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Exercise Echocardiography in Asymptomatic HCM

Exercise Capacity, and Not LV Outflow Tract Gradient Predicts Long-Term Outcomes

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OBJECTIVES This study sought to assess long-term outcomes in asymptomatic or minimally symptomatic patients with hypertrophic cardiomyopathy (HCM) who underwent exercise echocardiography, without invasive therapies for relief of left ventricular outflow tract (LVOT) obstruction.

BACKGROUND Many HCM patients present with LVOT obstruction, mitral regurgitation (MR), and diastolic dysfunction, often requiring invasive therapies for symptomatic relief. However, a significant proportion of truly asymptomatic patients can be closely monitored. In HCM patients, exercise echocardiography has been shown to be a useful assessment of functional capacity and risk stratification.

METHODS We included 426 HCM patients (44 ± 14 years; 78% men) undergoing exercise echocardiography, excluding hypertensive heart disease of elderly, ejection fraction <50% and invasive therapy (myectomy or alcohol ablation) during follow-up. Clinical, echocardiographic (LV thickness, LVOT gradient, and MR) and exercise variables (percent of age-sex predicted metabolic equivalents [METs] and heart rate recovery [HRR] at 1 min post-exercise) were recorded. A composite endpoint of death, appropriate internal defibrillator discharge, and admission for congestive heart failure was recorded.

RESULTS Patients were asymptomatic or minimally symptomatic on history, but 82% of patients achieved <100% of age-sex predicted METs, and 43% had ≥II+ post-stress MR. The mean LV septal thickness, post-exercise LVOT gradient, and HRR were 2.0 ± 0.5 cm, 62 ± 47 mm Hg, and 31 ± 14 beats/min, respectively. During a mean follow-up of 8.7 ± 3 years, there were 52 events (12%). Patients achieving >100% of age-sex predicted METs had 1% event rate versus 12% in those achieving <85%. On stepwise multivariate survival analysis, percent of age-sex predicted METs (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.64 to 0.90), abnormal HRR (HR: 0.89; 95% CI: 0.82 to 0.97), and atrial fibrillation (HR: 2.73; 95% CI: 1.30 to 5.74) (overall, $p < 0.001$) independently predicted outcomes.

CONCLUSIONS In asymptomatic or minimally symptomatic HCM patients, exercise stress testing provides excellent risk stratification, with a low event rate in patients achieving >100% of predicted METs. (J Am Coll Cardiol Img 2014;7:26–36) © 2014 by the American College of Cardiology Foundation

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Hypertrophic cardiomyopathy (HCM) is a heterogeneous inherited cardiomyopathy with variable phenotypic expression that ranges from asymptomatic status to heart failure to sudden death, which occurs in <1%/year (1–3). Disease progression is often due to diastolic dysfunction, mitral regurgitation (MR), and left ventricular outflow tract (LVOT) obstruction (4). All the above processes result in reduction of exercise capacity and could ultimately progress to congestive heart failure (CHF) and death. In intractably symptomatic HCM patients, invasive therapies to relieve LVOT obstruction (surgical myectomy with or without mitral valve surgery or alcohol septal ablation) are associated with excellent long-term outcomes (5–12). These therapies, when offered to symptomatic patients, result in long-term survival similar to that of a healthy population (5,10).

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Often, patients' perceptions about their symptoms can be misleading. In many situations, the symptoms are equivocal. In these instances, exercise testing can further aid in risk stratification for future events, as previously described in many populations (13–15). In general, patients with reduced exercise capacity have a worse prognosis as compared to those who have preserved capacity. Indeed, studies have demonstrated that exercise capacity, along with heart rate recovery (HRR), following exercise are predictive of long-term outcomes in various patient populations (13–16). In HCM, exercise echocardiography is deemed safe and is commonly used to assess: 1) patients with equivocal symptoms; 2) functional capacity prior to a corrective therapeutic procedure; and 3) risk stratification (3). We sought to assess the prognostic utility of various treadmill echocardiographic variables on long-term outcomes in a consecutive group of asymptomatic or minimally symptomatic HCM patients referred for clinical assessment and risk stratification and who did not undergo invasive therapies for relief of LVOT obstruction.

