Gender Differences in the Presentation of Adult Obstructive Hypertrophic Cardiomyopathy With Resting Gradient

— A Study of 122 Patients —

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The present study investigated gender differences among adult patients with obstructive hypertrophic cardiomyopathy (OHCM) and resting gradient. Using outflow gradients >10 mmHg and the presence of asymmetrical septal hypertrophy of the left ventricle as inclusion criteria, 122 patients were identified among patients referred for echocardiographic examinations between May 1990 and October 1996. Clinical, echocardiographical and follow-up data were compared between male and female patients. The female patients were significantly older than male patients (mean age $\pm$ SD 66.7 ± 10.5 vs 54.8 ± 12.5 years). The female patients had a smaller interventricular septal wall thickness, less frequent systolic anterior movement of the mitral valve, more frequent association with hypertension, and less frequent association with ischemic heart disease (IHD) and giant T wave inversion. In this study population, adult female patients presented with OHCM 12 years later than males. Whether this represents female patients' reluctance to seek medical attention early, a different disease process that affects predominantly elderly females, or a gender-specific end organ response to aging, hypertension, IHD and other processes, or the protective effects of estrogen remains to be determined. (*Jpn Circ J* 1999; 63: 859–864)

Key Words: Cardiomyopathy; Echocardiography; Gender; Hypertrophy

The natural history of hypertrophic cardiomyopathy (HCM) has been described in many large studies!^{1–4} However, gender differences among patients with obstructive hypertrophic cardiomyopathy (OHCM) have rarely been systematically analyzed. The present study attempted to define these differences in terms of clinical presentation, echocardiographic manifestation and outcome among adult patients with OHCM.

Methods

The hospital in which the study took place is a university-affiliated tertiary referral hospital in suburban Taipei, and the department receives patients from both inpatient wards and outpatient clinics. A total of 122 cases of OHCM were identified using the criteria of a peak systolic gradient of >10 mmHg (or a velocity of >1.6 m/s) in the left ventricular outflow tract (LVOT)⁵ and the presence of asymmetrical hypertrophy of the interventricular septum (IVS) (interventricular septal wall thickness/left ventricular posterior wall thickness >1.3). We included patients with a history of hypertension if they met these criteria. Their clinical profiles, such as age, gender, presenting symptoms, ECG and chest X-ray findings, current medications, echocardiographic and Doppler measurements, were

analyzed and follow-up data were obtained by either checking the hospital records or mailing a questionnaire to patients, followed by a telephone interview if the questionnaire was not returned within 10 days of mailing. In addition, to validate the completeness of follow-up, the patients' personal unique identification numbers were checked with the national death certificate registry to confirm those who died during the study period and the reported primary causes of death.

Echocardiographic Examination

Two-dimensional echocardiograms and Doppler studies were performed using a commercially available Hewlett-Packard 1500 or 2500 ultrasonic system equipped with a 2.5 MHz transducer, and 2-dimensional images were obtained in standard transducer positions (parasternal long- and short-axes and apical 2- and 4-chamber views). M-mode echocardiograms were derived from the 2-dimensional images. Cardiac dimensions were measured from M-mode echocardiograms according to the recommendations of the American Society of Echocardiography.⁶ Left ventricular outflow tract pressure gradients were estimated by the modified Bernoulli equation (4 times the square of the maximal velocity in the left ventricular outflow tract). Five minutes after sublingual administration of 0.6 mg of nitroglycerin, pressure gradient measurements were repeated.

