Symptom assessment and exercise impairment in surgical decision making in hypertrophic obstructive cardiomyopathy: Relationship to outcomes

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ABSTRACT

Objectives: We sought to assess the long-term outcomes in patients with hypertrophic cardiomyopathy and severe left ventricular outflow tract obstruction, in whom the decision regarding surgery (vs conservative management) was based on assessment of symptoms or exercise capacity.

Methods: This was an observational study of 1530 patients with hypertrophic cardiomyopathy (aged 50 ± 13 years, 63% were men) with severe left ventricular outflow tract obstruction (excluding those aged <18 years, with left ventricular ejection fraction $<50\%$, and with left ventricular outflow tract gradient <30 mm Hg). A composite end point of death (excluding noncardiac causes) and/or implantable defibrillator discharge was assessed.

Results: Coronary artery disease, family history of hypertrophic cardiomyopathy, and syncope were present in 15%, 17%, and 18% of patients, respectively, whereas 73% patients were in New York Heart Association class II or greater. Mean left ventricular ejection fraction, basal septal thickness, and left ventricular outflow tract gradient (resting or provokable) were $62\% \pm 5\%$, 2.2 ± 1 cm, and 101 ± 39 mm Hg, respectively. A total of 858 patients (56%) underwent exercise echocardiography, of whom 503 (59%) had exercise capacity impairment. At 8.1 ± 6 years, 990 patients (65%) underwent surgical relief of left ventricular outflow tract obstruction, and 540 patients (35%) did not. There were 156 events (10%) (134 deaths), with 0% 30-day mortality in the surgical group. On multivariable Cox proportional hazard analysis, increasing age (hazard ratio [HR], 1.20), coronary artery disease (HR, 1.68), worse New York Heart Association class (HR, 1.46), and atrial fibrillation (HR, 1.90) predicted higher events, whereas surgery (time-dependent covariate HR, 0.57) was associated with improved event-free survival (all $P < .01$).

Conclusions: In patients with hypertrophic cardiomyopathy and severe left ventricular outflow tract obstruction, in whom the decision regarding surgery was based on the presence of intractable symptoms and impaired exercise capacity, surgery was associated with significant improvement in long-term composite outcomes. (J Thorac Cardiovasc Surg 2015;150:928-35)

Outcomes of patients with HCM based on surgical myectomy versus conservative treatment.

Central Message

In HCM, surgical relief of severe LVOT obstruction resulted in improved freedom from long-term events versus conservative management.

Perspective

In patients with HCM and severe LVOT obstruction, in whom the decision regarding surgery (vs conservative management) was based on symptom assessment and exercise capacity, surgical relief of LVOT obstruction was associated with improved freedom from events (death or internal defibrillator discharge) when compared with conservative management.

See Editorial Commentary page 936.

Supplemental material is available online.

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Hypertrophic cardiomyopathy (HCM) is a commonly inherited cardiomyopathy with a varied phenotypic expression ranging from asymptomatic to congestive heart failure (CHF) to sudden death, which occurs in less than 1% per year.¹⁻⁴ Left ventricular outflow tract (LVOT) obstruction and concomitant mitral regurgitation (MR)⁵

Abbreviations and Acronyms

AF	= atrial fibrillation
CHF	= congestive heart failure
HCM	= hypertrophic cardiomyopathy
HR	= hazard ratio
ICD	= implantable cardioverter defibrillator
LV	= left ventricular
LVOT	= left ventricular outflow tract
METS	= metabolic equivalents
MR	= mitral regurgitation
NYHA	= New York Heart Association
VT	= ventricular tachycardia

result in reduced exercise capacity that, if uncorrected, can progress to CHF and death. LVOT obstruction is independently associated with adverse HCM-related outcomes.^{5,6} When evaluated carefully, LVOT obstruction is observed in approximately 70% of patients with HCM.⁷ Surgical myectomy provides excellent long-term survival and freedom from recurrent symptoms in patients with obstructive HCM.⁸⁻¹² However, most of these studies did not compare outcomes in patients with severe LVOT obstruction on the basis of whether surgical myectomy was performed or not.

