Risk of Death in Long-Term Follow-Up of Patients With Apical Hypertrophic Cardiomyopathy

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Apical hypertrophic cardiomyopathy (HC) has been considered a "benign" form of HC, with limited data on long-term outcome. We compared apical HC patients with a non-HC, age- and gender-matched Minnesota white population to identify outcomes and prognostic factors. Between 1976 and 2006, 193 patients (62% men) with apical HC were seen at our clinic. Their most recent echocardiographic examinations were reviewed. Mean ± SD age at first presentation was 58 ± 17 years. A family history of HC or sudden cardiac death (SCD) was reported by 43 patients (22%); coronary artery disease was known in 22 (11%). An apical pouch was present in 29 patients, including an apical aneurysm in 6 and apical dilatation with hypokinesis in 23. Median follow-up (187 patients [97%]) was 78 months (range, 1−350). Death from all causes occurred in 55 patients (29%; 33 women) at a mean age of 72 years (range, 20−92). During follow-up, more women had heart failure ($p = 0.001$), atrial fibrillation ($p = 0.009$), or died ($p < 0.001$) than men. Survival was worse than expected ($p = 0.001$); the observed versus expected 20-year survival was 47% versus 60%. SCD, resuscitated cardiac arrest, and/or defibrillator discharge was observed in 11 patients (6%) during follow-up. Multivariate predictors of decreased survival were higher age at baseline ($p < 0.001$), female gender ($p < 0.001$), and atrial fibrillation at baseline ($p = 0.06$). In conclusion, apical HC in this population was associated with increased mortality, especially in women. Because apical HC is less benign than previously suspected, careful longitudinal care is warranted. **(Am J Cardiol 2013;111:1784−1791)**

Apical hypertrophic cardiomyopathy (HC) is a phenotype variant of HC, with hypertrophy predominantly affecting the apex, that was initially described 30 years ago.[1,2] Patients with apical HC comprise approximately 25% of the total HC population in Asian populations and 1% to 10% in non-Asian populations.[3−5] Apical HC may have different clinical implications compared with other subsets of HC. In Asian populations, apical HC seems to have a more benign prognosis than other types of HC; in whites, outcome data are limited.[3,6−8] However, sudden cardiac death can occur in patients with HC,[9] and the incidence of sudden cardiac death did not differ between apical HC and other HC subtypes in 1 North American population.[3] In many risk-assessment studies, populations with HC either have not been analyzed separately,[5,10] or patients with apical HC were a minor subset of HC patients.[11,12] Recently, in a study of patients with apical HC and apical aneurysms, the adverse event rate was 10.5% per year during a mean ± SD of 4.1 ± 3.7 years of follow-up; adverse events included sudden death, appropriate implantable cardioverter-defibrillator (ICD) discharges, nonfatal thromboembolic stroke, and progressive heart failure and death.[13] Another recent study showed an increased rate of adverse outcomes in patients with apical HC and abnormal apical contractility.[14,15] The current study assessed the outcome of apical HC in a large population of patients evaluated at a tertiary care center in North America to identify predictors of adverse events.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. Patients were retrospectively identified through the HC and echocardiographic databases at Mayo Clinic (Rochester, Minnesota). From June 1976 through September 2006, 2,662 patients were referred to the HC clinic at our institution. Of these, 210 patients (7.9%) initially were classified as having apical HC by a clinical evaluator with subspecialty interest in HC.

For all patients, the most recent echocardiographic study and all medical records were reviewed. Patients were excluded if they had (1) a history of severe, chronic, uncontrolled arterial hypertension with evidence of end-organ disease, (2) hemodynamically significant moderate or severe aortic valve disease, (3) infiltrative disorders (e.g., amyloidosis, hypereosinophilic syndrome), or (4) were an elite endurance athlete. After echocardiographic review,

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Table 1
Baseline characteristics at the initial presentation

