Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 39, No. 4, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(01)01778-8

Long-Term Outcome in Patients With Apical Hypertrophic Cardiomyopathy

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OBJECTIVES The aim of this study was to describe long-term outcome in patients with apical hypertrophic cardiomyopathy (ApHCM) followed in a tertiary referral center.

BACKGROUND Apical hypertrophic cardiomyopathy is a relatively rare form of hypertrophic cardiomyopathy (HCM), first described in Japan. Initial reports, based on a limited number of patients, emphasized the benign nature of this condition.

METHODS A retrospective study of 105 patients with ApHCM diagnosed at the Toronto General Hospital from 1975 to 2000 was performed. Symptoms, clinical findings, mortality and cardiovascular morbidity were analyzed.

RESULTS The mean age at presentation was 41.4 ± 14.5 years. During a mean follow-up of 13.6 ± 8.3 years from presentation, cardiovascular mortality was 1.9% (2/105) and annual cardiovascular mortality was 0.1%. Overall survival was 95% at 15 years. Thirty-two patients (30%) had one or more major morbid events, the most frequent being atrial fibrillation (12%) and myocardial infarction (10%). Probability of survival without morbid events was 74% at 15 years. Three predictors of cardiovascular morbidity were identified: age at presentation <41 years, left atrial enlargement, and New York Heart Association (NYHA) class ≥II at baseline. Forty-four percent of the patients were asymptomatic at the time of last follow-up.

CONCLUSIONS Apical hypertrophic cardiomyopathy in North American patients is not associated with sudden cardiac death and has a benign prognosis in terms of cardiovascular mortality. Nevertheless, one third of these patients experience serious cardiovascular complications, such as myocardial infarction and arrhythmias. These data are likely to influence the counseling and management of patients with ApHCM. (J Am Coll Cardiol 2002;39:638–45) © 2002 by the American College of Cardiology

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease of the myocardium, caused by mutations in one of nine genes encoding sarcomeric proteins (1,2) and characterized by marked variability in morphological expression and natural history (3,4). Apical hypertrophic cardiomyopathy (ApHCM) is a relatively rare form of HCM, in which the hypertrophy of myocardium predominantly involves the apex of the left ventricle (LV) (5,6). The typical features of ApHCM, first described by Sakamoto (5) and Yamaguchi (6) and their associates, consist of "giant" T wave negativity in the electrocardiogram (5) and a "spade-like" configuration of the LV cavity at end-diastole on left ventriculography (6).

Studies of ApHCM in the Japanese population have indicated a benign prognosis in patients with this condition (5–8), with the exception of elderly patients (9). A less favorable outcome was initially reported from non-Japanese patients with all forms of HCM (10) and with ApHCM, in particular (11). More recent studies have found ApHCM to be associated with a rare occurrence of cardiovascular mortality and morbidity even in the Western population (12,13). However, severe clinical manifestations, including sudden cardiac death, severe arrhythmias and apical infarction with apical aneurysm, have frequently been described in case reports (14–20). Because the majority of long-term follow-up studies from non-Asian centers are based on small numbers of patients (11–13,21–25), the long-term prognosis of ApHCM in non-Japanese patients remains poorly defined. Therefore, this study was undertaken to investigate the clinical manifestations and the long-term mortality and morbidity in 105 patients with ApHCM, diagnosed in a large tertiary care referral center's HCM clinic.

METHODS

Study population and study design. The study subjects were identified through a registry of the HCM Clinic at the Toronto General Hospital, the University Health Network, which serves as a large tertiary referral center. We studied the clinical outcome of 105 consecutive patients with a diagnosis of ApHCM seen in the HCM clinic between January 1975 and December 2000. Data were abstracted on demographic characteristics, coronary risk factors, family history of HCM, symptoms and findings at physical exam-

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Manuscript received July 31, 2001; revised manuscript received October 29, 2001, accepted November 13, 2001.

