trials.^{10,11} Eligibility criteria included New York Heart Association (NYHA) functional class II-IV symptoms with objective evidence of HF, left ventricular ejection fraction 50% within 12

months of enrollment, and ability to walk and (in RELAX) complete cardiopulmonary exercise testing.^{10,11}

We compared subjects' baseline characteristics, exercise capacity, and quality of life (i.e., our analysis is unaffected by study randomization). Subjects completed a baseline medical history and physical examination, transthoracic echocardiogram, six-minute walk test (6MWT), and Minnesota Living with Heart Failure Questionnaire (MLHFQ).^{10,11} Anemia was defined as hemoglobin <13 g/dL for men and <12 g/dL for women.^{10,11}

Statistical analysis

We compared baseline characteristics by sex using the Student's *t*-test or Wilcoxon rank-sum test for continuous variables and the Pearson chi-squared or Fisher exact test for categorical variables as appropriate. Multiple imputation by chained equations was used to impute missing covariate data.

In exploratory analysis, we used generalized linear regression models to test associations between candidate predictors and 6MWT distance and MLHFQ score by sex. Variables were log₂-transformed where appropriate. We stratified analyses by sex (i.e., separate models were derived for men and women) rather than evaluating interactions with sex because the cohort was small relative to the number of degrees of freedom required to explore sex interactions in multivariable modeling. The univariable associations with candidate predictors (listed in Supplemental Tables 1–2) were assessed by sex after adjusting for clinical trial. For multivariable models, all candidate predictors were initially considered for inclusion, and backward variable selection with an inclusion criterion of *P*<0.10 was used to select key predictors for use in parsimonious multivariable models. All statistical analyses were performed in SAS 9.4 (SAS Institute; Cary, NC). *P*-values less than 0.05 indicate statistical significance.

Results

Baseline characteristics

The study cohort included 158 (48.9%) men and 165 (51.1%) women. All but 1 patient in each group had NYHA class II–III HF symptoms. As shown in Table 1, most patients were white and obese, with similar body mass index (BMI) between men and women (33.6 kg/m² vs. 33.3 kg/m², *P*=0.57). Men were more likely to have atrial arrhythmias (55.1% vs. 38.2%, *P*=0.002), ischemic heart disease (55.1% vs. 37.6%, *P*=0.002), diabetes (51.9% vs. 32.1%, *P*<0.001), and anemia (42.3% vs. 26.7%, *P*=0.003). Medication use was similar between sexes. Men were more likely than women to have concentric LV hypertrophy as measured by a relative wall thickness (i.e., the sum of septal and posterior wall thickness divided by LV end-diastolic diameter [LVEDD]) >0.41 (62.4% vs. 43.5%, *P*<0.001) and greater body surface area-indexed LV mass (88 g/m² vs. 72 g/m², *P*<0.001). 6MWT distance and MLHFQ score did not differ between men and women (Figure 1a–1b).

Predictors of exercise capacity

Results of a multivariable model for predicting 6MWT distance are presented in Figure 1c. Supplemental Table 1 lists univariable associations for all candidate predictors. Age, BMI, and anemia predicted 6MWT distance for both men and women. Atrial arrhythmias and diabetes independently predicted 6MWT distance for women. Left atrial (LA) volume index, medial e' , and medial E/e' were not associated with 6MWT distance in either sex. Higher pulmonary artery systolic pressure (PASP) was independently associated with lower 6MWT distance in women. N-terminal pro-B-type natriuretic peptide (NT-proBNP) level was significantly associated with exercise capacity for both sexes in univariable analysis but not after multivariable adjustment for co-morbidities and echocardiographic parameters.

Predictors of quality of life

Results of a multivariable model for MLHFQ score are shown in Figure 1d. BMI was negatively associated with quality of life in women. Ischemic heart disease predicted worse quality of life in men. Several echocardiographic parameters were independently predictive of MLHFQ score for men, including LVEDD, LA volume index, and medial E/e' . In univariable and multivariable analyses (Figure 1c–1d, Supplemental Tables 1–2), greater 6MWT distance was associated with more favorable MLHFQ score for men but not women.

