Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy: A propensity score–matched cohort

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ABSTRACT

Objectives: In patients with hypertrophic cardiomyopathy, obstruction of the left ventricular outflow tract can be relieved by surgical septal myectomy or alcohol septal ablation, but uncertainty remains regarding long-term results and comparative effectiveness of alcohol septal ablation. This study aims to compare short- and long-term outcomes of the 2 procedures.

Methods: Between December 1998 and September 2016, 2407 patients underwent septal myectomy and 211 patients underwent alcohol septal ablation at our institution. After 2:1 propensity score matching, the study cohort included 334 patients who underwent myectomy and 167 patients who underwent alcohol septal ablation.

Results: Median (interquartile range) ages of patients in the myectomy and alcohol septal ablation groups were 65 (58–71) years and 64 (56–73) years ($P = .9$), respectively. After intervention, median resting left ventricular outflow tract gradient at predischarge transthoracic echocardiography was 0 (0–10) mm Hg in the myectomy group ($n = 288$) and 21 (10–60) mm Hg in the alcohol septal ablation group ($n = 63$) ($P < .001$, tested at baseline gradients of 30 and 50 mm Hg). There were no differences in survival between the 2 groups (risk of death for alcohol septal ablation vs myectomy, hazard ratio, 1.5; 95% confidence interval, 0.9–2.6; $P = .1$). Survival of patients undergoing septal myectomy was better than that of an age-, sex-, and race-matched US population (82% vs 75% at 12 years, $P = .01$). Reintervention for left ventricular outflow tract obstruction was more likely to occur in patients who received alcohol septal ablation (hazard ratio, 33.3; 95% confidence interval, 4.4–250.6; $P < .001$).

Conclusions: There were no differences in survival of patients undergoing myectomy or alcohol septal ablation, but freedom from reintervention and early and late reduction of left ventricular outflow tract gradient are superior in patients undergoing septal myectomy. (J Thorac Cardiovasc Surg 2019;157:306–15)

Survival in the PS-matched groups.

Central Message

Septal myectomy remains the gold standard treatment for patients with obstructive HCM. ASA may be appropriate for elderly patients or patients considered at high risk for surgical myectomy.

Perspective

In patients with HCM, there are no differences in survival between the 2 propensity-matched groups who received septal myectomy or ASA. However, reintervention rates and gradient relief are superior after septal myectomy compared with ASA.

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Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac condition and has a prevalence of 1 in

500.¹ In the majority of patients, the left ventricular septum is abnormally thickened, which may lead to systolic anterior motion of the mitral valve, obstruction of the left ventricular outflow tract (LVOT), and mitral valve regurgitation. Symptomatic manifestations of HCM with LVOT obstruction include dyspnea, angina-like chest

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Abbreviations and Acronyms

ANCOVA	= analysis of covariance
ASA	= alcohol septal ablation
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter defibrillator
LVOT	= left ventricular outflow tract
NYHA	= New York Heart Association
PPM	= permanent pacemaker
PS	= propensity score
STS	= Society of Thoracic Surgeons

pain, and syncope. Initial medical management with beta-blockade, verapamil, or disopyramide can improve symptoms and functional capacity; however, there is a subset of patients in whom medical therapy is ineffective or associated with debilitating side effects, and in these patients invasive treatment for septal reduction is indicated.²

Currently, the 2 most common interventions for septal reduction are surgical septal myectomy and alcohol septal ablation (ASA). Transaortic septal myectomy involves resection of hypertrophied muscle, which, when performed by experienced surgical teams, reliably reduces the LVOT gradient and abolishes systolic anterior motion and mitral regurgitation. In high-volume experienced centers of excellence, operative risks are minimal (<1%)^{3,4} and long-term outcomes are well established. ASA is a less-invasive technique, where the hypertrophied septum is infarcted by injecting ethanol into a septal perforator of the left anterior descending coronary artery.⁵ Alcohol ablation is often reserved for patients who are considered to be at high risk for surgery.⁶⁻⁸

There is a paucity of comparative data on long-term results in large cohorts of patients undergoing septal reduction by surgery or alcohol ablation.^{7,9,10} Such analyses are problematic because ASA is often preferred for older patients with more comorbidities. In this study, we compared early and late outcomes of septal myectomy versus ASA in a single center and used propensity matching to identify patient cohorts with similar preoperative characteristics.

MATERIALS AND METHODS

Patient Selection and Propensity Score Matching

This study was approved by our Institutional Review Board (16-006116). From December 1998 to May 2016, 2407 patients underwent surgical myectomy for isolated subaortic obstruction at our institution, and 211 patients received ASA (Figure 1). Patients with previous septal reduction therapy or concomitant operative procedures (n = 895) were excluded, as well as those who underwent transapical incisions (n = 195) or refused research consent (n = 33). Before propensity matching, the surgical cohort consisted of 1284 patients, and the ASA group remained at 211 patients.

A propensity score (PS) model was used to match the myectomy and ASA groups for potential confounders. After 2:1 matching, the study

FIGURE 1. Flow diagram of the study population.

cohort included 334 patients who underwent myectomy and 167 patients who underwent ASA (Tables 1 and E1).

