Original Article

Gender-related differences in left atrial strain mechanics and exercise capacity in hypertrophic cardiomyopathy: a propensity-score matched study from the Cleveland Clinic

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Background: Male and female patients with hypertrophic cardiomyopathy (HCM) differ in physiologic characteristics and hemodynamics. Little is known about gender-related differences in left atrial (LA) strain and exercise capacity. The aim of this study was to assess the gender-related differences in the relationship between exercise capacity and cardiac function including LA function in patients with HCM.

Methods: Five hundred and thirty-two patients with HCM undergoing exercise stress echocardiography and cardiopulmonary exercise testing (CPET) were prospectively recruited between October 2015 and April 2019 as part of a cohort study in a quaternary referral center. To reduce potential confounding factors, propensity score (PS) matching was performed in 420 patients. LA strain mechanics were evaluated using speckle-tracking echocardiography.

Results: The majority of patients were male, comprising 58% of the total. Female HCM patients were older (54±14 *vs.* 50±15 years, P=0.002). After PS matching, percent-predicted peak VO_2 was similar between the genders (67.5%±20.7% *vs.* 65.8%±21.8%, P=0.41), even though female HCM patients had lower peak VO_2 (17.7±5.9 *vs.* 24.1±8.3 mL/kg/min, P<0.001). Left ventricular (LV) diastolic function was worse for female HCM patients. This is shown by worse E/e' ratio (15.0±5.9 *vs.* 12.9±6.4, P<0.001) and larger LA volume in respect to LV (0.88±0.35 *vs.* 0.74±0.31, P<0.001), compared with male HCM patients. The gender-related differences in LA reservoir strain were more evident for patients aged 60 years and older (27.5%±8.8% *vs.* 30.9%±9.1%, P=0.03). LA reservoir strain was found to have a significant association with exercise capacity in both male and female HCM patients (for females, β=0.27, P=0.001; for males, β=0.27, P<0.001), independent of LV diastolic dysfunction and stroke volume.

Conclusions: Gender-related differences in LA reservoir strain were increasingly evident for older HCM patients aged 60 years and older. LA reservoir strain was an independent determinant of percent-predicted peak VO_2 in male and female patients, underpinning the importance of LA function in determining exercise capacity in HCM.

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Keywords: Left atrial function (LA function); strain imaging; cardiopulmonary exercise testing (CPET); gender-related differences; hypertrophic cardiomyopathy (HCM)

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Introduction

Hypertrophic cardiomyopathy (HCM) is recognized as the most prevalent inherited cardiomyopathy, represented by left ventricular (LV) hypertrophy, associated with elevated risk of heart failure. Exertional dyspnea is a common symptom in HCM, and exercise capacity derived from exercise stress test is a determinant for prognosis. Decreased stroke volume and/or increased LV filling pressure are often implicated in symptoms experienced by HCM patients. Appropriate function of the left atrial (LA) function is critical in regulating LV filling pressure and ongoing maintenance of cardiac output, especially in LV cardiomyopathic conditions such as HCM. The role of LA function in exercise capacity has been increasingly recognized (1-3). HCM patients of both sexes vary in physiologic characteristics, with female patients having smaller LV cavity size, and worse diastolic dysfunction compared to male patients (4). The gender-related differences in physiology and cardiac function result in a lower exercise capacity in female HCM patients (5-7). The assessment of gender-related differences in LA function and exercise capacity may help us to better understand gender-related differences in reduced exercise capacity in HCM patients, with the understanding that all LA strain parameters are reduced in HCM (8). Thus, the aims of this study were to assess gender-related differences in LA function with exercise capacity in patients with HCM. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-147/rc).

Highlight box

Key findings

- Gender-related differences in left atrial (LA) reservoir strain have been found to hypertrophic cardiomyopathy (HCM), though LA reservoir strain was an independent determinant of exercise capacity in both male and female HCM patients.

What is known and what is new?

- Appropriate LA function is critical in regulating left ventricular (LV) filling pressure and ongoing maintenance of cardiac output.
- Male and female patients with HCM differ in physiologic characteristics and exercise capacity.
- The presents study shows that LA reservoir strain is an independent determinant of percent-predicted peak VO_2 in both male and female HCM patients, underpinning the importance of LA function in determining exercise capacity in HCM.

What is the implication, and what should change now?

- LA mechanical dysfunction may support exercise-induced diastolic dysfunction and inadequate increase in stroke volume during exercise as key determinants of impaired exercise capacity in HCM, and gender-related differences in LA mechanical function may be one of the factors underpinning the gender-related differences in exercise capacity in HCM, independent from resting LV diastolic dysfunction and stroke volume.

