

Clinical and Echocardiographic Determinants of Long-Term Survival After Surgical Myectomy in Obstructive Hypertrophic Cardiomyopathy

Anna Woo, MD, SM; William G. Williams, MD; Richard Choi, MD; E. Douglas Wigle, MD; Evelyn Rozenblyum; Katie Fedwick; Samuel Siu, MD, SM; Anthony Ralph-Edwards, MD; Harry Rakowski, MD

Background—Surgical myectomy has been the standard treatment for patients with drug-refractory obstructive hypertrophic cardiomyopathy. The clinical and echocardiographic predictors of long-term survival and freedom from cardiovascular morbidity after myectomy have been unclear.

Methods and Results—We studied a consecutive cohort of 338 adult patients (age at operation 47 ± 14 [range 18 to 77] years, 60% male) who underwent myectomy at our institution. Preoperative resting left ventricular outflow tract (LVOT) gradient was 66 ± 32 mm Hg (range 5 to 158 mm Hg). Early postoperative mortality was 1.5% (5 deaths); 4 deaths occurred between 1978 and 1992, and 1 death occurred between 1993 and 2002. During long-term follow-up, 83% of patients reported an improvement to functional class I or II. The majority of patients (98%) had no resting LVOT gradient. Long-term survival was excellent, with $98 \pm 1\%$ survival at 1 year, $95 \pm 1\%$ at 5 years, and $83 \pm 3\%$ at 10 years after myectomy. Multivariable Cox regression analysis identified 5 predictors of overall mortality: (1) age ≥ 50 years at surgery (hazard ratio [HR] 2.8, 95% CI 1.5 to 5.1, $P=0.001$), (2) female gender (HR 2.5, 95% CI 1.5 to 4.3, $P=0.0009$), (3) history of preoperative atrial fibrillation (HR 2.2, 95% CI 1.2 to 4.0, $P=0.008$), (4) concomitant CABG (HR 3.7, 95% CI 1.7 to 8.2, $P=0.001$), and (5) preoperative left atrial diameter ≥ 46 mm (HR 2.9, 95% CI 1.6 to 5.4, $P=0.0008$). Significant predictors of late major cardiovascular events found on multivariable analysis were (1) female gender (HR 3.3, 95% CI 2.0 to 5.4, $P<0.0001$), (2) history of preoperative atrial fibrillation (HR 1.9, 95% CI 1.1 to 3.3, $P=0.02$), and (3) preoperative left atrial diameter ≥ 46 mm (HR 2.5, 95% CI 1.5 to 4.3, $P=0.0008$).

Conclusions—Myectomy provides excellent relief for LVOT obstruction in patients with hypertrophic cardiomyopathy. Preoperative clinical and echocardiographic variables can predict long-term outcome after myectomy. (*Circulation*. 2005;111:2033-2041.)

Key Words: cardiomyopathy ■ hypertrophy ■ surgery ■ survival ■ echocardiography

Hypertrophic cardiomyopathy (HCM) is a disorder characterized by unique clinical, hemodynamic, and morphological features.¹⁻³ Surgical intervention was the first approach used to treat patients with drug-refractory left ventricular outflow tract (LVOT) obstruction.⁴⁻⁷ Myectomy consists of the resection of muscle from the subaortic region to enlarge the LVOT. It results in a decrease or abolition of mitral leaflet systolic anterior motion, which results in a decrease or elimination of the LVOT obstruction and the concomitant mitral regurgitation (MR).¹ However, there have been concerns that there were only a limited number of recognized centers worldwide with expertise in the performance of this procedure.⁸ Furthermore, other techniques, such as dual-chamber permanent pacing⁹ and nonsurgical septal reduction therapy (NSRT),¹⁰⁻¹² have emerged as alternative therapeutic options for patients with obstructive HCM.

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In addition to symptoms attributable to LVOT obstruction, patients with HCM have an increased risk of arrhythmias, arterial thromboembolic events, and congestive heart failure (CHF).^{2,3} Previous studies have suggested that echocardiographic variables such as the degree of left ventricular (LV) hypertrophy,¹³ the presence of resting LVOT obstruction,¹⁴ and the degree of left atrial (LA) enlargement¹⁵ are important predictors of mortality and morbidity in patients with HCM; however, it remains unproven whether direct surgical intervention to resect hypertrophied muscle and to relieve the hemodynamic burden of LVOT obstruction decreases the impact of these risk factors on the overall prognosis of HCM. Few studies have identified the clinical and morphological predictors of long-term benefit after myectomy. Therefore,

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From the Divisions of Cardiology and Cardiovascular Surgery, Toronto General Hospital, University of Toronto, Toronto, Canada.

Correspondence to Anna Woo, MD, SM, FACC, Division of Cardiology, Toronto General Hospital, 4N-506, 200 Elizabeth St, Toronto, Ontario, Canada M5G 2C4. E-mail anna.woo@uhn.on.ca

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the objectives of the present study were to determine the clinical and echocardiographic factors associated with mortality and long-term serious cardiovascular morbidity after myectomy in a large cohort of patients.

