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Comparison of Ethanol Septal Reduction Therapy With Surgical Myectomy for the Treatment of Hypertrophic Obstructive Cardiomyopathy

Sherif F. Nagueh, MD, FACC,* Steve R. Ommen, MD,† Nasser M. Lakkis, MD, FACC,* Donna Killip, RN,* William A. Zoghbi, MD, FACC,* Hartzell V. Schaff, MD, FACC,† Gordon K. Danielson, MD, FACC,† Miguel A. Quiñones, MD, FACC,* A. J. Tajik, MD, FACC,† William H. Spencer III, MD, FACC*

Houston, Texas and Rochester, Minnesota

OBJECTIVES This study was designed to compare the hemodynamic efficacy of nonsurgical septal reduction therapy (NSRT) by intracoronary ethanol with standard therapy (surgical myectomy) for the treatment of hypertrophic obstructive cardiomyopathy (HOCM).

BACKGROUND Nonsurgical septal reduction therapy has gained interest as a new treatment modality for patients with drug-refractory symptoms of HOCM; however, its benefits in comparison to surgery are unknown.

METHODS Forty-one consecutive NSRT patients at Baylor College of Medicine with one-year follow-up were compared with age- and gradient-matched septal myectomy patients at the Mayo Clinic. All patients had left ventricular outflow obstruction with a resting gradient ≥40 mm Hg and none had concomitant procedures.

RESULTS There were no baseline differences in New York Heart Association class, severity of mitral regurgitation, use of cardiac medications or exercise capacity. One death occurred during NSRT because of dissection of the left anterior descending artery. At one year, all improvements in both groups were similar. After surgical myectomy, more patients were on medications ($p < 0.05$) and there was a higher incidence of mild aortic regurgitation ($p < 0.05$). After NSRT, the incidence of pacemaker implantation for complete heart block was higher (22% vs. 2% in surgery; $p = 0.02$). However, seven of the nine pacemakers in the NSRT group were implanted before a modified ethanol injection technique and the use of contrast echocardiography.

CONCLUSIONS Nonsurgical septal reduction therapy resulted in a significantly higher incidence of complete heart block, but the risk was reduced with contrast echocardiography and slow ethanol injection. Surgical myectomy resulted in a significantly higher incidence of mild aortic regurgitation. Nonsurgical septal reduction therapy, guided by contrast echocardiography, is an effective procedure for treating patients with HOCM. The hemodynamic and functional improvements at one year are similar to those of surgical myectomy. (J Am Coll Cardiol 2001;38:1701–6) © 2001 by the American College of Cardiology

Surgical septal myectomy is the standard treatment for patients with hypertrophic obstructive cardiomyopathy (HOCM) who are refractory to medical therapy. Successful septal myectomy relieves symptoms and improves exercise tolerance in the great majority of these patients. Furthermore, the treatment's effects are usually sustained and, when performed in experienced centers, it is a safe procedure with low morbidity and mortality (1–6). Nonetheless, early results from several centers in Europe and the U.S. (7–10) suggest that nonsurgical septal reduction therapy (NSRT) is a similarly effective therapy. We sought to compare the hemodynamic efficacy, at one year, of both treatment modalities in two groups of patients matched for both age and left ventricular outflow tract (LVOT) gradient.

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METHODS

The first 41 consecutive HOCM patients at Baylor College of Medicine with a resting dynamic LVOT gradient ≥40 mm Hg who underwent NSRT were compared to 41 septal myectomy patients at the Mayo Clinic, matched for age and LVOT gradient. The presence of only a provokable gradient ($n = 40$ in the NSRT group) was the only reason for exclusion in this study. Also, no patients had to be excluded because of loss of follow-up. The surgery patients were identified from 148 patients with a resting gradient ≥40 mm Hg who underwent surgery during a similar time

From the *Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, Texas; and the †Divisions of Cardiology and Cardiothoracic Surgery, Mayo Clinic, Rochester, Minnesota. Supported in part by grants from the T. L. L. Temple Foundation, Lufkin, Texas; the Dunn Foundation, and The Methodist Hospital Foundation, Houston, Texas. Dr. Nagueh is supported by a Scientist Development Grant (0030235N) from the American Heart Association, National Center, Dallas, Texas.