Abbreviations and Acronyms

AF	= atrial fibrillation
ApHCM	= apical hypertrophic cardiomyopathy
ECG	= electrocardiogram
echo	= echocardiography
HCM	= hypertrophic cardiomyopathy
LV	= left ventricle
LVH	= left ventricular hypertrophy
NSVT	= non-sustained ventricular tachycardia
NYHA	= New York Heart Association
VT	= ventricular tachycardia

ination at the time of presentation and diagnosis of ApHCM, as well as at the most recent follow-up. In addition, the results of electrocardiogram (ECG), echocardiography, ambulatory ECG monitoring and cardiac catheterization were reviewed. Twenty-six patients in this study were included in a previous report on ApHCM from this institution (13). The study was approved by the Research Ethics Board of the Toronto General Hospital.

Diagnostic criteria. The diagnostic criteria for ApHCM included demonstration of asymmetric left ventricular hypertrophy (LVH), confined predominantly to the LV apex with an apical wall thickness ≥15 mm and a ratio of maximal apical to posterior wall thickness ≥1.5, based on two-dimensional echocardiography (echo) or MRI. Patients with ApHCM according to the previously stated criteria were further subdivided into two groups based on whether they had isolated asymmetric apical hypertrophy—"pure" ApHCM—or had a coexistent hypertrophy of the interventricular septum—"mixed" ApHCM. Patients with the "mixed" ApHCM pattern had to demonstrate the greatest wall thickness in the apical segments.

Follow-up. Late follow-up was obtained by direct contact with patients, their physicians or by clinic chart review. Additional medical records were obtained to confirm the timing and presence of cardiovascular complications.

Definition of mortality and morbidity. Mortality was classified as cardiovascular in origin if it was secondary to one of the following: myocardial infarction, intractable arrhythmia, congestive heart failure or stroke. Major morbid events included 1) atrial fibrillation or flutter, 2) sustained ventricular tachycardia (VT), defined as >30 consecutive ventricular beats or associated with hemodynamic instability, 3) ventricular fibrillation, 4) myocardial infarction, 5) stroke or transient ischemic attack, or 6) congestive heart failure. The diagnosis of myocardial infarction was established in the presence of characteristic symptoms, typical pattern on ECG and elevated cardiac enzymes, or by the appearance of a definite new wall motion abnormality on echocardiography, MRI or left ventricular angiography, in association with changes in ECG.

Electrocardiography. The initial and the most recent ECG were analyzed for the presence of LVH using the Sokolow-Lyon criteria (26). The corrected QT interval was measured in lead V_2 (27). "Giant" T wave negativity was defined as a voltage of negative T wave ≥1 mV (≥10 mm) in any of the leads. Maximum T wave inversion from any of the leads V_3, V_4, V_5 or V_6 and the sum of T wave amplitude in these leads in the initial and the most recent ECG were compared. Time-related changes in T wave amplitude were analyzed at mid-term (>4 and ≤8 years) and long-term (>8 years) follow-up. In the presence of an apical infarction, the last ECG before the infarction was used for comparison with the initial ECG tracing.

Echocardiography. Doppler echo studies were performed using commercially available ultrasound equipment. Left atrial dimension at end-systole and standard left ventricular dimensions at end-diastole and end-systole, as well as LV wall thickness were obtained from two-dimensional images according to the standards of the American Society of Echocardiography (28). The maximal apical wall thickness was obtained from the standard apical four- and two-chamber views at end-diastole. These views were available in all of our patients and used for comparisons throughout the follow-up. Doppler recordings of blood velocity at the apical, midventricular and outflow tract level were performed. Left atrium was considered enlarged if the left atrial diameter was ≥40 mm. We compared the results of the first and the most recent echo in patients who did not have any signs of myocardial infarction and in whom the interval between the two examinations was ≥4 years.

Ambulatory ECG monitoring. In 86 patients, all available ambulatory ECG monitoring covering at least a 24-h period was reviewed for the occurrence of non-sustained ventricular tachycardia (NSVT), defined as a minimum of three consecutive ventricular beats with a rate of ≥100 beats/min.

Radionuclide studies. Exercise myocardial perfusion imaging using either thallium-201 or technetium-99m-sestamibi was performed in 75 patients. In 24 patients, the results of myocardial scintigraphy and coronary angiography were compared.