METHODS

Study population. The study population was a part of an institutional review board–approved observational registry of HCM patients, with the initial visit between January 1997 and December 2007. In the current study, we included only HCM patients who were able to undergo treadmill echocardiography. No patient was a competitive athlete. The diagnosis of HCM was made by cardiologists experienced in this disease, on the basis of typical clinical, electrocardiographic, and echocardiographic features, with ventricular myocardial hypertrophy (LV wall thickness ≥15 mm) occurring in the absence of any other cardiac or systemic disease that could have been responsible for the hypertrophy (3). Additionally, in patients with borderline LV wall thickness (~15 mm), the presence of resting or provocable LVOT obstruction (LVOT gradient ≥30 mm Hg) also aided in the diagnosis (3). We excluded the following patients: 1) those age <18 years; 2) those with hypertensive heart disease of the elderly with concomitant LVOT obstruction (17–19); 3) those with ejection fraction <50%; 4) those with more than mild aortic or mitral stenosis on initial echocardiography; and 5) patients who underwent invasive therapies to relieve LVOT obstruction (surgical myectomy with or without mitral valve surgery or alcohol ablation) during follow-up. Hypertensive heart disease of the elderly with concomitant LVOT obstruction was defined as a long-standing history of hypertension and characteristic sigmoid-shaped basal septal hypertrophy, identified on echocardiography (17–20). These patients were excluded, after clinical/imaging evaluation, because they have different pathophysiologic and genetic profiles (20). The final study population consisted of 426 patients.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CHF = congestive heart failure
HCM = hypertrophic cardiomyopathy
HR = hazard ratio
HRR = heart rate recovery
ICD = implantable cardioverter-defibrillator
LVOT = left ventricular outflow tract
METs = metabolic equivalents
MR = mitral regurgitation
VT = ventricular tachycardia

Demographic, clinical, medication, and electrocardiographic data obtained at the time of initial and follow-up visits were recorded from electronic medical records. The presence of atrial fibrillation (AF) was recorded according to guidelines (21). Nonsustained ventricular tachycardia (VT), wide complex tachycardia at 120 beats/min or higher lasting >3 beats but <30 s, or sustained VT lasting >30 s, was recorded on the basis of history and Holter monitor data. The presence of an implantable cardioverter-defibrillator (ICD) and/or permanent pacemaker was ascertained.

Resting echocardiography. All patients underwent comprehensive echocardiography using commercially available instruments (HDI 5000, Philips Medical Systems, N.A., Bothell, Washington; and Acuson Sequoia, Siemens Medical Solutions Inc., Malvern, Pennsylvania). Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines (22). Resting LVOT peak velocity was measured by continuous-wave Doppler echocardiography, and

resting LVOT pressure gradient was estimated by using simplified Bernoulli equation. Care was taken to avoid contamination of the LVOT waveform by MR. In patients with resting LVOT gradients <30 mm Hg, provocative maneuvers, including Valsalva and amyl nitrite, were used to provoke LVOT gradient. The degree of resting MR was assessed (0 = none; 1+ = mild; 2+ = moderate; 3+ = moderately severe; and 4+ = severe) using multiple criteria (23). Grades of resting diastolic function were assigned in each individual on the basis of multiple criteria (E-to-A ratio, deceleration time, left atrial area, LV ejection fraction) (24). Tissue Doppler data were not uniformly available and hence not utilized.

Stress echocardiography. In conjunction with echocardiography, patients underwent a symptom-limited exercise treadmill test using either Bruce (standard or modified) or Cornell protocol, as previously described (25). Patients took their medications on the day of the test. BP, heart rate, and electrocardiographic measurements were made at rest, at 1-min intervals, and for at least 6 min in recovery. Resting and peak exercise rate-pressure product (systolic BP × heart rate), maximal predicted heart rate (220 − age), percent of predicted maximal heart rate, HRR (drop in heart rate from peak to 1 min post-exercise [16]), and number of metabolic equivalents (METs) (achieved as well as what would be expected on the basis of age and sex) were recorded. For men, we used the Veterans Affairs cohort formula (predicted METs = 18 − [0.15 × age]) (26), and for women we used the St. James Take Heart Project formula (predicted

Table 1. Baseline Characteristics of the Study Population

	All Patients (N = 426)	Asymmetric Septal Hypertrophy Without Obstruction (n = 116)	Asymmetric Septal Hypertrophy With Obstruction (n = 280)	Apical Hypertrophy (n = 30)	p Value
Age, yrs	44 ± 14	43 ± 14	45 ± 14	45 ± 15	0.4
Male	310 (73)	84 (72)	200 (71)	26 (87)	0.2
BSA, m^2	2.01 ± 0.3	1.99 ± 0.3	2.01 ± 0.3	2.04 ± 0.3	0.7
Disease history					
HTN	125 (32)	31 (27)	83 (30)	11 (37)	0.6
Syncope	69 (16)	21 (18)	44 (16)	4 (13)	0.7
AF	65 (15)	29 (25)	32 (11)	4 (15)	0.003
CAD	27 (6)	4 (3)	21 (8)	2 (7)	0.3
DM	21 (5)	2 (2)	16 (6)	3 (10)	0.1
Stroke	9 (2)	4 (3)	5 (2)	0 (0)	0.4
SCD	7 (1.6)	2 (1.7)	4 (1.4)	1 (3.3)	0.7
Family history of HCM	105 (25)	46 (40)	51 (18)	8 (27)	0.001
Treatment history					
Devices					
ICD	33 (8)	14 (12)	17 (6)	2 (7)	0.1
Pacemaker	30 (7)	9 (8)	19 (7)	2 (7)	0.7
Medications					
Beta-blocker	253 (60)	60 (52)	178 (63)	15 (50)	0.2
CCB	87 (20)	18 (16)	65 (23)	4 (13)	0.4
Disopyramide	12 (3)	2 (2)	10 (3)	0 (0)	0.7
Medical treatment after initial visit	387 (91)	93 (80)	267 (95)	27 (90)	0.002
NYHA functional class*					0.2
I	283 (66)	74 (64)	185 (66)	24 (80)	
II	143 (34)	42 (36)	95 (34)	6 (20)	

