Sexual dimorphism in the relationships between intramyocardial fat, myocardial fibrosis, and exercise intolerance in heart failure with preserved ejection fraction

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Sexual dimorphism in the relationships between intramyocardial fat, myocardial fibrosis, and exercise intolerance in heart failure with preserved ejection fraction

Heart failure with preserved ejection fraction (HFpEF) is characterized by exercise intolerance[1] and is commonly associated with obesity, diabetes, and increased interstitial myocardial fibrosis.[2–5] Women outnumber men in HFpEF, but the underlying mechanisms remain unclear.[6] Sorimachi *et al.*[7] recently showed that abdominal visceral adipose tissue (VAT) was increased in women with HFpEF compared to age and body mass index-matched control women, but no such difference was observed in men. Increased VAT was associated with greater increase in pulmonary capillary wedge pressures during exercise in women, but not men. This suggests a potential sexual dimorphism in the relationship between adipose tissue distribution and myocardial function in HFpEF. Increased accumulation of VAT is correlated with increases in ectopic fat elsewhere, including the heart.

We hypothesized that increases in myocardial steatosis would be associated with greater interstitial fibrosis in women with HFpEF, which may contribute to exercise intolerance. To test this hypothesis, we examined the relationship between left ventricular myocardial fat (LV-myoFat) and extracellular volume (ECV) as a measure of myocardial interstitial fibrosis in women and men with HFpEF by cardiac magnetic resonance (CMR) imaging, and their associations with aerobic capacity assessed by peak oxygen consumption (VO_2).

This study utilizes baseline data from patients participating the NIH-funded INABLE trial (NCT02713126), which showed that treatment with oral sodium nitrite did not enhance the benefits of exercise training in patients with HFpEF. The primary results, study protocol, and statistical analysis plan for this trial have been published.[8] A subgroup of 26 patients with confirmed HFpEF from the trial were recruited to an optional study where they underwent CMR at rest, and echocardiograms at rest and during maximal effort exercise testing. The study was approved by the Mayo Clinic Institutional Review Board while conforming to principles outlined in the Declaration of Helsinki.

Cardiac magnetic resonance was performed on a 1.5 T system. Myocardial steatosis (LV-myoFat fraction) was quantified using the multi-echo Dixon water and fat separated imaging with variable projection (VARPRO) sequence that was previously validated against the gold standard proton magnetic resonance spectroscopy.[5] Modified look-locker inversion recovery (MOLLI) T1 mapping sequence was used to derive ECV fraction which is the surrogate for interstitial fibrosis burden. All subjects received 0.1 mmol/kg of gadolinium diethylenetriamine penta-acetic acid.

Table 1 Baseline clinical, echocardiographic, cardiac magnetic resonance imaging, and cardiopulmonary exercise test characteristics