Methods

Study Design

Study Population and Data Collection

This study consisted of consecutive adult patients (≥ 18 years of age at the time of surgery) with obstructive HCM who underwent myectomy during a 25-year period (between March 1978 and November 2002) at the Toronto General Hospital. The diagnosis of HCM was established by the echocardiographic detection of septal hypertrophy, defined as a maximal septal thickness of at least 13 mm, in the absence of another cardiac or systemic disease that would cause the degree of LV hypertrophy identified.¹⁶ Indications for surgery were the presence of unacceptable symptoms despite maximally tolerated medications and/or previous dual-chamber pacing or NSRT. Data collection consisted of the review of clinical, echocardiographic, and hemodynamic information.

Cardiac Catheterization

Cardiac catheterization and coronary angiography were performed in 335 patients. Before 1987, patients also underwent LV angiography to assess the severity of MR.

Echocardiographic Studies

Patients had preoperative and postoperative transthoracic echocardiography studies performed with commercially available equipment. Measurements of myocardial wall thickness and cardiac chambers were obtained as described previously.^{17,18} LA diameter was determined from the parasternal long-axis view. Echocardiographic measurements were also indexed to body surface area (BSA). After the introduction of Doppler techniques in the 1980s, we evaluated the degree of MR using color flow imaging, continuous-wave Doppler, and, when available, pulmonary venous inflow assessment. We obtained the LVOT gradient by continuous-wave Doppler,¹⁸ which has been shown to correlate with the magnitude of LVOT obstruction obtained by cardiac catheterization.¹⁹ Measurements of LVOT gradient were performed at rest. If the resting LVOT gradient was < 30 mm Hg, the patient was given amyl nitrite, or a Valsalva maneuver was performed to assess for a provokable LVOT gradient.¹⁸

Surgical Procedures

Myectomy was performed during cardiopulmonary bypass with single right atrial cannulation and LA venting of the LV. Mild hypothermia was used during cardiopulmonary bypass with cardioplegia initiated at room temperature. Once normothermic cardioplegia arrested the heart, the cardioplegic solution was cooled and continued until the myocardial temperature reached 15°C to 17°C . Terminal warm cardioplegia was given before reperfusion. Septal myectomy was performed through an oblique aortotomy. The length of the septal myectomy ranged from 35 to 50 mm, the width ranged from 20 to 35 mm (wider toward the apex than at the subaortic region), and the depth of the resection was aimed at leaving 8 to 10 mm of residual thickness at the site of the myectomy. Concomitant surgical procedures were also performed if required. Intraoperative echocardiographic guidance of the procedure has been provided by transesophageal echocardiography since the late 1980s, and details about our intraoperative echocardiographic techniques have been published previously.²⁰

Follow-Up

The postoperative status of patients was determined by cross-sectional follow-up (with the most recent postoperative evaluation available in the last 2 years) in the Toronto General Hospital HCM Clinic or by the patients' other physicians. Documentation of death was obtained from hospital records or from physicians' offices.

Definition of Outcomes

A postoperative event was defined as an early event if it occurred within 30 days and as a late event if it occurred beyond 30 days after the myectomy. Survival analysis included the analysis of mortality (total, late, and cardiovascular) and of late major cardiovascular events. Mortality was attributed to a cardiovascular cause in the presence of one of the following: (1) death within 30 days of a cardiac surgical procedure, (2) sudden nontraumatic death, (3) CHF-related death, or (4) stroke-related death. Late major cardiovascular events included in the model were any of the following events: (1) CHF that required hospitalization, (2) stroke, (3) arterial thromboembolic event, (4) subsequent cardiac surgical procedure (repeat myectomy, repair of ventricular septal defect, valve surgery, or pericardiectomy), (5) cardiac transplantation, or (6) cardiovascular cause of death. The need for an implantable cardioverter defibrillator was not included as a late major cardiovascular event because the decision to insert an implantable cardioverter defibrillator was influenced by various other factors (eg, family history of sudden death or more widespread indications for implantable cardioverter defibrillator use).²¹

Ethics

The Research Ethics Board of the Toronto General Hospital approved this study.

Statistical Analysis

Statistical analysis was performed with SAS version 8.2. Continuous data are expressed as mean \pm SD and were analyzed by unpaired *t* or Wilcoxon rank sum tests, where appropriate. Differences between preoperative and postoperative values were compared with paired *t* or Wilcoxon signed rank tests. Categorical variables were analyzed by χ^2 or Fisher exact tests. Some continuous variables (eg, age, wall thickness, LA diameter, and LVOT gradient) were also dichotomized and treated as categorical variables. The point of dichotomization of these variables was determined by using clinically relevant cutoff points or the median value.

Estimates for long-term survival or freedom from cardiovascular morbidity were made by the Kaplan-Meier method.²² Differences in survival were assessed by the log-rank test, and a probability value of < 0.05 was considered statistically significant. We compared the survival of the study patients with the survival of age- and gender-matched controls from the population of Ontario, Canada (subjects without a history of ischemic heart disease). Survival estimates for the control population were obtained from the Central East Health Information Partnership (www.cehip.org).