Currently, it is a class I indication (level of evidence C) to offer invasive therapies (surgical myectomy $\pm$ mitral valve surgery or alcohol septal ablation), at an experienced center, to patients with severe LVOT obstruction who are intractably symptomatic (New York Heart Association [NYHA] class III-IV), despite maximally tolerated medical therapy.^{3,4} However, patients' perception of their symptoms is often misleading, and in many instances, symptoms are equivocal. In such scenarios, exercise stress testing can unmask latent symptoms and help decision making. Although stress testing has been shown to potentially aid in risk stratification,¹³ there are not much data regarding its role in helping decide on surgery versus medical management. We sought to assess the long-term outcomes in patients with HCM and severe LVOT obstruction, in whom the decision regarding surgery (vs conservative management) was based on symptom assessment and objective evaluation of exercise capacity (in patients with NYHA class I-II).

MATERIALS AND METHODS**Study Sample**

The study sample is part of an institutional review board–approved observational registry of patients with HCM, with the initial visit between 1997 and 2011. We included 1530 consecutive patients with HCM (aged ≥ 18 years) with significant LVOT obstruction who were evaluated at our tertiary care center, using the following exclusion criteria: (1) concomitant moderate or greater aortic/mitral stenosis on initial echocardiogram ($n = 151$); (2) left ventricular (LV) ejection fraction less than 50%

($n = 30$); (3) maximal (including provokable) LVOT obstruction less than 30 mm Hg ($n = 368$); (4) apical HCM variant ($n = 53$); and (5) hypertensive heart disease in elderly patients ($n = 639$).¹⁴⁻¹⁶ Hypertensive heart disease in elderly patients was defined as a long-standing history of hypertension and characteristic sigmoid-shaped septal hypertrophy.¹⁴⁻¹⁶ These patients were excluded because they have a different pathophysiologic and genetic profile. The diagnosis of HCM was made by experienced cardiologists on the basis of typical features, with ventricular myocardial hypertrophy (LV wall thickness ≥ 15 mm) occurring in the absence of any other disease responsible for hypertrophy.^{3,4} In addition, in patients with borderline LV wall thickness (~ 15 mm), the presence of resting/provocable LVOT obstruction (LVOT gradient ≥ 30 mm Hg) also aided in the diagnosis.^{3,4}

Baseline clinical data were manually extracted from electronic medical records. Follow-up information was collected by manual extraction from electronic medical records and phone calls. The presence of atrial fibrillation (AF) was recorded on the basis of history, electrocardiograms, and Holter data. Nonsustained ventricular tachycardia (VT), wide complex tachycardia at 120 beats or more per minute (lasting >3 beats but <30 seconds), and sustained VT (lasting >30 seconds) were recorded according to history and Holter data. The presence of an implantable cardioverter defibrillator (ICD) and permanent pacemaker was ascertained.

The primary indications to operate were (1) intractable symptoms (NYHA class III-IV, angina) despite maximal medical therapy; (2) exertional syncope (associated with elevated LVOT gradient); or (3) impaired exercise capacity on stress echocardiography, despite maximal medical therapy, defined as less than 7 metabolic equivalents (METS) or not achieving 85% of age- and gender-predicted METs.¹³ The decision regarding invasive therapies to relieve LVOT obstruction was made after a consensus between experienced cardiologists and cardiothoracic surgeons.