Angiography. Forty-two patients underwent selective coronary and LV angiography for symptoms of myocardial ischemia. The procedure included the evaluation of epicardial coronary artery disease, presence of a "spade-like" configuration on left ventriculogram, and the assessment of outflow tract obstruction at rest or with provocation (isoproterenol, extrasystoles, amyl nitrite).

Statistics. Continuous data are presented as the mean and one standard deviation (SD). Differences between groups were analyzed by unpaired or paired *t* tests, Fisher's exact test or the chi-square test, where appropriate. Longitudinal data were analyzed by Kaplan-Meier estimate (29). Information on survival of an age- and gender-matched Ontario population without ischemic heart disease, obtained from the Central East Health Information Partnership, Canada, was used for a qualitative comparison with our study patients. The time to death or a morbid event was calculated as the difference between the date of presentation and the

Table 1. Baseline Characteristics of the Study Population

Men/women	78/27
Age at presentation (yrs)	41.4 ± 14.5
Age at diagnosis (yrs)	46.1 ± 15.1
Family history of HCM	23 (22%)
Family history of SCD	10 (10%)
History of hypertension	27 (26%)
ECG	
LVH signs	68 (65%)
T wave inversion	98 (93%)
Giant T waves ≥10 mm	49 (47%)
Max T wave inversion (mm)	9.9 ± 5.6
Normal ECG	6 (6%)
QTc interval (ms)	445 ± 80
Echo	
IVS thickness (mm)	12.3 ± 3.3
PW thickness (mm)	10.6 ± 1.5
Apical thickness (mm)	19.0 ± 3.1
Ratio apical/PW thickness	1.8 ± 0.3
LV end-diastolic diameter (mm)	48.3 ± 5.2
LV end-systolic diameter (mm)	30.2 ± 5.5
Fractional shortening (%)	37.5 ± 9.2
LA end-systolic diameter (mm)	41.0 ± 5.9
NYHA class I/II/III and IV	64/41/0
S_4 audible/palpable	63 (60%)/34 (32%)
Systolic/diastolic blood pressure (mm Hg)	132 ± 21/78 ± 11

Data presented as number (%) or mean ± 1 SD.
ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; IVS = interventricular septum; LA = left atrial; LV = left ventricular; LVH = left ventricular hypertrophy; Max = maximum; NYHA = New York Heart Association; PW = posterior wall; QTc = corrected QT interval; SCD = sudden cardiac death; S_4 = fourth heart sound.

event date. In patients with multiple morbid events, only the time to the first event was entered into analysis.

Univariate predictors with a significance level of ≤0.1 were entered into multivariate Cox proportional hazards model using a backwards elimination algorithm. A p value <0.05 was considered significant. Statistical analyses were performed using Stat View (version 4.5, Macintosh; Abacus Concepts, Berkeley, California) and SPSS for Windows (version 10, SPSS Inc., Chicago, Illinois).

RESULTS

Baseline

Clinical characteristics. The 105 patients with a diagnosis of ApHCM represented approximately 7% of all HCM cases in our center. There were no patients of Japanese origin in the study population. Clinical and demographic variables at baseline are presented in Table 1. Eighty-six patients (82%) were between 20 and 59 years of age, and only 12 patients (11%) were 60 years or older at the time of presentation. Although 26% of patients had a history of treated hypertension, the blood pressure was well controlled. There was a delay between the initial presentation to a primary care provider and the final diagnosis of ApHCM, usually caused by interpretation of ECG changes as signs of coronary artery disease or athlete's heart.

A total of 57 patients (54%) were symptomatic at the first presentation. The main symptoms were angina (16%), atypical chest pain (14%), palpitations (10%), dyspnea (6%) and presyncope/syncope (6%). In 17 of these 57 symptomatic patients, the first manifestation was a morbid event including AF (n = 10), myocardial infarction (n = 5), exercise-induced ventricular fibrillation (n = 1) and congestive heart failure (n = 1). Two patients with AF presented with concomitant embolic events (transient ischemic attack/stroke). The remaining 48 asymptomatic patients (46%) presented with incidental findings, such as an abnormal ECG (n = 41), a new undiagnosed murmur (n = 3), abnormal echocardiography performed during evaluation for other reasons (n = 2) or screening for a family history of HCM (n = 2).