Statistical Methods

The collected data was then tabulated and analyzed using BMDP Dynamic Release 7.0 (BMDP Statistical Software 1990. Los Angeles, CA, USA). All continuous variables were expressed as mean $\pm$ standard deviation (SD). Univariate analyses using 2-tailed Student's t-test and chi-square tests were performed. A p value of <0.05

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Table 1 Gender differences in Baseline Clinical Presentation, Electrocardiogram, ChestX-ray, Echocardiographic Findings, Medications and Mortality During Follow-up

	Male (n=46)	Female (n=76)	p-value
Age (year)	54.8±12.5	66.7±10.5	0.0000*
Syncope	9/56 (19.6%)	21/76 (27.6%)	0.3160
Chest pain	18/46 (39.1%)	33/76 (43.4%)	0.6415
Family history	0/46 (0.0%)	1/76 (1.3%)	1.0000
Hypertension	17/46 (37.0%)	44/76 (57.9%)	0.0250*
Diabetes mellitus	1/46 (2.2%)	5/76 (6.6%)	0.5102
Ischemic heart disease	7/46 (15.2%)	1/76 (1.3%)	0.0086*
Palpitation	10/46 (21.7%)	10/76 (13.2%)	0.2147
Congestive heart failure	10/46 (21.76%)	14/76 (18.4%)	0.6550
Left ventricular hypertrophy (By ECG)	24/46 (54.3%)	34/76 (44.7%)	0.3032
Q waves on ECG	4/46 (8.7%)	7/76 (9.2%)	0.9233
Giant T waves	11/46 (23.9%)	4/76 (5.3%)	0.0059*
Atrial fibrillation	4/46 (8.7%)	11/76 (14.5%)	0.5109
Ventricular ectopy	6/46 (13.0%)	4/76 (5.3%)	0.2389
Ventricular tachycardia	2/46 (4.3%)	3/76 (3.9%)	1.0000
Cardiomegaly on X-ray	31/46 (67.4%)	51/76 (67.1%)	0.9740
Congestion on X-ray	6/46 (13.0%)	18/76 (23.7%)	0.1519
IVSt	23.4±6.2	21.4±4.9	0.0435*
LVPWt	11.6±3.8	10.4±2.3	0.0628
IVSt/LVPWt	2.1±0.7	2.1±0.6	0.8299
VLVOT	3.1±1.0	3.1±1.1	0.6436
ΔPLVOT	41.1±27.1	44.1±29.8	0.5801
LADs	30.0±9.90	31.5±11.2	0.2102
VLVOT[post NTG]	3.7±1.0	3.9±1.2	0.1803
ΔPLVOT[post NTG]	56.9±29.7	68.0±41.5	0.0891
SAM	36/46 (78.3%)	36/76 (47.4%)	0.0008*
Mitral regurgitation	3/46 (6.5%)	5/75 (6.7%)	0.9752
Beta-blockers	21/46 (45.7%)	24/76 (31.6%)	0.1184
Calcium channel blockers	20/46 (43.5%)	28/76 (36.8%)	0.4671
Norpace	1/46 (2.2%)	1/76 (1.3%)	1.0000
Digitalis	1/46 (2.2%)	8/76 (10.5%)	0.1760
Diuretics	3/46 (6.5%)	11/76 (14.5%)	0.2972
ACEI	4/46 (8.7%)	3/76 (3.9%)	0.4894
Mortality during follow-up	6/46 (13.0%)	12/76 (15.8%)	0.6785

IVSt, thickness of the interventricular septum; LVPWt, thickness of the left ventricular posterior wall; VLVOT, velocity across left ventricular outflow tract; ΔPLVOT, pressure gradient across left ventricular outflow tract; LADs, left atrial diameter at endsystole; NTG, nitroglycerin; SAM, systolic anterior movement of the mitral valve. LVH, Left ventricular hypertrophy; ACEI, angiotensin converting enzyme inhibitors.

*Statistically significant.

was considered statistically significant.

Results

The study group consisted of 122 patients (36% male and 64% female). The mean age at the time of diagnosis was 61.5± years (range, 16–85). The average follow-up period was 3.2 years. Most patients remained stable during the follow-up period from the cardiac point of view, with only a few reported new manifestations such as syncope (3 patients), palpitation (5 patients), chest pain (7 patients), and worsening of dyspnea (23 patients). During the follow-up period, there were 4 cardiac deaths and 14 deaths due to other causes such as diabetes mellitus (4 patients), liver diseases (3 patients), cerebrovascular diseases (2 patients), sepsis (2 patients), pneumonia, colon carcinoma, and renal failure (one patient each). The gender differences in baseline data are listed in Table 1; that is, clinical characteristics such as age, syncope, chest pain, family history, hypertension, diabetes mellitus, ischemic heart disease (IHD), palpitation, and congestive heart failure; echocardiographic findings such as left ventricular hypertrophy, pathological Q waves, giant T waves, atrial fibrillation, ventricular ectopy, and ventricular tachycardia; chest X-ray findings such as cardiomegaly, pulmonary congestion; echocardiographic findings such as interventricular septal wall thick-

