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Clinical Characteristics and Outcomes of Hypertrophic Cardiomyopathy in Taiwan—A Tertiary Center Experience

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Summary

Background: Most information concerning hypertrophic cardiomyopathy has been derived from western countries and Japan.

Hypothesis: Patients with hypertrophic cardiomyopathy in Taiwan may have a distinct morphology and clinical picture.

Methods: Information from 163 consecutive patients with hypertrophic cardiomyopathy at a medical center in Taiwan from 1990 through 2005 was retrospectively collected. The diagnosis of hypertrophic cardiomyopathy required echocardiographic demonstration of left ventricular hypertrophy (wall thickness $\geqslant 15$ mm during diastole) in a specific region or with diffuse distribution. Follow-up information was obtained from medical records.

Results: Among 163 patients (male, 52%), the mean follow-up period was 5.3 ± 4.1 years. Men had nearly a threefold increase in prevalence of apical hypertrophic cardiomyopathy (23.8% vs. 8.9%, p = 0.03), younger onset of initial evaluation (57.2 ± 12.9 vs. 64.8 ± 11.3, $p < 0.001$), and lower prevalence of hypertrophic obstructive cardiomyopathy (33.3% vs. 63.3%, $p < 0.001$) compared to women. Fifty-eight patients (35.6%) experienced cardiovascular events, of which pulmonary edema and paroxysmal atrial fibrillation were the most common (19.7% and 12.3%, respectively). The annual cardiovascular mortality rate was 0.8%. In multivariate analysis, left ventricular outflow obstruction [odds ratio (OR): 4.92, p = 0.001], atrial fibrillation (OR: 3.53, p = 0.014), and female gender (OR: 2.99, p = 0.043) were independent predictors of mortality.

Conclusions: Hypertrophic cardiomyopathy did not significantly increase cardiovascular mortality rate, but over one-third of patients with hypertrophic cardiomyopathy experienced cardiovascular events. High prevalence of left ventricular outflow obstruction especially in elderly women was observed. Left ventricular outflow obstruction, atrial fibrillation, and female gender were predictors of mortality.

Key words: hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, apical hypertrophic cardiomyopathy, prognosis

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac condition, which is characterized by clinical heterogeneity. Various epidemiologic investigations have estimated the rate of HCM among the general adult population as 0.2%,[1,2] and annual mortality rates were reportedly 0.6–6%.[3–5] In western countries, asymmetrical septal hypertrophic HCM is the predominant form, and the apical variant is approximately 1%.[6] In contrast, apical HCM is 12–25% in Japan, and is

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typically associated with a better prognosis.[7,8] Gender difference is an important clinical feature of a variety of acquired cardiovascular conditions, such as coronary artery disease.[9] Therefore, the purpose of this study was to describe the clinical features and to determine if gender influenced the clinical presentation and outcome in a Taiwanese cohort of HCM patients.

Methods

Study Population and Study Design

Between 1990 and 2005, 163 consecutive patients with echocardiographically documented HCM were evaluated in a tertiary referral center in Taiwan. All patients were assessed clinically on at least two separate occasions. Data were collected retrospectively regarding demographic characteristics, symptoms, electrocardiogram results, and the patient's functional status at presentation. The results of transthoracic echocardiography and cardiac catheterization were also reviewed. In this study, patients diagnosed with HCM and later developed hypertension during the follow-up period were included. All patients were clinically evaluated for at least 6 months; the mean duration of follow-up was 5.3 ± 4.1 years.

Definitions

A diagnosis of HCM was based on the echocardiographic identification of a hypertrophic, nondilated left ventricle (wall thickness $\geqslant$ 15 mm) in the absence of other cardiac or systemic diseases capable of producing the observed magnitude of hypertrophy (such as aortic stenosis, uncontrolled arterial hypertension or infiltrative cardiomyopathy).[6] The diagnostic criteria for apical HCM included asymmetric left ventricular apex hypertrophy with a wall thickness $\geqslant$ 15 mm and a ratio of apical to posterior wall thickness $\geqslant$ 1.5 based on transthoracic echocardiography.[8] Giant negative T waves were defined as $\geqslant$ 10 mm deep, in addition to tall R waves in the left precordial leads.[10] Electrocardiographic diagnosis of left ventricular hypertrophy was based on Sokolow–Lyon criterion ($SV_1 + RV\ (LVH)_{5-6} \geqslant$ 35 mm).