Electrocardiography. The analyses of initial ECG recordings are presented in Table 1. The maximal T wave negativity was most frequently seen in lead V_4 (n = 41), followed by V_5 (n = 35) and V_3 (n = 13). "Giant" T wave negativity, with mean value 14.4 ± 4.3 mm, was seen in 49 patients (47%). There was no difference in age or history of hypertension between patients with and without "giant" T waves. The mean value of T wave negativity for the remaining patients was 5.6 ± 2.2 mm. There was no significant difference in distribution of ECG abnormalities between the "pure" and the "mixed" ApHCM on initial ECG. There was a weak correlation between the degree of apical thickness and both the maximal T wave negativity ($r = 0.231$, $p = 0.018$) and the sum of T wave amplitudes in precordial leads ($r = 0.269$, $p = 0.006$). No significant correlation was found between the maximal T wave negativity and other echocardiographic variables, e.g., the septal thickness or the ratio of apical to septal thickness.

Echocardiography. The echocardiographic variables at baseline are presented in Table 1. No patient had left ventricular outflow tract obstruction, either at rest or following provocative maneuvers. There were 89 patients (85%) with the "pure" form of ApHCM, with hypertrophy limited to the apical portion of LV, and 16 patients (15%) with the "mixed" form of ApHCM, with extension of the hypertrophy beyond the apical segments. The "mixed" group demonstrated a significantly worsened functional NYHA class, as well as increased interventricular septum, posterior wall and apical thickness ($p < 0.05$) at baseline. There were no significant differences in length of follow-up, blood pressure, age, gender, presence of coronary risk factors or family history between the "pure" and the "mixed" forms of ApHCM.

The final diagnosis of ApHCM was established using echo in 96 patients (91%), although in 14 patients (13%) the initial suspicion of ApHCM occurred during left ventriculography, performed for other reasons before an echo examination, and by MRI in 9 patients (9%). The nine patients who were diagnosed by MRI scan all had a "pure" ApHCM and an initially non-diagnostic echo study. When echo was repeated to look specifically for ApHCM, echo confirmed the diagnosis in all nine patients.

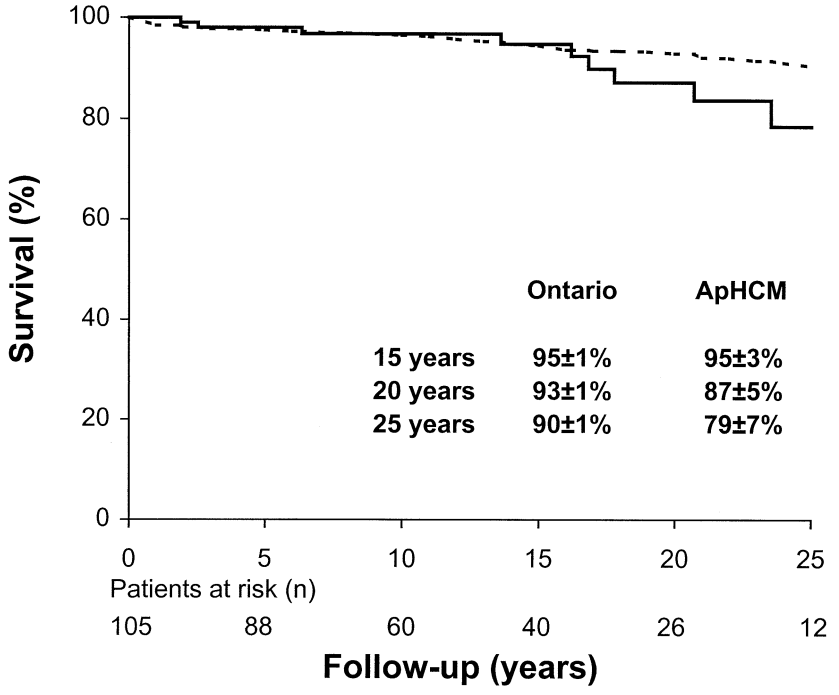

Figure 1. Kaplan-Meier plot of overall survival since initial presentation of 105 patients with apical hypertrophic cardiomyopathy (ApHCM) **(solid line)** in comparison to an age- and gender-matched Ontario population (Ontario) **(dotted line)**. Probability of survival ± 1 standard error at 15, 20 and 25 years of follow-up are shown.