ness (IVSt), left ventricular posterior wall thickness (LVPWt), Doppler velocity and pressure gradient across left ventricular outflow tract at rest (VLVOT, and ΔPLVOT) and after sublingual nitroglycerin (VLVOT[post NTG] and ΔPLVOT[post NTG]), left atrial dimension at end systole (LADs), systolic anterior movement of mitral valve (SAM), mitral regurgitation; the use of medications such as -blockers, calcium channel blockers, disopyramide (Norpace), digitalis, diuretics, angiotensin converting enzyme inhibitors (ACEI); and mortality during the follow-up period. There were statistically significant gender differences in several variables. Female patients were much older than male (mean age±SD; 66.7±10.5 vs 54.8±12.5 years, $p<0.0001$). The IVSt of male patients was larger than that of female patients (23.4 mm vs 21.4 mm, $p=0.0435$). Male patients had significantly more SAM, giant T wave inversion, and IHD, but less association with hypertension than female patients. There were no statistically significant gender differences among the other variables.

Discussion

Features of This Study

Gender differences in patients with OHCM have rarely been systemically analyzed; a literature search yielded only a few articles focusing only on a few items (Table 2). Male

Table 2 Gender Differences in Patients With Hypertrophic Cardiomyopathy

Studies	Gender differences
Brugada ⁷	More LVH in male
Russel ⁸	Less stroke risk in male
Aurigemma ⁹	Elderly female with aortic stenosis developed more LVH
Pelliccia ¹⁰	Athletic training was a stimulus for LVH in male but not in female
Maron ¹¹	Sudden death on the athletic field is uncommon in young women
Dimitrow ¹²	Delayed onset of symptoms in women with HCM compared with men.
Present study	Male patients were younger, had thicker IVS, more negative giant T wave, more ischemic heart disease, and less hypertension.

Abbreviations: As in Table 1.

patients had more left ventricular hypertrophy (LVH) and gender accounted for 4.8–5.4% of the variability of the phenotypic expression of LVH in patients with HCM⁷; although female gender was associated with an increased risk of stroke in patients with HCM⁸; elderly females with aortic stenosis developed more marked concentric LVH⁹; athletic training was not a stimulus for LVH in women athletes as opposed to male athletes,¹⁰ and sudden death on the athletic field is uncommon in young women¹¹; women with HCM had a delayed onset of symptoms compared with men.¹² Our study, through systematic analyses, revealed the following gender differences: the male patients were younger, had thicker IVS, more giant negative T waves, SAM and IHD, but less hypertension. However, it should be pointed out that, our patients represented a subset of OHCM patients with a resting LVOT gradient, therefore the data and interpretation may not be applicable to all OHCM patients. We believe that the presence of a resting LVOT gradient might be more specific than the presence of SAM, because the latter can occur in cases with redundant mitral valve, which is by no means rare in the elderly population. Of course, the adoption of resting rather than provoked gradient as one of the inclusion criteria would improve specificity, but decrease sensitivity. We believe these findings might shed light on the pathophysiology and progression of OHCM as discussed next.

Interventricular Septal Wall Thickness

In the present study, the male patients had significantly thicker IVS (23.4 ± 6.2 vs 21.4 ± 4.9 mm, $p=0.0435$) and thicker, though not statistically significant, LVPW (11.6 ± 3.8 vs 10.4 ± 2.3 mm, $p=0.0628$) than the female patients. This can be explained by the fact that the male patients were significantly younger than the female patients (mean age 54.8 ± 12.5 vs 66.7 ± 10.5 years, $p=0.0000$) because it has been well demonstrated that there is an inverse relation between left ventricular wall thickness and age in HCM.¹³ Our results are also consistent with other published studies, which demonstrated statistically significant thicker IVS and LVPW in youthful patients with HCM than in the elderly.^{4,15} In fact, after adjustment for age, we found that the difference in IVSt became statistically insignificant ($p=0.1948$).