Multivariable Models

Individual analyses of the predictors of mortality and of the combined end point of late major cardiovascular events were performed with the Cox model. Individual predictors with a significance level of ≤ 0.10 were entered into multivariable Cox proportional hazards regression models²³ with a backward selection algorithm. The level of significance for the multivariable models was set at 0.05. We verified the proportional hazards assumption for the models using time-varying covariates.

Results

Baseline Characteristics

Surgical myectomy was performed in 338 adult patients during the study period. The mean age was 47 ± 14 years (range 18 to 77 years), and males composed 60% of the study cohort. The majority of patients (72%) reported New York Heart Association (NYHA) class III or IV symptoms before surgery. This operative procedure was a repeat intervention in 14 patients (5 patients had a previous myectomy, and 9 underwent a previous myectomy at other institutions). Preoperative resting LVOT gradient was 66 ± 32 mm Hg (range 5 to 158 mm Hg). Septal thickness was 22 ± 5 mm (1 patient had

TABLE 1. Baseline Characteristics of Study Cohort

Preoperative Characteristics	Results
Demographic data at surgery	
Age, y	47±14 (18–77)
Weight, kg	78.5±16.5 (42.0–133.5)
BSA, all patients, m ²	1.9±0.2 (1.2–2.6)
BSA, male patients, m ²	2.0±0.2 (1.5–2.6)
BSA, female patients, m ²	1.7±0.2 (1.2–2.4)
Clinical status	
Shortness of breath	282 (83)
Chest pain	207 (61)
Syncope	131 (39)
NYHA class III or IV symptoms	243 (72)
History of prior myotomy/myectomy	14 (4)
History of prior AF	59 (17)
Drug therapy	
β-Blockers	149 (44)
Disopyramide	182 (54)
Calcium channel blockers	27 (8)
Preoperative echocardiographic data	
Septal thickness, mm	22.5±5.1 (13–42)
Septal thickness/BSA, mm/m ²	12.1±3.1 (6.3–26.7)
Maximal LV wall thickness, mm	22.7±5.2 (13–42)
Posterior wall thickness, mm	12.8±3.4 (6–30)
LV end-diastolic diameter, mm	42.1±6.0 (23–59)
LV end-systolic diameter, mm	23.4±5.9 (11–40)
LA diameter, mm	46.1±7.0 (27–66)
LA size indexed to BSA, mm/m ²	24.6±4.3 (14.3–42.0)
Resting LVOT gradient, mm Hg	65.6±32.2 (5–158)
LVOT gradient ≥50 mm Hg, n (%)	227 (67)
Concomitant operative procedures	
Aortic cross clamp time, min	55.9±20.9 (21–153)
CABG	44 (13)
Unroofing of coronary artery	25 (7)
Mitral valve repair or replacement	13 (4)
Aortic valve repair or replacement	8 (2)
Right ventricular myectomy	7 (2)

Values are mean±SD (range) or n (%).

septal thickness of 13 mm; for the remainder of the cohort, it ranged from 15 to 42 mm). Mean LA size was 46±7 mm (range 27 to 66 mm) and was not significantly related to the magnitude of the LVOT gradient. Myectomy was performed by 1 of 2 surgeons (WGW [317 cases, 94%] or ARE [21 cases, 6%]). Other baseline preoperative and intraoperative characteristics are summarized in Table 1.

There was a prior history of atrial fibrillation (AF) in 59 patients (17.5%). Patients with prior AF were older (51±12 years versus 46±14 years, respectively; $P=0.002$) and had larger LA diameters (48±6 versus 46±7 mm, respectively; $P=0.006$) than patients with no history of AF. There was no difference between these 2 groups in magnitude of the LVOT gradient, degree of MR, or septal thickness. Female patients were similar to male patients in terms of age, absolute septal

and maximal LV wall thickness, and need for other surgical procedures at the time of myectomy; however, female patients had a greater prevalence of class III or IV symptoms (78% versus 68%, $P=0.04$), a higher resting LVOT gradient (71±32 versus 62±32 mm Hg, $P=0.004$), greater septal thickness indexed to BSA (13.0±3.4 versus 11.4±2.7 mm/m², $P<0.0001$), and greater maximal LV wall thickness indexed to BSA (13.1±3.5 versus 11.5±2.7 mm/m², $P<0.0001$) than male patients. Although the mean absolute preoperative LA diameter was greater in male than in female patients (48±7 versus 44±7 mm, $P<0.0001$), female patients had a significantly larger LA diameter indexed to BSA (25.5±4.6 versus 24.0±4.0 mm/m², $P=0.005$).

Early Surgical Outcomes

There were 5 deaths that occurred in the early postoperative period (1.5%): 4 deaths occurred between 1978 and 1992, and 1 death occurred in the last decade of the study period. No early deaths have occurred in the last 145 cases performed. There were 2 deaths among the 249 patients (0.8%) who underwent myectomy alone, and 3 deaths in the 89 patients (3.4%) who had any concomitant surgical procedure ($P=0.09$). Age, gender, preoperative AF, and preoperative echocardiographic findings (LVOT gradient, LA size, and septal thickness) were not significantly associated with early postoperative death. Other early postoperative complications are summarized in Table 2.