Characteristic	All Patients (n = 193)	Men (n = 120)	Women (n = 73)	p Value
Mean ± SD age (yrs)	58 ± 17	55 ± 18	62 ± 15	0.009
Family history				
HC	31 (16%)	19 (16%)	12 (16%)	0.91
Sudden cardiac death	19 (10%)	11 (9%)	8 (11%)	0.69
HC and/or sudden cardiac death	43 (22%)	27 (23%)	16 (22%)	0.92
Coronary artery disease	29 (15%)	13 (11%)	16 (22%)	0.04
Arterial hypertension	58 (30%)	29 (24%)	29 (40%)	0.02
Smoker (current or previous)	96 (50%)	61 (51%)	35 (48%)	0.70
Hyperlipidemia	128 (66%)	78 (65%)	50 (68%)	0.62
Diabetes mellitus	15 (8%)	5 (4%)	10 (14%)	0.02
New York Heart Association functional class				
I	96 (50%)	66 (55%)	30 (41%)	0.16
II	63 (33%)	36 (30%)	27 (37%)	
III/IV	34 (18%)	18 (15%)	16 (22%)	
Dyspnea on exertion	74 (38%)	39 (33%)	35 (48%)	0.03
Angina pectoris	55 (28%)	34 (28%)	21 (29%)	0.95
Syncope	22 (11%)	13 (11%)	9 (12%)	0.75
Heart failure	16 (8%)	6 (5%)	10 (14%)	0.03
Stroke	13 (7%)	8 (7%)	5 (7%)	0.96
Proven coronary artery disease	22 (11%)	14 (12%)	8 (11%)	0.88

patients were excluded from this study if (1) criteria for apical HC were not fulfilled (n = 9) or (2) features were compatible with isolated left ventricular noncompaction (n = 3), endocardial fibroelastosis (n = 3), restrictive cardiomyopathy (n = 1), or pheochromocytoma (n = 1). The remaining 193 patients constituted the study cohort.

The following data were abstracted from the clinical record: demographic characteristics, family history of HC, presenting symptoms (including New York Heart Association classification), coronary risk factors, proof of coronary artery disease at the initial presentation, details of ICD implantation, and follow-up findings.

Echocardiographic images and data were retrieved from the prospectively acquired echocardiographic database. The most recent echocardiographic examination for each patient was reviewed. For patients who had undergone apical myectomy (n = 16) or heart transplantation (n = 1), the last echocardiographic examination before that intervention was reviewed. The following criteria for apical HC were applied: (1) hypertrophy predominantly involving the apex, (2) hypertrophy that may extend from the apex to the level of the papillary muscles, and (3) hypertrophy without predominant basal left ventricular involvement. Wall thickness had to be at least 12 mm in a single segment. Patients were not excluded if they additionally showed hypertrophy of the basal septum or other basal segment, provided there was no evidence of left ventricular outflow tract obstruction. All patients in the study had nonobstructive HC, with predominant apical hypertrophy; those with typical asymmetric basal septal HC were excluded.

We assessed data on wall thickness of basal septum, basal posterior wall, maximal apical wall thickness, ejection fraction, presence of hypokinetic segments, midventricular or apical obstruction, presence of an apical pouch, and left atrial size. Left atrial dilatation was defined as either left atrial dilatation in the parasternal long axis by M-mode measurement (>4 cm) or in the apical views by biplane measurement of the left atrial volume (left atrial volume index >28 mL/m^2 body surface area).[16] Diastolic function was assessed as previously described.[17] Right atrial pressure was estimated as previously described.[18] Pulmonary hypertension was defined as an estimated right ventricular systolic pressure >35 mm Hg.

We reviewed the 12-lead electrocardiograms that were recorded closest to the echocardiographic examination. We measured standard intervals, the number of leads showing negative T waves, and voltage of negative T waves in precordial leads. The ST-T wave segments were studied to determine whether T-wave inversion was present; when it was, the maximum T-wave depth in any anterior lead was recorded. Giant T-wave negativity was defined as a negative T-wave voltage of at least 10 mm (≥1 mV).

Last follow-up was obtained in 187 patients (97%) by clinical visits (n = 69), by other contact (e.g., a computer search, telephone contact, letter from outside physicians, prescription refill [n = 22]), by survey (n = 40), or by notice of death (n = 55) or heart transplantation (n = 1). End of follow-up was censored on September 30, 2006.