Echocardiography

All patients underwent comprehensive echocardiograms using commercially available instruments (Philips, Bothell, Wash; General Electric, Milwaukee, Wis; and Siemens, Malvern, Pa). Maximal end-diastolic LV wall thickness, LV dimensions, and left atrial area were measured according to guidelines.¹⁷ Resting LVOT peak velocity was measured by continuous-wave Doppler echocardiography, and pressure gradient was estimated by using the simplified Bernoulli equation. Care was taken to avoid contamination of LVOT waveform by MR. In patients with resting LVOT gradients less than 30 mm Hg, provocative maneuvers, including Valsalva and amyl nitrite, were used. In patients with low resting gradients or NYHA class I-II symptoms, we performed exercise echocardiography to assess for impairment of exercise capacity, blood pressure response, and maximal postexercise LVOT gradient, as described.¹³ In patients with resting peak LVOT gradient greater than 100 mm Hg, provocative maneuvers were not used. Maximal LVOT gradient was recorded and defined as the highest recorded gradient (resting or provoked, including exercise) in a patient.¹⁸ The degree of resting MR was assessed (none-severe) using multiple criteria.¹⁹ Grades of resting diastolic function were assigned on the basis of multiple criteria (E to A ratio, deceleration time, left atrial area, LV ejection fraction).²⁰ Tissue Doppler data were incorporated where available.

Outcomes Assessment

The duration of follow-up ranged between initial office visit to event or last follow-up. Death notification was confirmed by observation of death certificate or verification with a family member. The cause of death was ascertained as sudden cardiac death, noncardiac death, or unknown after a review of records or discussion with family. Sudden death was defined as unexpected sudden collapse occurring less than 1 hour from symptom onset in otherwise stable patients.²¹ In addition, we recorded successful resuscitation from cardiac arrest or appropriate ICD shocks (with

defibrillation threshold of >200 beats on electrocardiogram reviews).²¹ For the composite end point, we included sudden death (excluding documented noncardiac death due to cancer, liver failure, primary respiratory, or neurologic issues, but censoring at the time of event) and appropriate ICD discharge. Patients with an unknown cause of death were included as part of the composite outcome, as previously described.¹¹ Admission for CHF was recorded. In addition, the presence and cause of stroke (transient or permanent) were recorded on the basis of clinical neurologic evaluation and appropriate neuroimaging. Arrhythmias, occurring during follow-up (AF, VT, and nonsustained VT), were recorded.

In patients who had undergone surgery to relieve LVOT obstruction, the date and type of surgical procedures performed were recorded: (1) myectomy, (2) myectomy + mitral valve repair/replacement, (3) myectomy + coronary artery bypass grafting, and (4) myectomy ± coronary artery bypass grafting ± valve surgery. The details of the surgical techniques by our group have been described.^{9,12,22} The basic technique of myectomy involved muscle resection below the membranous septum, removing muscle over both papillary muscles, and often extending to both trigones. In patients requiring mitral repair, the most common technique involved plication of A2 scallop of the anterior leaflet.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median and compared using analysis of variance (normal distribution) or Mann-Whitney test (non-normal distribution). Categorical data are expressed as percentage and compared using the chi-square test. To assess outcomes, Cox proportional hazards analysis was used. Forward stepwise multivariable survival analysis was performed, adjusting for relevant variables associated with outcomes in patients with HCM (*P* value threshold <.1 was an entry cutoff). Myectomy and alcohol ablation were included as time-dependent covariates in Cox survival analysis. For each patient undergoing these procedures, the analysis time was modeled so that only the person-time after the procedure was included in the invasive group. The person-time before invasive therapy was included in the nonsurgical category. Hazard ratios with 95% confidence intervals were calculated. In addition, adjusted survival curves were generated from the Cox model to determine the cumulative proportion of events as a function over time. For the surgical patients, date of surgery was considered as “time-zero” on survival analysis. The discriminative ability of survival models was compared using the c-statistic.²³ Statistical analysis was performed using SPSS version 11.5 (SPSS Inc, Chicago, Ill), Stata version 10.0 (StataCorp LP, College Station, Tex), and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria).

RESULTS

The clinical, rest, and stress echocardiographic data are shown in Tables 1 and 2. A total of 1425 patients (93%) had a maximal LVOT gradient 50 mm Hg or greater (437 [81%] in the nonsurgical group and 990 [100%] in the surgical group).