Operative Technique

Surgical septal myectomy. Our preferred surgical technique of septal myectomy has been described in detail.^{11,12} Briefly, after median sternotomy, we measure the pressure gradient between the left ventricle and the aorta at rest and after a premature ventricular contraction. After initiation of cardiopulmonary bypass, the aorta is crossclamped and cold blood cardioplegia is administered. We incise the aorta obliquely and extend this incision toward the noncoronary sinus. A Number 10 knife blade is used to incise the septum beginning just to the right of the nadir of the right aortic sinus toward the anterior leaflet of the mitral valve and further lengthened toward the left ventricular apex. After bypass, we again measure the gradient between the left ventricle and the aorta at rest and after provocation to confirm adequate reduction of LVOT gradient.

Alcohol septal ablation. As previously reported, we measure hemodynamic LVOT gradients at rest and with provocation using trans-septal puncture or retrograde catheterization.^{9,13} A slightly oversized, over-the-wire angioplasty balloon is placed in a proximal septal perforator artery. The balloon is inflated, and angiographic and echocardiographic contrast are injected to identify the perfusion bed of the septal perforator artery. After confirming the targeted myocardium, 1 to 3 mL of ethanol are injected over 3 to 5 minutes, followed by a normal saline flush (1 mL over 2 minutes). Additional septal arteries may be treated if there is significant residual LVOT obstruction and if other septal arteries are accessible.

Among patients in this study, median volume of ethanol used was 1.8 (1.5-2.0) mL, and injection into 1 coronary artery was performed in 83.2% (139/167); the remaining patients had ethanol injected into 2 septal branches of the left anterior descending coronary artery.

Data Collection

We collected data from a prospectively maintained surgical database at the Mayo Clinic and retrospective review of electronic health records. To

TABLE 1. Baseline characteristics of myectomy and alcohol septal ablation groups after propensity score matching

Variable	Myectomy (n = 334)	ASA (n = 167)	P value	Standardized difference
Age at intervention, median (IQR), y	65.4 (57.7-71.1)	64.0 (56.0-73.0)	.64	−0.024
Male	153 (45.8%)	74 (44.3%)	.75	−0.030
Procedure year, median (IQR)	2008 (2005-2011)	2006 (2003-2011)	.67	−0.070
NYHA class, median (IQR)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	.75	−0.032
Chronic lung disease	59 (17.7%)	29 (17.4%)	.93	−0.008
Cerebrovascular accident	9 (2.7%)	4 (2.4%)	.85	−0.019
Renal failure	6 (1.8%)	4 (2.4%)	.66	0.042
Diabetes	40 (12.0%)	20 (12.0%)	>.99	0.000
Hypertension	192 (57.5%)	98 (58.7%)	.79	0.024
Coronary artery disease	47 (14.1%)	25 (15.0%)	.78	0.025
Beta-blocker	258 (77.2%)	131 (78.4%)	.76	0.029
Calcium channel blocker	130 (38.9%)	70 (41.9%)	.51	0.061
Previous percutaneous coronary intervention	27 (8.1%)	12 (7.2%)	.73	−0.034
Previous coronary artery bypass graft surgery	4 (1.2%)	1 (0.6%)	.54	−0.064
Maximum LVOT gradient (resting or provoked), median (IQR), mm Hg	85 (70-104)	88 (67-105)	.83	0.039
PS, median (IQR)	−1.3 (−2.1 to −0.7)	−1.3 (−2.1 to −0.5)	.43	0.067

ASA, Alcohol septal ablation; IQR, interquartile range; NYHA, New York Heart Association; LVOT, left ventricular outflow tract; PS, propensity score.

ensure consistency of data collection before propensity matching, we used the Society of Thoracic Surgeons (STS) database to abstract information from the myectomy cohort and adhered strictly to STS criteria when collecting data for the ASA cohort. After propensity matching, outcomes were determined using the electronic medical records, and chart abstraction was consistently performed by 1 co-author (A.N.). Vital status was ascertained through LexisNexis Accurint (New York City, NY).

Statistical Analysis

Details regarding the PS estimation, matching, and outcome analysis are described in the [Supplementary Material](#). Briefly, we attempted to caliper match 2 patients in the myectomy group to each patient in the ASA group within a small tolerance (0.2 standard deviations of the logit of the PS) using the optimal matching algorithm. Baseline differences between the 2 treatment groups were assessed before matching using the Wilcoxon rank-sum test or Pearson chi-square test. Group comparisons on the same data after the match were performed with univariate conditional logistic regression models, stratified on the matched sets.

For outcomes analysis, unadjusted event-free rates for all-cause mortality and reintervention were estimated using the Kaplan–Meier method. In addition, Cox regression models stratified on PS-matched sets were used to investigate differences in cumulative mortality and length of stay. Because of some missing data, reintervention was analyzed using a propensity-adjusted Cox model with a robust variance estimator to account for partially matched data. Binary logistic regression, estimated with generalized estimating equations, was used to model risk of postoperative complications.

To compare changes in LVOT measurements at early or late follow-up, LVOT gradient outcomes were analyzed in subgroups of patients for whom both pre- and postprocedural measurements were available. We used semi-parametric analysis of covariance (ANCOVA) models based on proportional odds ordinal logistic regression. Similar ANCOVA ordinal regression models were applied to New York Heart Association (NYHA) outcomes. In general, when only a subset of the matched sample had the outcome measurement, the analysis adjusted for treatment selection bias by including PS as a covariate in the model.

