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Chapter 5

Relationship Between Sex, Shape, and Substrate in Hypertrophic Cardiomyopathy

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) is a disease characterized by substantial genetic, morphologic and prognostic heterogeneity. Recently, sex-related differences in HCM were reported with females being older at diagnosis and exhibiting greater left ventricular outflow tract obstruction than men. We sought to evaluate the influence of sex on the HCM phenotype in a large cohort of unrelated patients with genetically and morphologically classified HCM.

Methods: Comprehensive genotyping of 13 HCM-susceptibility genes encoding myofilament and Z-disc proteins of the cardiac sarcomere was performed previously on 382 unrelated patients with HCM. Blinded to the genotype, the septal morphology was graded as reverse curvature-, sigmoidal-, apical-, or neutral contour-HCM by echocardiography.

Results: Overall, females were a) significantly older at diagnosis (45.1 ± 20 vs. 35.8 ± 17 years; $p<0.001$), b) had greater left ventricular outflow tract obstruction (53.5 ± 45 vs. 41.7 ± 42 mmHg; $p = 0.009$), c) were more likely to have concomitant hypertension (19% vs. 11%, $p = 0.02$), and d) had a higher rate of surgical myectomy (49% vs. 36%, $p = 0.01$) than men. Interestingly, these sex-based differences were apparent only among patients with sigmoidal-HCM ($p < 0.001$).

Conclusions: In this largest cohort of comprehensively genotyped and morphologically classified patients with clinically diagnosed HCM, we observed that the striking sex-related differences in the clinical phenotype are confined largely to the subset of mutation negative, sigmoidal-HCM. Whereas mutations within the sarcomere appear to dominate the disease process, in their absence, sex has a significant modifying effect, specifically noted in cases of sigmoidal-HCM.

Keywords

Sex, hypertrophy, hypertrophic cardiomyopathy, septum, echocardiography

Abbreviations

FH	Family history
HCM	Hypertrophic cardiomyopathy
LVEDD	Left ventricular end-diastolic dimension
LVH	Left ventricular hypertrophy
LVOT(O)	Left ventricular outflow tract (obstruction)
MLVWT	Maximum left ventricular wall thickness
SCA	Sudden cardiac arrest

Background

Affecting 1 in 500 persons, hypertrophic cardiomyopathy (HCM) is a disease or diseases characterized by marked genetic and prognostic heterogeneity[1]. Characterized by unexplained myocardial hypertrophy in the absence of precipitating factors, HCM is the most common cause of sudden death in young athletes[1, 2]. Since the sentinel discovery of the first locus linked to familial HCM[3] and the first HCM-associated mutations identified in the MYH7-encoded β-myosin heavy chain[4], hundreds of mutations scattered among 16 HCM-associated genes encoding sarcomeric proteins have been identified.

In a pre-genomics study by Lever *et al*, a striking correlation between the echocardiographically classified reverse- and sigmoidal septal contour, and age of onset was described[5]. This observation was followed by an early shape-genetic substrate analysis by Seidman *et al*. showing a correlation between reverse septal curvature and the presence of an HCM-associated MYH7 mutation[6]. Recently, a strong relationship between the genetic substrate comprised by all 8 myofilament genes underlying HCM and the morphological subtype was elucidated in a large cohort of genotyped patients with HCM[7]. The morphology of the left ventricle and septum were much more closely related to the presence or absence of an underlying myofilament mutation than to the age of the patient. In fact, multivariate analysis revealed reverse septal contour to be the strongest independent predictor of a myofilament mutation, with an odds ratio of 21[7].

Over the past several years, several studies have described sex differences in HCM[8, 9, 10, 11]. Most recently, significant sex related differences were reported in a large cohort of American and Italian patients with HCM. This study, in which women were underrepresented, showed that women were older and more symptomatic at the time of initial diagnosis[11]. Furthermore, the aforementioned study noted that women, usually with left ventricular outflow tract obstruction (LVOTO), were more likely to progress to advanced heart failure and stroke[11]. The relative contributions between sex, genetic substrate, and anatomical shape could not be ascertained because this analysis was performed on a cohort of genetically undefined and morphologically unclassified patients with HCM. Due to the heterogeneous nature both at the level of the genotype as well as the specific anatomical morphology, we sought to further evaluate the influence of sex on the HCM phenotype in a large cohort of unrelated patients with genetically and morphologically classified HCM.