During follow-up, 990 patients (65%) underwent surgical relief of LVOT obstruction. Within the surgical group, the type of cardiac surgeries was as follows: isolated myectomy (*n* = 663, 67%), myectomy plus mitral surgery (*n* = 226, 23%), myectomy plus coronary artery bypass grafting (*n* = 89, 9%), and myectomy plus coronary artery bypass plus additional surgery (*n* = 12, 1.2%). In the subgroup with concomitant mitral surgery, only 36 patients (16%) underwent valve replacement; the rest underwent

TABLE 1. Baseline characteristics of study sample

Variable	Total n = 1530	No surgery n = 540	Surgery n = 990	<i>P</i> value
Age, y	50 ± 13	50 ± 14	50 ± 12	.9
Male gender	965 (63%)	346 (64%)	619 (63%)	.3
Body surface area (m ²)	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	.3
Hypertension	633 (41%)	217 (40%)	416 (42%)	.3
Diabetes mellitus	166 (11%)	60 (11%)	106 (11%)	.4
History of significant CAD	235 (15%)	57 (11%)	178 (18%)	<.001
Family history of HCM	254 (17%)	80 (15%)	174 (18%)	.1
History of sudden death	16 (1%)	19 (1.5%)	9 (0.8%)	.2
Unexplained syncope	271 (18%)	74 (14%)	197 (20%)	.001
History of AF	220 (14%)	60 (11%)	160 (16%)	.004
History of stroke	51 (3%)	17 (3%)	34 (3%)	.5
Implantable defibrillator	128 (8%)	50 (9%)	78 (8%)	.5
Permanent pacemaker	164 (11%)	52 (10%)	112 (11%)	.2
Beta-blockers	1127 (74%)	359 (67%)	768 (78%)	<.001
Calcium channel blocker	507 (33%)	166 (31%)	341 (34%)	.08
Disopyramide	81 (5%)	4 (0.7%)	64 (7%)	<.001
Angina	181 (12%)	50 (9%)	131 (13%)	<.001
NYHA class				<.001
I	418 (27%)	264 (49%)	154 (16%)	
II	803 (52%)	210 (39%)	593 (60%)	
III	307 (21%)	66 (12%)*	241 (24%)	
IV	2 (0.1%)	0	2 (0.2%)	

CAD, Coronary artery disease; HCM, hypertrophic cardiomyopathy; AF, atrial fibrillation; NYHA, New York Heart Association. *These patients underwent alcohol septal ablation.

transaortic repair. During follow-up, 29 patients (3%) needed a repeat surgical procedure to relieve LVOT obstruction (24 or 83% requiring an additional mitral valve procedure). Also, 119 patients (8%) had invasive therapies (surgical Maze or pulmonary vein isolation) for relief of AF. The median time from initial evaluation to surgery was 45 days (1-5140 days). The indications for surgery were as follows: NYHA class III/IV or intractable angina (*n* = 374), exertional syncope with severe (>50 mm Hg) LVOT obstruction (*n* = 113), and impaired exercise capacity (*n* = 503). Patients in the surgical group, deemed in NYHA class I, had additional reasons (ie, exertional syncope with severe LVOT obstruction or impaired exercise capacity) to recommend surgery.

In the nonsurgical group, 49% of patients were in NYHA class I at initial presentation and remained asymptomatic during follow-up. The 12% of patients (*n* = 66) in the nonsurgical group who reported NYHA class III symptoms underwent alcohol septal ablation during follow-up. Within the nonsurgical group, the remaining patients (those with NYHA class II [*n* = 210] or angina [*n* = 50] at baseline) were not offered surgery because the symptoms were adequately controlled with medical therapy. Likewise, in the nonsurgical patients with a history of syncope, 31 patients with LVOT obstruction greater than 50 mm Hg underwent alcohol ablation, whereas the remainder had an