Postoperative Long-Term Clinical Status and Echocardiographic Follow-Up

Mean follow-up time after myectomy was 7.7±5.7 years (range 1 day to 25.8 years). There were 8 patients (2%) lost to follow-up. The majority of patients experienced a significant improvement in symptoms after myectomy, with 83% reporting NYHA class I or II functional capacity ($P<0.0001$ compared with preoperative status). Patients ≥50 years old at the time of surgery (odds ratio [OR] 2.7, 95% CI 1.5 to 5.0, $\chi^2=11.6$, $P=0.0007$) and female patients (OR 3.6, 95% CI 2.0 to 6.7, $\chi^2=18.7$, $P<0.0001$) were significantly more likely to report postoperative class III or IV symptoms. Follow-up echocardiographic data were available in 332 patients (98%), and the most recent postoperative echocardiogram was performed 5.5±5.3 years after myectomy (range 1 day to 25.6 years). There was no significant resting LVOT gradient (defined as resting LVOT gradient ≥16 mm Hg or LVOT velocity ≥2 m/s) in 326 patients (98%) at the time of the most recent echocardiographic examination. In the remaining 6 patients, the resting LVOT gradient was 29±18 mm Hg (range 16 to 59 mm Hg), which included 2 patients with resting LVOT gradients ≥30 mm Hg. There was no significant association between postoperative NYHA class III or IV symptoms and the presence of a postoperative LVOT gradient.

Overall Survival

Kaplan-Meier estimates of overall survival in the study patients and in the control group are shown in Figure 1. There were a total of 56 deaths in this cohort of 338 patients (17%). Overall survival was 98±1% at 1 year, 95±1% at 5 years,

TABLE 2. Postoperative Major Cardiovascular Events

Complications	n (%)
Early (within 30 days of myectomy)	
Postoperative death	5 (1.5)
Isolated myectomy group (n=249)	2 (0.8)
Myectomy and any concomitant surgical procedure(s) (n=89)	3 (3)
Permanent pacemaker	21 (6)
Ventricular septal defect	6 (2)
Early postoperative AF	102 (30)
Late (>30 days after myectomy)	
Subsequent surgical procedures	
Repeat myectomy	1 (0.3)
Ventricular septal defect repair	1 (0.3)
Mitral valve replacement	8 (2)
Pericardiectomy	1 (0.3)
Implantable cardioverter defibrillator	14 (4)
Cardiac transplantation	5 (1.5)
Serious cardiovascular events	
Congestive heart failure requiring hospitalization	44 (13)
Stroke	20 (6)
Arterial thromboembolic events	5 (1.5)
Cardiovascular cause of death	
Early postoperative death (during initial hospitalization for myectomy)	5 (1.5)
Sudden cardiac death	13 (4)
After myocardial infarction	2 (0.6)
Associated with congestive heart failure	15 (4)
After stroke	7 (2)
Early after cardiac transplantation	1 (0.3)
Total cardiovascular deaths	43 (13)

and $83 \pm 3\%$ at 10 years after myectomy. The survival of age- and gender-matched controls was $97 \pm 0.2\%$ at 1 year, $96 \pm 0.2\%$ at 5 years, and $94 \pm 0.4\%$ at 10 years. Cardiovascular deaths accounted for the majority of deaths after myectomy (43 deaths [77% of total deaths]; Table 2), and the remaining deaths were secondary to a definite noncardiac cause. Cardiovascular survival was $98 \pm 1\%$ at 1 year, $96 \pm 1\%$ at 5 years, and $87 \pm 3\%$ at 10 years. Individual analyses of clinical and echocardiographic variables and their association with overall mortality are shown in Table 3.

TABLE 3. Clinical and Echocardiographic Predictors of Overall Mortality Among 338 Patients Who Underwent Myectomy

Variable	Individual Analysis HR		Multivariable Analysis HR	
	(95% CI)	P	(95% CI)	P
Age ≥ 50 y*	3.3 (1.9–5.8)	<0.0001	2.8 (1.5–5.1)	0.0008
Female gender*	1.7 (1.0–2.8)	0.06	2.5 (1.5–4.3)	0.0009
History of preoperative AF*	2.7 (1.6–4.8)	0.0004	2.2 (1.2–4.0)	0.008
LA diameter ≥ 46 mm*	2.9 (1.6–5.3)	0.0005	2.9 (1.6–5.4)	0.0008
Septal/posterior thickness ratio ≥ 1.8 *	0.5 (0.3–0.8)	0.009	0.8 (0.4–1.5)	0.5
Concomitant CABG*	4.8 (2.3–10.2)	<0.0001	3.7 (1.7–8.2)	0.001

*The group of patients without the indicated feature represents the reference category for the calculation of risk.