Cause of death was classified as cardiovascular if it was attributable to myocardial infarction, arrhythmia, sudden cardiac death, congestive heart failure, or stroke. Sudden cardiac death was defined as instantaneous and unexpected death within 1 hour after a previously stable condition.

We also noted whether the patient had any of the following morbidity parameters: atrial fibrillation or flutter, ventricular tachycardia or ventricular fibrillation, transient ischemic attack or stroke, or congestive heart failure. Implantation of an automatic ICD was noted when present.

Continuous data values were expressed as mean ± SD. Contingency tables were analyzed for association with a chi-squared or Fisher exact test (where appropriate). Comparison of continuous variables was made with the appropriate

Table 2
Electrocardiogram findings and arrhythmias*,†

Finding or Arrhythmia	All Patients (n = 176)	Men (n = 111)	Women (n = 65)	p Value
Mean ± SD heart rate (beats/min)	65 ± 13	64 ± 13	66 ± 13	0.28
Sinus rhythm	152 (86%)	97 (87%)	55 (85%)	0.60
Mean ± SD QRS duration (ms)	101 ± 17	102 ± 17	100 ± 17	0.28
Any negative T wave	158 (90%)	103 (93%)	55 (85%)	0.08
Mean ± SD number of negative T waves	3.8 ± 1.7	4.1 ± 1.7	3.3 ± 1.8	0.007
Mean ± SD maximal negative T wave (mm)	5.1 ± 4.2	5.8 ± 4.5	4.0 ± 3.4	0.007
Giant T wave (>10 mm)	19 (11%)	16 (14%)	3 (5%)	0.04
Any Q wave	16 (9%)	8 (7%)	8 (12%)	0.26
Previous ventricular tachycardia	21/193 (11%)	13/120 (11%)	8/73 (11%)	0.98
Previous automatic ICD	4/193 (2%)	2/120 (2%)	2/73 (3%)	0.61
Previous atrial fibrillation, any	43/193 (22%)	18/120 (15%)	25/73 (34%)	0.002
Paroxysmal	28/193 (15%)	10/120 (8%)	18/73 (25%)	0.002
Chronic	15/193 (8%)	8/120 (7%)	7/73 (10%)	0.46

* Patient percentages for categories "All Patients," "Men," and "Women" were calculated using the denominator 176, 111, and 65, respectively, unless otherwise indicated.

† Electrocardiograms to measure or analyze QT interval and T-wave negativity were available in 176 patients (4 patients had pacemaker rhythm; 13 patients with missing data).

Table 3
Echocardiographic findings

Finding	All Patients		Men (n = 120)		Women (n = 73)		p Value
	n	Value	n	Value	n	Value	
Mean ± SD age at echocardiographic examination (yrs)	193	61 ± 17	120	59 ± 17	73	65 ± 15	0.02
Mean ± SD LV end-diastolic diameter (mm)	156	48 ± 6	95	50 ± 6	61	47 ± 7	0.002
Mean ± SD septal wall thickness (mm)	160	15 ± 5	96	15 ± 5	64	14 ± 4	0.12
Mean ± SD posterior wall thickness (mm)	152	12 ± 3	91	13 ± 3	61	12 ± 4	0.03
Apical wall thickness (mm)	177						
≥20		72 (41%)	112	51 (46%)	65	21 (32%)	0.08
≥25		17 (10%)	112	13 (12%)	65	4 (6%)	0.24
≥30		2 (1%)	112	2 (2%)	65	0	0.53
Mean ± SD maximal thickness	177	20 ± 5	112	20 ± 5	65	19 ± 4	0.07
LV hypertrophy only at apex	193	73 (38%)	120	47 (39%)	73	26 (36%)	0.65
Mean ± SD ejection fraction (%)	191	67 ± 9	118	67 ± 8	73	67 ± 11	0.55
Mean ± SD LA end-systolic diameter (mm)	119	47 ± 9	73	46 ± 8	46	48 ± 11	0.79
Mean ± SD LA volume index (mL/m^2 body surface area)	84	43 ± 18	54	42 ± 16	30	46 ± 22	0.57
LA dilatation	186	133 (72%)	116	77 (66%)	70	56 (80%)	0.05
Abnormal diastolic function	125	95 (76%)	85	63 (74%)	40	32 (80%)	0.47
Regional wall motion abnormality	193	16 (8%)	120	12 (10%)	73	4 (5%)	0.27
Elevated pulmonary artery systolic pressure (mm Hg)	125	78 (62%)	75	37 (49%)	50	41 (82%)	<0.001
Apical wall motion abnormality	193		120	18 (15%)	73	11 (15%)	0.99
Apical aneurysm		6 (3%)					
Apical dilatation with hypokinesis		23 (12%)					
Systolic apical gradient	186	75 (40%)	116	45 (39%)	70	30 (43%)	0.58
Diastolic gradient	186	27 (15%)	116	17 (15%)	70	10 (14%)	0.94
Clinically significant valvular heart disease	193	12 (6%)	120	2 (2%)	73	10 (14%)	<0.001