Discussion

In this pooled secondary analysis of two prospective HFpEF trials, we found baseline differences in clinical and echocardiographic parameters between women and men with HFpEF. In contrast with prior HFpEF studies,^{4,7,8} women and men had similar age and BMI, while men had more co-morbidities. Also in contrast to prior reports,⁴ we found that women had less ventricular hypertrophy.

While baseline 6MWT distance and HF-related quality of life were similar between sexes, we found sex differences in predictors of these measures. For example, we found that the relationship between exercise limitation and quality of life may differ between men and women with HFpEF. This finding is relevant given a recent analysis of sex differences in HFrEF which found women had worse quality of life and disability compared to men, despite having fewer co-morbidities and better survival.¹² Prior work suggested a strong association between exercise capacity in HFpEF and quality of life.¹³ In our study, 6MWT distance was associated with quality of life for men but not women, aligning with a study which found quality of life was more strongly associated with NYHA class and natriuretic peptide levels in men.⁹ This potential sex difference is important to recognize because prior studies and HF guidelines have implicitly assumed that improving exercise capacity will improve quality of life.

Reasons for the apparently attenuated association between exercise capacity and quality of life in women are currently unknown. Unmeasured psychosocial factors may contribute. Sex differences in perception of disease severity and its impact on physical function have been proposed. For example, women with HFpEF appear to have higher rates of depression than men,¹⁴ and depression has been shown to impact patient perceptions of HF severity and

quality of life independent of objective disease severity.¹⁵ Lack of data on co-morbid depression is a limitation of this analysis. Further, it is possible that social determinants of health (e.g., economic circumstances, caregiver burden, sexism) may differentially affect women and men with HF. It is striking that few factors predicted quality of life in women and that the multivariable model for HF-related quality of life performed worse in women vs. men (R^2 0.178 vs. 0.38). Further research is needed to understand these factors with the ultimate goal of optimizing patients' overall quality of life.

Our findings should be interpreted in the context of limitations. The sample size, while similar to recent HFpEF trials, was small relative to the number of candidate predictors, limiting power. By fitting separate models for men and women, we cannot directly compare differences in estimated associations with candidate predictors. Inclusion criteria in RELAX and NEAT-HFpEF included ability to walk/exercise, potentially limiting generalizability. Data on comorbidities beyond those routinely ascertained in HFpEF trials were not available. Finally, our study population was predominantly white and therefore our findings may not be generalizable to other racial or ethnic minorities with HFpEF.

Conclusions

In this pooled HFpEF cohort from the RELAX and NEAT-HFpEF clinical trials, men with HFpEF had more co-morbidities and LV hypertrophy than women. Ischemic heart disease, echocardiographic parameters of diastolic function, and exercise capacity predicted quality of life in men, whereas none of these factors was significantly associated with quality of life in women. Further research is needed to identify determinants of quality of life in women with HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrfEF	Heart failure with reduced ejection fraction
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal pro-B-type natriuretic peptide

NYHA	New York Heart Association
6MWT	Six-minute walk test
LA	left atrium
PASP	pulmonary artery systolic pressure

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Figure 1. Baseline six-minute walk test distance (a) and Minnesota Living with Heart Failure Questionnaire total score (b) for men and women, and predictors of these measures from backward-selected regression models (c and d).

Table 1.

Characteristics of the study population by sex.