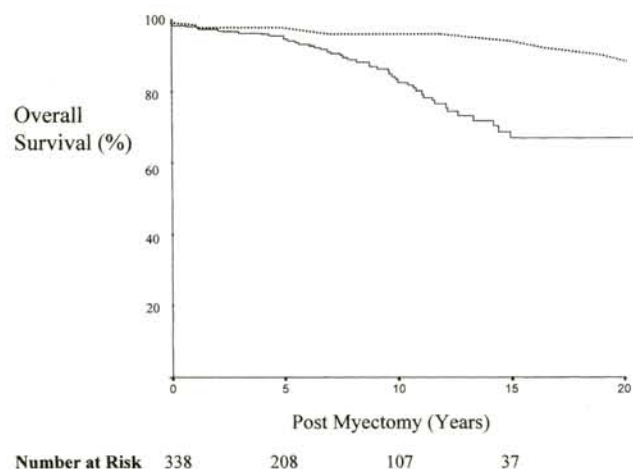


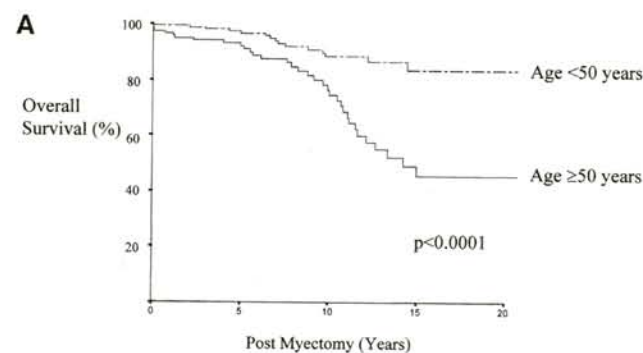
Figure 1. Kaplan-Meier survival curve for total mortality in 338 patients who underwent myectomy (solid line). Overall survival was $98 \pm 1\%$ at 1 year, $95 \pm 1\%$ at 5 years, and $83 \pm 3\%$ at 10 years after myectomy. Overall survival for age- and gender-matched Ontario, Canada population is depicted by dashed line.

Determinants of Mortality

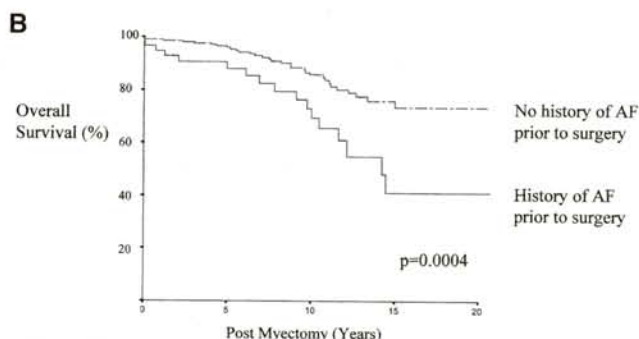
Results of the multivariable analysis are shown in Table 3. The significant predictors of overall mortality were (1) age ≥ 50 years at surgery (hazard ratio [HR] 2.8, 95% CI 1.5 to 5.1, $P=0.001$), (2) female gender (HR 2.5, 95% CI 1.5 to 4.3, $P=0.0009$), (3) history of preoperative AF (HR 2.2, 95% CI 1.2 to 4.0, $P=0.008$), (4) concomitant coronary artery bypass grafting (CABG) (HR 3.7, 95% CI 1.7 to 8.2, $P=0.001$), and (5) preoperative LA diameter ≥ 46 mm (median LA dimension: HR 2.9, 95% CI 1.6 to 5.4, $P=0.0008$; Figure 2 and Figure 3). The same 5 variables were found to be significant predictors for late mortality (excluding all early postoperative deaths) and for cardiovascular mortality.

Echocardiographic Predictors of Mortality

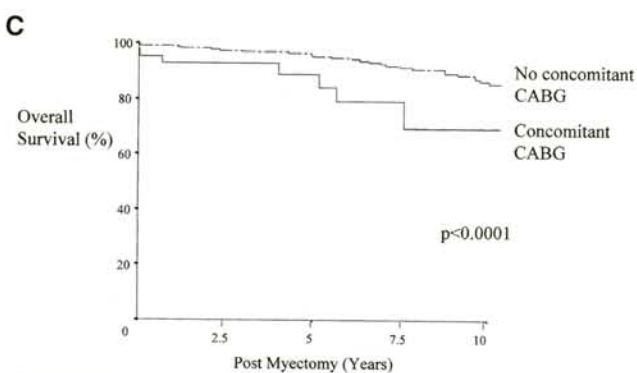
The only preoperative echocardiographic parameter that was predictive of overall mortality was LA diameter. When the preoperative LA dimension was analyzed as a continuous variable, it remained a significant variable on multivariable analysis (HR 1.04, 95% CI 1.003 to 1.08, $P=0.04$). To account for the effects of body size, the LA diameter indexed to BSA was also analyzed and was found to be a significant variable on multivariable analysis when it was treated as a continuous variable (HR 1.1, 95% CI 1.1 to 1.2, $P=0.0006$),



Number at Risk	0	5	10	15	20
Age <50 years	192	122	67	25	
Age ≥50 years	146	86	40	12	