Values are mean ± SD or n (%). *Because excluded patients who subsequently needed invasive therapies were excluded, none of the patients had NYHA functional class III or IV disease.

AF = atrial fibrillation; BSA = body surface area; CAD = coronary artery disease; CCB = calcium channel blocker; DM = diabetes mellitus; HCM = hypertrophic cardiomyopathy; HTN = hypertension; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; SCD = sudden cardiac death.

Table 2. Resting and Exercise Echocardiographic Parameters of the Study Population

	All Patients (N = 426)	Asymmetric Septal Hypertrophy Without Obstruction (n = 116)	Asymmetric Septal Hypertrophy With Obstruction (n = 280)	Apical Hypertrophy (n = 30)	p Value
Resting echocardiography					
LVEF, %	61 ± 5	61 ± 5	61 ± 5	62 ± 5	0.3
Maximal LV thickness, cm	2.0 ± 0.5	2.1 ± 0.5	2.0 ± 0.5	1.6 ± 0.6	<0.001
Left atrial dimensions, cm	4.2 ± 0.8	4.2 ± 0.8	4.2 ± 0.7	4.1 ± 0.7	0.4
Resting MR					0.02
None	45 (11)	19 (16)	22 (8)	4 (13)	
1+	332 (78)	91 (78)	216 (77)	25 (83)	
II+	40 (9)	6 (5)	33 (12)	1 (3)	
III+	9 (2)	0 (0)	9 (3)	0 (0)	
Diastolic function					0.06
Impaired relaxation	399 (93)	106 (91)	266 (95)	27 (90)	
Pseudonormal	24 (6)	7 (6)	14 (5)	3 (10)	
Restrictive filling	3 (1)	3 (3)	0 (0)	0 (0)	
Resting LVOT gradient, mm Hg					<0.001
Mean ± SD	28 ± 32	7 ± 4	32 ± 29	15 ± 18	
Median (IQR)	12 (8–35)	7 (5–9)	18 (10–54)	9 (6–44)	
Resting SAM of mitral valve	105 (25)	0 (0)	105 (38)	0 (0)	< 0.001
Treadmill exercise echocardiography					
Post-stress LVOT gradient, mm Hg					<0.001
Mean ± SD	62 ± 47	12 ± 9	86 ± 39	26 ± 38	
Median (IQR)	59 (20–93)	12 (6–24)	81 (58–110)	11 (0–36)	
Peak-stress SAM of mitral valve	233 (55)	0 (0)	233 (83)	0 (0)	<0.001
Peak-stress MR					0.2
None	45 (11)	19 (16)	22 (8)	4 (13)	
1+	197 (46)	52 (45)	131 (47)	14 (47)	
II+	137 (32)	38 (33)	89 (32)	10 (33)	
III+	43 (10)	7 (6)	34 (12)	2 (7)	
IV+	4 (1)	0 (0)	4 (1)	0 (0)	
Peak heart rate, beats/min	150 ± 26	149 ± 27	150 ± 25	153 ± 30	0.8
Peak BP, mm Hg					
SBP	168 ± 35	162 ± 41	170 ± 33	175 ± 30	0.07
DBP	80 ± 14	79 ± 16	81 ± 14	79 ± 13	0.4
Peak rate-pressure product	26,223 ± 10,372	24,906 ± 7,894	26,063 ± 6,717	32,794 ± 8,943	0.001
Abnormal BP drop at peak exercise	5 (1.2)	1 (0.9)	4 (1.4)	0 (0)	0.7
Peak METs achieved	8.4 ± 2.6	8.4 ± 2.8	8.2 ± 2.4	9.6 ± 3.2	0.02
Age-sex predicted METs					0.09
<85%	268 (63)	76 (63)	177 (66)	15 (50)	
85%–100%	82 (19)	22 (19)	56 (20)	4 (13)	
>100%	76 (18)	18 (16)	47 (17)	11 (37)	
Abnormal chronotropic reserve index	149 (35)	48 (41)	93 (33)	8 (27)	0.2
Heart rate recovery, beats/min	31 ± 14	31 ± 15	31 ± 14	32 ± 11	0.8

Values are mean ± SD, n (%), or median (IQR).
BP = blood pressure; DBP = diastolic blood pressure; IQR = interquartile range; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; METs = metabolic equivalents; MR = mitral regurgitation; SAM = systolic anterior motion; SBP = systolic blood pressure.