Methods

Patient population

Consecutive HCM patients undergoing exercise stress echocardiography and cardiopulmonary exercise testing (CPET) between October 2015 and April 2019 at the Cleveland Clinic were prospectively recruited. The diagnosis of HCM was defined by typical criteria including a normal sized LV with LV hypertrophy and wall thickness ≥15 mm (or ≥13 mm and a positive family history), without an alternate concurrent condition that would be associated with LV hypertrophy (9). Patients with apical HCM, significant (at least moderate) left-sided valvular lesions, atrial arrhythmia at the time of the echocardiogram and LV ejection fraction <50% were excluded. Finally, patients with imaging suboptimal for the analysis of LA function were excluded. The electronic medical records were searched to obtain the clinical characteristics of the study cohort. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The protocol for the present study was approved by the Institutional Review Board (IRB) of the Cleveland Clinic (IRB: 19-1184). Individual consent was waived as part of the approved IRB protocol, because

identified information was not used in the analysis and writing of this work.

CPET assessment

The patients in this study underwent assessment with treadmill Bruce protocol exercise CPET, which was symptom-limited. The peak oxygen consumption during exercise (peak VO_2) was recorded at each stage of exercise and measured by respiratory gas analysis as a parameter of exercise capacity. Ventilatory thresholds were determined from gas exchange data. Based on variables of age and sex, the percent-predicted peak VO_2 was derived (10).

Echocardiographic assessment

Dedicated echocardiographers carried out comprehensive echocardiographic examinations in accordance with contemporary guidelines (utilizing Vivid E9/E95, GE Healthcare, Milwaukee, WI, USA) (11). The different morphological types of HCM including apical and mid-ventricular HCM, reverse curvature HCM, sigmoid HCM and neutral septum HCM, were determined based on a meticulous review of echocardiographic data (12). We calculated the ratio of the peak early diastolic velocity of transmitral flow and the peak early diastolic mitral annular tissue motion velocities (E/e' ratio). LV outflow tract obstruction was recorded when there is a peak LV outflow tract pressure gradient ≥30 mmHg at rest or following physiological provocation (9).

Biplane method of disks using the transthoracic apical four- and apical two-chamber views was used to calculate the maximum LA volume. The LA volume index (LAVI) was derived from adjustment of LA volume according to body surface area (11). The pulmonary veins and the LA appendage, where visualized, were excluded from transthoracic echocardiographic images, during the tracing of the LA endocardium. We calculated the ratio of maximum LA volume and LV end-diastolic volume (LA/LV ratio).

Assessment of LA strain mechanics

The standard transthoracic apical four-chamber view was used to measure LA strain parameters. The analysis was performed using echocardiography vendor-independent speckle tracing echocardiographic software (Velocity Vector Imaging, Siemens, Mountain View, CA, USA). R wave on electrocardiogram was set as the zero-strain reference. The LA endocardium was carefully traced according to standard methodology manually. The analytic software then performed strain analysis throughout the cardiac cycle. LA conduit strain was defined as the difference in strain between mitral valve opening and LA contraction onset; LA contractile strain was defined as the difference between LA contraction onset and end-diastole, and LA reservoir strain was defined as the sum of LA conduit strain and LA contractile strain (13).

LA strain measurements reproducibility

Two blinded physicians performed analysis of LA strain mechanics for twenty unique patients on two different occasions to evaluate intra-observer and inter-observer variability (14). Intra-observer variability was measured as the standard error of measurement (SEM_{intra}), and inter-observer variability was measured as SEM_{inter}. Each observer conducted all measurements without knowledge of previous measurements and those of the other observer. SEM_{intra} and SEM_{inter} were 2.1% and 2.6%, respectively for LA reservoir strain. SEM_{intra} and SEM_{inter} were 1.4% and 1.5%, respectively for LA conduit strain. SEM_{intra} and SEM_{inter} were 1.2% and 2.0%, respectively for LA contractile strain.

Statistical analysis

For continuous variables with a normal distribution, the data were expressed as mean ± standard deviation. For variables with skewed distribution, the data were expressed as median and interquartile ranges. Numbers and percentages were used to describe categorical data variables. Unpaired *t*-test were used to test differences between male and female HCM patients for normally distributed variables. For variables with skewed distribution, the Mann-Whitney *U* test was used for continuous variables, whereas the Chi-squared test was used for categorical variables. To assess the effect of menopause on cardiac function including LA strain mechanics, female patients were categorized according to if they were younger or older than 60 years of age, at which most female subjects are expected to experience menopause (15). To assess for potential impact of gender-related differences after controlling for potential confounding factors, propensity score (PS) matching was performed. A multivariable logistic-regression model was used to determine PS, using sex as the dependent variable and the individual clinical characteristics as covariates,