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Abbreviations and Acronyms

ANOVA = analysis of variance
CCS = Canadian Cardiovascular Society
EDD = end-diastolic dimension
ESD = end-systolic dimension
HOCM = hypertrophic obstructive cardiomyopathy
ICD = implantable cardiac defibrillator
LVOT = left ventricular outflow tract
METS = metabolic equivalents
NSRT = nonsurgical septal reduction therapy
NYHA = New York Heart Association
V_{O_2} peak = maximal oxygen consumption

interval. All patients had asymmetric left ventricular hypertrophy with a septal thickness of at least 1.5 cm. Left ventricular outflow tract obstruction was due to septal-leaflet contact (from systolic anterior motion of the mitral valve). Because of different techniques of provoking LVOT obstruction at the two institutions, patients with only provokable gradients were not enrolled in an attempt to achieve similar and comparable samples. Likewise, those with concomitant midventricular gradients, primary structural valvular abnormalities or anomalous insertion of the papillary muscles were not included in this series. All enrolled patients had been on beta-blocker agents, calcium channel blockers and/or disopyramide, and remained symptomatic.

Clinical and echocardiographic evaluation. Patients were interviewed by experienced cardiologists who determined their New York Heart Association (NYHA) classification, Canadian Cardiovascular Society (CCS) angina class and the presence of presyncope and/or syncopal episodes. Echocardiographic studies were performed, as previously reported (10), at baseline and one year. Observers who were blinded to clinical data performed the echocardiographic interpretation and, to ensure consistency, a random sample of 20 postprocedure studies from each institution was re-reviewed by two investigators (S. F. N., S. R. O.).

Measurements of septal thickness, maximum end-diastolic (EDD) and end-systolic (ESD) dimensions and left ventricular ejection fraction were performed according to the recommendations of the American Society of Echocardiography (11). Left ventricular outflow tract gradient was measured with color-guided continuous-wave Doppler of the outflow tract (12). Care was taken to avoid contamination with the mitral regurgitation jet. The severity of mitral and aortic regurgitation was assessed by color-Doppler techniques evaluating the size of the regurgitant jet to the receiving chamber (13,14). All patients in the NSRT group had follow-up data one year after NSRT. The mean follow-up in the surgery group was 398 ± 492 days.

Exercise protocols. Before and one year after NSRT, 25 patients who could exercise at baseline underwent stress testing on a standard Bruce protocol. Previously validated regression equations (15) were used to estimate the maximal oxygen consumption (V_{O_2} peak) and the metabolic equivalents (METS). There were 23 patients in the myectomy group who could exercise at baseline and therefore performed symptom-limited maximal treadmill exercise testing according to a standard Mayo Clinic protocol (16), with simultaneous respiratory gas analysis. Standard algorithms (adjusted for age, gender and activity level) were applied to predict V_{O_2} peak for each patient in both groups, and the achieved value was then expressed as percent of the predicted value.

NSRT. Each patient provided informed consent before NSRT, in accordance with a protocol approved by the institutional review board of Baylor College of Medicine. In patients without a pre-existing permanent pacemaker, temporary pacing wires were placed according to standard technique. Two-dimensional and Doppler echocardiography were used throughout the NSRT procedure. A 2 × 10 mm balloon catheter was introduced over a 0.014-in standard wire into the septal perforator artery and inflated. Subsequently, Omnipaque (Nycomed, Princeton, New Jersey) was injected through the balloon lumen to delineate the course of the septal branch and to ensure the lack of spillage into the left anterior descending coronary artery. After the first seven patients in this series, the procedure was modified and contrast echocardiography was utilized (after Omnipaque injection, 1.5 ml Albunex [Mallinckrodt, St. Louis, Missouri] diluted in an equal volume of saline). Depending on the size of the vascular territory of the cannulated septal branch, 2 ml to 5 ml of absolute ethanol were instilled through the inflated balloon catheter and left in place for 5 min. This ethanol injection technique was modified after the first 12 patients in this series such that ethanol was injected slowly, at 1 ml/min. The electrocardiogram was closely monitored for evidence of bradycardia and heart block, and the ethanol injection was aborted upon the development of high-grade atrioventricular block.