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Table 3. Univariate Cox Proportional Hazards Survival Analysis of Composite Events (N = 426)

	HR (95% CI)	p Value
Age (10-year increment)	1.13 (0.85–1.50)	0.4
Sex	1.09 (0.49–2.43)	0.8
BSA	0.73 (0.18–2.88)	0.5
HTN	1.49 (0.74–3.00)	0.2
DM	1.79 (0.09–33.1)	0.6
CAD	1.60 (0.37–6.84)	0.4
Family history of HCM	1.32 (0.62–2.79)	0.4
Syncope	1.23 (0.50–3.04)	0.6
Medical treatment for HCM	1.10 (0.70–1.71)	0.6
NYHA functional class at first visit	1.63 (0.84–3.16)	0.13
VT	1.65 (0.67–4.05)	0.2
Pacemaker	1.73 (0.68–4.44)	0.2
AF	2.39 (1.05–5.42)	0.03
Maximal LV thickness	1.40 (0.85–2.32)	0.2
LVEF	0.98 (0.92–1.04)	0.6
Left atrial area	1.38 (0.83–2.32)	0.3
Resting LVOT gradient (10-mm Hg increment)	1.05 (0.91–1.21)	0.5
Post-stress LVOT gradient (10-mm Hg increment)	1.01 (0.93–1.09)	0.9
Diastolic dysfunction	1.51 (0.72–3.02)	0.3
Resting MR	1.57 (0.88–1.75)	0.12
Peak post-stress MR	1.27 (0.87–1.85)	0.2
Apical variant	1.58 (0.80–3.13)	0.2
Abnormal BP response at peak stress	1.96 (0.20–3.27)	0.4
Ventricular arrhythmias during stress test	1.25 (0.51–3.10)	0.6
Peak METs achieved	0.73 (0.63–0.85)	0.001
% Age-sex predicted METs achieved	0.73 (0.62–0.86)	0.001
Abnormal chronotropic reserve index	0.72 (0.41–1.26)	0.7
Abnormal heart rate recovery at 1 min in recovery	0.86 (0.79–0.92)	0.001

CI = confidence interval; HR = hazard ratio; VT = ventricular tachycardia; other abbreviations as in Tables 1 and 2.

METs = 14.7 − [0.13 × age]) (27). These formulas have been previously demonstrated to perform best, in respective sexes, in their ability to predict outcomes (28). Using that, we calculated the following ratio: (METs achieved/predicted METs) × 100. Abnormal HRR was defined as <12-beat drop over 1 min in recovery (16). We also calculated chronotropic reserve index as follows (29): peak heart rate − resting heart rate/220 − age. Abnormal chronotropic reserve index was defined as <0.62 if on beta-blockers and <0.8 if not on beta-blockers. Abnormal BP response, defined as a 20-mm Hg drop in systolic BP at peak stress, was recorded (30,31).

Table 4. Stepwise Multivariate Cox Proportional Hazards Survival Analysis for Composite Events (N = 426)

	HR (95% CI)	p Value
% Age-sex predicted METs achieved*	0.76 (0.64–0.90)	0.001
Abnormal heart rate recovery at 1 min in recovery	0.89 (0.82–0.97)	0.007
AF	2.73 (1.30–5.74)	0.007

Defibrillators were not included in this analysis because defibrillator discharge was one of the primary endpoints. Overall chi-square: 34; $p < 0.001$. *Because % of age-gender predicted METs incorporated absolute METs achieved along with age and sex, it was used in stepwise multivariate model. Abbreviations as in Tables 1 and 3.

Prior to initiating the stress test, resting echocardiographic views were recorded, as per guidelines (32). In addition to resting wall motion abnormalities, presence/absence of systolic anterior motion of mitral valve was ascertained, and presence and degree of MR and resting LVOT gradient were recorded. Immediately following exercise, regional wall motion abnormalities, MR, and peak exercise LVOT gradient (and presence of systolic anterior motion of mitral valve) were recorded. Major events (sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) and minor events (decrease in BP, transient symptoms, or non-sustained arrhythmias) were recorded.

Outcomes assessment. Death notification was confirmed by observation of death certificate or verification with a family member. The duration of follow-up ranged between the initial stress test to December 2012. The primary endpoint was a composite of death, appropriate ICD discharges, resuscitated sudden death, and admission for CHF. The cause of death was ascertained as sudden death, death due to progressive CHF, or "other," after review of electronic records and/or discussion with family members. Sudden death was defined as unexpected sudden collapse occurring <1 h from the onset of symptoms in patients who had previously experienced a relatively stable clinical course (33). In addition, we recorded successful resuscitation from cardiac arrest or appropriate ICD shocks (with defibrillation threshold of >200 beats documented by electrocardiogram reviews) because they were regarded as equivalents of sudden death (33). Stroke (transient or permanent neurological impairment and disability due to vascular causes, including episodes lasting <24 h) was recorded, along with its cause, either ischemic or embolic.