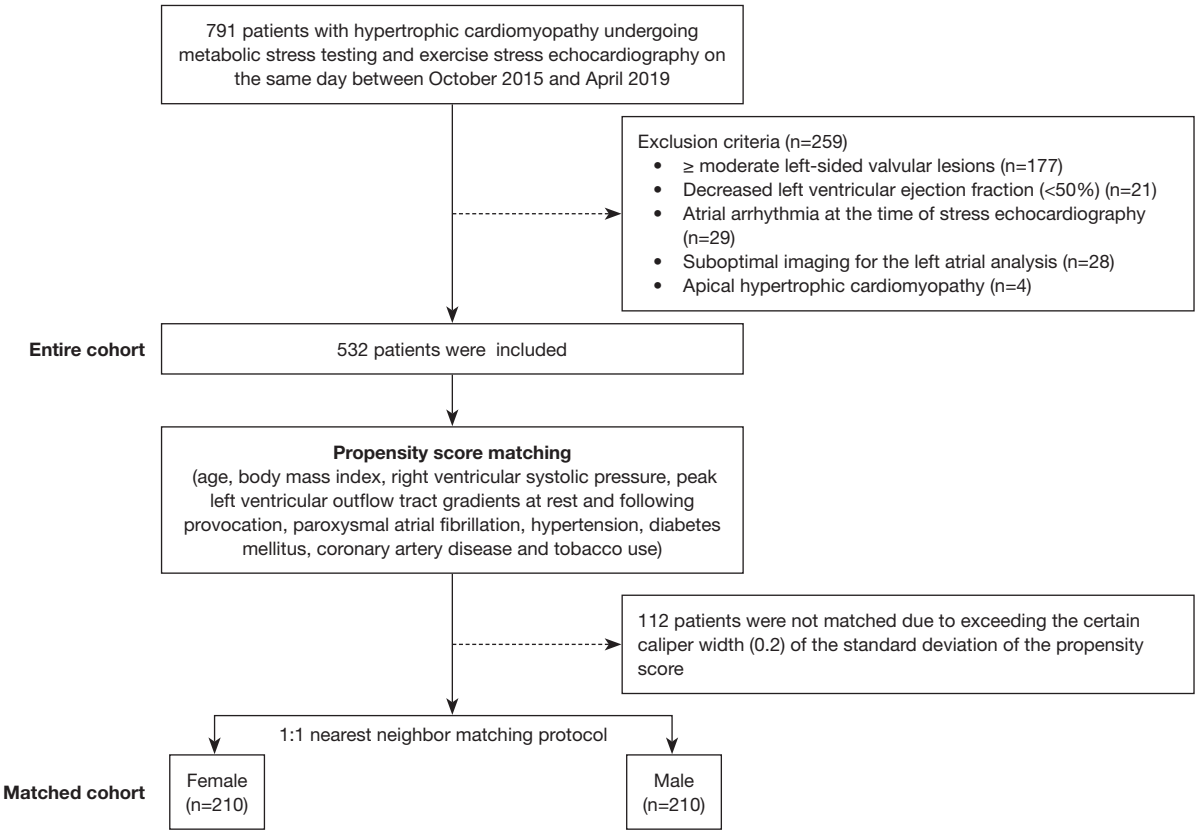

Figure 1 Flow chart outlining the study design.

as illustrated in *Figure 1*. PS matching was performed to derive two subgroups (female and male HCM patients) with the equal number of subjects, which were comparable and balanced in baseline clinical characteristics, utilizing a 1:1 nearest neighbor matching protocol without replacement and a caliper width equal to 0.2 of the standard deviation of the PS. Multiple linear regression was performed to assess the gender-related differences in independent contributions to exercise capacity. The pre-specified variables described in the published literature as showing an important relationship with impaired exercise capacity were included in the models, along with LA reservoir strain (16-18). Because body weight and age were used to calculate the predicted-percent peak VO_2 (objective variable), body mass index (BMI) and age were excluded from the multivariate models (19). For a sample size that was 210 in each group, multiple linear regression was sufficiently powered for inclusion of 10 predictors. Participants with missing data were excluded from analysis of each variable. Statistical analysis in this study was performed using commercially available software packages: SPSS version 25 (SPSS Inc., Chicago, IL, USA) and R 3.6.1 (R foundation for Statistical Computing, Vienna, Austria). P values <0.05 were interpreted as statistically significant.