Analyses were conducted using SAS software (version 9.4; SAS Institute Inc, Cary, NC) and R programming language (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Baseline Characteristics

A total of 1495 patients met initial inclusion criteria. Compared with the myectomy group, patients in the ASA group were older, treated earlier in the study period, and more likely to be female and to have comorbidities ([Table E1](#)). PS analysis matched 334 patients who underwent myectomy to 167 patients who underwent ASA. As expected, this resulted in similar distribution of PSs ([Figures 2 and E1](#)) and baseline characteristics ([Table 1](#)), with minimal standardized differences.

Early Outcomes

Procedure-related morbidity and mortality were similar in the 2 groups. There were no in-hospital deaths after septal myectomy or ASA. Nonfatal complications (tamponade, sustained ventricular tachycardia/cardiac arrest, reoperation, or cerebrovascular accident) occurred in 18 patients (5.4%) undergoing septal myectomy and 12 patients (7.2%) undergoing ASA ($P = .43$). There were no differences in implantable cardioverter defibrillator (ICD) placements (7.2% in patients undergoing myectomy vs 9.6% in patients undergoing ASA, $P = .37$), but the need for permanent pacemaker (PPM) insertion was significantly lower in the myectomy group (3.9% vs 17.4%, $P < .001$). In-hospital length of

FIGURE 2. Distribution of PS in the original sample and the PS-matched subset.

stay was longer in patients undergoing surgical myectomy (6.0 [5.0-7.0] days vs 3.0 [3.0-4.0] days, $P < .001$).

Gradient Relief

As shown in Table 2, the direct manometric LVOT gradient at rest decreased from a median of 60.0 (32.0-85.0) mm Hg to 0.0 (0.0-3.0) mm Hg in the septal myectomy group and from 65.0 (29.0-100.0) mm Hg to 5.0 (0.0-15.0) mm Hg in the ASA group. Modeled estimates of postoperative LVOT gradients indicated that, at higher baseline gradients, predicted gradient relief was better after myectomy compared with ASA (Figure 3, A, $P < .001$ for interaction between group and baseline gradient). This is further supported by testing at 2 prespecified baseline thresholds, which showed no treatment difference at a baseline gradient of 30 mm Hg ($P = .67$) but a beneficial effect of myectomy at 50 mm Hg ($P = .001$) (Table 2).

On Doppler transthoracic echocardiography performed in 351 patients (70.1%) before hospital dismissal, median resting LVOT gradient after septal myectomy was 0.0 (0.0-9.5) mm Hg compared with 21.0 (10.0-60.0) mm Hg in those who had ASA. Again, there was evidence of a differential treatment effect (interaction $P = .04$; treatment difference, $P < .001$ at both pregradient thresholds), and the estimated benefit of myectomy was superior to ASA

at higher baseline gradients (Figure 3, B). Late postprocedural transthoracic echocardiography assessed in 125 patients (25.0%) at a median of 7.3 (3.7-13.6) months after intervention revealed resting gradients of 0.0 (0.0-0.0) mm Hg in surgical patients and 18.0 (0.0-46.0) mm Hg in ASA patients (treatment difference, $P < .001$) (Figure 3, C).

Survival and Freedom From Reintervention

In the overall cohort, survival was superior in patients undergoing septal myectomy (Figure 4, A). However, after PS matching, survival was not different between the 2 groups (risk of death for ASA vs myectomy, hazard ratio, 1.52; 95% confidence interval, 0.89-2.60; $P = .13$) (Figure 4, B). Further sensitivity analyses for the matched comparisons that were adjusted for any residual imbalance in PS yielded the same results as those presented.

From the matched cohort, we identified 269 patients (53.7%) who had adequate follow-up (2.6 [0.6-7.2] years) to ascertain repeat intervention. Compared with the 239 patients who were lost to follow-up, these patients were more likely to originate from the ASA group and were treated earlier in the study period, but were otherwise similar (Table E2). In this unmatched subgroup, reintervention for LVOT obstruction was more likely to occur in the ASA group compared with the myectomy group (hazard ratio,

TABLE 2. Changes in left ventricular outflow tract gradient in myectomy and alcohol septal ablation groups

	Myectomy	ASA	P value
Postprocedure gradient (catheter/pressure), median (IQR), mm Hg	n = 299	n = 145	
Observed baseline value	60.0 (32.0-85.0)	65.0 (29.0-100.0)	
Observed follow-up value	0.0 (0.0-3.0)	5.0 (0.0-15.0)	
Interaction {Group $\times$ baseline value} [*]			<.001
Predicted follow-up value [†]			
At baseline value = 30 mm Hg	0.0 (0.0-2.8)	0.0 (0.0-3.4)	.67
At baseline value = 50 mm Hg	0.0 (0.0-4.0)	2.9 (0.0-8.7)	.001
TTE gradient at early follow-up (<30 d), median (IQR), mm Hg	n = 288	n = 63	
Observed baseline value	61.0 (25.5-92.0)	74.0 (25.0-100.0)	
Observed follow-up value	0.0 (0.0-9.5)	21.0 (10.0-60.0)	
Interaction {Group $\times$ baseline value} [*]			.04
Predicted follow-up value [†]			
At baseline value = 30 mm Hg	0.0 (0.0-6.5)	15.6 (3.9-27.7)	<.001
At baseline value = 50 mm Hg	0.0 (0.0-11.8)	23.2 (12.9-50.1)	<.001
TTE gradient at late follow-up (30 d to 2 y), median (IQR), mm Hg	n = 54	n = 71	
Baseline value	64.0 (27.0-92.0)	67.0 (25.0-100.0)	
Follow-up value	0.0 (0.0-0.0)	18.0 (0.0-46.0)	
Interaction {Group $\times$ baseline value} [*]			.42
Predicted follow-up value [†]	0.0 (0.0-0.0)	17.3 (5.7-41.6)	<.001