Methods

Between April 1997 and December 2001, a total of 382 unrelated patients (210 male, mean maximum left ventricular wall thickness (MLVWT, 21.5 ± 6mm) underwent clinical evaluation including echocardiography in Mayo Clinic's HCM Clinic, a tertiary referral center for HCM and surgical septal myectomies. Furthermore, comprehensive genetic testing for 8 myofilament- and 5 Z-disc-associated, HCM-susceptibility genes was completed for all patients in Mayo Clinic's Windland Smith Rice Sudden Death Genomics Laboratory[12, 13, 14, 15, 16, 17, 18]. Informed consent for this IRB-approved study was obtained from all patients or parents, if underage.

Evaluation of septal curvature and cavity contour was previously performed and blinded to genotype, patients were classified morphologically into sigmoidal-, reverse curve-, apical-, and neutral contour-HCM[7]. The diagnosis of HCM was based on the echocardiographic demonstration of increased left ventricular wall thickness in the absence of clear etiology. Data on symptomatic status at initial visit (angina, dyspnea) was collected and scored in severity using the New York Heart Association (NYHA) - class, while the overall NYHA-class was assessed as well.

As hypertension is a common disease in the US population, some patients in this cohort also had mild concomitant hypertension. In these cases, the diagnosis of HCM was felt to be the appropriate diagnosis, by experienced clinicians dedicated to the care of patients with HCM, as the severity of hypertrophy was out of proportion to the concomitant hypertension. As a reference, 317 patients were referred to the Mayo HCM clinic during this time period and were felt to have either significant hypertension or aortic valve stenosis rather than HCM, and were therefore not included in this cohort.

Statistical analysis

Student's *t* tests and Fisher's exact tests were applied to calculate overall differences between the males and females, as well as sex differences for the four difference morphological subgroups using JMP Statistical Software (JMP 6.0, SAS Institute Inc. 2005). For characteristics with multiple levels, multivariate analyses (χ^2) were performed to assess the distribution of the given character between sexes, and therefore a single p-value was reported. Multiple logistic and linear regression analyses which included the sex-by-shape interaction effect were used to assess whether the difference between sexes were, in fact, dependent on morphology. A p-value <0.05 was considered statistically significant.

Results

The demographics of the entire cohort as well as the independent analysis of males and females are shown in **Table 1**. Overall, there were 382 patients (210 male) diagnosed at an average age of 41.5 ± 19 years with females being significantly older at diagnosis than males (45.1 ± 20 vs. 35.8 ± 17 years; $p < 0.001$). As inquired during the interview, one third of patients had a family history of HCM and 20% of patients had a family history of sudden cardiac arrest (SCA). Fifty-two patients (14%) were found to have concomitant hypertension at their evaluation at Mayo Clinic (mean systolic blood pressure, SBP, 123 ± 17 mmHg), which was more common in women. Nineteen percent of women (31/172) had concomitant hypertension compared to 11% of males (21; $p = 0.02$). Clinically, women were more symptomatic at diagnosis with respect to dyspnea ($p = 0.002$) and overall NYHA-class ($p = 0.0006$). During mean follow-up of 24 months (range 0.1 – 88 months), 25 patients died of HCM-associated causes, but no sex-differences were observed in these small numbers.