Systolic Anterior Movement of the Mitral Valve (SAM)

In elderly patients with HCM, the mild hypertrophy of the left ventricle is generally confined to the septum, giving the left ventricular cavity an elliptical shape and the SAM appears less pronounced than in youthful patients with HCM, in whom a crescent-shaped left ventricular cavity

and a reversed curvature of the interventricular septum predominates and the SAM appears more commonly.^{14,15} Our study results of significantly more SAM in male than female patients (78.3 vs 47.4%, $p=0.0008$) can be accounted for, at least in part, by the age differential between the present male and female patients. After adjustment for age, we found that the difference in the prevalence of SAM became marginally significant ($p=0.0670$). Therefore, whether gender plays an additional role in the prevalence of SAM remains to be determined.

Giant T Wave Inversion

Classical cases of apical HCM associated with giant T wave inversions on ECG are exceeding rare outside Japan.^{16,17} Because we selected only cases with asymmetrical septal hypertrophy and an outflow gradient, none of our patients had isolated apical hypertrophy of the left ventricle. Therefore, the different prevalence of giant T inversions of male and female patients may represent the degree of left ventricular hypertrophy, or is related to IHD, both of which are more prevalent and pronounced in male patients than in female patients. The exact mechanism remains unclear.

Ischemic Heart Disease (IHD)

Recent studies have shown significant gender differences in coronary heart disease.^{18,19} Death due to IHD occurs 5–10 years later in women than in men.²⁰ The lower prevalence of IHD in women can be partially attributed to risk factors such as lipid profiles,²⁰ smoking,²¹ and the probable protective effects of estrogen.²² Our study showed that, although the male patients with HCM were younger, they had significantly more IHD than the female patients. Thus, the gender differences of IHD prevail even in the presence of HCM.

Hypertension

In our study population, the prevalence of hypertension was significantly higher among female patients than male patients. There are several possible explanations: First, the female patients were significantly older than the male patients and the prevalence of hypertension tends to rise with age.²³ Second, according to a national survey in the USA,²³ the prevalence of hypertension in men is greater than in women at ages under 65; however, the prevalence of hypertension in women exceeds that of men at ages over 65. In the present study, the female patients had a mean age of 66.7 years as compared with the male patients' 54.8 years and this might account for the difference. Third, in a small subset of patients, predominantly elderly females,

Table 3 Mean Age and Gender Predominance Among Studies of Hypertrophic Cardiomyopathy

	No. of Patients	Follow-up (years)	Mean age (years)	% Male (%)
Shah et al ³²	190	5.2	33.6	60
McKenna et al ²	254	6	34	59.8
Maron et al ³³	99	3	38	75.8
Romeo et al ⁴	125	7.6	34	63.2
Seiler et al ³⁴	139	10.3	37	81.3
Kofflard et al ³⁵	113	7.3	37	53.1
Spirito et al ³⁶	25	4.4	44	68
Fananapazir et al ³⁷	230	2.3	39	57
Yoshida et al ³⁸	83	6.7	51.2	79.5
Koga et al ³	314	5	42	72.9
Cannan et al ³⁹	37	7.7	59	43
Lewis et al ⁴⁰	52	3.4	69	13
Fay et al ²⁸	95	4.2	71.8	39
Present study	122	2.2	61.5	35.9

Table 4 Differences of Mean Age Between Male and Female Patients With HCM

	Patients Number	Obstructive (%)	% Male (%)	Mean Age (years)				
				Total	Male	Female	Diff.*	p-value
Frank ¹ (Familial)	40	80	55	26.8	20.0	35.1	15.1	<0.01
Frank ¹ (Sporadic)	86	80	72	32.7	29.3	41.3	12.0	<0.001
Motamed ⁴¹ (>40 year)	100	(-)	43	56.9	53.5	59.5	6.0	(-)
Level ¹⁴	56	70	66	49	44.6	57.5	12.9	(-)
Dimitrow ¹²	94	(-)	59	(-)	26.7	31.3	4.6	<0.05
Present study	122	100	35.9	61.5	54.8	66.7	11.9	<0.001

Abbreviation: (-) data not available. *difference between male and female mean age.