Statistical analyses. Continuous variables are expressed as mean ± SD and/or median and were compared using Student *t* test (for parametric variables) or Mann-Whitney test (for nonparametric variables). Categorical data are expressed as percent frequency and were compared with chi square. Cox proportional hazards survival models for composite

endpoints were then constructed using bootstrapping (1,000 bootstrapped models were generated and variables that entered the model at least 75 times were considered significant). We utilized bootstrapping to increase reliable assessment of risk factors by improving the precision of estimate. In this manner, univariate hazard ratios (HRs) for various predictors of composite outcomes were initially generated individually. Subsequently, a stepwise multivariate model for composite outcomes was generated. Data are reported as HRs with 95% confidence intervals (CIs). Cumulative event rates as a function over time were obtained by the Kaplan-Meier method, and different event curves were compared using the log-rank test. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois). A p value <0.05 was considered significant.

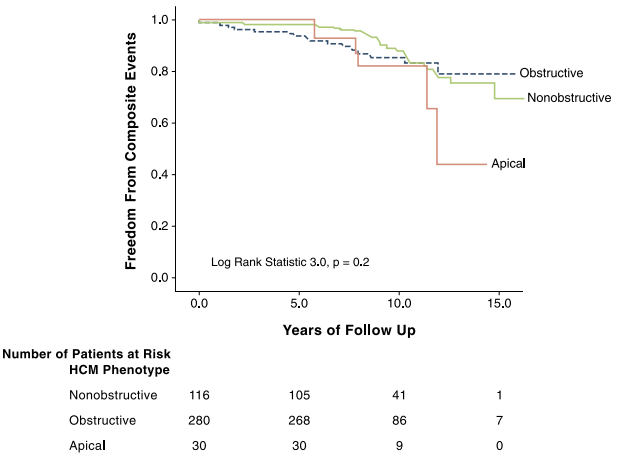

Figure 1. Outcomes by HCM Phenotype

Kaplan-Meier curves demonstrating long-term outcomes, by hypertrophic cardiomyopathy (HCM) phenotype.

RESULTS

The baseline data of the study population are shown in Table 1. These were also divided into 3 subgroups on phenotypic basis: asymmetrical septal hypertrophy with maximal LVOT obstruction ≥30 mm Hg, nonobstructive asymmetrical septal hypertrophy (<30 mm Hg), and apical hypertrophy variant. Although approximately one-third had a history of hypertension, it was not deemed severe enough to cause the degree of ventricular hypertrophy. A significantly higher proportion of patients in the obstructive subgroup were on HCM-related medical therapy. Because we excluded patients that subsequently needed invasive therapies, there were no patients in New York Heart Association functional class III or IV.

Resting and stress echocardiographic variables, for the entire study population as well as by phenotype, are shown in Table 2. There was no peak-stress evidence of ischemia (suggested by a new echocardiographic wall motion abnormality at peak stress). Because of the use of beta-blockers, only 262 patients (62%) achieved ≥85% predicted maximal heart rate (64 [55%] in the nonobstructive subgroup, 179 [64%] in the obstructive subgroup, and 16 [53%] in the apical hypertrophy subgroup; $p = 0.2$). The number of achieved METs and peak rate-pressure product were significantly higher in the apical variant. Twenty-five patients (6%) had an abnormal HRR (11 [10%] in the nonobstructive subgroup, 13 [5%] in the obstructive subgroup, and 1 [3%] in the apical hypertrophy subgroup; $p = 0.2$). Because of baseline abnormalities, no electrocardiogram was diagnostic for ischemia. There were no significant arrhythmias, syncope, deaths, or ICD discharges during the stress test. Five patients (2 in the obstructive subgroup, 2 in the nonobstructive subgroup, and 1 in the apical subgroup) had a short run of nonsustained VT that spontaneously resolved.

Follow-up data. During follow-up, 40 patients (9%) had nonsurgical therapy for management of AF (all had direct current cardioversions, and 25 had pulmonary vein isolations). However, 52 patients (12%) remained in AF during follow-up and were treated with amiodarone (28 [24%] in the nonobstructive subgroup, 20 [7%] in the obstructive subgroup, and 4 [13%] in the apical hypertrophy subgroup; $p = 0.3$). Of the entire population, 299 patients (70%) had Holter monitoring performed. Nonsustained VT and sustained VT (on Holter monitoring) were noted in 64 (15.0%) and 3 (0.7%) patients, respectively, with no differences within subgroups. Also during follow up, there were an additional 13 patients (3%) with pacemaker implantation, resulting in a total of 43 (10%) patients (16 [14%] in the nonobstructive subgroup, 24 [9%] in the obstructive subgroup, and 3 [10%] in the apical hypertrophy subgroup; $p = 0.3$). Similarly, during follow up, there were an additional 74 patients (17%) with ICD implantation, resulting in a total of 107 patients (25%) (39 [34%] in the nonobstructive subgroup, 59 [21%] in the obstructive subgroup, and 9 [30%] in the apical hypertrophy subgroup; $p < 0.01$).