LA = left atrial; LV = left ventricular.

2-sample test: a 2-sample *t* test when the variable distributions were symmetric and a Wilcoxon rank-sum test otherwise. Survival was evaluated by Kaplan-Meier analysis, with 95% confidence intervals. Expected survival was calculated on the basis of rates observed in the Minnesota white population with the same age and gender distribution as those in the study group. Cox proportional hazards regression was used to test for associations with long-term survival. Stepwise selection techniques were used to identify variables independently associated with the end points in these analyses, including age, gender, functional class III or IV symptoms, hypertension, family history of HC, family history of sudden cardiac death, giant negative T waves, maximal left ventricular wall thickness, history of syncope, and chronic or paroxysmal atrial fibrillation. For all analyses, statistical significance was established as $p \leq 0.05$.

Results

The study group consisted of 193 patients (mean ± SD age, 58 ± 17 years; 120 men [62%]). The demographic and clinical characteristics at initial presentation are listed in

Table 4
Follow-up data

Variable	All (n = 187)	Men (n = 114)	Women (n = 73)	p Value
Mean ± SD age (yrs)	64 ± 18	62 ± 19	66 ± 16	0.13
Mean ± SD length of follow-up (mos)	94 ± 76	106 ± 79	76 ± 67	0.005
New York Heart Association functional class				0.22
I or II	147 (79%)	93 (82%)	54 (74%)	
III or IV	40 (21%)	21 (18%)	19 (26%)	
Atrial fibrillation	54 (29%)	25 (22%)	29 (40%)	0.009
Heart failure	35 (19%)	13 (11%)	22 (30%)	0.001
History of ventricular tachycardia	37 (20%)	23 (20%)	14 (19%)	0.87
Coronary artery disease	39 (21%)	26 (23%)	13 (18%)	0.41
AICD implantation				
Ever	21 (11%)	13 (11%)	8 (11%)	0.93
During follow-up	16 (9%)	10 (9%)	6 (8%)	0.90
Discharge during follow-up	5 (3%)	5 (4%)	0	0.16
Syncope	28 (15%)	18 (16%)	10 (14%)	0.70
Stroke	21 (11%)	12 (11%)	9 (12%)	0.70
Death*				
Any death	55 (29%)	22 (19%)	33 (45%)†	<0.001‡
Cardiac death or stroke	9 (5%)	5 (4%)	4 (5%)	0.56
Cardiac death	7 (4%)	4 (4%)	3 (4%)	0.57
SCD	5 (3%)	3 (3%)	2 (3%)	>0.99
AICD discharge	5 (3%)	5 (4%)	0 (0%)	0.16
Resuscitated cardiac arrest	3 (2%)	3 (3%)	0 (0%)	0.29
SCD, AICD discharge, or resuscitated cardiac arrest	11 (6%)	9 (8%)	2 (3%)	0.11
SCD, AICD discharge, stroke, or resuscitated cardiac arrest	20 (11%)	14 (12%)	6 (8%)	0.63

AICD = automatic internal converter-defibrillator; SCD = sudden cardiac death.
* The categories for death are not mutually exclusive (patients can be counted in >1 subgroup).
† One patient with heart transplantation.
‡ Kaplan-Meier survival curve.