Results

Study cohort

Two hundred and fifty-nine patients were excluded out of an initial total of 791 patients [the reasons for exclusion included: moderate or greater left-sided valvular disease (n=177), atrial arrhythmia including atrial fibrillation and atrial flutter at time of echocardiogram (n=29), LV ejection fraction <50% (n=21), apical variant HCM (n=4), or suboptimal imaging quality for strain analysis (n=28)], leading to a final cohort of 532 patients. Following PS matching, due to exceeding the defined caliper width of the standard deviation of the PS, 112 patients were excluded. The remaining 420 HCM patients (210 females and 210 males) were included in the matched cohort (*Figure 1*).

Table 1 Clinical characteristics and cardiopulmonary exercise testing variables of the entire cohort versus propensity score matched cohort

Variables	Entire cohort					Propensity score matched cohort			
	All patients (n=532)	Female (n=221)	Male (n=311)	P value	Std diff	Female (n=210)	Male (n=210)	P value	Std diff
Age, years	51±15	54±14	50±15	0.002*	0.27	53±14	52±14	0.60	0.071
Age ≥60 years	169 [32]	82 [37]	87 [28]	0.03*	0.19	74 [35]	67 [32]	0.54	0.085
Body mass index, kg/m^2	30.4±6.3	31.3±7.3	29.9±5.3	0.01*	0.22	31.4±7.7	30.4±5.5	0.12	0.078
Hypertension	245 [46]	107 [48]	138 [44]	0.38	0.08	100 [48]	97 [46]	0.85	0.04
Diabetes mellitus	55 [10]	29 [13]	26 [8]	0.08	0.16	27 [13]	20 [10]	0.35	0.094
Paroxysmal atrial fibrillation	93 [17]	42 [19]	51 [16]	0.49	0.08	42 [20]	36 [17]	0.53	0.078
Coronary artery disease	45 [8]	14 [6]	31 [10]	0.16	0.15	14 [7]	14 [7]	>0.99	–
Tobacco	175 [33]	73 [33]	102 [33]	>0.99	–	72 [34]	69 [33]	0.84	0.021
β-blocker	70 [13]	165 [75]	205 [66]	0.04*	0.20	156 [74]	142 [68]	0.16	0.13
ACE-I/ARB	108 [20]	38 [17]	70 [23]	0.16	0.15	35 [17]	50 [24]	0.09	0.17
Calcium channel blocker	90 [17]	42 [19]	48 [15]	0.29	0.11	37 [18]	34 [16]	0.80	0.053
Diuretics	74 [14]	46 [21]	28 [9]	<0.001*	0.34	44 [21]	26 [12]	0.03*	0.24
NT-proBNP, ng/L[#]	437 [153–843]	539 [195–1,025]	345 [113–723]	0.001*	0.24	520 [186–968]	386 [101–717]	0.01*	0.30
Cardiopulmonary exercise testing variables									
Heart rate, bpm	64±11	65±12	62±10	0.003*		65±12	63±10	0.02*	
Resting systolic blood pressure, mmHg	125±18	124±17	126±18	0.34		124±17	127±18	0.10	
Resting diastolic blood pressure, mmHg	80±11	79±11	81±11	0.13		79±11	82±11	0.07	
Maximal heart rate, bpm	142±27	135±27	147±25	<0.001*		135±27	144±25	<0.001*	
Maximal systolic blood pressure, mmHg	164±29	156±26	170±29	<0.001*		156±26	170±29	<0.001*	
Maximal diastolic blood pressure, mmHg	82±12	81±12	83±13	0.052		81±12	83±13	0.058	
Respiratory exchange ratio	1.15±0.12	1.11±0.12	1.18±0.10	<0.001*		1.11±0.12	1.18±0.11	<0.001*	
VE/VCO_2	31.9±5.0	33.0±4.8	31.2±5.1	<0.001*		33.0±4.8	31.3±5.2	0.001*	
Metabolic equivalents of task	6.3±2.4	5.0±1.7	7.2±2.5	<0.001*		5.1±1.7	6.9±2.4	<0.001*	
Peak VO_2, mL/kg/min	22.0±8.5	17.5±5.8	25.2±8.7	<0.001*		17.7±5.9	24.1±8.3	<0.001*	
Percent-predicted peak VO_2, %	66.7±21.2	67.4±20.3	66.1±21.8	0.48		67.5±20.7	65.8±21.8	0.41	

Data are presented as mean ± standard deviation, n [%] or median [interquartile range]. *, statistically significant; [#], available in 276 patients. Std diff, standardized difference; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NT-proBNP, N-terminal pro-brain natriuretic peptide; VE/VCO_2, ventilatory equivalent for carbon dioxide.