Follow-up

Mortality. The mean follow-up from the time of presentation was 13.6 ± 8.3 years (median 12.9, range 0.2 to 32.2) and from the time of diagnosis was 8.8 ± 6.1 years (median 7.8, range 0.1 to 24.7). Eleven patients died during follow-up; thus, the overall mortality in this study was 10.5%. There were nine noncardiac deaths and two cardiovascular deaths, one caused by myocardial infarction and another caused by congestive heart failure, consistent with a cardiovascular mortality of 1.9% and an annual cardiovascular mortality of 0.1%. Figure 1 shows Kaplan-Meier estimates of overall survival since presentation for patients with ApHCM in comparison to an age- and gender-matched Ontario population.

Major morbidity. There were 40 morbid cardiovascular events, AF (n = 13), myocardial infarction (n = 11), congestive heart failure (n = 5), transient ischemic attack (n = 4), stroke (n = 3), VT (n = 3) and ventricular fibrillation (n = 1). These morbid events occurred in 32/105 patients (30%). Kaplan-Meier event-free survival curve for patients without any major cardiac morbidity is shown in Figure 2. Seventeen patients (16%) presented with a morbid event. There was no significant association between morbidity and gender, history of hypertension, "pure" or "mixed" type of ApHCM, apical wall thickness, apical to posterior wall thickness ratio or "giant" T wave negativity when tested by a univariate Cox regression analysis. Age at presentation <41 years, left atrial enlargement and NYHA class ≥II at baseline were significantly associated with higher risk for cardiovascular morbidity by a univariate Cox regression analysis, and all three were also found to be the independent predictors of cardiovascular morbidity by a multivariate Cox regression analysis: age at presentation <41 years with Hazard ratio 4.8 (95% CI 2.0 to 11.7), left atrial enlargement Hazard ratio 3.0 (95% CI 1.4 to 6.6), and NYHA class ≥II at baseline Hazard ratio 3.4 (95% CI 1.5 to 7.6) ($p < 0.05$).

Thirteen patients (12%) developed AF during follow-up. A univariate Cox regression analysis identified left atrial enlargement at baseline as the only predictor of AF (Hazard ratio 6.5, $p = 0.017$).

Eleven patients (10%) suffered a myocardial infarction, which was apical in location in nine patients. The degree of wall motion abnormality varied from a large apical aneurysm to apical hypokinesis. Four patients suffered an asymptomatic apical infarction. The development of myocardial infarction was usually associated with a loss of "giant" T wave negativity, development of new pathological Q waves, decrease in R wave amplitude, ST elevation or a new RBBB (one patient). Coronary angiography was performed in 10 of the 11 patients with infarction, showing normal coronary arteries in 9 patients and concomitant coronary artery disease in only 1 elderly patient, who subsequently died of congestive heart failure. We identified age <41 years at the time of presentation (Hazard ratio 12, $p = 0.005$) as a predictor of myocardial infarction. During follow-up, one patient with a large apical aneurysm and normal coronary arteries underwent a surgical aneurysmectomy eight years after infarction for management of recurrent VT.