Table 1. The cohort was 91% white, 3% Asian, and 6% black or other race. Women were older than men at the time of their first visit. The prevalence of diabetes mellitus and hypertension were slightly higher in women ($p = 0.02$ for both); otherwise, no gender-based differences in personal cardiovascular risk factors or known coronary artery disease were identified. Compared with men, a greater proportion of women had a family history of coronary artery disease ($p = 0.04$) and reported dyspnea and a history of heart failure.

Electrocardiogram findings are summarized in Table 2. Ninety percent of patients had the typical negative T waves. Compared with women, men had a greater number of leads with negative T waves ($p = 0.007$), deeper negative T waves ($p = 0.007$), and more frequently met criteria for giant negative T waves ($p = 0.04$). At baseline, there was no difference between men and women in the history of known ventricular tachycardia or prior ICD implantation. A greater proportion of women had a history of atrial fibrillation at baseline ($p = 0.002$), especially paroxysmal atrial fibrillation. More patients with an apical pouch formation had a family history of sudden cardiac death ($p = 0.03$).

Echocardiographic characteristics are summarized in Table 3. Both men and women had small left ventricles and significantly enlarged left atrial size. Men had a larger left ventricular end-diastolic diameter and a slightly greater posterior wall thickness than women. There were no sex-related differences in apical wall thickness, involvement of the midventricle, left atrial size, diastolic function, intraventricular systolic or diastolic gradients, or presence of an apical pouch. Pulmonary artery pressures were elevated in both genders. Pulmonary artery pressure could be calculated in 125 patients (mean ± SD, 41 ± 15 mm Hg). Women had higher pulmonary artery pressure compared with men (mean ± SD, 48 ± 18 vs 36 ± 10 mm Hg; $p \leq 0.001$) and consequently more often had clinically significant valvular heart disease because of moderate or severe tricuspid regurgitation (10% and 0% in women and men, respectively; $p < 0.001$). Diastolic dysfunction was frequent (79%); in the subset of 89 patients for whom pulmonary artery pressure could be estimated, we observed no association between elevated pulmonary artery pressure and diastolic dysfunction ($p = 0.61$).

Follow-up was available in 187 patients (97%; Table 4). Median age at follow-up was 72 years (range, 20–92). More episodes of heart failure were observed in women than men ($p = 0.001$). Women had a higher incidence of atrial fibrillation ($p = 0.009$). There were no gender-based differences in documented ventricular tachycardia events, proven coronary artery disease, implantation of ICD, or stroke. However, when considering the combined end point of sudden cardiac death, ICD discharge, and resuscitated cardiac arrest, more men tended to be affected than women, although the difference was not significant ($p = 0.11$). The annual rate of sudden cardiac death and/or ICD discharge was 0.5% per year.

Overall, there were 55 deaths, occurring at a mean age of 72 years (range, 20–92). Twenty-one deaths had noncardiac causes (cancer [n = 10], infection or septicemia [n = 4], stroke [n = 2], amiodarone toxicity with respiratory failure