Clinical characteristics

The baseline characteristics including CPET variables in the entire cohort versus the PS matched cohort are outlined in *Table 1*. In the entire cohort, the majority of patients were male, comprising 58% of the total. The mean age of the study patients was 51±15 years. Female HCM patients were older at the time of evaluation than the male counterparts (54±14 *vs.* 50±15 years, P=0.002) with significantly higher BMI (31.3±7.3 *vs.* 29.9±5.3 kg/m^2, P=0.01) and a higher probability of β-blocker use (75% *vs.* 66%, P=0.04) and diuretic use (21% *vs.* 9%, P<0.001).

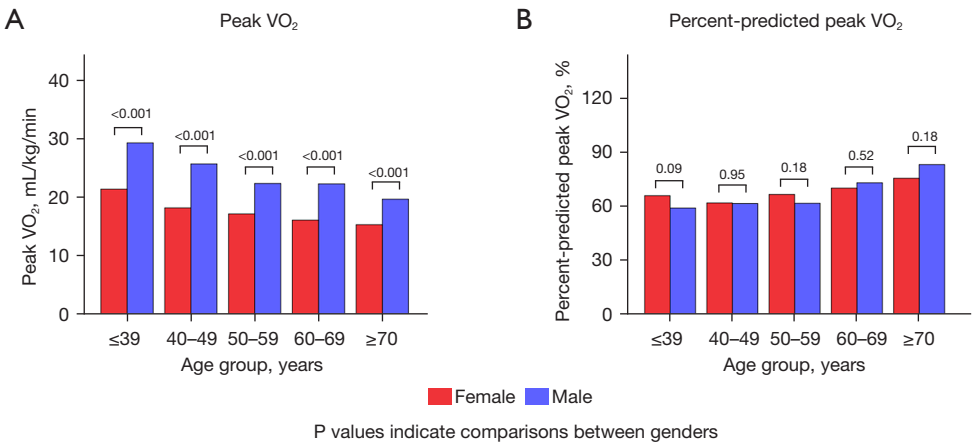

Figure 2 Impact of ageing on exercise capacity by sex in HCM. There were significant gender-related differences in peak VO_2 (A), but not in percent-predicted peak VO_2 (B). HCM, hypertrophic cardiomyopathy.

CPET variables

While female patients had higher ventilatory equivalent for carbon dioxide (VE/VCO_2) (33.0±4.8 *vs.* 31.2±5.1, P<0.001) and lower peak VO_2 (17.5±5.8 *vs.* 25.2±8.7 mL/kg/min, P<0.001), the percent-predicted peak VO_2 was similar between HCM patients of both sexes (67.4%±20.3% *vs.* 66.1%±21.8%, P=0.48). *Figure 2* shows the effect of ageing on exercise capacity in the matched cohort. Female patients had statistically significantly lower peak VO_2 than male patients in each age-group, although there was a greater age-associated decline in peak VO_2 in male patients. On the other hand, the percent-predicted peak VO_2 was comparable between sexes in each age-group.

Echocardiographic characteristics

Echocardiographic variables in the entire cohort versus the matched cohort are shown in *Table 2*. The HCM morphological subtype did not differ significantly between the sexes in the matched cohort. Compared with male patients, female patients had significantly lower LV mass index (113±43 *vs.* 121±41 g/m^2, P=0.042), smaller LV end-diastolic volume index (45±12 *vs.* 52±13 mL/m^2, P<0.001) and LV stroke volume index (28±8 *vs.* 33±8 mL/m^2, P<0.001), and worse E/e' ratio (15.0±5.9 *vs.* 12.9±6.4, P<0.001), even after PS matching. There were no gender-related differences in the presences of LV outflow tract obstruction and at least moderate mitral regurgitation during exercise. While LAVI was comparable between the sexes, LA/LV ratio in female HCM patients was significantly larger (0.88±0.35 *vs.* 0.74±0.31, P<0.001). No statistically significant gender-related difference in LA strain parameters were recorded after PS matching, while the LA strain parameters were likely to be worse in female patients compared to male patients.

Figure 3 shows the gender-related differences in the impact of ageing on echocardiographic variables. Maximum LAVI increased consistently with ageing in both sexes, and there was no significant gender-related difference in each age-group. E/e' and LA/LV ratio increased with ageing, but there were gender-related differences in these variables in both younger age-group and older age-group following menopause (for younger age-group, E/e' ratio 13.8±5.6 *vs.* 12.3±8.4, P=0.03, LA/LV ratio 0.83±0.35 *vs.* 0.70±0.28, P=0.001; for older age-group, E/e' ratio 17.2±5.9 *vs.* 14.1±6.4, P=0.004, LA/LV ratio 0.98±0.32 *vs.* 0.81±0.35, P=0.003). On the other hand, while LA reservoir strain consistently decreased with ageing in both sexes, older female patients had significantly lower LA reservoir strain than male patients (27.5%±8.8% *vs.* 30.9%±9.1%, P=0.03).