Ambulatory Electrocardiographic Monitoring and Treadmill Exercise Test

All HCM patients presenting with syncope, near-syncope or with heart palpitations were subjected to a 24-h holter monitoring. For patients presenting with typical chest pain (but without ST segment depression on electrocardiography) proceeding with treadmill exercise. Patients with hypertrophic obstructive cardiomyopathy did not receive the treadmill exercise test.

Echocardiography: Echocardiographic studies were performed with a 2.5 MHz transducer connected to an ultrasound system (Hewlett-Packard Sonos 2500; Andover, MA, U.S.A). Transthoracic echocardiography was performed according to the recommendations of the American Society of Echocardiography. Left ventricular outflow tract obstruction was defined as a peak instantaneous outflow gradient at least 30 mmHg from the apical five-chamber view.[11] Systolic anterior motion of the mitral valve was evaluated using the M-mode image. The apical wall thickness was evaluated on apical two-chamber or apical four-chamber views.

Statistical analysis: Data were expressed as mean $\pm$ standard deviation. Statistical analysis was performed using Student's *t*-test for continuous variables or chi-square test for categorical variables. Multivariate regression analyses were performed using a stepwise forward regression model in which each variable with a p value $\leqslant 0.1$ in the univariate analysis was entered into the model. The clinical endpoint employed in this study was death due to cardiovascular causes. The annual mortality rate was calculated using all available follow-up data. For all tests, $p < 0.05$ was considered significant. All analyses were performed with SPSS software, 10.0 (Chicago, Illinois).

Results

Clinical Characteristics

The clinical features of the 163 patients with HCM are listed in Table 1 and the distribution of age at initial evaluation is presented in Fig. 1. Male patients were significantly younger at the time of evaluation than their female counterparts (57.2 ± 12.9 vs. 64.8 ± 11.3 years, $p < 0.001$), and Taiwanese men were found to have a higher percentage of coronary heart disease than women (22.9% vs. 11.4%, $p = 0.063$).

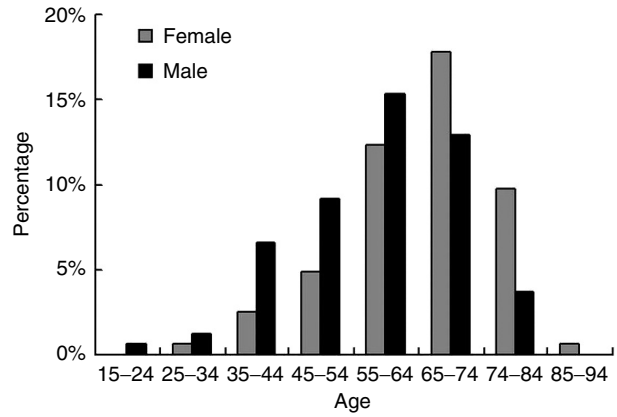

FIG. 1 Age at initial evaluation in 163 patients with hypertrophic cardiomyopathy.

TABLE 1 Initial demographic and clinical characteristic of the study patients

Features	Men (n = 84)	Women (n = 79)	P value
Demographics			
Age at presentation, yr	57.2 ± 12.9	64.8 ± 11.3	<0.001
Symptoms			
Dyspnea, %	71.4	79.7	NS
Exertional chest tightness, %	60.7	54.4	NS
Palpitation, %	16.9	16.5	NS
Near-syncope and syncope, %	12.0	11.4	NS
Underlying disease			
Diabetes mellitus, %	15.7	21.5	NS
Hypertension, %	17.9	16.5	NS
Coronary artery disease, %	22.9	11.4	0.06
Medications			
Beta-blockers, %	42.9	38.0	NS
Calcium channel blockers, %	57.1	58.2	NS
Amiodarone, %	7.1	6.3	NS
Electrocardiography			
Normal tracing, %	9.5	8.9	NS
Atrial fibrillation, %	22.6	17.7	NS
Left ventricular hypertrophy, %	85.7	82.3	NS
ST depression, %	67.9	65.8	NS
Giant negative T waves, %	28.6	8.9	0.001
Echocardiography			
Left atrium, cm	3.78 ± 0.65	3.85 ± 0.70	NS
Interventricular septum thickness (cm)	1.82 ± 0.47	1.88 ± 0.41	NS
Posterior wall thickness (cm)	1.11 ± 0.28	1.11 ± 0.24	NS
Apex thickness (cm) (n = 52)	1.91 ± 0.27	1.83 ± 0.17	0.06
LVEDD (cm)	4.58 ± 0.52	4.30 ± 0.54	0.001
LVESD (cm)	2.46 ± 0.49	2.36 ± 0.45	NS
SAM, %	36.9	62.0	0.003
Mitral regurgitation (1 ~ 2+/3 ~ 4+), %	92.9 / 7.1	84.8 / 15.2	0.02
Resting LVOT gradient ⩾ 30 mmHg, %	33.3	63.3	<0.001

LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; SAM = systolic anterior motion of mitral valve; LVOT = left ventricular outflow tract.

On electrocardiography, 84.6% of patients showed left ventricular hypertrophy voltage. Men had higher percentages of giant negative T waves than women (28.6% vs. 8.9%, p = 0.001). Among the 46 patients who had ambulatory electrocardiographic monitoring, 7 (15.2%) patients had nonsustained ventricular tachycardia, 8.7% had paroxysmal atrial tachycardia, 26.1% had greater than 10 atrial ectopic beats, and 23.9% had greater than 10 ventricular ectopic beats. On transthoracic echocardiography, mean interventricular septum thickness was 1.83 ± 0.44 cm and the mean ratio of interventricular septum and posterior wall was 1.65. Significant left ventricular outflow obstruction was found in approximately half of the study subjects (48.1%). Female patients had smaller left ventricular cavity, higher percentage of left ventricular outflow obstruction, and systolic anterior motion of mitral valve (Table 1). Figure 2 shows the distribution of the different types of HCM identified in this study. Male patients had nearly a threefold higher prevalence of pure apical HCM (23.8% vs. 8.9%, p = 0.012) compared to women.

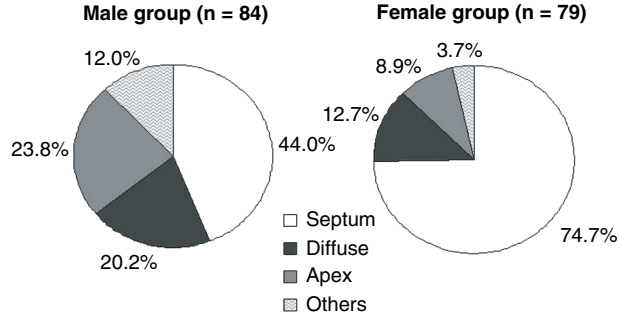

FIG. 2 Percentages of different morphologic forms of hypertrophic cardiomyopathy in male and female patients, respectively.

During the follow-up period, 18 patients received treadmill exercise tests and 64 patients received selective coronary angiograms to determine if myocardial ischemia was present. Not one of the 18 treadmill patients developed ventricular arrhythmia during the exercise test; however 8 (44%) patients had positive

TABLE 2 Major cardiovascular events and mortality among 163 patients with HCM during the follow-up period

Event or intervention	Number of patients
Myetomy and MVR, n	8
TASH, n	3
Syncope without identified causes, n	15
Acute pulmonary edema, n	32
Paroxysmal atrial fibrillation, n	20
Ventricular arrhythmia, n	5
Ischemic stroke with atrial fibrillation, n	10
Acute myocardial infarction, n	5
Infective endocarditis, n	1
Mortality causes	
Ventricular arrhythmia, n	2
Refractory heart failure, n	2
Acute mitral regurgitation, n	1
Ischemic stroke with atrial fibrillation, n	2
Sepsis, n	13
Malignancy, n	4

MVR = mitral valve replacement; TASH = transcoronary ablation of septal hypertrophy.