Table 1: Sex differences among patients with clinically diagnosed HCM

	Total	Male	Female	*p*-value
N	382	210	172	
Age at Dx (years)	41.5 ± 19	35.8 ± 17	45.1 ± 20	< 0.001
Age > 50 (%)	125 (33)	55 (26)	70 (41)	0.003
Angina* n(%)	151 (40)	80 (38)	71 (45)	0.2
Dyspnea* n(%)	250 (65)	126 (60)	134 (78)	0.002
NYHA-class n(%)				
Class I	116 (30)	82 (39)	34 (20)	
Class II	74 (19)	48 (23)	26 (45)	0.0006
Class III	164 (43)	76 (36)	88 (51)	
Class IV	8 (2)	4 (2)	4 (2)	
FH HCM (%)§	117 (31)	62 (30)	55 (32)	0.7
FH SCA (%)§	53 (14)	34 (17)	19 (11)	0.2
Hypertension (%)	52 (14)	21 (11)	31 (19)	0.02
SBP (mmHg)	123 ± 17	122 ± 16	124 ± 19	0.4
DBP (mmHg)	72 ± 11	73 ± 11	71 ± 12	0.1
Septal myectomy (%)	159 (42)	75 (36)	84 (49)	0.01
Septal ablation (%)	15 (4)	5 (2)	10 (6)	0.1
Echocardiography				
MLVWT (mm)	21.5 ± 6	21.7 ± 6	21.4 ± 7	0.7
Patients w/ obstruction (%)	294/382 (77)	153 (73)	141 (82)	0.04
Resting gradient (mm Hg)	47.3 ± 42	41.7 ± 40	53.5 ± 45	0.009
EF (%)	72.7 ± 8	72.5 ± 8	73.1 ± 8	0.4
Morphology				
Sigmoid	181 (47)	102 (49)	79 (46)	
Reverse	131 (35)	69 (33)	62 (36)	0.83
Apical	37 (10)	22 (10)	15 (9)	
Neutral	33 (8)	17 (8)	16 (9)	
Genotype positive	157 (41)	86 (41)	71(41)	1.0
Mutation location				
Thick filament (%)	57 (15)	23 (11)	34 (20)	
Intermediate filament (%)	57 (15)	37 (18)	20 (11)	
Thin filament (%)	12 (3)	9 (5)	3 (2)	0.06
Z-disc (%)	12 (3)	7 (3)	5 (3)	
Multiple (%)#	19 (5)	10 (4)	9 (5)	

Dx, diagnosis; DBP, diastolic blood pressure; DT, deceleration time; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LA, LVEDD, left ventricular end-diastolic dimension; MLVWT, maximum left ventricular wall thickness; SBP, systolic blood pressure SCA, sudden cardiac arrest defined as unexpected death, nocturnal or within one hour of witnessed collapse
* Symptomatic status as classified by NYHA-class, data shown are class II, III and IV combined; §In a first-degree relative; #Patients harboring more than one HCM mutation, (double/compound heterozygotes)

Although there was no difference in mean MLVWT between men and women (21.7 ± 6 vs. 21.4 ± 7 mm; p = 0.7), a slightly greater portion of women than men (141/172 (82%) vs. 153/210 (73%); p = 0.04) had obstructive HCM with a significantly higher LVOT gradient (53.5 ± 45 vs. 41.7 ± 40 mm Hg; p = 0.009). Overall, sigmoidal-HCM (181 patients, 47%) and reverse curve-HCM (131 patients, 35%) represented the two major morphological subtypes **(Figure 1)**; only 37 patients (10%) had apical-HCM and 33 patients (8%) had neutral contour-HCM. As shown previously, only 14% of patients with sigmoidal-HCM had a probable disease causing mutation following comprehensive open reading frame/splice site genetic testing of the 13 HCM-susceptibility genes compared to 79% of the patients with reverse curve-HCM[7, 17]. Overall, there was no statistical difference in the distribution of each morphological subtype of HCM or distribution of mutations between men and women.