ASA, Alcohol septal ablation; IQR, interquartile range; TTE, transthoracic echocardiography. ^{*}An interaction was included in the model to test if the difference of treatments varied across baseline gradients. [†]If the interaction was significant, model-predicted follow-up gradients were estimated and tested for a treatment difference at fixed baseline gradients of 30 and 50 mm Hg. Otherwise, the model was refit without the interaction term to assess the average treatment effect.

33.25; 95% confidence interval, 4.41-250.57; $P < .001$) (Figure 5). Repeat intervention was necessary in 1 patient after myectomy and 21 patients after ASA. In those who had undergone ASA, myectomy was the preferred choice of repeat intervention and was performed in 16 of 21 patients (76.2%).

Functional Outcomes

In a subset of 268 patients (53.5%) with available data, functional status as expressed by NYHA class was stratified into less than 1 year, 1 to 5 years, and more than 5 years follow-up. As shown in Table E3, functional status was generally comparable late after operation, but during early follow-up (<1 year), NYHA class was better in patients who underwent septal myectomy ($P = .003$); 98.0% of surgical patients were in NYHA class I or II compared with 78.4% of patients after ASA.

DISCUSSION

Rationale of Study and Important Findings

Important findings from our study comparing septal reduction by surgical myectomy or ASA are that overall survival of propensity-matched patients does not differ, but freedom from reintervention and LVOT gradient relief are superior after septal myectomy. The degree of symptomatic improvement over the first year also favors myectomy, although this benefit does not appear sustained thereafter. Further, incidence of postprocedural pacemaker implantation is significantly lower in those undergoing surgical myectomy.

Overall Survival

Most previous studies comparing surgical myectomy and ASA for patients with obstructive HCM have found little difference in outcomes between the 2 procedures, including 30-day mortality and all-cause long-term mortality.^{9,10,14} However, there are fundamental differences in methods. ASA results in a variable degree of septal necrosis and scarring, which might be a substrate for ventricular arrhythmias.^{15,16} Indeed, ten Cate and coauthors¹⁷ reported that among patients undergoing ASA, survival free from death and aborted sudden cardiac death (including appropriate ICD therapy) was reduced compared with patients who underwent surgical myectomy. In a multicenter study of 566 patients undergoing septal myectomy or ASA, Vriesendorp and colleagues⁷ noted a lower risk of sudden cardiac death in those who had septal myectomy.

In the present study, we focused on overall mortality after septal reduction therapy, and among all patients (unadjusted), surgical myectomy was associated with a significant survival benefit compared with ASA (Figure 4, A). It has been our practice to discuss both treatments with patients who are candidates for septal reduction therapy, and patients who choose surgical myectomy are generally younger and healthier than patients who choose ASA. After PS matching to account for potential confounders including age, there was no significant difference in overall survival (despite a hazard ratio for death of 1.52 after ASA). Of note, long-term survival in matched patients who received septal myectomy may be favorable compared with a nationwide population with similar demographics (Figure 4, B).

A

B

C

FIGURE 3. Predicted follow-up LVOT resting gradient in myectomy and ASA cases, based on preprocedure gradients. A, Predicted postprocedural gradients using catheter/pressure measurements. B and C, Predicted early (<30 days after procedure) and late transthoracic echocardiography gradients (>30 days to 2 years after septal reduction therapy). LVOT, Left ventricular outflow tract; TTE, transthoracic echocardiography.

Postprocedural Complications

Both surgical myectomy and ASA can be performed with a low risk of procedural complications. Among propensity-matched patients, there were no in-hospital mortalities. Nonfatal complications, including cardiac tamponade, sustained ventricular tachycardia, cardiac arrest, reoperation, or cerebrovascular accident, occurred in 5.4% of patients receiving septal myectomy and 7.2% of patients undergoing ASA, and did not differ among the 2 groups. However, Steggerda and colleagues¹⁰ described a significantly higher rate of postprocedural complications in surgical patients compared with ASA patients. The increased risk of nonfatal complications in their surgical patients appears to be due to the higher than expected rate of repeat thoracotomy for bleeding and tamponade.