TABLE 3 Predictors of mortality among 163 patients with HCM

Parameters	Univariate analysis odds ratio (95% confidence interval)	P value
LVOT obstruction	3.46 (1.48–7.63)	0.005
Atrial fibrillation	2.88 (1.13–7.33)	0.023
Female	4.99 (1.77–14.08)	0.002
Acute pulmonary edema	3.80 (1.50–9.63)	0.006
Ventricular arrhythmia	4.12 (0.65–26.08)	0.16
Marked LVH	3.81 (1.15–12.55)	0.036
Apical HCM	0.30 (0.07–1.33)	0.07
Use of beta-blockers	0.25 (0.08–0.77)	0.012

Parameters	Multivariate analysis odds ratio (95% CI)	P value
LVOT obstruction	4.92 (1.84–13.54)	0.001
Atrial fibrillation	3.53 (1.25–8.22)	0.014
Female	2.99 (1.13–9.87)	0.043

LVOT = denotes left ventricular outflow obstruction; marked LVH stands for interventricular septal wall thickness $\geqslant$ 2.5 cm.

exercise test for ischemia. A significant epicardial coronary artery lesion of $\geqslant$ 50% was found in 28 patients (44.4%), with 14.3% having myocardial bridging of the coronary artery.

Clinical Outcome

During the follow-up period, 24 patients died (mean age was 72.8 years), although only 7 died of cardiovascular-related issues (Table 2). The overall mortality rate in this study (i.e. due to all causes of death) was 14.7% and the annual all-cause mortality rate was 2.8%. In contrast, the overall mortality rate attributable to cardiovascular causes was only 4.3%. The annual cardiovascular mortality rate was 0.8%, and the annual sudden death rate was 0.2%.

Table 2 demonstrates that 20.3% of the patients had atrial fibrillation on initial evaluation. Further, 39.4% of patients developed ischemic stroke and 4 patients (12.1%) suffered recurrent ischemic stroke during follow-up. Among the patients without atrial fibrillation at the time of initial evaluation, 14.6% later developed ischemic stroke and 2.3% of these patients suffered from recurrent stroke.

Using multivariate logistic regression analysis, determinants of death in patients with HCM included left ventricular outflow obstruction, atrial fibrillation, and being female (Table 3).

Discussion

There are several unique findings in this retrospective study of hypertrophic cardiomyopathy in this Asian country. First, the age of the Taiwanese patients with HCM at evaluation was much older than that reported in western countries (average 61 years vs. 45 years in western countries).[4,6] Second, a high prevalence of apical HCM was observed in Taiwanese patients with 24.5% of the entire HCM population affected. Third, approximately 48% of patients with HCM demonstrated a sizeable left ventricular outflow gradient, which was much higher than the previously reported 25%.[6] Fourth, cardiovascular outcome was surprisingly favorable in this referral center. Finally, gender differences in clinical presentations and outcome were observed.

Clinical Presentations

The apical HCM reported in Japanese patients was approximately 13–25% and 3–11% in western populations.[4,12,13] The finding reported herein suggest that the apical variant is the more common subtype of hypertophic cardiomyopathy in Oriental populations. This higher prevalence of left ventricular outflow obstruction observed in Taiwanese may be partly due to selection bias in the tertiary center study. Women with HCM had a relatively thick basal interventricular septal wall, a higher percentage of systolic anterior motion of mitral valves, and a smaller left ventricular cavity. Therefore, higher ratio of left ventricular outflow obstruction was observed in women. The study by Maron *et al*. (1995) reported that the elderly HCM patients were predominantly women, also with higher prevalence of left ventricular outflow obstruction.[14] Ho *et al*. also found that being female

TABLE 4 Differences of annual mortality rate among studies of hypertrophic cardiomyopathy

Author-country/year	Patient no.	Follow-up/ year	Annual all-cause mortality rate	Annual HCM mortality rate
Present study—Taiwan	163	5.3	2.8%	0.8%
Ho[16]-China/2004	118	5.8	1.6%	1.5%
Maron[4]-USA/1999	277	8.1	2%	1.3%
Kofflard[5]-Netherlands/2003	225	8	1.3%	0.8%
Koga[7]-Japan/1984	136	5.1	4.3%	3.7%

was the only independent predictor of major cardiovascular events associated with HCM.[15] One explanation for this gender difference in clinical features and outcome could be due to the higher prevalence of left ventricular outflow obstruction and the lower prevalence of apical HCM among the female population. During the follow-up period of this study, many patients died of sepsis or an unstable hemodynamic status due to sepsis. These conditions could potentially worsen the severity of left ventricular outflow obstruction (predominantly identified in women) and therefore, women had a worse clinical outcome.