TABLE 2. Echocardiographic parameters of study sample

Variable	Total (n = 1530)	No surgery n = 540	Surgery n = 990	P value
LV ejection fraction (%)	62 ± 5	62 ± 5	62 ± 5	.3
Indexed LV end-diastolic dimension (cm/m ²)	2.1 ± 0.3	2.1 ± 0.4	2.0 ± 0.3	.1
Indexed LV end-systolic dimension (cm/m ²)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	.9
Maximal LV thickness (cm)	2.0 ± 0.3	2.0 ± 0.2	2.0 ± 0.2	.3
Indexed left atrial dimensions (cm/m ²)	2.2 ± 0.4	2.2 ± 0.4	2.3 ± 0.4	.1
Resting MR				<.001
None	64 (4%)	30 (6%)	34 (3%)	
I+	921 (60%)	368 (68%)	553 (56%)	
II+	387 (25%)	108 (20%)	279 (28%)	
III+	134 (9%)	26 (5%)	108 (11%)	
IV+	24 (1.6%)	8 (1.5%)	16 (1.6%)	
Diastolic function				.005
Impaired relaxation	1392 (91%)	509 (94%)	883 (89%)	
Pseudonormal	132 (8%)	31 (6%)	101 (10%)	
Restrictive filling	6 (1%)	0	6 (0.6%)	
Resting LVOT gradient (mm Hg)	51 ± 41	39 ± 36	58 ± 42	<.001
Maximal LVOT gradient mm Hg	101 ± 39	100 ± 50	102 ± 41	.1
Systolic anterior motion of mitral valve	1329 (87%)	438 (81%)	891 (90%)	<.001
Exercise echocardiography	858 (56%)	355 (66%)	503 (51%)	<.001
Maximum METs <7*	503 (59%)	0	503 (100%)	<.001
>100% age- and gender-predicted METs	503 (59%)	0	503 (100%)	<.001
Maximum METs achieved	6.6 ± 1.3	8.1 ± 1.1	5.2 ± 1	<.001
Abnormal blood pressure response to exercise	9 (0.5%)	3 (0.5%)	6 (0.6%)	.5

LV, Left ventricle; MR, mitral regurgitation; LVOT, left ventricular outflow tract; METs, metabolic equivalents. *The percentages represent only those patients who underwent stress echocardiography.

LVOT gradient of less than 50 mm Hg, and thus invasive therapies were not offered. The 3 patients in the nonsurgical group with abnormal blood pressure response underwent alcohol ablation.

A total of 282 patients (18%) (74 [14%] in the nonsurgical group, of whom 64 were in NYHA class I/II at baseline, and 208 [24%] in the surgical group, $P < .001$) had evidence of AF during long-term follow-up and were treated with medications (263 with amiodarone, 7 with dofetilide, and the rest using rate control). Nonsustained and sustained VT were noted in 154 patients (10%) and 8 patients (0.9%), respectively, with no difference between groups. Also, during follow-up, there were an additional 172 patients (11%) with pacemakers, resulting in a total of 266 patients (17%) (74 [14%] in the nonsurgical group and 192 [19%] in the surgical group, $P = .003$). Likewise, there were an additional 276 patients (18%) with ICDs, resulting in a total of 404 patients (26%) (113 or 21% in the nonsurgical group and 291 patients or 29% in the surgical group, $P = .01$).

During a mean follow-up of 8.1 ± 6 years, 22 patients (1.4%) progressed to NYHA class III-IV (7 [1%] in the surgery group and 15 [3%] in the nonsurgery group, $P = .04$), whereas 44 patients (2%) had a stroke, with no difference between subgroups (1.8% vs 2.1%, $P = .4$). The 15 patients in the nonsurgical group who progressed

to NYHA class III-IV did not have LVOT obstruction greater than 50 mm Hg to justify surgery. A total of 156 patients (10%) met the composite end point. The composite outcome included the following: 134 deaths (9%) (89 documented sudden cardiac deaths and 45 unknown) and 31 appropriate ICD discharges (2%). In patients in whom multiple end points developed, time to first event was used as an event time cutoff. An additional 17 patients (1%) died of documented noncardiac causes during follow-up and were not included in the survival analysis (but were censored at time of death). The breakdown of composite events in patients who underwent surgery versus those who did not was as follows: 82 of 990 (8%) versus 74 of 540 (14%) ($P < .001$). There were no deaths in 30 days (or before hospital discharge) after myectomy. Twelve patients (18%) in the group who underwent isolated alcohol septal ablation ($n = 66$) had an event during long-term follow up.