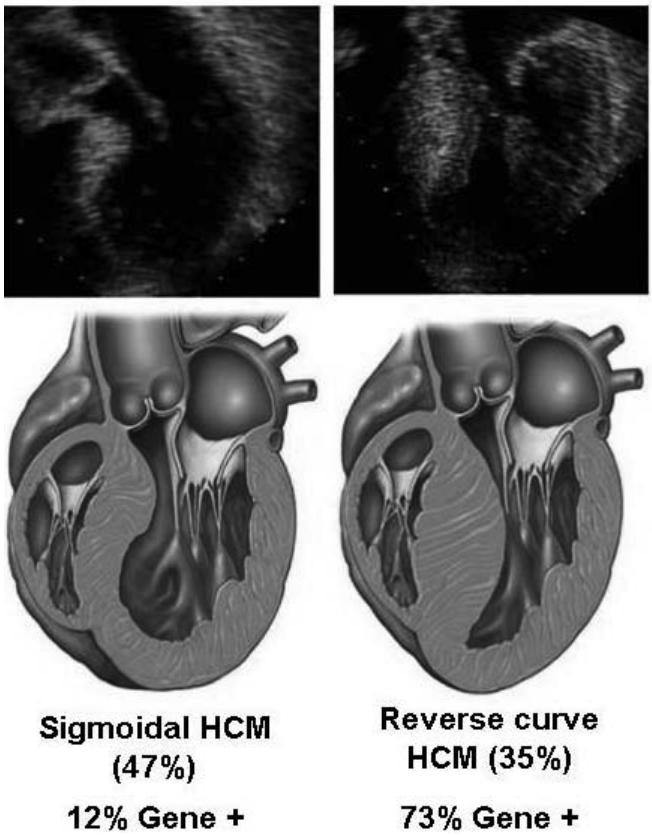

Figure 1: Two most common morphologic subtypes of HCM. Echocardiographic picture and graphic depiction of the 2 most common morphologic subtypes of HCM: sigmoidal-HCM (47%) and reverse curve-HCM (35%). Gene + = presence of HCM-associated mutation.

To investigate the influence of septal contour, we subdivided the cohort into the four septal contour subgroups and further analyzed the sex-related based differences of the two major sub-groups of sigmoidal- and reverse curve-HCM. Strikingly, the effect of sex on clinical phenotype that was first observed for the cohort at large was present only among patients with sigmoidal-HCM **(Table 2)**. Akin to the initial observations gleaned from the entire cohort, women with sigmoidal-HCM were older at diagnosis (56.0 ± 15 vs. 42.6 ± 16 years old; $p < 0.001$), were more likely to show obstructive HCM (75/79, 95% vs. 83/102, 84%; $p = 0.007$), had higher LVOT gradient (63.9 ± 40 vs. 49.7 ± 42 mm Hg; $p = 0.02$), and were more likely to have concomitant hypertension ($p = 0.05$) compared to men with sigmoidal-HCM. Although not statistically significant, more women (52%) than men (40%) underwent surgical septal myectomy ($p = 0.1$).

In contrast to the overall observation, no statistical differences were seen in symptomatic status (angina, dyspnea and overall NYHA-class) between sexes and the two morphological subgroups. Specifically, the clinical presentation in women was similar between obstructive sigmoidal HCM and obstructive reverse curve-HCM suggesting that symptoms stem from the degree of obstruction regardless of the morphological substrate for that obstruction. No statistical differences were observed between men and women in MLVWT ($p = 0.6$), EF (0.08) or the presence or location of a HCM-associated mutation ($p = 0.1$). Sex had no demonstrable effect for patients with reverse curve-HCM.

To assess whether the observed differences between sexes were dependent specifically on the morphology, multiple linear and logistic regression analyses were performed. For women, age at diagnosis ($p = 0.01$), systolic blood pressure ($p = 0.008$), and presence of LVOTO ($p = 0.04$) were in fact directly dependent on the sigmoidal morphology whereas prevalence of myectomy no longer achieved statistical significance.