Clinical Outcome

Approximately 36% of the patients with HCM experienced at least one episode of a cardiovascular event during the follow-up period. Acute pulmonary edema and paroxysmal atrial fibrillation were the most commonly encountered events. It is possible that impaired left ventricular diastolic function, which was frequently observed in patients with HCM, contributed to progressive left atrial enlargement and subsequent atrial fibrillation.[16] In addition, patients with left ventricular outflow obstruction appeared to be highly dependent on the active contribution of the atrium for adequate left ventricular filling and appeared to be associated with mitral regurgitation. In these patients, left ventricular outflow obstruction could easily have resulted in congestive heart failure.[6,17]

In the patients described herein, the initial prevalence of atrial fibrillation was 20.3%, which was similar to several reported HCM populations (which range from 10% to 28%).[4,6] Among patients with atrial fibrillation in this study, the relative risk of ischemic stroke was 2.7-fold greater than among those patients in sinus rhythm. The relative risk of recurrent ischemic stroke was 5.3-fold greater in atrial fibrillation patients than those in sinus rhythm. Higashikawa *et al*. reported that among HCM patients with atrial fibrillation, the risk of ischemic stroke was eightfold greater than among patients in sinus rhythm.[18] Therefore, aggressive anticoagulation therapy should be considered in this special patient population.

In this study, the annual cardiovascular mortality rate was 0.8% and the annual sudden cardiac death rate was 0.23%. According to the 2004 annual health statistics report of UNICEF (http://www.unicef.org) and Taiwan (http://www.doh.gov.tw/statistic), the crude annual mortality of the general population ranged from 0.6 to 0.9% in the United States, European countries, Japan and Taiwan. The annual cardiovascular mortality rate for HCM in tertiary referral centers were reportedly 1.5 to 3.2%;[6,7,13,16] however, the annual cardiovascular mortality rate for HCM in community-based populations was only 1%.[4,5] Kitaoka *et al*. reported that apical HCM in Japanese or western populations had been associated with a good prognosis and there was no HCM-related death reported during the follow-up period.[14] The high prevalence of apical HCM and no HCM-related mortality in this group might explain why the annual cardiovascular death rate reported in this current trial was lower than the annual cardiovascular death rate in referral centers and similar to the rate reported in nonreferral centers (Table 4).

Predictors of Outcome

In this retrospective report, female patients with left ventricular outflow obstruction, and atrial fibrillation were predictors of mortality. Several clinical parameters including left ventricular outflow obstruction at rest, atrial fibrillation, sustained or nonsustained ventricular arrhythmia, recurrent syncope, and extreme left ventricular hypertrophy (wall thickness $\geqslant$ 3 cm) have previously been documented as predictors of mortality for HCM.[6] Sepsis and atrial fibrillation could easily contribute to unstable hemodynamic status in elderly patients with left ventricular outflow obstruction. The female patients in our study were older and had a high prevalence of left ventricular outflow obstruction, which may explain why female patients had a poorer clinical outcome than the male patients. Few patients with an extremely thick septal wall and sustained ventricular arrhythmia were identified thereby making it difficult to identify these as possible predictors of mortality.

Limitations

A small number of limitations were noted in this trial that warrant discussion. First, myocardial biopsies were

not routinely performed in cardiac patients to confirm the final diagnosis of HCM. Instead, the diagnosis of HCM was based on guidelines published in previous studies.[6,10] Second, the selected patients did not represent the general population with HCM in Taiwan. Nonetheless, our findings suggest that the outcome of the general Taiwanese population with HCM is remarkably optimistic. Third, a 24-hour electrocardiographic monitoring and treadmill exercise were not routinely administered to every patient with HCM. As a result, some patients with asymptomatic arrhythmia and exercise-induced hypotension may not have been identified.

Conclusions

This retrospective study of HCM in a tertiary referral center in Taiwan demonstrated that HCM has a relatively benign clinical course in terms of cardiovascular-related mortality. Taiwanese hypertrophic cardiomyopathy appears to have a distinct morphology and clinical picture compared to HCM patients from other countries and.gender may contribute to differences in clinical features and outcome. The data presented here identified left ventricular outflow obstruction, atrial fibrillation, and female gender as predictors of mortality. Early diagnosis and treatment (particularly in women), control of left ventricular outflow obstruction, and adequate management of atrial fibrillation are important issues to be considered in patients with HCM.

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