Fig 1. Mean age and male percentage of the study population. *Numbers in the graph refer to reference numbers in the text, p is the present study.

hypertension has been demonstrated to cause severe concentric hypertrophy of the left ventricle, a small ventricular cavity, and supernormal indexes of systolic function.²⁴ Patients can even present with left ventricular outflow obstructions similar to that seen in HCM.^{25,26} But most believe that hypertension is not the primary cause of HCM although it may coexist with or aggravate HCM.^{24,27,28} In our study, the high prevalence of hypertension among female patients maybe due to one, 2 or all of aforementioned factors.

Age Differences

The most striking finding of the present study is the age differential between the male and female patients. There is evidence of the impact of gender on the development of many disease processes. Men tend to develop symptoms of schizophrenia 5 years earlier,^{29,30} but develop symptoms of rheumatoid arthritis 5 years later than women.³¹ In review-

ing the literature, we also found that men appear to develop symptoms of HCM or are diagnosed to have HCM earlier than women. As listed in Table 3, most published reports on HCM showed a male predominance (>50%) in the young population (mean age <55 years)^{2-4,32-38} and a female predominance in the elderly population (mean age >55 years),^{28,39,40} as demonstrated in Fig 1. And, as listed in Table 4, women appear to present with HCM 5-15 years later than their male counterparts.^{1,12,14,41} In other studies, it was found that HCM in the elderly appeared to be a subset with distinctive left ventricular morphology and female predominance. They have a relatively small heart, an ovoid left ventricular cavity contour, a reduced left ventricular outflow tract, anterior displacement of the mitral valve and sizable deposits of calcium in the region of the mitral annulus.^{14,40} They generally have a favorable prognosis.²⁸ These studies, and the present data, suggest that gender may play an important role in the natural development, presentation, and progression of HCM. There are several possible explanations for the apparent difference. First, female patients may tend to seek medical attention later than their male counterparts. Second, HCM in the elderly may be the result of a different pathologic process from that active in younger patients, one that begins during or before middle age, yet is compatible with long life and this process affects females predominantly. Third, it may represent a gender-specific end organ response to the same disease process because growth, aging, systemic hypertension and coronary artery disease, etc. can affect quite differently male or female patients with the same genetic background. In the original study of Frank and Braunwald,¹ males were significantly younger than females in both the familial and sporadic forms of the disease (Av.=20.0 years vs 35.1 years in the familial and Av.=29.3 years vs 41.3 years in the sporadic group). Kitzman et al reported

that the mean value of indexed heart weights increased significantly in woman between the 3rd and 10th decades of life ($p < 0.01$) and yet remain relatively constant with time in men.⁴² In aortic stenosis, with chronic left ventricular pressure overload, female patients develop more marked concentric hypertrophy, lower levels of wall stress, and higher indices of systolic function than their male counterparts.^{9,43,44} These studies tend to favor the explanation that the age difference seen in male and female patients with HCM represents the gender-specific end organ response to aging and the underlying disease process. Dimitrow et al's postulation that endogenous estrogen may delay the development of HCM in females as compared with males is quite interesting.¹² The exact mechanisms of estrogen's cardiovascular protective effects remain unclear, but estrogen's favorable effects on circulating lipoproteins,²⁰ its calcium-channel blocking properties⁴⁵⁻⁴⁹ and the effect on endothelium-derived relaxing factors⁵⁰⁻⁵² have been postulated to play important roles. Further studies are needed, particularly longitudinal studies of patients with documented genetic aberration, as well as studies of the cardiovascular effects of estrogen, to clearly elucidate the impact of gender and estrogen on the natural course of HCM and the mechanism of the different progression patterns among male and female patients.

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