Seven patients suffered stroke or transient ischemic attack

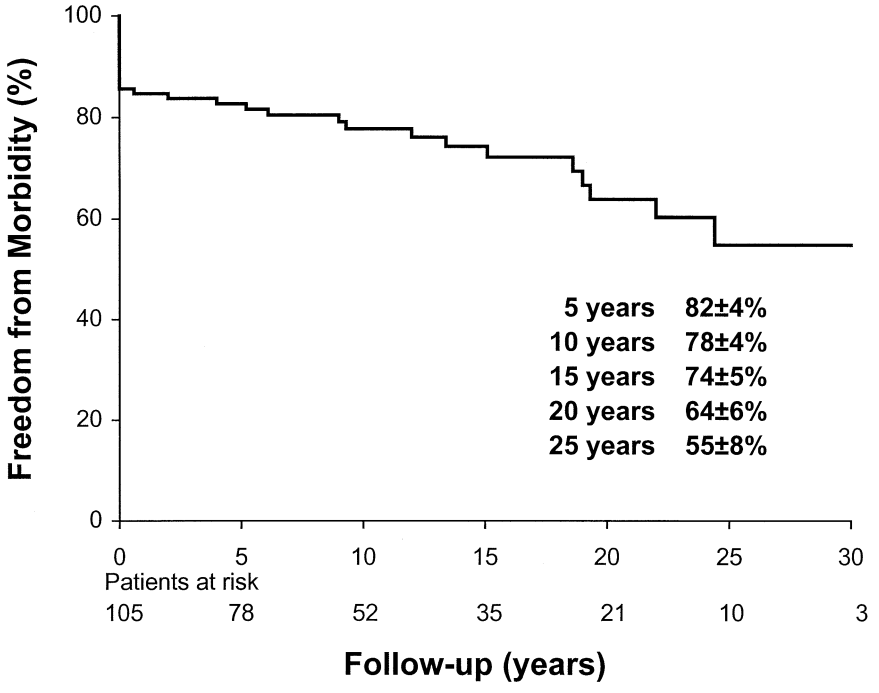

Figure 2. Kaplan-Meier analysis of freedom from major cardiac morbidity with probability of event-free survival ± 1 standard error at 5, 10, 15, 20 and 25 years of follow-up are shown.

during follow-up. A univariate Cox regression analysis identified only two significant predictors of cerebrovascular events, LA size (Hazard ratio 1.2, p = 0.005) and presence of AF (Hazard ratio 5.5, p = 0.026).

Clinical findings at follow-up. Forty-four percent of the patients were asymptomatic at the last follow-up, whereas 56% reported symptoms such as dyspnea on exertion (38%), palpitations (21%), typical angina (18%), atypical chest pain (14%), presyncope (10%) and syncope (6%). At the last follow-up, 62 patients were in NYHA functional class I, 35 patients in class II, 7 patients in class III and 1 in class IV. Twenty-one of 105 patients (20%) deteriorated in their functional class; 70 patients (66%) were unchanged, and 14 patients (14%) improved by one class.

The analysis of all available Holter monitor recordings revealed single or multiple short runs of NSVT with a mean 7 ± 5 beats at a mean heart rate of 146 ± 41 beats/min in 20 out of 86 monitored patients (23%). Only one patient was symptomatic with syncopal episodes associated with NSVT.

Forty-four patients (42%) did not take any cardiac medications at the last follow-up, while the remaining patients were on beta blockers (n = 30), calcium channel blockers (n = 34) or antiarrhythmic therapy (n = 13).

ECG and echocardiography. Two patterns of ECG changes during midterm (4 to 8 years) and long-term (>8 years) follow-up were observed (Table 2). In patients presenting with "giant" T wave negativity (>10 mm), a statistically significant decrease in the maximum T wave amplitude was seen (p < 0.05). In contrast, in patients presenting with "non-giant" T waves, there was a significant increase in the sum of negative precordial T waves (p = 0.027). Furthermore, five patients presenting with only minor T wave changes developed "giant" T wave negativity during follow-up.