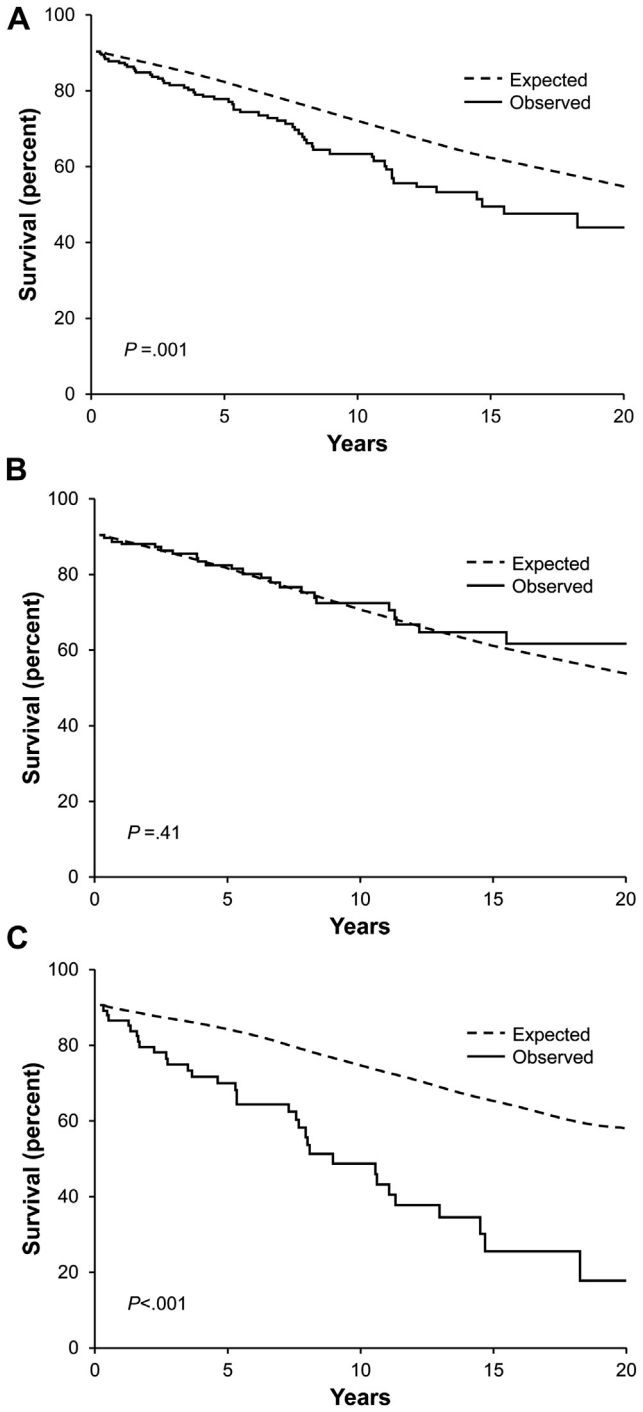

Figure 1. Kaplan-Meier survival curves. *(A)* Survival in all patients with apical HC. Ten- and 20-year survival was lower than expected (p <0.001). *(B)* Overall survival in men with apical hypertrophic cardiomyopathy was equivalent to age- and gender-matched controls (p = 0.41). *(C)* In women with apical HC, 10- and 20-year survival was much worse than an age- and gender-matched population (p <0.001).

[n = 1], renal failure [n = 1], respiratory failure [n = 1], pulmonary emboli [n = 1], postoperative multiorgan failure [n = 1]), 27 were from unknown causes, and 7 were cardiac causes. The rate of deaths was significantly higher in women than men (p <0.001).

Table 5
Univariate predictors of survival (Cox models)

Factor	Hazard Ratio	95% CI	p Value
Unadjusted Predictors			
Age at first visit	1.06	1.04−1.09	<0.001
Age at diagnosis	1.05	1.03−1.08	<0.001
Age at diagnosis, <50 yrs	0.27	0.12−0.64	0.003
Female gender	3.23	1.88−5.56	<0.001
Chronic atrial fibrillation, first visit	3.82	1.82−8.03	<0.001
Heart failure, first visit	3.24	1.56−6.70	0.001
Stroke, first visit	2.24	1.01−4.97	0.05
Family history of HC	0.29	0.09−0.93	0.04
Family history of HC or sudden cardiac death	0.42	0.19−0.98	0.04
Age- and Gender-Adjusted Predictors			
Chronic atrial fibrillation, first visit	2.18	1.01−4.74	0.05
Stroke, first visit	2.11	0.93−4.75	0.07
Heart failure, first visit	2.04	0.96−4.32	0.06
Family history of HC	0.67	0.20−2.27	0.52
Family history of HC or sudden cardiac death	0.96	0.38−2.40	0.93

CI = confidence interval.

Table 6
Multivariate predictors of survival

Factor	Hazard Ratio	95% CI	p Value
Female gender	2.78	1.59−4.86	<0.001
Age, first visit	1.05	1.02−1.05	<0.001
Chronic atrial fibrillation, first visit	2.10	0.96−4.57	0.06
Stroke, first visit	2.01	0.88−4.58	0.10

CI = confidence interval.