Determinant of exercise capacity in male and female patients

As shown in *Table 3*, multiple linear regression analyses demonstrated that LA reservoir strain had a significant association with percent-predicted peak VO_2 in both females and males (for females, β=0.27, P=0.001; for males, β=0.27, P<0.001), independent of other clinical and echocardiographic variables, such as LV stroke volume, E/e' and right ventricular systolic pressure at rest. For female patients, the presence of diabetes mellitus and tobacco use

Table 2 Echocardiographic variables of the entire cohort versus propensity score matched cohort

Variables	Entire cohort				Propensity score matched cohort		
	All patients (n=532)	Female (n=221)	Male (n=311)	P value	Female (n=210)	Male (n=210)	P value
Hypertrophic cardiomyopathy morphological subtypes				0.045*			0.08
Reverse curvature septum	357 [67]	160 [72]	197 [63]		152 [72]	136 [65]	
Sigmoid septum	101 [19]	39 [18]	62 [20]		38 [18]	39 [19]	
Neutral septum	74 [14]	22 [10]	52 [17]		20 [10]	35 [17]	
LV mass index, g/m^2	118±41	113±42	121±40	0.042*	113±43	121±41	0.042*
LV end-diastolic volume index, mL/m^2	50±13	45±11	53±13	<0.001*	45±12	52±13	<0.001*
LV stroke volume index, mL/m^2	32±9	29±8	34±8	<0.001*	28±8	33±8	<0.001*
LV ejection fraction, %	64±5	65±5	63±5	0.02*	64±5	64±5	0.12
Right ventricular systolic pressure, mmHg	29±8	30±8	29±8	0.17	30±8	29±8	0.88
TMF-E, cm/s	82±25	84±23	79±25	0.03*	83±23	80±27	0.27
e', cm/s	6.6±2.4	6.0±2.3	7.1±2.4	<0.001*	6.1±2.3	6.9±2.3	<0.001*
E/e' ratio	13.7±6.2	15.4±6.2	12.4±5.9	<0.001*	15.0±5.9	12.9±6.4	<0.001*
Peak LV outflow tract pressure gradient							
At rest, mmHg	24±27	29±31	20±23	<0.001*	25±26	23±26	0.37
During exercise, mmHg	67±53	66±54	67±53	0.85	62±51	62±52	0.98
LV outflow tract obstruction	321 [60]	128 [58]	193 [62]	0.37	122 [58]	117 [56]	0.69
≥ moderate MR during exercise	94 [18]	37 [17]	57 [18]	0.73	34 [16]	36 [17]	0.90
Maximum LA volume index, mL/m^2	37.9±13.0	37.7±12.3	36.8±11.9	0.44	37.5±12.4	36.4±11.4	0.34
LA/LV volume ratio	0.8±0.33	0.89±0.35	0.73±0.3	<0.001*	0.88±0.35	0.74±0.31	<0.001*
LA reservoir strain (%)	31.6±10.1	30.1±9.8	32.6±10.2	0.005*	30.4±9.9	32.3±10.5	0.06
LA conduit strain (%)	−17.5±7.1	−16.5±6.7	−18.3±7.2	0.003*	−16.6±6.8	−17.8±7.2	0.09
LA contractile strain (%)	−14.1±4.9	−13.7±5.0	−14.4±4.8	0.11	−13.8±5.1	−14.5±5.0	0.17

Data are presented as mean ± standard deviation or n [%]. *, statistically significant. LV, left ventricular; TMF, transmittal flow; MR, mitral regurgitation; LA, left atrial.

were associated with percent-predicted peak VO_2, but not for male patients.

Discussion

The present PS matched study, in which non-sex related differences were accounted for as much as possible, reveals that (I) although female HCM patients had lower peak VO_2 than male counterparts, percent-predicted peak VO_2 was comparable between sexes; (II) female HCM patients had worse LV diastolic dysfunction evidenced by higher E/e' ratio, and larger LA volume in respect to LV volume, compared with male patients; (III) although there were no statistically significant gender-related differences in LA strain parameters in the entire study cohort, gender-related differences in LA reservoir strain were increasingly notable for HCM patients aged 60 years and older; and (IV) LA reservoir strain was an independent determinant of percent-predicted peak VO_2 in both sexes.