Long-term changes in echocardiographic variables are

Table 2. Changes in ECG Variables During Mid-Term and Long-Term Follow-up

	Baseline	Mid-Term	p Value	Baseline	Long-Term	p Value
Giant T wave at baseline						
Follow-up (yr)	6.0 ± 1.3			11.9 ± 4.0		
Patients (n)	n = 16			n = 20		
Maximum T wave (mm)	15.6 ± 5.3	11.7 ± 5.2	0.003	13.5 ± 4.2	10.5 ± 5.5	0.036
Sum of T waves (mm)	43.7 ± 18.1	34.9 ± 14.5	0.029	37.7 ± 14.4	28.7 ± 15.7	0.051
Non-giant T wave at baseline						
Follow-up (yr)	5.3 ± 1.7			16.0 ± 5.8		
Patients (n)	n = 15			n = 23		
Maximum T wave (mm)	5.4 ± 5.9	4.7 ± 3.2	0.62	4.3 ± 2.9	6.1 ± 4.1	0.056
Sum of T waves (mm)	8.8 ± 15.9	9.5 ± 19.9	0.86	8.4 ± 11.1	16.1 ± 14.3	0.027

Data presented as number or mean ± 1 SD.

Table 3. Changes in Echocardiographic Variables in 44 Patients With Apical Hypertrophic Cardiomyopathy During a Mean Follow-Up of 9.0 ± 4.6 Years

Echocardiographic Variable	Baseline	Follow-Up	p Value
LV end-diastolic diameter (mm)	48.0 ± 5.9	51.2 ± 6.2	<0.001
LV end-systolic diameter (mm)	29.2 ± 7.0	30.9 ± 6.9	0.045
Fractional shortening (%)	39.5 ± 11.0	39.9 ± 8.9	0.83
IVS thickness (mm)	12.2 ± 3.5	12.6 ± 3.5	0.27
PW thickness (mm)	10.3 ± 1.4	10.6 ± 1.4	0.40
Apex thickness (mm)	19.0 ± 3.4	19.2 ± 4.6	0.77
LA end-systolic diameter (mm)	40.9 ± 6.8	43.7 ± 6.8	0.001

Mean ± 1 SD.
IVS = interventricular septum; LA = left atrial; LV = left ventricular; PW = posterior wall.

summarized in Table 3. There was a significant increase in LV diastolic and systolic dimensions and left atrial diameter during follow-up.

Radionuclide studies. Thirty-nine of 75 patients (52%), who underwent myocardial scintigraphy had abnormal scans, showing reversible perfusion defects in 28 patients, fixed defects in 4 patients and both reversible and fixed defects in 7 patients. In 32 of 39 cases the apical segment was involved, showing either reversible (27 patients) or fixed (5 patients) perfusion defects. There was no difference in the apical thickness and the magnitude of T wave negativity between patients with and without abnormal perfusion scan.

Angiography. During follow-up, 42 patients underwent selective coronary and LV angiography for symptoms of myocardial ischemia. A "spade-like" configuration of the LV cavity at end-diastole on left ventriculogram was present in 29 of 42 patients (69%). A significant epicardial coronary artery lesion of ≥50% was detected in eight patients, and compression of coronary arteries was observed in three patients. Thus, 31 patients (74%) had no evidence of coronary artery disease on coronary angiography, despite symptoms suggesting myocardial ischemia. No significant LVOT gradient was detected at rest. Twenty-four patients underwent both coronary angiography and myocardial scintigraphy scans. Nineteen of these patients (79%) had abnormal myocardial scintigraphy scans. In 10 patients (53%) with abnormal perfusion scan and all patients with normal scan, the coronary arteries were normal.

DISCUSSION

In the present study, we characterized clinical findings, mortality and morbidity in, to the best of our knowledge, the largest reported North American series of patients with ApHCM. ApHCM was first described in Japan (5,6), where it represents 13% to 25% of the entire HCM population (7,10,30–32). Outside Japan, ApHCM is less common and has been reported in 3% to 11% of all HCM patients (3,10,12,33).