Permanent Pacemaker Insertion

Complete heart block requiring PPM insertion is a well-known complication of septal reduction therapy. In our propensity-matched cohort, PPM insertion was necessary in 3.9% of surgical patients, but this rate was more than 4-fold higher in patients undergoing ASA (17.4%, $P < .001$). Our results differ from studies using data from the National Inpatient Sample in which rates of PPM implantation after septal reduction by surgery or ASA were 8% to 9%.^{18,19} We suspect the lower risk of pacemaker implantation in our surgical patients reflects experience and familiarity with subaortic myectomy and can be achieved in other dedicated HCM centers. Although implantation of transvenous pacemakers is a relatively minor procedure, pacemaker dependency and late lead complications are important considerations for young patients with long life expectancy.²⁰⁻²² In addition to the cost and potential for early morbidity of pacemakers, device implantation may have an effect on late survival after septal reduction. Greason and colleagues²³ reported that among 5842 patients undergoing aortic valve replacement followed for a median of 11 years, early pacemaker implantation was independently associated with an increased risk of death (hazard ratio, 1.49; $P < .001$).

Relief of Left Ventricular Outflow Tract Gradient

An important finding of this study is that LVOT gradient relief is more complete after septal myectomy than ASA. Indeed, at both early and late follow-up, resting LVOT gradients were on average lower after myectomy compared with ASA (Table 2). This finding is similar to data from Nogie and colleagues,²⁴ who reported persistent postprocedure gradients of more than 20-50 mm Hg, suggesting that ASA may not adequately relieve LVOT obstruction in some patients. In our surgical patients, postintervention gradient

FIGURE 4. Survival in original sample and PS-matched groups. A, Unadjusted survival in the original sample for myectomy and ASA groups. B, Survival of the PS-matched myectomy and ASA groups. The *dashed line* depicts expected survival in an age-, sex-, and race-matched population.

was independent of severity of preoperative LVOT obstruction, but with ASA, early follow-up gradient was strongly related to preprocedure gradient (Figure 3). This finding

may be helpful in selecting septal reduction therapy; ASA may be an appropriate treatment choice for selected patients with preprocedure resting gradients of 40 mm Hg or less,

FIGURE 5. Freedom from reintervention in myectomy and ASA groups.

but may not be adequate for those with higher LVOT gradients.^{25,26}

Reintervention

Incomplete relief of LVOT gradient after septal reduction therapy may lead to recurrent or persistent symptoms and need for reintervention. In our propensity-matched cohort, we observed overall reintervention rates (over 10 years) of 1.0% for patients undergoing myectomy and 35.0% for patients undergoing ASA; the hazard ratio for repeat procedure after ASA compared with myectomy was 33.3 (Figure 5). The study findings add to accumulating evidence that alcohol ablation is associated with a significantly higher rate of repeat intervention.²⁷ Some authors have reported that residual LVOT gradients may affect late patient survival.²⁸ In a previous study from our institution, Sorajja and colleagues⁹ observed that a residual LVOT gradient 10 mm Hg or more was associated with worse survival in ASA cases. In the present study, which reflects our more recent experience, there was no association between residual LVOT gradient and overall mortality.

Septal Myectomy After Unsuccessful Ablation

In this series, surgical myectomy rather than repeat ASA appeared to be the favored intervention for residual outflow tract obstruction after unsuccessful ASA; however, operation in this setting can be problematic.^{29,30} In a review of 31 patients who underwent septal myectomy after failed alcohol ablation, Quintana and coauthors³¹ noted a higher

risk of postoperative complete heart block in patients who had prior ASA compared with a control group of patients who had myectomy without a history of ASA (19.4% vs 1.6%). The increased risk of heart block observed with septal myectomy after ASA may be explained by the differential effects of each procedure on the conduction system. A right bundle branch block develops in approximately one third of patients after ASA, and 40% of patients develop left bundle branch block after septal myectomy.³² Quintana and colleagues also noted that early mortality was increased in patients who underwent septal myectomy after prior ASA and hypothesized that the interstitial endocardial fibrosis observed in these patients may contribute to decreased ventricular compliance resulting in diastolic dysfunction and heart failure.

Functional Outcomes

Functional outcomes after septal reduction therapy improve after both surgical myectomy and ASA.³³ However, most prior investigations comparing functional status after the 2 therapies are limited by small sample size and short duration of follow-up. Among patients in our study for whom data were available, early (<1 year) relief of symptoms was superior after surgical myectomy. Over later follow-up intervals, functional outcomes were generally similar, and this may be explained by 2 observations. First, patients in either group with persistent symptoms after initial septal reduction received medical therapy and were considered for repeat procedures. There was a relatively

high incidence of reintervention, primarily surgical myectomy, in the ASA group, which would be expected to improve late outcome. Second, the median age of patients in the propensity-matched cohort was 64 to 65 years, and late functional status of both groups is likely influenced by comorbidities associated with aging.

Study Limitations

This study is a retrospective review from a single tertiary center, and our analysis may be limited by inherent selection and referral bias; the results may not be generalizable to other institutions. Information on survival is available for all patients, but follow-up data on echocardiographic measurements, functional status, and reintervention are not complete. Further, propensity matching restricted our analyses to patients with myectomy who had similar baseline characteristics as patients with ASA. As a result, these patients are older and likely sicker than typical myectomy cases, which could limit the generalizability of our results. Finally, propensity analysis is susceptible to unmeasured confounders, and we have assumed any such missed covariates do not lead to significant bias in our findings.