Table 2: Sex differences in the two most common morphological subgroups

	Sigmoidal-HCM (n = 181)			Reverse Curve-HCM (n = 131)			Multi regr. model (*p*)
	Male	**Female**	***p***	**Male**	**Female**	***p***	
N	102	79		69	62		
Age at Dx (years)	42.6 ±16	56.0 ± 15	<0.001	29.2 ± 16	33.3 ± 18	0.2	0.01
Age > 50yrs (%)	36 (35)	47 (59)	0.002	5 (7)	10 (16)	0.2	0.9
Angina* n(%)	49 (48)	35 (44)	0.8	20 (29)	27 (44)	0.4	0.2
Dyspnea* n(%)	73 (72)	67 (85)	0.1	35 (51)	43 (69)	0.03	0.4
NYHA-class n (%)							
Class I	29 (28)	10 (13)		33 (48)	17 (27)		
Class II	23 (23)	21 (26)	0.07	18 (26)	19 (31)	0.07	0.7
Class III	49 (48)	47 (59		16 (23)	25 (40)		
Class IV	1 (1)	2 (3)		2 (3)	1 (2)		
FH HCM (%)*	25 (25)	14 (18)	0.4	29 (42)	30 (48)	0.5	0.2
FH SCA (%)*	13 (13)	5 (6)	0.2	15 (22)	10 (16)	0.5	0.5
Hypertension (%)	13 (13)	20 (26)	0.05	2 (3)	4 (7)	0.4	0.1
SBP (mmHg)	124 ± 16	131 ± 30	0.01	118 ± 17	115 ± 13	0.2	0.008
DBP (mmHg)	73 ± 10	73 ± 11	0.6	71 ± 11	69 ± 11	0.3	0.7
Septal myectomy	41 (40)	41 (52)	0.1	27 (39)	26 (42)	0.9	0.4
Echocardiography							
MLVWT (mm)	19.8 ± 5	19.4 ± 5	0.6	24.5 ± 7	24.6 ± 7	0.9	0.9
Patients w/ obstruction (%)	83 (84)	75 (95)	0.007	51 (74)	47 (76)	0.8	0.04
Resting gradient (mmHg)	49.7 ± 42	63.9 ± 40	0.02	38.1 ± 37	50.3 ± 49	0.1	0.9
EF (%)	73.1 ± 6	74.6 ± 5	0.08	71.7 ± 9	72.6 ± 9	0.6	0.8
Genotype positive	15 (15)	10 (13)	0.8	58 (84)	47 (76)	0.3	0.6
Mutation location							
Thick filament (%)	0 (0)	4 (5)	0.04	17 (25)	23 (37)	0.1	
Intermediate filament (%)	6 (6)	2 (3)	0.5	26 (38)	14 (23)	0.09	
Thin filament (%)	1 (1)	1 (1)	1.0	7 (10)	2 (3)	0.2	0.3
Z-disc (%)	7 (7)	3 (4)	0.5	0 (0)	0 (0)	-	
Multiple (%)#	1 (1)	0 (0)	1.0	8 (12)	8 (13)	1.0	

Dx, diagnosis; DBP, diastolic blood pressure; DT, deceleration time; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; LA, left atrial LVEDD, left ventricular end-diastolic dimension; MLVWT, maximum left ventricular wall thickness; SBP, systolic blood pressure SCA, sudden cardiac arrest, defined as unexpected death, nocturnal or within one hour of witnessed collapse.
* Symptomatic status as classified by NYHA-class, data shown are class II, III and IV combined
§In a first-degree relative; #Patients harboring more than one HCM mutation, (double/compound heterozygotes)

Our prior demonstration that reverse curve-HCM is predominantly genotype positive whereas sigmoidal-HCM is mostly genotype negative, prompted us to further homogenize the two most common subsets of morphological/genetic HCM by comparing patients with mutation positive/reverse curve-HCM (N = 105) to patients with mutation negative/sigmoidal-HCM (N = 156). Herein, sex-based differences in age at diagnosis, LVOT gradient and presence of concomitant hypertension were significantly higher among women than men for the largest subtype of HCM, i.e. mutation negative/sigmoidal-HCM (**Figure 2**).