Outcomes and survival data. During a mean follow-up of 8.7 ± 3.0 years, a total of 52 patients (12%)

Table 5. Clinical and Exercise Echocardiographic Variables, Separated on % Age-Sex Predicted METs Achieved (N = 426)

	<85% (n = 268)	85%–100% (n = 82)	>100% (n = 76)	p Value
Age	42 ± 14	45 ± 14	51 ± 11	<0.001
Sex	202 (75)	57 (70)	51 (67)	0.2
BSA	2.04 ± 0.3	1.95 ± 0.2	1.94 ± 0.2	0.008
HTN	69 (26)	25 (31)	31 (41)	0.2
CAD	20 (8)	3 (4)	4 (5)	0.4
History of AF	49 (18)	10 (12)	6 (8)	0.06
Beta-blocker	173 (65)	44 (54)	36 (47)	0.06
CCB	62 (23)	17 (21)	8 (11)	0.2
NYHA functional class				<0.001
I	147 (55)	71 (87)	65 (86)	
II	121 (45)	11(13)	11 (14)	
LVEF, %	62 ± 5	61 ± 5	61 ± 5	0.3
Maximal LV thickness, cm	2.1 ± 0.6	1.9 ± 0.5	1.8 ± 0.4	<0.001
Left atrial dimensions, cm	4.3 ± 0.8	4.0 ± 0.8	4.0 ± 0.1	0.002
Resting MR				0.6
None	24 (9)	9 (11)	12 (16)	
1+	212 (79)	62 (19)	58 (76)	
II+	25 (9)	10 (12)	5 (7)	
III+	7 (3)	1 (1)	1 (1)	
Resting LVOT gradient, mm Hg	27 ± 29	21 ± 22	20 ± 23	0.08
Phenotypic subtypes				0.09
Asymmetric septal hypertrophy without obstruction	76 (28)	22 (27)	18 (24)	
Asymmetric septal hypertrophy with obstruction	177 (66)	56 (68)	47 (62)	
Apical variant	15 (6)	4 (5)	11 (15)	
Post-stress LVOT gradient, mm Hg	63 ± 48	65 ± 46	55 ± 47	0.4
Peak-stress MR				0.2
None	24 (9)	9 (11)	12 (16)	
1+	127 (47)	31 (38)	39 (51)	
II+	85 (32)	30 (37)	22 (29)	
III+	29 (11)	12 (15)	2 (3)	
IV+	3 (1)	0 (0)	1 (1)	
Abnormal chronotropic reserve index	114 (43)	19 (23)	16 (21)	<0.001
Heart rate recovery, beats/min	30 ± 15	32 ± 10	33 ± 11	0.13

Values are mean ± SD or n (%).
Abbreviations as in Tables 1 and 2.

met the composite endpoint. The breakdown of individual endpoints was as follows: 27 deaths (6%), 13 appropriate ICD discharges (3%), and 19 patients (4%) who developed CHF requiring hospital stay during follow-up. There were no sudden death resuscitations during follow-up. The breakdown of deaths was as follows: 17 sudden deaths, 7 due to progressive CHF, 1 due to ICD infection, and 2 uncertain etiologies. In the same patient with multiple endpoints, time to first event was utilized as a censoring cutoff. In addition, 8 patients (2%) also developed a stroke (all embolic) during follow-up. In patients who experienced events during follow-up, the resting and maximal LVOT gradients were not sufficiently elevated to recommend surgery, measuring 24 ± 22 mm Hg and 34 ± 32 mm Hg, respectively.

Using the composite endpoint, the data on univariate and stepwise multivariate Cox proportional hazards survival analysis are shown in Tables 3 and 4, respectively. Percent age-sex predicted METs achieved, HRR at 1 min in recovery, and AF independently predicted composite events. During follow-up, there were no significant differences in event rates within subgroups (16 [14%] in the nonobstructive subgroup, 30 [11%] in the obstructive subgroup, and 6 [20%] in the apical hypertrophy subgroup; p = 0.3). Kaplan-Meier curves demonstrating the composite outcomes of the 3 phenotypic subgroups are shown in Figure 1. We also performed survival analysis using "hard events" (death and ICD discharge, excluding CHF admission). The findings were similar, with percent of age-sex predicted METs achieved (HR: 0.81; 95% CI: 0.71 to 0.94; p = 0.001), HRR at 1 minute in recovery (HR: 0.92; 95% CI: 0.85 to 0.98; p = 0.03) and AF (HR: 2.2; 95% CI: 1.06 to 4.59; p = 0.03) independently predicting hard events on stepwise multivariate regression analysis.