CONCLUSIONS

Septal myectomy and ASA are important treatment modalities to relieve LVOT obstruction in symptomatic patients undergoing HCM. In a propensity-matched cohort, survival is not different between myectomy and ASA cases. However, freedom from reintervention, early and late reduction of LVOT gradient relief, and short-term symptomatic improvement are superior in patients undergoing septal myectomy.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

References

- Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation*. 1995;92:785-9.
- Elliott PM, Anastakis A, Borger MA, Borggreve M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014; 35:2733-79.
- Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Nishimura RA, et al. Low operative mortality achieved with surgical septal myectomy: role of dedicated hypertrophic cardiomyopathy centers in the management of dynamic sub-aortic obstruction. *J Am Coll Cardiol*. 2015;66:1307-8.
- Maron BJ. Controversies in cardiovascular medicine. Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. *Circulation*. 2007;116:196-206; discussion 206.
- Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet*. 1995;346:211-4.
- Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124: e783-831.
- Vriesendorp PA, Liebrechts M, Steggerda RC, Schinkel AFL, Willems R, Ten Cate FJ, et al. Long-term outcomes after medical and invasive treatment in patients with hypertrophic cardiomyopathy. *JACC Heart Fail*. 2014;2:630-6.
- Nishimura RA, Seggewiss H, Schaff HV. Hypertrophic obstructive cardiomyopathy: surgical myectomy and septal ablation. *Circ Res*. 2017;121:771-83.
- Sorajja P, Ommen SR, Holmes DR Jr, Dearani JA, Rihal CS, Gersh BJ, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation*. 2012;126:2374-80.
- Steggerda RC, Damman K, Balt JC, Liebrechts M, ten Berg JM, van den Berg MP. Periprocedural complications and long-term outcome after alcohol septal ablation versus surgical myectomy in hypertrophic obstructive cardiomyopathy: a single-center experience. *JACC Cardiovasc Interv*. 2014;7:1227-34.
- Kotkar KD, Said SM, Dearani JA, Schaff HV. Hypertrophic obstructive cardiomyopathy: the Mayo Clinic experience. *Ann Cardiothorac Surg*. 2017;6:329-36.
- Said SM, Schaff HV. Surgical treatment of hypertrophic cardiomyopathy. *Semin Thorac Cardiovasc Surg*. 2013;25:300-9.
- Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, et al. Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation*. 2008;118:131-9.
- Nagueh SF, Ommen SR, Lakkis NM, Killip D, Zoghbi WA, Schaff HV, et al. Comparison of ethanol septal reduction therapy with surgical myectomy for the treatment of hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol*. 2001;38:1701-6.
- Valeti US, Nishimura RA, Holmes DR, Araoz PA, Glockner JF, Breen JF, et al. Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol*. 2007;49:350-7.
- Noseworthy PA, Rosenberg MA, Fifer MA, Palacios IF, Lowry PA, Ruskin JN, et al. Ventricular arrhythmia following alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am J Cardiol*. 2009;104:128-32.
- Ten Cate FJ, Soliman OI, Michels M, Theuns DAMJ, de Jong PL, Geleijnse ML, et al. Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. *Circ Heart Fail*. 2010;3:362-9.
- Panaich SS, Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, et al. Results of ventricular septal myectomy and hypertrophic cardiomyopathy (from Nationwide Inpatient Sample [1998-2010]). *Am J Cardiol*. 2014;114: 1390-5.
- Chothani A, Panaich SS, Patel N, Patel NJ, Arora S, Deshmukh A, et al. Septal ablation and hypertrophic obstructive cardiomyopathy: 7 years US experience. *J Interv Cardiol*. 2016;29:505-12.
- Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186-94.
- Udo EO, Zuithoff NPA, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm*. 2012;9: 728-35.
- Lin G, Nishimura RA, Connolly HM, Dearani JA, Sundt TM III, Hayes DL. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J Am Coll Cardiol*. 2005;45:1672-5.
- Greason KL, Lahr BD, Stulak JM, Cha Y-M, Rea RF, Schaff HV, et al. Long-term mortality effect of early pacemaker implantation after surgical aortic valve replacement. *Ann Thorac Surg*. 2017;104:1259-64.
- Nogic J, Koh Y, Bak M, Gooley RP, Meredith IT, McCormick LM. Alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a 16-year Australian single centre experience. *Heart Lung Circ*. 2018;27:1446-53.
- Sorajja P, Binder J, Nishimura RA, Holmes DR Jr, Rihal CS, Gersh BJ, et al. Predictors of an optimal clinical outcome with alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Catheter Cardiovasc Interv*. 2013; 81:E58-67.
- McCully RB, Nishimura RA, Bailey KR, Schaff HV, Danielson GK, Tajik AJ. Hypertrophic obstructive cardiomyopathy: preoperative echocardiographic predictors of outcome after septal myectomy. *J Am Coll Cardiol*. 1996;27:1491-6.