The data on forward stepwise multivariable Cox proportional hazard analysis are shown in Table 3. Alcohol septal ablation did not independently affect outcomes (hazard ratio, 1.35 [0.74-2.40], $P = .3$). For association with composite events, the c-statistic for baseline predictors (age, CAD, and NYHA class) was 0.62 (0.57-0.68). Addition of AF during follow-up increased the c-statistic to 0.68 (0.62-0.76) ($P = .02$). Further addition of surgical

TABLE 3. Forward stepwise multivariable Cox proportional hazard analysis for composite end points

Variable	HR	P value
Model with relevant predictors associated with outcome in patients with HCM		
Age (for 10-y increase)	1.20 (1.02-1.40)	.02
Coronary artery disease	1.68 (1.13-2.51)	.01
NYHA class	1.46 (1.15-1.86)	.002
Surgery to relieve LVOT obstruction (time-dependent covariate)	0.57 (0.40-0.79)	.001
AF	1.90 (1.32-2.72)	<.001

Chi-square for the model 51, $P < .001$

The following variables were considered for the stepwise multivariable model: age, gender, NYHA class at initial visit, syncope, family history of HCM, history of sudden death, hypertension, cardiac medications at or after initial visit, maximal LV wall thickness, indexed left atrial area, maximal LVOT gradient, VT, AF, alcohol septal ablation (as a time-dependent covariate), surgery to relieve LVOT obstruction (as a time-dependent covariate), and time to surgery. *HR*, Hazard ratio; *HCM*, hypertrophic cardiomyopathy; *NYHA*, New York Heart Association; *LVOT*, left ventricular outflow tract; *AF*, atrial fibrillation.

relief of LVOT obstruction increased the c-statistic to 0.75 (0.70-0.79) ($P = .01$).

The proportion of events increased significantly with worsening baseline NYHA class (30/418 [7%] in class I, 84/805 [10%] in class II, and 42/307 [14%] in class III/IV, $P < .001$). The survival curves, separated on the basis of worsening baseline NYHA class, adjusted for variables listed in Table 3, are shown in Figure 1. In patients who presented with NYHA class I and II at baseline, the proportion of long-term events was 10% and 17% in the nonsurgical group compared with 4.5% and 8% in the surgical group, respectively (both $P < .001$).

The survival curves, separated on the basis of having undergone surgical relief of LVOT obstruction, adjusted for variables listed in Table 3, are shown in Figure 2. Likewise, the proportion of events was significantly lower in patients who remained free of AF versus those who had AF during follow-up (107/1248 [9%] vs 49/282 [17%], $P = .001$). The adjusted survival curves of patients based on the presence of AF during follow are shown in Figure 3.

Additional survival analyses (ie, excluding patients with alcohol septal ablation or significant coronary artery disease and only patients with maximal LVOT gradient ≥ 50 mm Hg) are shown in the Appendix.

DISCUSSION

In the current study of patients with HCM with significant dynamic LVOT obstruction, in whom the decision regarding surgery (vs conservative management) was based on symptom assessment or objective evaluation of exercise capacity, we demonstrate that patients who underwent surgical relief of LVOT obstruction had significantly improved long-term outcomes versus those managed conservatively. Despite a higher proportion of

NYHA Class					
I	418	378	244	88	14
II	805	706	479	179	27
III/IV	307	253	148	68	4

FIGURE 1. Adjusted survival curves demonstrating long-term outcomes, separated on the basis of NYHA class. *NYHA*, New York Heart Association.

risk factors (symptoms, AF, and CAD) and poorer exercise capacity in the surgical versus nonsurgical group, the outcomes were significantly better after surgery.