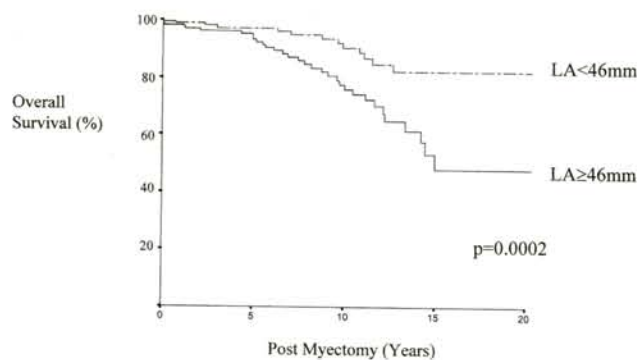
Number at Risk	0	5	10	15	20
No history of AF	279	175	88	31	
History of AF	59	33	19	6	



Number at Risk	0	2.5	5	7.5	10
No CABG	294	240	189	148	
CABG	44	26	19	7	

Figure 2. Kaplan-Meier plots of overall postmyectomy survival stratified by different variables: (A) age <50 years or ≥age 50 years at time of surgery ($P<0.0001$), (B) history of preoperative AF ($P=0.0004$), and (C) need for concomitant CABG surgery ($P<0.0001$).

when it was dichotomized at the median value of 24 mm/m² (HR 2.6, 95% CI 1.4 to 4.9, $P=0.002$), and when the indexed LA dimension was divided into quartiles (HR 1.4, 95% CI 1.1 to 1.9, $P=0.01$ for each quartile). Although the degree of asymmetrical hypertrophy (defined as the ratio of maximal septal to posterior wall thickness), dichotomized at the median value of 1.8, was found to be a significant predictor of survival on individual analysis (HR 0.5, 95% CI 0.3 to 0.8, $P=0.009$), it was not significant on multivariable analysis ($P=0.5$). Furthermore, other preoperative markers of disease severity, such as resting LVOT gradient, septal thickness



Number at Risk	0	5	10	15	20
LA <46mm	161	102	54	23	
LA ≥46mm	177	106	53	14	

Figure 3. Kaplan-Meier plot of overall postmyectomy survival stratified by preoperative LA diameter, dichotomized at median value of 46 mm ($P=0.0002$).

(absolute thickness and thickness indexed to BSA), and maximal LV wall thickness, were not significant predictors of mortality.

Late Major Cardiovascular Events

Subsequent cardiac surgical procedures after myectomy were performed in 11 patients at 8.8 ± 7.3 years (range 1.5 to 20.5 years; Table 2). The most frequent long-term serious cardiovascular complication was CHF, with the first episode of CHF that required hospitalization occurring 9.8 ± 6.1 years after myectomy. There was no association between development of CHF and the persistence of a postoperative resting LVOT gradient. Major cardiovascular events occurred in 70 patients (21%) during long-term follow-up. The following preoperative variables were found on multivariable analysis to be significant predictors of postoperative late major cardiovascular events: (1) female gender (HR 3.3, 95% CI 2.0 to 5.4, $P<0.0001$), (2) history of preoperative AF (HR 1.9, 95% CI 1.1 to 3.3, $P=0.02$), and (3) preoperative LA diameter ≥ 46 mm (HR 2.5, 95% CI 1.5 to 4.3, $P=0.0008$).

Verification of Proportional Hazards Assumption

The multivariable models were developed based on the proportional hazards assumption. Time-varying covariates for all of the variables identified by multivariable analysis were nonsignificant ($P>0.2$), and the HR approached 1.0 for each time-varying covariate, which suggests that the proportional hazards assumption was valid.

The Importance of Late Postoperative AF

Late Postoperative AF in Patients With Preoperative AF

In the subset of 57 patients who had a history of preoperative AF and who survived the early postoperative period, myectomy was successful in keeping 26 patients (46%) in sinus rhythm throughout the postoperative period (excluding the first 30 days after surgery). The other 31 patients (54%) had recurrent AF after surgery (onset of first episode was 5.4 ± 4.3 years after myectomy). There was no difference in age at surgery or preoperative LA diameter between patients who were in postoperative sinus rhythm versus those who experienced late AF. In addition, LA size did not change signifi-

cantly between the preoperative echocardiogram and the most recent follow-up echocardiogram in either group.

New-Onset Late Postoperative AF

There were 276 patients without any history of preoperative AF who survived the early postoperative period. During postoperative follow-up, 58 patients (21%) developed late AF (onset of first episode was 6.5 ± 5.7 years after myectomy), whereas 218 patients (79%) remained in sinus rhythm. There was no significant difference in age at the time of surgery between these 2 groups; however, these 2 groups differed in terms of the changes in LA size before and after surgery. In the patients who stayed in sinus rhythm, LA diameter decreased from 45 ± 7 to 43 ± 7 mm (before versus after surgery, $P=0.004$). In contrast, there was no significant change in LA diameter after myectomy in the patients who developed new postoperative AF (49 ± 7 versus 51 ± 9 mm before versus after myectomy, $P=0.24$).