Variables	All participants ($n = 26$)	Men ($n = 14$)	Women ($n = 12$)	*p*-value
Demographics				
Age (years)	69 ± 9	67 ± 10	70 ± 9	0.45
Body mass index (kg/m^2)	35.2 ± 7.5	36.1 ± 6.9	34.3 ± 8.4	0.56
Type 2 diabetes (%)	34.6	35.7	25.0	0.68
Hypertension (%)	84.6	92.9	75.0	0.31
Dyslipidaemia (%)	73.1	85.7	58.3	0.19
Medications (%)				
Antiplatelets	36.0	50.0	18.2	0.21
ACEI/ARB	34.6	35.7	33.3	>0.99
Beta-blockers	53.8	64.3	41.7	0.25
Calcium channel blockers	46.2	57.1	33.3	0.23
Diuretics	84.6	78.6	91.7	0.60
HMG-CoA inhibitors	69.2	78.6	58.3	0.40
Insulin	29.2	30.8	27.3	>0.99
Biochemical				
HbA1c (%)	7.1 ± 1.3	7.0 ± 1.3	7.2 ± 1.6	0.83
Total cholesterol (mg/dl)	170 ± 39	162 ± 43	186 ± 27	0.12
High-density lipoprotein (mg/dl)	58 ± 19	50 ± 19	70 ± 15	0.025
Low-density lipoprotein (mg/dl)	89 ± 19	81 ± 19	97 ± 19	0.08
Triglyceride (mg/dl)	124 ± 89	133 ± 106	115 ± 62	0.64
eGFR (ml/min/1.73 m^2)	64 ± 17	69 ± 15	59 ± 18	0.15
Cardiac magnetic resonance imaging				
LV mass index (g/m^2)	44.1 ± 7.7	46.7 ± 7.6	41.0 ± 6.9	0.06
LV end-diastolic volume index (ml/m^2)	56.7 ± 12.2	57.2 ± 11.1	56.0 ± 13.9	0.81
LV end-systolic volume index (ml/m^2)	23.6 ± 7.2	25.8 ± 6.5	21.1 ± 7.3	0.10
LV ejection fraction (%)	57.3 ± 8.6	54.7 ± 8.8	60.4 ± 7.6	0.09
LV-myoFat fraction (%)	9.0 ± 3.6	11.1 ± 5.3	8.0 ± 2.1	0.06
ECV fraction (%)	25.5 ± 4.0	24.5 ± 3.7	26.4 ± 4.1	0.24
Cardiopulmonary exercise test				
Resting				
Resting heart rate (bpm)	74 ± 12	80 ± 9	67 ± 13	0.019
Resting systolic blood pressure (mmHg)	124 11	126 ± 7	121 ± 15	0.36
Resting average mitral E/e′ ratio	10.6 ± 4.1	10.4 ± 3.3	10.8 ± 4.6	0.83
Peak exercise				
Peak heart rate (bpm)	119 ± 24	131 ± 18	106 ± 24	0.018
Peak systolic blood pressure (mmHg)	175 ± 31	183 ± 35	164 ± 22	0.17
Peak average mitral E/e′ ratio	10.9 ± 3.8	10.7 ± 3.0	11.2 ± 4.9	0.76
Peak VO_2 (L/min)	1.6 ± 0.7	1.9 ± 0.8	1.3 ± 0.3	0.032
Peak respiratory exchange ratio	1.02 ± 0.08	1.04 ± 0.08	1.00 ± 0.08	0.18
V_E/VCO_2 slope	35.5 ± 8.0	36.2 ± 8.4	32.5 ± 5.0	0.27

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LV, left ventricular; LV-myoFat, left ventricular myocardial fat; VO_2, oxygen consumption; V_E/VCO_2, minute ventilation to carbon dioxide or ventilatory efficiency.

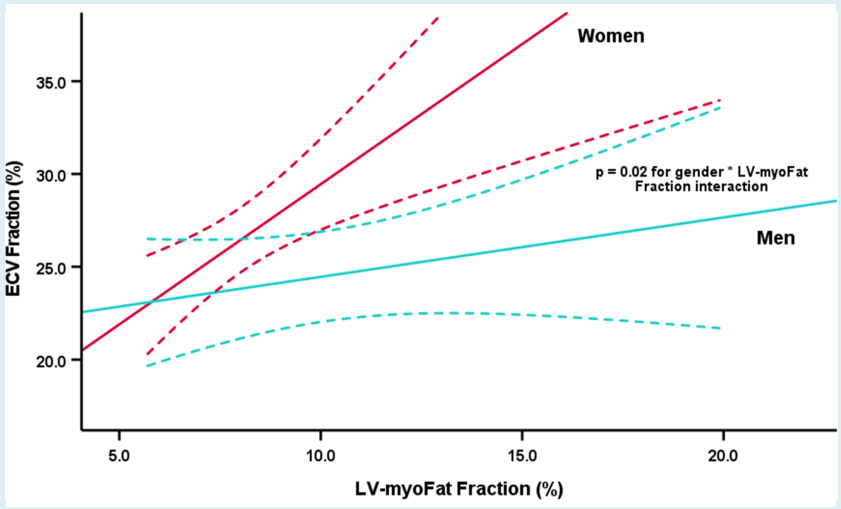

Figure 1 Correlation between left ventricular myocardial fat (LV-myoFat) fraction and extracellular volume (ECV) fraction. Women had greater increase in ECV fraction with progressively higher LV-myoFat compared to men.