Characteristic	Men (N=158)	Women (N=165)	P-value ⁺
Demographics			
Age, years: mean (SD)	69 (9.4)	68 (10.3)	0.39
Self-reported white race: n (%)	149 (94.3%)	143 (86.7%)	0.02
Clinical Assessment			
Body mass index, kg/m ² : median (Q1, Q3)	33.6 (29.1, 40.0)	33.3 (28.9, 40.0)	0.57
New York Heart Association functional classification: n (%)			0.30
II	82 (51.9%)	76 (46.1%)	
III	75 (47.5%)	88 (53.3%)	
Systolic blood pressure, mmHg: median (Q1, Q3)	126 (116, 138)	126 (113, 141)	0.63
Heart rate, beats/min: mean (SD)	70 (12.1)	70 (12.0)	0.81
Peripheral edema, trace+: n/N (%)	98 / 157 (62.4%)	92 / 165 (55.8%)	0.22
Medical History			
Hypertension: n (%)	138 (87.3%)	142 (86.1%)	0.74
Atrial fibrillation or flutter: n (%)	87 (55.1%)	63 (38.2%)	0.002
Ischemic heart disease: n (%)	87 (55.1%)	62 (37.6%)	0.002
Diabetes mellitus: n (%)	82 (51.9%)	53 (32.1%)	<.001
Chronic kidney disease, stage 3+: n/N (%)	78 / 157 (49.7%)	92 / 165 (55.8%)	0.28
Chronic obstructive pulmonary disease: n (%)	35 (22.2%)	23 (13.9%)	0.06
Anemia: n/N (%)	66 / 156 (42.3%)	44 / 165 (26.7%)	0.003
Medications at Enrollment			
Loop diuretic: n (%)	122 (77.2%)	113 (68.5%)	0.08
Beta-blocker: n (%)	124 (78.5%)	115 (69.7%)	0.07
Angiotensin converting enzyme inhibitor or angiotensin II receptor blocker: n (%)	110 (69.6%)	110 (66.7%)	0.57
Aldosterone antagonist: n (%)	21 (13.3%)	28 (17.0%)	0.36
Calcium channel blocker: n (%)	51 (32.3%)	49 (29.7%)	0.62
Echocardiographic Data			
Left ventricular ejection fraction, %: mean (SD) [N]	60 (7.6) [156]	63 (7.9) [164]	0.004
Left ventricular end diastolic dimension, cm: mean (SD) [N]	4.9 (0.67) [124]	4.6 (0.51) [143]	<.001
Left ventricular mass / body surface area, g/m ² : median (Q1, Q3) [N]	88 (67, 109) [123]	72 (60, 84) [138]	<.001
Left ventricular mass / body surface area $\geq$ 95 g/m ² (women) or 115 g/m ² (men): n/N (%)	22 / 123 (17.9%)	17 / 138 (12.3%)	0.21
Relative wall thickness $>$ 0.41: n/N (%)	79 / 123 (64.2%)	60 / 138 (43.5%)	<.001
Left atrial volume index, mL/m ² : median (Q1, Q3) [N]	44 (33, 61) [103]	40 (31, 52) [134]	0.03
Medial e', m/s: median (Q1, Q3) [N]	0.06 (0.05, 0.08) [144]	0.06 (0.05, 0.08) [155]	0.32
Medial E/e': median (Q1, Q3) [N]	14 (11, 20) [137]	15 (11, 20) [152]	0.38
Pulmonary artery systolic pressure, mmHg: median (Q1, Q3) [N]	40 (32, 49) [78]	36 (30, 49) [105]	0.54

Characteristic	Men (N=158)	Women (N=165)	P-value ⁺
Laboratory Biomarkers			
NT-proBNP, pg/mL: median (Q1, Q3) [N]	622 (214, 1333) [156]	446 (141, 1187) [164]	0.11
Outcomes			
Six-minute walk distance, m: mean (SD) [N]	311 (115.2) [158]	299 (112.2) [164]	0.32
MLHFQ total score [^] : mean (SD) [N]	46 (23.6) [148]	44 (22.3) [151]	0.61
Physical dimension score (range 0-40): median (Q1, Q3) [N]	22 (15, 30) [152]	24 (14, 30) [162]	0.55
Emotional dimension score (range 0-25): median (Q1, Q3) [N]	8 (3, 14) [157]	9 (5, 15) [163]	0.12

Values are displayed as median (interquartile range) [N], mean (SD) [N], or n/N (%) when data are missing in a given cell.

⁺ Continuous variables reported as median (interquartile range) were compared using the Wilcoxon rank-sum test. Continuous variables reported as mean (SD) were compared using the Student's *t*-test.

[^] Higher scores on the Minnesota Living with Heart Failure Questionnaire correspond to worse health status.

61/507 (57.0%) subjects in NEAT and 104/216 (48.1%) subjects in RELAX were female (P=0.13).

NT-proBNP=N-terminal pro b-type natriuretic peptide; MLHFQ = Minnesota Living with Heart Failure Questionnaire