Several studies show that female HCM patients are less represented than male patients, ranging from 41% to 45%, and female patients are older at first evaluation and diagnosis (5,20-22). These findings are consistent with the findings of our study. In our study, female patients were

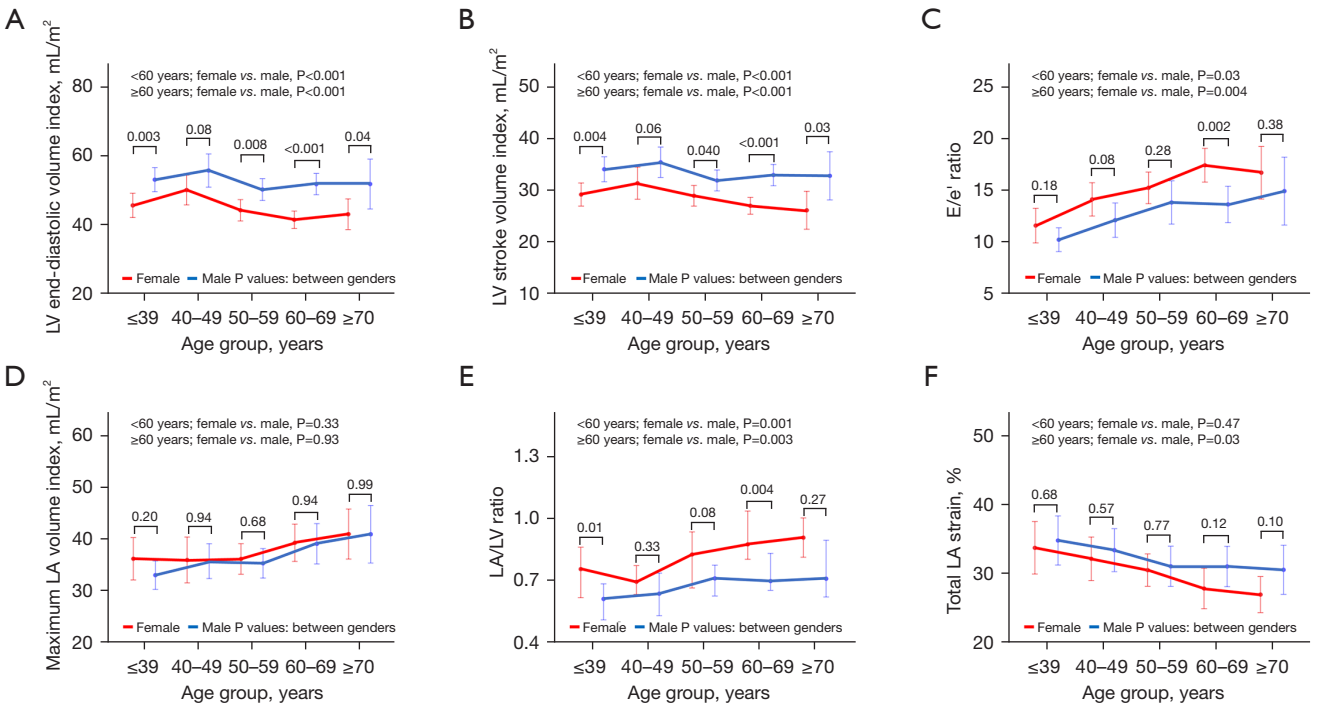

Figure 3 Impact of ageing on LV end-diastolic volume index (A), LV stroke volume index (B), E/e' ratio (C), maximum LA volume index (D), LA/LV ratio (E), LA reservoir strain (F) for female and male HCM patients. LV, left ventricular; LA, left atrial; HCM, hypertrophic cardiomyopathy.

Table 3 Multivariable linear regression analysis by gender for associations with percent-predicted peak VO_2

Variables	Female		Male	
	Standardized β	P value	Standardized β	P value
Hypertension	−0.10	0.15	0.03	0.66
Diabetes mellitus	−0.22	0.002*	−0.06	0.37
Tobacco use	−0.15	0.03*	−0.06	0.35
LV stroke volume index	0.07	0.33	0.06	0.30
LV mass index	−0.08	0.29	−0.06	0.37
LV outflow tract obstruction	−0.07	0.34	−0.02	0.75
≥ moderate MR during exercise	0.10	0.17	0.01	0.86
Right ventricular systolic pressure	−0.07	0.37	−0.082	0.19
E/e' ratio	−0.02	0.84	−0.16	0.08
Left atrial reservoir strain	0.27	0.001*	0.27	<0.001*

*, statistically significant. LV, left ventricular; MR, mitral regurgitation.

under-represented in the cohort (42%), and around 4 years older than male patients at the time of evaluation. Female HCM patients had smaller LV volume and stroke volume than male patients, even after adjusting for body surface area. This is concordant with a prior study using cardiac magnetic resonance imaging analysis (4).