Clinical Sequelae of Late Postoperative AF

In total, there were 89 patients with late postoperative AF; 16 had a singular episode, 41 had intermittent episodes (≥ 2 separate episodes), and 32 were in permanent AF. Patients with a history of late postoperative AF were more likely to have postoperative NYHA class III or IV symptoms (OR 2.3, 95% CI 1.2 to 4.1, $\chi^2=7.3$, $P=0.007$). Of the 70 patients who had a significant late major cardiovascular event, 47% had a history of preceding or concurrent AF in the time period after myectomy. There was no association between the development of postoperative AF and the presence of a resting LVOT gradient.

Discussion

Summary of Study Results

In the present study, the following preoperative clinical and echocardiographic findings were associated with overall, late, and cardiovascular mortality: age ≥ 50 years at surgery, female gender, history of preoperative AF, concomitant CABG, and preoperative LA size. The observation that increased age is a significant long-term risk factor is relevant because increased age is usually thought to be a significant risk factor for early perioperative morbidity. Advanced age has been identified as an independent predictor of cardiovascular morbidity or mortality in other studies of HCM cohorts.^{15,24} The need for CABG at the time of myectomy was a significant risk factor for long-term mortality in the present study. Concomitant epicardial coronary artery disease in patients with HCM has been found to be an independent risk factor for mortality.²⁵ Patients with coronary atherosclerosis likely have additional mechanisms for developing myocardial ischemia, which is a feature of HCM in the absence of known coronary artery disease.²⁶ Previous studies have shown that ischemia adversely affects prognosis in patients with HCM.²⁷

Role of Gender

The impact of female gender in the long-term outcome of patients after myectomy has not been described previously. There have been few studies assessing gender differences in HCM. Two previous studies demonstrated that women with HCM presented with symptoms at a later age than men.^{28,29} In

the present study, the female patients had features suggestive of more advanced obstructive HCM than the male patients: women had more symptoms, a higher LVOT gradient, greater septal thickness and maximal LV wall thickness (indexed to BSA), and larger LA size (indexed to BSA). There was no significant difference between the 2 groups in terms of age. After surgery, functional class is worse and the risk of cardiovascular events and death is higher in women. These findings have a few important implications. First, some clinical and experimental studies have suggested that females affected with HCM have generally less hypertrophy than males.^{30,31} Therefore, the female patients in the present cohort who were referred for surgery may have a more aggressive form of this condition, and these factors contributing to greater disease severity persist in the postoperative period. Second, gender differences have been demonstrated in animal models of pressure-overload hypertrophy.³² Consequently, male and female patients may differ in their adaptive response to relief of the LVOT gradient after myectomy. Finally, because women had markers of increased disease magnitude at the time of surgery, it is possible that they may have developed more irreversible changes, such as increased LV stiffness or diastolic dysfunction, that do not normalize in the postoperative period.

Echocardiographic Predictors of Mortality

LA enlargement is a marker of disease severity and reflects the extent of MR, which has been correlated to the degree of LVOT obstruction,³³ abnormal diastolic filling,^{34,35} and elevation in LA and LV pressures. Because there was no significant relationship between preoperative LVOT gradient and LA diameter in the present study, this suggests that patients with greater LA diameters may have had more advanced diastolic dysfunction or higher filling pressures at the time of surgery. LA size was the only significant preoperative echocardiographic determinant of postoperative mortality in the present study. Given that the main direct effect of myectomy is the abolition of LVOT obstruction, poorer outcomes would be expected in those patients who have other abnormalities, such as impaired LV filling, which are not definitively treated with subaortic muscle resection. Although the degree of hypertrophy is regarded as a prognostic marker in HCM,¹³ preoperative septal thickness was not a significant predictor of postoperative mortality in the present study. This is likely because preoperative septal thickness may not reflect the total burden of preoperative LV hypertrophy nor the amount of residual hypertrophy after subaortic muscle resection, which limits the usefulness of this preoperative variable as a predictor of postoperative long-term outcomes.

Effects of Myectomy on AF

Previous studies of patients with HCM have demonstrated a significant relationship between LA size and the development of AF.^{15,36} The onset of AF frequently is associated with clinical deterioration.^{15,24} Few studies have addressed the effects of relieving LVOT obstruction on LA enlargement and the subsequent risk of AF. One study of 37 patients showed a reduction in LA diameter after surgery in younger

patients (<40 years of age at surgery).³⁷ There was also an increased incidence of postoperative AF in patients with postoperative LA enlargement during a relatively short follow-up period (mean of 11 months). Another study demonstrated significant changes in LA volume and function at 6 months after NSRT.³⁸ The results of the present study support and extend these findings. Patients with preoperative AF were older and had greater LA enlargement than patients in sinus rhythm. Myectomy abolished further AF in 46% of the patients who had preoperative AF. This represents a greater reduction in the incidence of recurrent AF during postoperative follow-up than has been reported previously.³⁹ In the group of patients with both preoperative and late postoperative AF, patients remained free of AF for an average of >5 years after surgery. There was no accompanying change in LA size after surgery in patients with preoperative AF. In contrast, LA size appeared to influence the development of new postoperative AF. Patients who remained in postoperative sinus rhythm had smaller LA diameters than those with new postoperative AF. Moreover, patients in sinus rhythm had a significant reduction in LA diameter after surgery, an effect that was not observed in patients who developed new postoperative AF. Although the present study did not specifically examine the differences in the long-term risks of AF with earlier timing of myectomy, our results suggest that a lower threshold for surgical intervention in patients with preoperative AF may be warranted.