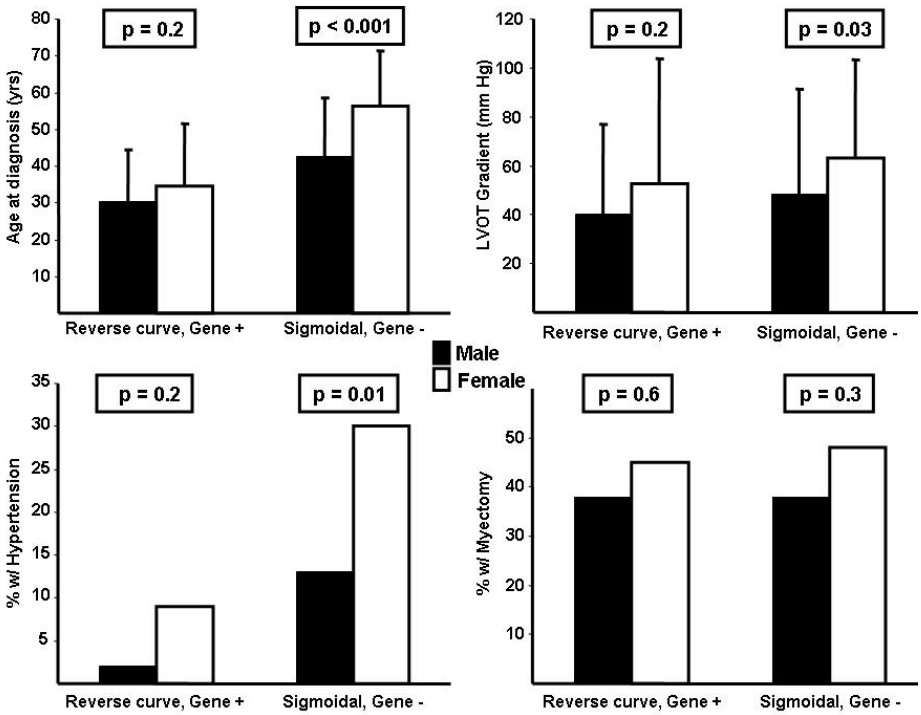

Figure 2: Male-female comparisons among patients with genotype positive, reverse curve-HCM and patients with genotype negative, sigmoidal-HCM. Bar diagrams showing the sex differences between males and females with HCM in the specific subgoups of reverse-curve, genotype positive (gene +), reverse curve-HCM and genotype negative (gene-), sigmoidal-HCM on age at diagnosis **(top left panel)**, resting left ventricular outflow tract gradient **(top right panel)**, percentage with surgical myectomy **(bottom right panel)**, and percentage with mild hypertension **(bottom left panel)**.

To investigate the potential confounding influence of concomitant hypertension, the analysis of sex-differences per septal subgroup was repeated excluding the patients diagnosed with concomitant hypertension. As shown in **Table 3**, all previously observed, statistically significant differences that were confined to the sigmoidal-HCM subgroup – age at diagnosis, number of patients with obstruction, degree of LVOT obstruction and rate of surgical myectomies – persisted, and no new statistically significant differences were seen (data not shown). Again, logistic regression models showed a clear female sex-sigmoidal shape dependence with respect to age at diagnosis ($p = 0.006$) and presence of LVOTO ($p = 0.02$). Overall, patients with sigmoidal-HCM and concomitant hypertension were less likely to undergo surgical myectomy than patient without hypertension (21% vs. 52%; $p < 0.001$), explaining the increase of significance in surgical myectomies when hypertension was excluded from the analysis.

Table 3: Sex differences in the two most common morphological subgroups after exclusion of patients with mild hypertension

	Sigmoidal-HCM (n = 148)			**Reverse Curve-HCM** (n = 125)			Multiple regr. models (*p*)
	Male	Female	*p*	Male	Female	*p*	
N	89	59	-	67	58	-	-
Age at Dx	40.9 ± 16	53.8 ± 15	0.001	29.4 ± 16	31.6 ± 16	0.5	0.006
Patients w/ obstruction n(%)	72 (81)	57 (97)	0.005	50 (75)	44 (75)	1.0	0.02
Resting gradient (mm Hg)	50.0 ± 42	66.1 ± 39	0.02	38.4 ± 37	49.0 ± 49	0.2	0.06
Septal myectomy n(%)	37 (42)	38 (64)	0.008	26 (39)	24 (41)	0.9	0.1