Angiography was repeated after balloon deflation both to confirm the patency of the left anterior descending coronary artery and occlusion of the target septal branch. If present, other similarly sized vessels were injected whenever the LVOT gradient (as determined by Doppler echocardiography) was ≥16 mm Hg. After our experience in the first 100 cases, repeat injection of other amenable arteries was considered only in the presence of a residual gradient >30 mm Hg. This change was adopted because of further gradient reduction following postintervention remodeling. A 6F multipurpose catheter was used to measure the LVOT gradient at baseline and after NSRT. Patients were observed in the coronary care unit for 24 h and, in the absence of high-degree atrioventricular block, the pacer wire was removed. Patients were transferred to a telemetry unit for the remainder of their hospital stay (total hospitalization averaged three days).

Surgery. Standard cardiopulmonary bypass and myocardial preservation techniques were used. After aortotomy, excision of the septum was initiated with two parallel longitudinal incisions: one beneath the nadir of the right coronary

Table 1. Baseline Characteristics of the NSRT and Surgery Groups

	NSRT (n = 41)	Surgery (n = 41)
Age (yrs)	49 ± 17	49 ± 16
LVOT gradient (mm Hg)	76 ± 23	78 ± 30
NYHA class		
I and II		9 (22%)
II	4 (10%)	
III and IV	37 (90%)	32 (78%)
Angina class		
I	16 (39%)	16 (39%)
II	15 (37%)	10 (24%)
III	10 (24%)	15 (37%)
Presyncope	24/41 (59%)*	23/41 (56%)†
Permanent pacemaker‡	9/41 (22%)	16/41 (39%)
Cardiac medications		
Beta-blockers	31/41 (76%)	26/41 (63%)
Calcium antagonists	19/41 (46%)	18/41 (44%)
Disopyramide	8/41 (20%)	4/41 (10%)
Amiodarone	3/41 (7%)	4/41 (10%)
Sotalol	3/41 (7%)	None

*18 with syncope. †6 with syncope. ‡In both groups, pacemakers were placed as therapy for HOCM and not for heart block. There were no statistically significant differences between the two groups ($p > 0.1$).

HOCM = hypertrophic obstructive cardiomyopathy; LVOT = left ventricular outflow tract; NSRT = nonseptal surgical reduction therapy; NYHA = New York Heart Association.

cusp and the other beneath the commissure separating the left and right cusps. The mass of myocardium extending to the posteromedial papillary muscle was then excised. Additional muscle mass was excised toward the lateral attachment of the anterior mitral leaflet. Before the aortotomy was closed, the LVOT was inspected and palpated for completeness of the resection.

Adequacy of myectomy was confirmed through measurement of simultaneous left ventricular and aortic pressures before and after cardiopulmonary bypass. Intraoperative transesophageal echocardiography was utilized in all cases.

Statistics. We present baseline and follow-up values for each of the two groups, with data expressed as mean ± standard deviation. For statistical analysis, the clinical, hemodynamic and echocardiographic results of surgery and NSRT were analyzed using a two-way repeated measures analysis of variance (ANOVA). The factors considered were time (baseline vs. follow-up) and the type of procedure (surgery vs. NSRT). We report the p value for each main effect. Further, we test whether the time data are dependent on the procedure performed (interaction p value). Chi-square or Fisher exact tests were applied to compare categorical variables. Statistical significance was present with a $p \leq 0.05$.

RESULTS

There were 41 patients in each group; Table 1 shows their baseline clinical characteristics. Twelve patients in the surgery group and 11 in the NSRT group were at least 60 years old. The patient groups at baseline were similar except for a higher prevalence of pre-existing dual-chamber pacemakers in the surgery group ($p = 0.15$). All patients were severely limited by dyspnea or angina (at least class III), or had recurrent, limiting presyncope/syncope. At the time of the procedures, similar proportions of patients were receiving cardiovascular medications (Table 1). None of the patients with NSRT in the present cohort had previous cardiac surgery; likewise, none of the surgery patients had undergone NSRT or any other surgical procedure (including surgical procedures for HOCM).