Previous Studies of Myectomy in Management of HCM

Ventricular myotomy or myectomy has been performed for the past 4 decades for the management of severe obstructive HCM.²⁻⁸ The present study represents one of the largest cohorts of patients who have undergone surgical myectomy.³⁹⁻⁴² The perioperative mortality rates of this procedure at other centers are variable. Existing data have shown substantial symptomatic improvement and abolition of the LVOT gradient in the majority of patients during long-term follow-up.³⁹⁻⁴³ In terms of long-term survival, the present results are consistent with other studies that have identified increased age and the need for concomitant surgical procedures as significant predictors for late death.⁴⁰⁻⁴² The study by Heric et al⁴⁰ also found the presence of preoperative syncope (or near syncope) and postoperative complete heart block to be risk factors for late death. It is possible that syncope may reflect an increased incidence of arrhythmias, which may not be eliminated by myectomy. The development of complete heart block may be a marker for increased age, preexistent conduction abnormalities, additional cardiac lesions that require concomitant surgical procedures, or more severe HCM that necessitated a larger subaortic resection.⁴⁰ Unlike the present study, other investigators have not found significant parameters on echocardiography to have long-term prognostic significance.⁴¹ However, 1 study did find 3 preoperative echocardiographic characteristics that were associated with improved symptoms 1 year after surgery: the presence of asymmetrical hypertrophy, severe systolic anterior motion, and a prolonged isovolumic relaxation time.⁴⁴

Other Treatment Options in Obstructive HCM

Patients with obstructive HCM and intractable symptoms (despite pharmacological therapy) are candidates for dual-chamber permanent pacing, NSRT, or myectomy.^{2,3} Nonrandomized studies of medical therapy versus myectomy⁴⁵ and of dual-chamber pacing versus myectomy⁴⁶ have suggested more favorable overall outcomes with myectomy. Since the introduction of NSRT as a nonsurgical strategy in the mid-1990s,¹⁰ there have been multiple studies that examined the outcomes of NSRT and its effects on patients' clinical status and LVOT obstruction.^{3,11,12} Three nonrandomized studies have directly compared the results of NSRT versus myectomy.⁴⁷⁻⁴⁹ In all 3 studies, there was a significant reduction in the magnitude of the resting LVOT gradient after both interventions. Nevertheless, 2 of these studies showed that patients who underwent myectomy were more likely to have complete abolition of their LVOT gradient.^{48,49} There were 6 patients (25%) in the NSRT group in the study by Qin et al⁴⁸ who required a repeat intervention (5 had myectomy, 1 had second NSRT) owing to residual symptomatic obstruction. All 3 studies showed similar improvements in NYHA functional class after these interventions⁴⁷⁻⁴⁹; however, the study by Firoozi et al⁴⁹ demonstrated that oxygen consumption and other exercise parameters were better in the myectomy group. Although NSRT has the advantage of being less invasive than myectomy, there was a significantly higher need for permanent pacemaker implantation in the patients who underwent NSRT (15% to 24% for NSRT groups versus 2% to 8% for myectomy groups).⁴⁷⁻⁵⁰ Importantly, there are potential late complications that may occur after NSRT, such as the development of ventricular arrhythmias, which necessitate ongoing vigilance and long-term follow-up studies.^{3,8,50}

Study Limitations

The data collection of baseline and perioperative characteristics was retrospective. Because all clinical and echocardiographic evaluations could not be performed entirely at our institution, the data are subject to interobserver variability. Assessment of LA size was limited to measurement of LA diameter (in the anteroposterior plane) by transthoracic echocardiography. Determination of preoperative and postoperative filling pressures would have provided further data on the hemodynamic changes after myectomy; however, given the assembly of this cohort over the past 25 years, the comprehensive assessment of diastolic filling parameters was not feasible in the present study. Finally, this study involved the experience of a single tertiary-care referral center. Therefore, as with many procedures that require clinical and technical expertise, its outcomes may not be generalizable to other centers.

Conclusions

In summary, surgical myectomy for the abolition of LVOT obstruction is associated with excellent perioperative and long-term outcomes. Surgical myectomy should remain the standard to which all newer interventions for obstructive HCM are compared. Multivariable models identified risk factors that previously had not been associated with mortality and serious cardiovascular morbidity after myectomy. Increased age, female gender, concomitant CABG, and preop-

erative AF are the clinical determinants of overall, late, and cardiovascular mortality. Preoperative LA size was the only significant echocardiographic predictor of postoperative outcome. This study contributes to our understanding and our management of patients with obstructive HCM.

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