Discussion

Long considered a disease of the sarcomere or, more specifically, a disease of the myofilament, the discovery of mutations in multiple proteins outside the myofilament has caused an expansion of the spectrum of genetically-mediated pathways culminating in the disease phenotype that clinicians diagnose as HCM. Currently, over 18 HCM-susceptibility genes have now been published, with 8 of these genes encoding the essential cardiac myofilaments for which HCM genetic testing is now commercially available. With this large number of putative pathogenetic genes, a variety of genes yielding rare mutations, it is intriguing that 30 to 50% of adults with clinically diagnosed HCM remain genetically unexplained[19]. Binder *et al*. recently described an important genotype-phenotype relationship linking the genotypic substrate to the morphological shape. The analysis of a large cohort of genotyped – and echocardiographically characterized patients reveal that nearly 80% of patients with reverse curve-HCM have a positive genetic test for myofilament-HCM whereas the same genetic test is positive in fewer than 10% of patients clinically diagnosed with HCM but having a sigmoidal contour (i.e. sigmoidal-HCM) [7]. More recently, the yield for sigmoidal-HCM increased from 8% to 14% with the inclusion of 5 Z-disc associated genes[17]. Conversely, myofilament-HCM preferentially yields reverse curve-HCM whereas Z-disc-HCM predisposes to the development of sigmoidal-HCM[20].

Now, this present study examines the influence of sex in the interplay between genetic substrate and anatomical shape. Overall, this cohort mirrors previously published studies that examined the effect of sex on a presumably heterogeneous cohort of HCM lacking both morphological and genetic sub-classification[9, 10, 11]. Moreover, the data presented herein suggest that the differences are largely confined to sigmoidal-HCM which constitutes the anatomical phenotype of nearly half of the patients with clinically diagnosed HCM in our institution. Furthermore, it shows that specifically for age at diagnosis, systolic blood pressure and presence of LVOTO, there is a direct sex-by-morphology interaction for women with sigmoidal-HCM.

These observations among distinct subtypes of HCM generate several questions regarding the influence of sex in the phenotypic expression of disease. More specifically, it suggests that gender does not seem to be a significant modifier in reverse curve-HCM. This is supported by our original morphological data that the underlying genotype rather than sex appears to be the predominant determinant of septal morphology[7]. Thus, in reverse curve-HCM, the presence of a structural myofilament mutation is the driver of the phenotype, whereas in sigmoidal-HCM, a multi-factorial process culminates in a clinical expression of HCM, with significant male – female differences.

The presence of mild, concomitant hypertension may be a contributing factor in the pathogenesis of sigmoidal-HCM in women as 1 of 4 females within this morphological classification of HCM were mildly hypertensive. Several studies have shown that in response to pressure-overload, sex differences in the hypertrophic response patterns can be seen. Krumholz *et al*. showed that in isolated hypertension, significant sex differences can be observed in cardiac adaptation. In contrast to our findings, they show females predominantly develop a concentric hypertrophy, whereas a more eccentric pattern was observed in men[21]. Similar patterns of sex-dependent hypertrophy were observed in aortic stenosis[22, 23] and as a response to hemodynamic overload after myocardial infarction[24]. Furthermore, the presence of concomitant hypertension could mean there has always been a presence of low-grade hypertension and therefore a higher afterload in these patients. These factors combined with a (undefined) genetic susceptibility for HCM by means of a pathogenetic mutation or a LVH-promoting polymorphism [25], or endocrine factors [26] could all converge in the phenotype of clinically diagnosed, sigmoidal-HCM.

Although recent studies have shown that the prevalence of LVOTO is far more prevalent than previously believed [27, 28], our study may be biased with its higher prevalence of patients with obstructive HCM at rest due to our role as tertiary referral center for the surgical treatment of HCM. This is reflected in higher prevalence of patients with resting LVOTO (75% vs. ~35-40% in other published HCM cohorts)[27, 28] as well as a higher rate of surgical myectomies (42% vs. ~5-10% in other published HCM cohorts)[29]. Our observations might therefore be less applicable to a broader spectrum of patients with HCM, particularly non-obstructive HCM. On the other hand, the conclusions regarding these important sex-substrate differences appear robust for the subset of patients with obstructive disease.

Conclusions

In this large cohort of comprehensively genotyped and morphologically classified, unrelated patients with clinically diagnosed HCM, we observed that the striking and previously noted sex-related differences in HCM are confined largely to the subset of patients with mutation negative, sigmoidal-HCM. Sex does not appear to be a significant genetic modifier in myofilament-HCM.

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