Table 2. One-Year Results in the NSRT and Surgery Groups

	NSRT (n = 41)	Surgery (n = 41)
LVOT gradient (mm Hg)	8 ± 15	4 ± 7
NYHA class		
I	36 (88%)	32 (78%)
II	5 (12%)	8 (20%)
III		1 (2%)
Angina class		
I	41 (100%)	38 (93%)
II		3 (7%)
Presyncope	2/41 (5%)	7/41 (17%)
Permanent pacemaker	18/41 (44%)	17/41 (41%)
Due to heart block	9/41	1/41*
Cardiac medications		
Beta-blockers	7/41 (17%)	24/41 (59%)*
Calcium antagonists	1/41 (2%)	8/41 (20%)*
Disopyramide	3/41 (7%)	1/41 (2%)
Amiodarone	None	3/41 (7%)
Sotalol	2/41 (4%)	None

*$p < 0.05$ vs. NSRT.
Abbreviations as in Table 1.

Outcome after NSRT and surgery. HEMODYNAMICS. Analysis using two-way repeated-measures ANOVA showed that at one year, the LVOT gradient had decreased significantly (baseline: 77 ± 25 vs. follow-up: 6 ± 10; $p < 0.05$). However, there was no significant difference with respect to the type of procedure (NSRT: 42 ± 19 vs. surgery: 41 ± 18.5; $p > 0.3$). Analysis for interaction revealed that the effect of time was not dependent on the procedure ($p > 0.1$). Therefore, the hemodynamic benefits derived with NSRT and surgery were comparable.

SYMPTOMS. Improvements in NYHA and CCS angina class were similar in both groups. All NSRT patients and 40 of 41 surgery patients were in NYHA class I or II one year following the procedures. Likewise, there was a similar reduction in presyncope/syncopal episodes after both NSRT and surgery (Table 2). The improvement at follow-up was not dependent on the type of procedure.

No significant differences were present in the use of antiarrhythmics after either NSRT or surgery. Although more patients in the surgery group were receiving beta-blocker ($p < 0.001$) and calcium channel antagonist ($p = 0.029$) therapy following surgery, 29 of 41 in this group were receiving no cardiac medications or were on lower doses postsurgery. Of note, postprocedural medical therapy was institution-specific and not related to the reduction in LVOT gradient.

Table 3. Exercise Tolerance in the NSRT and Surgery Groups

	Pre-NSRT	Post-NSRT	Pre-Surgery	Post-Surgery
Exercise duration (s)	289 (188–422)	417* (301–589)	330 (294–525)	480* (393–600)
Peak V_{O_2} (ml/kg/min)	20.8 ± 4.9	26.2 ± 6.5*	18.9 ± 5.7	22.2 ± 5.3*
METS	5.9 ± 1.4	7.5 ± 1.9*	5.3 ± 1.7	6.5 ± 1.5*
% Maximal predicted V_{O_2}	55 ± 15	72.5 ± 18.4*	57 ± 11.5	69 ± 17*

*$p < 0.05$ vs. baseline.
METS = metabolic equivalents; NSRT = nonsurgical septal reduction therapy; V_{O_2} = oxygen consumption.

EXERCISE TOLERANCE. Peak V_{O_2} , METS and % of maximum predicted V_{O_2} were similar at baseline in both NSRT and surgical myectomy groups. These parameters and exercise duration increased at one year in both groups (Table 3). On analysis of the effect of time by two-way repeated-measures ANOVA, the increase in V_{O_2} peak (baseline: 19.6 ± 5.3 vs. follow-up: 24 ± 5.4, $p < 0.05$), METS (baseline: 5.6 ± 1.6 vs. follow-up: 7 ± 1.7, $p < 0.05$) and % of maximum V_{O_2} peak (baseline: 56 ± 13 vs. follow-up: 71 ± 16, $p < 0.05$) at one year were all significant. In the analysis for the other main variable, the results of surgery versus NSRT, however, were comparable for each parameter (at V_{O_2} peak, NSRT: 23.5 ± 5.7 vs. surgery: 21 ± 5.5; METS, NSRT: 6.7 ± 1.55 vs. surgery: 6 ± 1.6; percent of maximum V_{O_2} peak, NSRT: 63.75 ± 16.7 vs. surgery: 63 ± 14; all $p > 0.3$). At one-year postprocedure, the magnitude of improvement in all parameters (exercise duration, V_{O_2} peak and percent of maximum V_{O_2} peak) was similar irrespective of the intervention (interaction: $p > 0.2$).