27. Singh K, Qutub M, Carson K, Hibbert B, Glover C. A meta analysis of current status of alcohol septal ablation and surgical myectomy for obstructive hypertrophic cardiomyopathy. *Catheter Cardiovasc Interv*. 2016;88:107-15.
28. Veselka J, Jensen MK, Liebrechts M, Januska J, Krejci J, Bartel T, et al. Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry. *Eur Heart J*. 2016;37:1517-23.
29. Quintana E, Bajona P, Arguis MJ, Prat-González S. Septal myectomy after failed septal alcohol ablation. *Ann Cardiothorac Surg*. 2017;6:394-401.
30. ElBardissi AW, Dearani JA, Nishimura RA, Ommen SR, Stulak JM, Schaff HV. Septal myectomy after previous septal artery ablation in hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2007;82:1516-22.
31. Quintana E, Sabate-Rotes A, Maleszewski JJ, Ommen SR, Nishimura RA, Dearani JA, et al. Septal myectomy after failed alcohol ablation: Does previous percutaneous intervention compromise outcomes of myectomy? *J Thorac Cardiovasc Surg*. 2015;150:159-67.e1.
32. Talreja DR, Nishimura RA, Edwards WD, Valeti US, Ommen SR, Tajik AJ, et al. Alcohol septal ablation versus surgical septal myectomy: comparison of effects on atrioventricular conduction tissue. *J Am Coll Cardiol*. 2004;44:2329-32.
33. Samardhi H, Walters DL, Raffel C, Rateesh S, Harley C, Burstow D, et al. The long-term outcomes of transcatheter ablation of septal hypertrophy compared to surgical myectomy in patients with symptomatic hypertrophic obstructive cardiomyopathy. *Catheter Cardiovasc Interv*. 2014;83:270-7.

Key Words: alcohol septal ablation, hypertrophic cardiomyopathy, myectomy

SUPPLEMENTAL MATERIAL

Statistical Analysis

PS analysis was performed to control for covariate imbalance between the 2 treatment groups via matching. To estimate the PS, a multivariable logistic regression model was fitted with group membership as the dependent variable and 15 baseline covariates as the independent variables (see variables listed in Table 1). To avoid casewise deletion of patients in the propensity model, we imputed a small percentage of patients with missing NYHA (2.5%) and LVOT (0.5%) data points by assigning the corresponding median values from the observed data. Continuous covariates were included in the PS model as restricted cubic spline functions (3 knots) to permit nonlinear relationships. As defined on the logit scale, PS is the predicted log odds of being treated with ASA instead of myectomy given the set of baseline covariates. The goal of then matching patients from the 2 treatments on the basis of their PS is to produce subgroups with similar baseline characteristics. Because of the limited number in the ASA group, we attempted to sample all of these patients and twice as many myectomy cases as ASA cases. Our matching procedure used the optimal algorithm to caliper match patients with myectomy to those with ASA within a small tolerance on PS, prespecified as 0.2 standard deviations of logit PS. Covariate balance after PS matching was assessed by back-to-back histogram and standardized difference plots, as well as by statistical testing.

Unadjusted event-free rates for all-cause mortality and reintervention outcomes were estimated as a function of time after the index intervention using the Kaplan-Meier method. Length of stay was also defined as a censored outcome based on the time from intervention until successful discharge. Cox regression models stratified on PS-matched sets were used to investigate differences in cumulative mortality and length of stay between the matched groups. Because follow-up for reintervention was available in a subset of patients, some of whom remained matched and others became unmatched, we formulated the Cox model with a robust variance estimator to account for the partially matched data and included PS as a covariate to control for residual imbalance. Binary logistic regression models, estimated with the generalized estimating equations method to take into account the clustering by matched sets, were used to model risk of 3 separate complication outcomes based on treatment group. These short-term outcomes included placement of PPM, placement of ICD, and a composite outcome of other nonfatal complications that was formed because of sparse counts in the other individual complications of interest: tamponade, sustained ventricular tachycardia, reoperation, cardiac arrest, and stroke or transient ischemic attack.

To determine if measurements at early or late follow-up differed between the 2 groups after adjustment for baseline values, LVOT gradient outcomes were analyzed in subgroups of patients for whom both pre- and postprocedural measurements were available. Because distributions of LVOT gradient are typically skewed with heavy ties at zero, the analysis was subjected to a robust rank-based approach that is invariant to data transformation. This involved semiparametric ANCOVA based on the proportional odds ordinal logistic regression model, with the follow-up gradient as the dependent variable and treatment group, baseline gradient, and PS as covariates. To allow for a differential treatment effect on the follow-up gradient according to baseline measurement, an interaction term was included in the model and tested for significance. Predicted mean gradient values were plotted as a function of baseline gradient and treatment group to illustrate the modeled effects. When the test for interaction indicated a varying treatment effect across baseline gradients, we constructed tests for treatment difference fixing the baseline gradient at 30 and 50 mm Hg.

Similar ANCOVA-type ordinal regression models were applied to functional status outcomes defined by the latest follow-up NYHA measurement per patient. However, because these measurement times were highly variable, we stratified the data into 3 follow-up intervals and fit the ANCOVA ordinal model within each interval. The proportional odds assumption was assessed by calculating the cumulative logits for each ordinal class and checking for parallelism in these curves plotted against predictors. In general, outcome models included PS as a covariate (modeled flexibly using restricted cubic splines with 3 knots) when only an unbalanced subset of the matched sample was available, whereas models generated using the entire sample accounted for the matched design and did not initially include PS as a covariate. For sensitivity analysis, we repeated these matched analyses with PS included in the models as a covariate because matching on a continuous variable is not exact and may result in some residual imbalance. Analyses were conducted in SAS software (version 9.4; SAS Institute Inc, Cary, NC), with the exception of the model fits and plots of predicted mean gradients that were obtained with R programming language (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria).