The number of patients meeting the composite endpoint was significantly higher in the group that achieved <7 METs (median) as compared to those who achieved ≥7 METs (39 of 215 [18%] vs. 13 of 211 [6%]; p = 0.001). Because exercise capacity is highly dependent on age and sex, we further divided patients into 3 subgroups on the basis of ratio of achieved METs to age-sex predicted METs, as follows: >100%, 85% to 100%, and <85%. Relevant data in these 3 subgroups are shown in Table 5. As expected, patients achieving <85% predicted METs had a greater body surface area, greater beta-blocker use, greater maximal LV thickness and left atrial area. However, patients achieving <85% were significantly younger and less likely to be hypertensive. Of note, 55% of patients who achieved <85% of predicted METs reported no symptoms (NYHA functional class I). The event rates of these 3 subgroups were significantly different (1 of 76 [1%], 8 of 82 [10%], and 31 of 268 [12%], respectively; p < 0.001). The Kaplan-Meier curves of patients separated into these 3 subgroups are shown in Figure 2. In patients who achieved

>100% of their age-sex predicted METs, the event rate was extremely low.

The number of patients meeting the composite endpoint was significantly higher in the group with abnormal versus normal HRR (8 of 25 [32%] vs. 31 of 401 [8%]; $p < 0.001$). The Kaplan-Meier curves of patients separated on the basis of abnormal HRR are shown in Figure 3. Similarly, the event rate was significantly higher in patients with AF versus those without (15 of 52 [29%] vs. 37 of 374 [10%]; $p < 0.03$). The Kaplan-Meier curves of patients separated on the basis of the presence of AF during follow-up are shown in Figure 4.

DISCUSSION

In the current study of HCM patients undergoing stress echocardiography, we demonstrated that functional capacity was an independent predictor of outcomes. To avoid the confounding effect of invasive therapies to relieve LVOT obstruction, we excluded patients with intractable symptoms who required such therapies (surgical myectomy with or without mitral valve surgery or alcohol ablation) because these patients have excellent outcomes (5–12). We also excluded elderly patients with hypertensive heart disease and concomitant LVOT obstruction because they have pathophysiologic and genetic profiles different from those of typical HCM patients (17–20). Patients with impaired exercise capacity (achieved METS < median) were 3 times as likely to have events versus those with a preserved functional capacity. In fact, if the patients achieved 100% of age-sex predicted METs, the event rate was 1% during follow-up, versus those achieving ≤85% of expected METs, who had an event rate of 12% during follow-up. This is important because no patient was deemed symptomatic enough to recommend surgery or alcohol ablation. Also, in patients with subsequent events, the resting and maximal LVOT gradients remained low during follow-up, justifying the recommendation to not perform invasive therapies. More importantly, the current study demonstrates that patients' perceptions about their symptoms can be misleading because all of the patients deemed themselves asymptomatic or minimally symptomatic (NYHA functional class I–II) at the time of initial presentation. In these instances, exercise testing can further aid in risk stratification for future events. This is similar to what has been previously described in other populations (13–15).

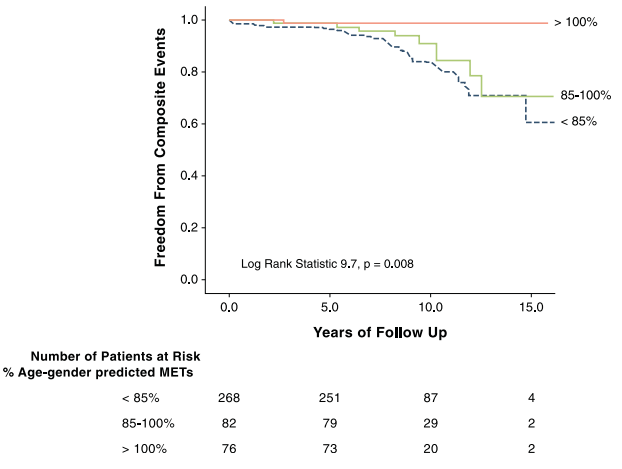

Figure 2. Outcomes by Predicted METs

Kaplan-Meier curves demonstrating long-term outcomes, by percent of predicted metabolic equivalents (METs) achieved.