Outcome and prognosis in patients with ApHCM. Our study showed a benign long-term prognosis in the North American patients with ApHCM in terms of cardiovascular mortality. The probability of survival during the first 15 years of follow-up for patients with the apical form of HCM was similar to the age- and gender-matched Ontario population. There was no sudden cardiac death during follow-up, and long-term cardiovascular mortality for ApHCM in our study was 1.9% with an annual mortality of 0.1%. This is lower than the annual mortality of 1.4% for the entire HCM spectrum in a nonreferral-based patient population recently reported by Maron et al. (34) and the cardiovascular annual mortality of up to 4% previously reported from other tertiary referral centers (3,35). Furthermore, our results are similar to those reported from Japan, where ApHCM is usually associated with a good prognosis (7,8,32), often better than in other forms of HCM (31). In addition, the presence of "giant" T wave inversion in the Japanese HCM patients has been identified as a predictor of favorable outcome (31). In contrast, the initial, small North American study reported more serious clinical course with 28% mortality in patients with ApHCM (11). However, their study population differed significantly with regard to the magnitude of T wave negativity and LV configuration, both from the Japanese (5,6) and the other Western ApHCM patients including our cohort (12,13,22,23).

The most frequent morbid events in our study were AF and myocardial infarction. Atrial fibrillation occurred in 12% of the patients. Left atrial enlargement on the baseline echo was identified as the only predictor of AF. Impaired LV relaxation in patients with HCM, including ApHCM, has been previously proposed as a mechanism for progressive left atrial enlargement and subsequent AF (3,13).

Apical myocardial infarction in the presence of normal coronary arteries was found in about 10% of our patients. The mechanisms responsible for ischemia in ApHCM are still unclear, although there is some evidence of a limitation in coronary flow reserve (21). Decreased capillary myocardial ratio, small vessel disease and other mechanisms (3,32) may also result in regional apical ischemia and be involved in development of apical infarction and aneurysm. Apical segmental dysfunction with midventricular obstruction has been previously described as a typical wall motion abnormality seen in 11% of patients with ApHCM (32). We found various degrees of abnormal apical segments, ranging from a large apical aneurysm requiring surgical removal to apical hypokinesis.

Presentation. The clinical characteristics of our study population were similar to those described by Japanese and other investigators, with similar age at presentation (5,12,13,23), male predominance (7,12,21,23), a high percentage of asymptomatic patients (7,8,21), "giant" T wave negativity in the ECG (5) and a "spade-like" LV configuration at end-diastole (6). As previously described (6,7,13), a fourth heart sound, reflecting impaired LV relaxation, is not only frequently audible but also palpable, as shown in the present study. Thus the phenotypic expression of ApHCM in the North American patients seems identical to that seen in the Japanese patients with this form of HCM.

Diagnosis. The correct diagnosis of this form of HCM is of major importance because many of these patients present at a relatively young age with chest pain and dramatic T wave inversions that frequently result in hospitalization for suspected coronary artery disease. The use of echocardiography in the diagnosis of HCM has been widely recognized (36); however, adequate visualization of the LV apex may be difficult, and measurements of the apical thickness are subject to variability depending on the echocardiographic view (37). In our study, echo established a correct diagnosis in 91% of the patients and failed to initially diagnose ApHCM in nine patients in whom MRI clearly demonstrated asymmetric hypertrophy of the apical LV segment. The recent study by Pons-Llado et al. (38) showed that MRI allowed better overall assessment of the degree and extent of LVH in HCM patients than did echo. The apical segment was adequately visualized in all patients by MRI but only in 60% of the patients by echo (38). Furthermore, MRI allows the early diagnosis of ApHCM by identifying even a small quantity of hypertrophied myocardium in different apical locations in a "non-spade" variety of ApHCM (39). The recent development of intravenous contrast agents for echocardiographic image enhancement may improve the diagnostic accuracy of echo in patients with ApHCM (40). Therefore, in patients with suspicion of ApHCM and inadequate echo images, the use of contrast echocardiography or MRI should be considered.

CONCLUSIONS

Apical hypertrophic cardiomyopathy in North American patients is very similar, if not identical, to that in Japanese patients, is not associated with sudden cardiac death and has a benign prognosis in terms of cardiovascular mortality. However, one third of ApHCM patients may develop unfavorable clinical events and potentially life-threatening complications, such as myocardial infarction, arrhythmias, and stroke. Despite this significant morbidity, the majority of patients do not show any deterioration in their functional class, and approximately half remain totally asymptomatic during follow-up. These data are likely to influence the counseling and management of patients with ApHCM.

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