Kaplan-Meier survival analysis showed that the overall survival was significantly worse than expected (Figure 1A). The expected (observed) survival rate at 5, 10, and 20 years was 91% (86%), 79% (70%), and 60% (47%), respectively. The annualized rate of cardiac death was 0.5% (95% confidence interval, 0.2%−1.0%). Notably, overall survival in men with apical HC was equivalent to age- and gender-matched controls (Figure 1B), but women with apical HC had a significantly higher rate of all-cause mortality compared with controls (Figure 1C). Expected (observed) 10- and 20-year survival in women was 82% (52%) and 63% (17%), respectively (p <0.001); in contrast, expected (observed) 10- and 20-year survival in men was 78% (80%) and 58% (37%; p = 0.40).

Univariate predictors of survival are shown in Table 5. After controlling for age and gender, factors that continued to show association with survival were chronic atrial fibrillation, stroke at first visit, and congestive heart failure at first visit (p <0.10). The increased risk of mortality associated with chronic atrial fibrillation and stroke at baseline was maintained even when both variables were entered into the model together. Table 6 shows multivariate predictors of survival.

Discussion

Apical HC in this predominantly North American patient group was associated with an increased overall mortality

Table 7
Comparison of previously published outcome studies in apical HC

Study	No. of Patients	Mean Age at First Visit (yrs)	Female Gender	Duration of Follow-Up (mo)*	Giant Negative T Waves	CAD	Apical Pouch	Mortality
Sakamoto et al[21]	31	47	4 (13%)	24−156	31 (100%)	—	—	0 (0%)
Moro et al[12]	11	49	4 (36%)	72	6 (55%)	0/6 (0%)	0 (0%)	0 (0%)
Abinader[8]	11	57	5 (45%)	60-720	11 (100%)	2 (18%)	1 (9%)	0 (0%)
Eriksson et al[3]	105	41	27 (26%)	163 ± 100	49 (47%)	8/42 (19%)	—	12 (11%)
Lee et al[22]	40	56	10 (25%)	72 ± 60	21 (53%)	16 (40%)	0 (0%)	0 (0%)
Chen et al[14]	47	60	29 (61%)	35 ± 24	28 (60%)	17 (36%)	4−16 (9%−34%)	4 (8.5%)
Moon et al[7]	454	61	138 (70%)	43 ± 20	NR	NR	NR	39 (9%)
Present study	193	58	73 (38%)	100 ± 75	21 (11%)	39 (20%)	29 (15%)	56 (29%)

CAD = coronary artery disease.
* Data are reported as mean only, range only, or mean ± SD.

rate and yearly rate of cardiac death, approaching what has been reported for other phenotypes of HC.[19,20] The excess overall mortality from apical HC was seen exclusively in women, likely because more had atrial fibrillation and pulmonary hypertension.

To our knowledge, only 7 published studies on outcomes in apical HC have included more than 10 patients; the findings of those studies are summarized in Table 7. The patients in our study were older than those from the study by Eriksson et al[3] but were otherwise comparable to patients in other studies. One striking difference was the percentage of patients with giant negative T waves, which was much higher in other studies compared with ours (Table 7). Giant negative T waves can also diminish considerably with age,[3] and given our older patient population, age differences could also explain this disparity. Giant negative T waves are known to occur more rarely in whites than in Asians.[6]

The apical pouch formation rate in the smaller studies, when reported, was 0%,[12] 0%,[22] and 10%[8] versus 13% in our study. The higher incidence rate might be due to improved echocardiographic imaging techniques. In the recent study by Chen et al,[14] apical aneurysm was observed in 4 of 47 patients, with an additional 10 showing "apical sequestration" that resembled the apical pouch formation in our patients, as previously described.[15] In total, 14 of the 47 patients (30%) had abnormal apical wall motion in the study by Chen et al.[14]

Maron et al[13] have suggested that patients with apical HC have a better prognosis, not because they represent a distinct population, but because they are characterized by less hypertrophy, similar to that seen in mild HC confined to the basal septum. Our study supports this impression, emphasizing that patients with apical HC rarely have massive hypertrophy (only 2 men [1%] had an apical wall thickness exceeding 30 mm). However, wall thickness alone likely is not the most important criterion for assessment of cardiac risk.