Multiple previous reports have suggested that an elevated LVOT gradient is associated with worse long-term outcomes.^{5,6} In patients with LVOT obstruction, the survival was better in patients with NYHA class I than in those with class II and III/IV (91% vs 83% and 82.6%, respectively, $P < .05$).⁶ Another study demonstrated that LVOT obstruction increased the risk of HCM-related death.⁴ If evaluated diligently using provocative maneuvers, an elevated LVOT gradient is seen in approximately 70% of patients.⁷ Also, patients commonly misjudge their symptoms, and stress testing can help further elucidate their functional capacity. In a recent study, 82% of patients with HCM, despite claiming to be asymptomatic, did not achieve 100% of their age- and gender-predicted METs,¹³ with those achieving less than 100% faring significantly worse than those who did.

Because surgical myectomy provides excellent long-term freedom from symptoms and outcomes,⁸⁻¹² current guidelines give it a class I indication in patients with obstructive HCM, if performed at an experienced

FIGURE 2. Adjusted survival curves demonstrating long-term outcomes, separated on the basis of surgical relief of LVOT obstruction.

center.^{3,4} However, it is recommended only in those patients who present with advanced intractable symptoms (NYHA class III-IV, angina, and syncope).³ This recommendation is based on a level of evidence C, implying a consensus opinion based on small studies. Most of the previous studies that reported outcomes in patients undergoing myectomy did not use a strategy in which the decision regarding surgery (vs conservative management) was based on symptom assessment or objective evaluation of exercise capacity. Two prior reports have attempted to compare outcomes in patients with obstructive HCM, based on whether they underwent surgical relief of LVOT obstruction or not. In one study, the authors compared the outcomes in 3 HCM subgroups: nonobstructive (n = 820), obstructive without subsequent myectomy (n = 228), and obstructive with subsequent myectomy (n = 289).⁸ They demonstrated that the patients who underwent myectomy had the best outcomes, whereas the patients with obstructive HCM without myectomy had the worst outcomes. However, in addition to having a smaller sample size of patients with obstructive HCM, 78% of patients were evaluated at centers with large cohorts but not with specialized surgical experience in this disease. Another study by Ball and colleagues,¹¹ evaluating 649 patients with HCM with resting LVOT obstruction treated invasively versus conservatively, demonstrated that

FIGURE 3. Adjusted survival curves demonstrating long-term outcomes, separated on the basis of AF during follow-up. AF, Atrial fibrillation.

overall survival was greater in the invasive group.¹¹ However, invasive therapy did not independently predict HCM-related events. Unlike the previous report,⁸ a major strength of the study by Ball and colleagues¹¹ was that it was conducted in a single center with substantial experience in all forms of invasive therapies. However, the entry criteria were primarily based on resting LVOT gradient. Furthermore, pacing (used as a first-line invasive therapy) could have adversely affected outcomes. Also, the study was likely underpowered to detect differences in HCM-based outcomes. The current study was conducted in a single center with substantial experience in all forms of invasive therapies with a larger sample size. In addition, stress echocardiography was used as a strategy to further elucidate symptoms and help decide on the timing of surgery in selected patients. We also demonstrate that in the nonsurgical group, despite a low rate of progression of patients with NYHA class I/II at baseline to NYHA class III/IV during follow-up, the composite event rate was twice as high as in similar patients in the surgical group. The current study also underscores the importance of experience in the invasive management of patients with HCM with severe LVOT obstruction. In a recent analysis of the Nationwide Inpatient Sample, the authors demonstrated a 30-day mortality of 5.9% in patients undergoing surgical myectomy

for relief of LVOT obstruction.²⁴ This database represents the largest publically available all-payer US inpatient database, and the study population represents approximately 20% sample of US community hospitals. The results of that study underscore the importance of having myectomy performed at experienced centers.^{7,9,11} In fact, a sizable proportion of patients with symptomatic HCM with severe LVOT obstruction, especially those with basal septal thickness less than 1.8 cm, have mitral valve abnormalities contributing to LVOT obstruction. As shown recently, more than 50% of such patients would require a concomitant surgical procedure (most likely anterior mitral leaflet repair or papillary muscle surgery) to relieve LVOT obstruction, further underscoring the importance of an experienced center.^{12,22,25}