Gender-related differences in exercise capacity

Impaired physical activity and exercise capacity in patients with HCM have been previously reported (23). Ghiselli *et al.* report that female HCM patients have more impaired exercise performance, using metabolic equivalents (METs) as a parameter of exercise capacity (24). While METs represents the body's ability to use oxygen, peak VO_2 measures represent the body's ability to deliver oxygen to the muscles during activity, which reflects ability to pump oxygen to the muscles. There is limited literature regarding the gender-related differences in quantitative exercise capacity derived by CPET (4,5). A large cohort of 3,673 HCM patients showed that females have reduced peak VO_2 and percent-predicted peak VO_2, compared with males (5). However, although the present study shows that female HCM patients had a reduced exercise capacity than male patients when evaluating by using peak VO_2 only, no significant gender-related difference was found in the percent-predicted peak VO_2 (5). This difference may be explained by the fact that the previous study included an older population with a more advanced stage of disease, compared to the current study. In addition, we used PS matching to minimize confounding factors. Therefore, the present study provides incremental data on the gender-related pathophysiology of HCM to the current available literature (5). Furthermore, gender-related differences on the impact of ageing on exercise capacity were shown in the present study. There was no significant gender-related difference in percent-predicted peak VO_2, although male patients had a greater age-associated decline in peak VO_2. Using the percent-predicted peak VO_2 or sex specific cut-off values of exercise capacity are likely more appropriate, compared to peak VO_2 alone, when assessing exercise capacity in HCM.

Pivotal role of LA mechanics on exercise capacity

LA passively and actively transfers blood into the LV during diastole, and therefore LA function is critically important in regulating LV filling pressure and cardiac output (25). When the compensatory function of LA for maintaining LV filling pressure is disrupted, the pulmonary artery pressure may easily increase through pressure and volume overload, such as during exercise (26,27). The previous studies report that female HCM patients have a greater degree of LV diastolic dysfunction than male patients (28,29). The findings from the present study that female HCM patients had higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and E/e', lower e' and increased diuretic use, compared with male patients also support that worse LV diastolic dysfunction in female patients is associated with impaired exercise capacity. In addition, stroke volume will be reflected by the dimensional changes in LA wall during diastole (30). The fact that female HCM patients had worse LA function in addition to smaller LV cavities supports the hypothesis that impaired exercise capacity in female patients may be related to an inadequate increase in stroke volume during exercise. Of note, in the present study, resting E/e' and stroke volume themselves were not predictors of reduced exercise capacity, indicating LA strain may be a more sensitive predictor for exercise capacity in HCM. In summary, the results from the present study suggest that LA mechanical dysfunction may support exercise-induced diastolic dysfunction and inadequate increase in stroke volume during exercise as key determinants of impaired exercise capacity in HCM, and gender-related differences in LA mechanical function may be one of the factors underpinning the gender-related differences in exercise capacity in HCM, independent from resting LV diastolic dysfunction and stroke volume.

Effect of ageing on LA mechanics

LA myocardial fibrosis in females is reported to be greater with various cardiac pathologies, based on magnetic resonance imaging or pathological analysis, suggesting a possible mechanism for the gender-related differences in LA mechanics (31,32). Of note, the impact of ageing on LA dysfunction differed between the sexes, with female patients having a more rapid deterioration in LA reservoir strain in the older age-group following menopause, and the gender-related differences in LA dysfunction then became more obvious. This gender-related difference in the effect of ageing on LA dysfunction may be explained by differences in sex hormones. A protective effect of estrogen on the development of myocardial hypertrophy and fibrosis has been shown in animal models (33). Postmenopausal endocrine changes may impact on gender-related differences for disease progression (34), leading to myocardial degeneration and fibrosis of LA itself or LV diastolic dysfunction. The present study suggests that we should consider the aging effect on the gender-related differences when assessing LA reservoir strain.

Study limitations

This was a single center study from a quaternary referral center. Therefore, there are inherent selection biases. The findings of the present study suggest that older female HCM patients may have more advanced LA myopathy; this needs to be confirmed in future studies, using cardiac magnetic resonance and/or pathological correlation. Furthermore, this study did not address potential prognostic value of gender-related differences in impaired exercise capacity and LA dysfunction, due to the small number of cardiac events in our cohort. Recent data show the utility of mavacamten in obstructive HCM with equal efficacy for both male and female patients in terms of the study endpoints (35). However, the present study did not include any patients treated with mavacamten.

Conclusions

The present study shows that gender-related differences in LA reservoir strain are increasingly notable for patients with HCM aged 60 years and older. LA reservoir strain was an independent determinant of percent-predicted peak VO_2 in HCM for both sexes.

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Footnote

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