In a study by Elliott et al,[23] the 5-year risk of sudden cardiac death or ICD implantation was 5% for patients if a wall thickness of at least 30 mm was the only criterion present, but it increased to 34% if 3 additional risk factors were included. In that study, 630 patients had HC (mixed morphology, with 3% described as having apical HC); after a mean ± SD follow-up of 59 ± 34 months (range, 1 day−157 months), there were 91 events (e.g., death, appropriate ICD discharge), which was a higher rate than that found in our study.

A more recent report by Maron et al[13] described 28 of 1,288 patients with HC and an apical aneurysm who had a considerably increased adverse outcome compared with patients with HC but without an apical aneurysm. The morphologic description suggests that many of these patients originally had apical HC. Apical aneurysms occurred in 6 patients in our study, but due to the small number of events and apical aneurysms, it was not a significant predictor of adverse outcome in our study. However, we agree that careful surveillance is needed in patients with HC and an apical wall motion abnormality because of increased risk of embolic events and sudden cardiac death.

The differences in outcome were striking when comparing men and women in our study. Previous studies have reported clinically significant differences between women and men in cardiovascular disease with regard to heart failure, coronary artery disease, aortic stenosis, and sustained ventricular arrhythmias.[24−29] Women may be underrepresented in HC studies, perhaps reflecting hormonal or other gender-specific influences that might have a major impact on the phenotype and outcome in this autosomal-dominant disease affecting the myocardium. Although this is only speculative, our study nevertheless raises the concern that further investigation is needed to better understand gender differences in apical HC.

Among patients with coronary artery disease, women are less likely than men to have ventricular arrhythmias.[29] Conversely, for children with HC, rates of sudden cardiac death peak earlier in girls (around age 10−11 years) than in boys.[30] For adults, this has not been described. Male gender is associated with a higher risk of sudden cardiac death in normal populations (without heart disease) and also in young adults with HC. In our study, men with apical HC were more likely to have an ICD discharge (no women experienced ICD discharge); however, this difference was not statistically significant. Women in our study had considerably worse overall survival compared with men: 10- and 20-year survival rates were 52% and 17% for women versus 80% and 67% for men. This was similar to findings reported by Olivotto et al[31]; in that study of HC,

more women than men were symptomatic, had heart failure, excess mortality, and outflow tract obstruction.

Atrial fibrillation is more common in women with apical HC. It is known to affect HC patient outcome because of increased heart failure, stroke, and resultant excess mortality.[31]

Women in this study had a significantly increased incidence of pulmonary hypertension compared with men. This was accompanied by a higher incidence of tricuspid regurgitation. To our knowledge, no previous studies to date have described pulmonary hypertension occurring more often in women with HC. Generally, only limited data are available on the prevalence of pulmonary hypertension in patients with HC; however, we suspect that pulmonary hypertension may be attributable to diastolic dysfunction, although the association was not statistically significant in the current study.

The echocardiographic images analyzed for this study were not the images initially obtained at our institution because many of these studies had limited image quality. Thus, the patient age at the index echocardiogram was slightly older than that at the time when baseline data were obtained. However, we reviewed comprehensive echocardiographic examinations to be able to include only patients with definite apical HC.

Genetic testing for sarcomeric mutations was not performed routinely in these study patients, reflecting the length of the study period, the patient preference for or against testing, and insurance coverage issues. Thus, we cannot determine to what extent the distribution of such mutations in our population differed from those with other phenotypes of HC. However, to date, genetic mutations have not provided reliable information on outcome.

Magnetic resonance imaging may be considered the diagnostic standard for assessing wall thickness in patients with apical HC. This was not routinely performed for patients in the study (only 30 [16%] were imaged) because we included those who were treated before the introduction of routine cardiac magnetic resonance imaging. In 6 of the 10 patients with a visible scar on magnetic resonance imaging, it involved the apex.

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Disclosure

The authors have no conflicts of interest to disclose.

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