There are many potential reasons for improvement in HCM-related outcomes after surgery. An obvious reason is LVOT obstruction and symptomatic relief, with resultant increased exercise capacity and improved longevity. Another potential reason is that an extensive surgical myectomy removes a substantial amount of hypertrophied muscle. Previous reports have demonstrated that there is a significant association between LV hypertrophy and associated myocardial fibrosis.¹⁸ Thus, septal debulking could indirectly reduce the burden of myocardial fibrosis, which could be associated with a reduced incidence of VT.²⁶

Study Limitations

This was an observational study from a single tertiary center, which could have selection bias. The results of all testing were available to all clinicians at the time of decision-making, introducing further bias. However, to truly understand the impact of surgical relief versus watchful waiting on outcomes, a large-scale prospective study would have to be conducted in patients with HCM with severe LVOT obstruction. However, a prospective, randomized trial in HCM has many inherent challenges.²⁷ By study design, patients with LV dysfunction were not included in the study, and thus the results cannot be extrapolated to those groups. In addition, given the overall expertise involved with both the conservative and the invasive management of HCM, our results might not be generalizable to other lesser-experienced centers.²⁴ We do not have stress echocardiographic data during follow-up.

CONCLUSIONS

In a large group of patients with HCM and significant LVOT obstruction, in whom the decision regarding surgery (vs conservative management) was based on a combination of symptom assessment and objective evaluation of exercise capacity (especially in patients who perceive themselves as not very symptomatic), surgical relief of LVOT obstruction was associated with significantly improved long-term freedom from composite end points of HCM-related death

and appropriate ICD discharge when compared with conservative management.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: hypertrophic cardiomyopathy, outcomes, surgical myectomy

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APPENDIX

When isolated alcohol septal ablation was removed from the analysis (total $n = 1464$, number of composite events = 144), the results of the forward stepwise multivariable Cox proportional hazard survival analysis were similar and as follows: Age (hazard ratio [HR], 1.17 [1.02-1.38]), coronary artery disease (CAD) (HR, 1.62 [1.11-2.43]), worsening New York Heart Association (NYHA) class (HR, 1.39 [1.10-1.91]), and atrial fibrillation (AF) (HR, 1.79 [1.22-2.58]) predicted higher events, whereas surgery as a time-dependent covariate (HR, 0.63 [0.44-0.84]) was associated with improved event-free survival (all $P < .01$).

When only patients with maximal left ventricular outflow tract (LVOT) gradient 50 mm Hg or greater were included in the analysis ($n = 1425$, number of events = 147), the results

of forward stepwise multivariable Cox proportional hazard survival analysis were similar and as follows: Age (HR, 1.23 [1.03-1.48]), CAD (HR, 1.91 [1.28-2.86]), worsening NYHA class (HR, 1.54 [1.19-1.99]), and AF (HR, 1.95 [1.36-2.82]) predicted higher events, whereas surgery as a time-dependent covariate (HR, 0.49 [0.34-0.70]) was associated with improved event-free survival (all $P < .05$).

Likewise, when patients with known significant CAD were excluded from the analysis ($n = 1295$, number of events = 116), the results of the forward stepwise multivariable Cox proportional hazard survival analysis were similar and as follows: Age (HR, 1.26 [1.05-1.51]), worsening NYHA class (HR, 1.68 [1.25-2.23]), and AF (HR, 1.61 [1.06-2.45]) predicted higher events, whereas surgery as a time-dependent covariate (HR, 0.46 [0.31-0.70]) was associated with improved event-free survival (all $P < .05$).