Exercise intolerance is related to an inability to increase stroke volume due to impaired LV contractile reserve to overcome afterload in obstructed patients and impaired filling in those who are not. Previous studies have demonstrated safety and incremental utility of performing exercise stress echocardiography in HCM patients (25,34). In a previous study, exercise echocardiography was deemed safe, with a major event rate of 0.04% and a minor event rate of 23% (25). In another study, the incidence of arrhythmias during exercise echocardiography was 45%, without any major adverse events at the time of testing (34). According

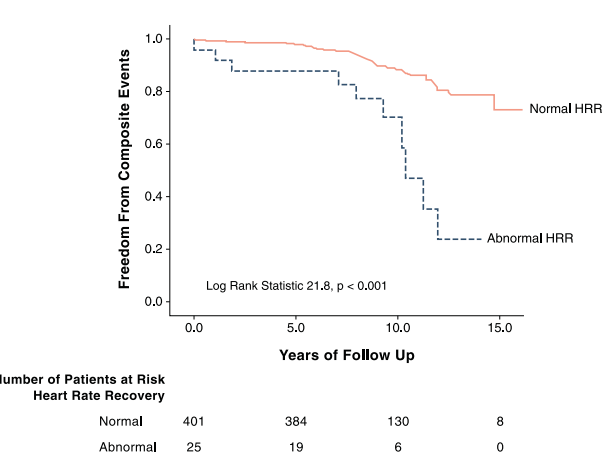

Figure 3. Outcomes by HRR

Kaplan-Meier curves demonstrating long-term outcomes, by normal or abnormal heart rate recovery (HRR).

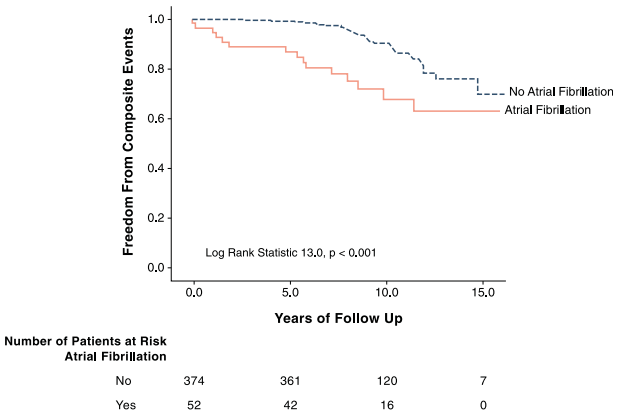

Figure 4. Outcomes by Atrial Fibrillation

Kaplan-Meier curves demonstrating long-term outcomes, by atrial fibrillation in follow-up.

to recent guidelines, exercise echocardiography is recognized as an important adjunct in the management of patients with HCM (3). Also, previous reports have utilized stress echocardiography to predict outcomes in HCM patients. In one study, abnormal exercise capacity and LV function were associated with worse outcomes (35). In another study, severity of resting LVOT gradient and percent of predicted peak myocardial oxygen consumption during exercise were predictive of outcomes (36). However, these were relatively small studies with much shorter follow-up. For the current study, to account for potential differences in exercise capacity, on the basis of age and sex, we also calculated a percentage of age-sex predicted METs in every individual, rather than utilizing absolute METs achieved or only age-based correction. We utilized previously validated formulas that have been demonstrated to have the most optimal performance to predict age-based METs, separately in men and women (28).

Also, abnormal HRR was predictive of long-term outcomes, similar to previous reports (16). HRR during the first minute of recovery is reflective of vagal reactivation, which tends to be blunted in patients with CHF. Previous smaller reports have indeed demonstrated that HCM patients with VT have a reduction in parasympathetic activity (37). This could potentially explain the association between sudden death (or ICD discharges) and abnormal HRR. It appears that impaired exercise capacity and abnormal HRR identify HCM patients who have a higher risk of death, malignant arrhythmias, or progression to CHF, which in part could be mediated by cardiac autonomic dysfunction (38,39). Previous reports have demonstrated AF to predict outcomes in HCM patients (5,40–43); however, none evaluated a large cohort undergoing exercise echocardiography, as in the current study. In our study, previously reported HCM-related variables, including standard clinical risk factors, diastolic function, LV thickness, resting/provocable LVOT gradient, resting/post-stress MR, or abnormal BP response to stress, were not predictive of long-term outcomes (3). One potential reason for this is that these patients represented a less sick cohort.

Study limitations. This was an observational experience from a single tertiary center, which could have potential selection bias because we included only patients who were able to undergo exercise echocardiography. Tissue Doppler indices for the assessment of diastolic function (i.e., E/e′) were not uniformly available in the study population and hence not reported. Because cardiopulmonary exercise data were not uniformly available in patients seen during the early part of the study, variables such as Vo_2 max are not reported. Right ventricular systolic pressure at peak stress was not uniformly available in all patients and hence is not reported. We utilized a composite endpoint that weighted the development of CHF admission similar to sudden death or its surrogates.

CONCLUSIONS

We demonstrate that in asymptomatic or minimally symptomatic HCM patients who did not undergo invasive therapies for relief of LVOT obstruction, reduced exercise capacity and abnormal HRR on exercise echocardiography independently predict composite endpoints, in addition to the presence of AF. We also demonstrate that patients who achieved ≥100% of age-sex predicted METs had excellent long-term outcomes, with a very low event rate, regardless of the degree of LVOT obstruction or other HCM-related risk factors. In asymptomatic or minimally symptomatic HCM patients, exercise stress testing is a safe and useful tool that enables excellent risk stratification of individuals.

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