Volumes of oxygen consumed (VO_2) and carbon dioxide produced (VCO_2) were measured during peak exercise at baseline prior to exercise training and study drug administration using a low resistance, open circuit, automated metabolic system integrated with a mass spectrometer as described.[8] Peak VO_2 was determined as the mean of the highest 30-s interval achieved during upright cycling on an ergometer. Patients underwent a 5-min rest period before cycling at 20 W for 5 min, followed by incremental increases in workload until volitional fatigue, administered by trained exercise physiologists.

Transthoracic echocardiography was performed at rest in the upright position and during upright peak exercise, and images were analysed offline (Vivid E9, EchoPAC version 113, GE-Vingmed, Horten, Norway) according to guideline recommendations.[8] Transmitral E-wave velocities were recorded using pulsed-wave Doppler in the apical four-chamber view using a 2 mm sample volume placed at the mitral leaflet tips. Mitral annular early diastolic (e′) velocity was recorded using tissue Doppler imaging at the septal and lateral mitral annulus. Transmitral E wave to the average mitral septal and lateral annular e′ velocity (average E/e′) ratio was calculated at rest and during peak exercise.

Multiple linear regression was used to identify independent variables associated with ECV fraction and peak VO_2 using the backward elimination method. Significant variables with $p < 0.05$ were entered as covariates. A tolerance of >0.5 was used to avoid multicollinearity. A two-tailed p-value < 0.05 was considered significant.

The cohort (12 women, 14 men) displayed typical characteristics of HFpEF including older age (69 ± 9 years), elevated body mass index (35.2 ± 7.5 kg/m^2), and high prevalence of comorbidities including diabetes, hypertension, and dyslipidemia (*Table 1*). There were no significant sex differences in age, body mass index, cardiac risk factors, left ventricular mass index, volumes, ejection fraction, upright E/e' at rest and exercise, or myocardial ECV fraction on CMR.

The mean ECV fraction was $25.5 \pm 4.0\%$. Increasing age was positively correlated with higher ECV fraction among men and women with HFpEF ($r = 0.67$, $p = 0.001$). Similarly, increasing LV-myoFat fraction was significantly correlated with higher ECV fraction after adjusting for sex (partial $r = 0.49$, $p = 0.021$). There was a significant interaction between ECV fraction and LV-myoFat fraction, such that women with HFpEF had greater increase in ECV fraction with progressively higher LV-myoFat fraction compared to men (*Figure 1*). There was also a significant positive correlation between the resting average mitral E/e' ratio and ECV fraction ($r = 0.49$, $p = 0.017$). On multivariable analysis, only age and the sex*LV-myoFat fraction interaction terms were significantly related to ECV fraction (model $R^2 = 0.58$). On multivariable analysis, peak average mitral E/e' ratio and ECV were independently related to peak VO_2, explaining most of the variance in aerobic capacity (model $R^2 = 0.64$).

The present study showed that increases in ECV were correlated with increasing age, higher E/e′ ratio at rest, and poorer exercise capacity as measured by absolute peak VO_2. ECV was correlated with LV-myoFat fraction to a greater extent in women with HFpEF than men (*Figure 1*). On multivariable analysis, increasing age and female sex*LV-myoFat fraction interaction were both independently associated with higher ECV fraction. This finding may help explain why the risk of HFpEF with obesity is greater among women.[7] Estimated left ventricular filling pressures during exercise and ECV were independent correlates of lower aerobic capacity. These data emphasize the pathophysiologic importance of interstitial fibrosis and intramyocardial fat in HFpEF and identify for the first time a potentially important sex difference in the relationship between myocardial steatosis and interstitial fibrosis, suggesting that increases in intramyocardial fat are even more detrimental in women.

The present study does have limitations, including a modest sample size, and the lack of an intervention on myocardial fibrosis or steatosis, which would have allowed for greater insight into causal relationships, and the lack of a control group without heart failure, to determine whether these relationships are specific to HFpEF. Nevertheless, these data call for further study into the interaction between cardiac lipid accumulation and myocardial composition and function in patients with HFpEF, and suggest the potential for myocardial steatosis as a novel treatment target in patients with the obesity phenotype of HFpEF.

Conflict of interest: none declared.

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