ECHOCARDIOGRAPHIC RESULTS. Analysis for the effect of time by two-way repeated-measures ANOVA showed a significant increase in left ventricular dimensions at follow-up (EDD, baseline: 42.5 ± 5.3 vs. follow-up: 45.75 ± 5; ESD, baseline: 22 ± 4.8 vs. follow-up: 26 ± 5; both $p < 0.05$), along with a decrease in septal thickness (baseline: 22.3 ± 6.3 vs. follow-up: 12.5 ± 4; $p < 0.05$). Analysis for the effect of NSRT versus surgery showed no statistically significant difference between the two procedures in the same parameters (EDD, NSRT: 44.6 ± 5.1 vs. surgery: 43.2 ± 5.3; ESD, NSRT: 23 ± 4.3 vs. surgery: 25.6 ± 5.5; septal thickness, NSRT: 17.4 ± 4.6 vs. surgery: 17.35 ± 6.7; all $p > 0.3$). Testing for interaction revealed that the effect of time on echocardiographic measurements did not depend on whether NSRT or surgery was the therapeutic intervention ($p > 0.2$). Left ventricular ejection fraction was preserved after both procedures (Table 4). Likewise, mitral regurgitation was significantly less after these interventions, with a comparable improvement ($p > 0.2$).

COMPLICATIONS. One NSRT death occurred acutely in the catheterization laboratory because of dissection of the left anterior descending coronary artery while the vessel was negotiated with a standard wire. There were no deaths in the surgery group.

Nine patients underwent implantation of a permanent pacemaker because of complete heart block after NSRT. Seven of these implants occurred before we modified our technique (i.e., contrast echocardiography and slow injection of ethanol). One surgical patient became pacemaker dependent following the procedure. Overall, the incidence of new complete heart block was higher in the NSRT group ($p = 0.014$ vs. surgery).

Implantable cardiac defibrillators (ICDs) were placed because of ventricular dysrhythmias in four surgery patients and one NSRT patient. One of the ICDs in the surgery group was placed because of preoperative ventricular fibrillation, whereas the others were placed postoperatively as primary prevention, based on risk factor profiles and not necessarily clinical events. The NSRT patient received an ICD for treatment of sustained ventricular tachycardia. Eight of the 41 surgery patients (20%) developed transient atrial fibrillation after surgery, but all were discharged in

Table 4. Echocardiographic Parameters in the NSRT and Surgery Groups

	Pre-NSRT	Post-NSRT	Pre-Surgery	Post-Surgery
EDD (mm)	42.8 ± 5	46.5 ± 5.3*	41.5 ± 5.5	45 ± 4.8*
ESD (mm)	21 ± 4.7	25 ± 4*	23.4 ± 5	27.8 ± 6*
Ejection fraction (%)	73 ± 9	70 ± 12	73 ± 14	68 ± 7
Septal thickness (mm)	22.6 ± 5.8	12.2 ± 3.4*	22 ± 7.3	12.7 ± 6.1*
Mitral regurgitation (grade 0 to 4)				
None		29 (71%)		19 (46%)
I		12 (29%)		20 (49%)
II				1 (5%)
I and II	36 (88)		34 (83%)	
III				1 (5%)
III and IV	5 (12%)		7 (17%)	

*$p < 0.01$ vs. baseline
EDD = end-diastolic dimension; ESD = end-systolic dimension; NSRT = nonsurgical septal reduction therapy.

normal sinus rhythm. There were no episodes of atrial fibrillation post-NSRT.

None of the patients in either group developed worsening mitral regurgitation. Aortic regurgitation of mild or moderate severity occurred in 11 patients (27%) following surgical myectomy (mild in 10 and moderate in 1; $p < 0.001$ vs. before surgery). Post-NSRT, new aortic regurgitation of mild severity was present in three patients (7%) ($p = 0.65$ vs. pre-NSRT). The incidence of aortic regurgitation was significantly higher after surgery ($p = 0.04$ vs. NSRT).

There were no cerebrovascular accidents, ventricular septal defects or cardiac tamponade after either NSRT or surgery.