Vital status was determined using LexisNexis Accurint (New York City, NY), which links data from a number of sources, including the Social Security Death Master File and state death records. If death from any cause was indicated in these records, the reported death date was used. Otherwise, patients were considered to be alive and were censored at 2 weeks before the date their vital status was searched.

FIGURE E1. PS between the 2 groups; back-to-back histograms of the PS distributions before and after matching shown on probability and logit scale. ASA, Alcohol septal ablation.

TABLE E1. Baseline characteristics of myectomy and septal ablation groups before propensity score matching

Variable	Myectomy (n = 1284)	ASA (n = 211)	P value	Standardized difference
Age at intervention, median (IQR), y	53.8 (42.9-63.8)	68.0 (58.0-76.0)	<.001	0.997
Male	712 (55.5%)	88 (41.7%)	<.001	-0.278
Procedure year, median (IQR)	2010 (2007-2013)	2006 (2003-2011)	<.001	-0.511
NYHA class, median (IQR)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	.40	0.082
Chronic lung disease	99 (7.7%)	49 (23.2%)	<.001	0.439
Cerebrovascular accident	17 (1.3%)	5 (2.4%)	.25	0.077
Renal failure	8 (0.6%)	8 (3.8%)	<.001	0.217
Diabetes	117 (9.1%)	27 (12.8%)	.09	0.118
Hypertension	632 (49.2%)	129 (61.1%)	.001	0.241
Coronary artery disease	99 (7.7%)	44 (20.9%)	<.001	0.382
Beta-blocker	943 (73.4%)	173 (82.0%)	.008	0.207
Calcium channel blocker	430 (33.5%)	86 (40.8%)	.040	0.151
Previous percutaneous coronary intervention	74 (5.8%)	18 (8.5%)	.12	0.108
Previous coronary artery bypass graft surgery	8 (0.6%)	6 (2.8%)	.002	0.171
Maximum LVOT gradient (resting or provoked), median (IQR), mm Hg	85 (64-104)	88 (67-105)	.18	0.068
PS, median (IQR)	-2.8 (-3.6 to -1.9)	-0.9 (-1.8 to 0.1)	<.001	1.412

ASA, Alcohol septal ablation; IQR, interquartile range; NYHA, New York Heart Association; LVOT, left ventricular outflow tract; PS, propensity score.

TABLE E2. Comparison of subsets with and without reintervention follow-up

Variable	Follow-up not available (n = 232)	Follow-up available (n = 269)	P value*
Treatment group: ASA	52 (22.4%)	115 (42.8%)	<.001
Age at procedure, median (IQR), y	65 (57-71)	65 (57-72)	.739
Male	107 (46.1%)	120 (44.6%)	.735
Procedure year	2009 (2005-2012)	2006 (2004-2011)	.004
NYHA class, median (IQR)	3 (3-3)	3 (3-3)	.339
Chronic lung disease	40 (17.2%)	48 (17.8%)	.860
Cerebrovascular accident	8 (3.4%)	5 (1.9%)	.264
Renal failure	3 (1.3%)	7 (2.6%)	.296
Diabetes	31 (13.4%)	29 (10.8%)	.375
Hypertension	137 (59.1%)	153 (56.9%)	.623
Coronary artery disease	38 (16.4%)	34 (12.6%)	.234
Beta-blocker	182 (78.4%)	207 (77.0%)	.688
Calcium channel blocker	93 (40.1%)	107 (39.8%)	.944
Previous percutaneous coronary intervention	18 (7.8%)	21 (7.8%)	.984
Previous coronary artery bypass graft surgery	3 (1.3%)	2 (0.7%)	.537
Maximum LVOT gradient (resting or provoked), median (IQR), mm Hg	85 (67-100)	88 (67-108)	.284

ASA, Alcohol septal ablation; IQR, interquartile range; NYHA, New York Heart Association; LVOT, left ventricular outflow tract. *P value from Wilcoxon rank-sum test or Pearson chi-square test.

TABLE E3. Functional outcomes (New York Heart Association Class) in myectomy and alcohol septal ablation groups during follow-up

NYHA class	Myectomy	ASA	P value*
<1 y follow-up	n = 50	n = 37	.003
I	39 (78.0%)	19 (51.4%)	
II	10 (20.0%)	10 (27.0%)	
III	1 (2.0%)	8 (21.6%)	
IV	0 (0.0%)	0 (0.0%)	
1-5 y follow-up	n = 43	n = 43	.89
I	26 (60.5%)	26 (60.5%)	
II	7 (16.3%)	6 (14.0%)	
III	9 (20.9%)	10 (23.3%)	
IV	1 (2.3%)	1 (2.3%)	
>5 y follow-up	n = 60	n = 35	.84
I	36 (60.0%)	20 (57.1%)	
II	12 (20.0%)	9 (25.7%)	
III	12 (20.0%)	5 (14.3%)	
IV	0 (0.0%)	1 (2.9%)	

NYHA, New York Heart Association; ASA, alcohol septal ablation. *P value from multivariable proportional odds logistic regression model fitted for ordinal NYHA class in the 3 subsets defined by time of follow-up measure; baseline NYHA and PS were included in each model as covariates.