DISCUSSION

Left ventricular outflow tract obstruction is present in 20% to 30% of patients with HCM. A number of patients remain symptomatic despite optimal medical therapy, and surgical myectomy is usually recommended for these patients. Myectomy reduces or eliminates LVOT obstruction in most individuals and its effects are usually sustained (1–6). Sigwart noticed that inflating an angioplasty balloon catheter in the septal perforator resulted in a significant decrease in outflow obstruction (7). Subsequently, intracoronary (septal perforator) ethanol injection gained popularity in treating patients with HOCM who are refractory to medical therapy. In this study, we compared NSRT with surgical myectomy, the standard for treating refractory HOCM. The study had >85% power to detect a difference of 20 ± 15 mm Hg between the two groups at an alpha level of 0.05.

Comparative performance of NSRT and surgery in eliminating LVOT obstruction. The two groups of patients reported in this investigation had identical gradients at baseline and achieved a similar hemodynamic improvement after either procedure. This may be related to the similar mechanisms for eliminating obstruction that both procedures share. As noted in the previous text, a similar reduction in basal septal thickness was noted after both surgery and NSRT. We recently observed that the long-term improvement in obstruction by NSRT is related to widening in the LVOT and a reduction in the angle between the mitral valve leaflets and the direction of blood flow (17). These observations are similar to the mechanisms by which successful surgery relieves LVOT obstruction (18,19).

Effects of NSRT and surgery on symptoms and exercise tolerance. The two patient groups had similar baseline NYHA and CCS class. Also, a similar number in either group suffered from presyncope and/or syncope at baseline.

After surgery 98% of the patients were in NYHA class I or II, and after NSRT, 100% of the patients were in these two classes. These results are well representative of the previously reported (1–10) benefits achieved by both surgery and NSRT. Although a placebo effect cannot be excluded, this effect appears unlikely given the sustained improvement in symptomatology as well as the corroboration provided by exercise testing. Importantly, at baseline there were no statistically significant differences between the two groups' Vo_2 peak, METS or percentage achieved maximum predicted Vo_2; at follow-up both groups increased their exercise tolerance to a similar extent. This improvement in exercise parameters is likely related to improvement in mitral regurgitation as well as to improvement in left ventricular relaxation and stiffness (20,21).

Effects of NSRT and surgery on left ventricular size and function. We observed an increase in left ventricular EDD and ESD after both NSRT and surgery. The change was similar in both groups and, importantly, the left ventricular ejection fraction was preserved after both procedures. The decrease in the severity of mitral regurgitation, as assessed by color Doppler, is another important result of both procedures. In patients with more severe mitral regurgitation (grade III to IV), improvement of this valvular lesion may have accounted for the lower left ventricular filling pressures and the elimination of heart failure symptoms after the successful relief of obstruction.

Complications of NSRT and surgery. One death occurred acutely in the NSRT group. This resulted from a guide-wire-induced dissection of the left anterior descending coronary artery. After this episode we modified our approach and now use the high-torque floppy wire. As expected, percutaneous interventions in older patients carry more risk because of the presence of atherosclerotic lesions that make their vessels more vulnerable to dissection. This is also true for surgery, where mortality is higher in older patients; however, no deaths were observed in the surgery group.

Complete heart block necessitating permanent pacing occurred in 22% of the NSRT group. Seven of the nine cases of heart block occurred before modifying our technique as detailed above (see Methods and Results). Since then, the incidence of heart block in a subsequent group of 160 patients has fallen to 8.6%. As previously reported, the incidence of aortic regurgitation (albeit mild) and the incidence of postoperative transient atrial fibrillation were significantly higher after surgery. However, neither of these has been previously associated with adverse long-term morbidity or mortality. With NSRT, ventricular dysrhythmias are also a potential risk following the induction of infarction. Interestingly, in our study the use of ICDs was comparable in both groups.

Study limitations. Our results may not be generalizable; we compare the performance of two procedures at two well-experienced centers. Also, this was not a randomized trial and there may be differences in practice patterns between the two institutions. However, our two groups were well matched at baseline in several important variables, including age, LVOT gradient, NYHA and CCS class, use of cardiac medications and ventricular function.

Different exercise protocols were used at the two institutions, rendering direct comparison of exercise times imprac-

tical. Also, in the NSRT group, regression equations were used to arrive at the peak V_{O_2} and number of METS achieved. Although there are some difficulties with the use of these regression models, the equations adopted have been previously well validated in a large population of 1,074 patients (15). Furthermore, the peak V_{O_2} values in the NSRT group were very similar to those of the surgery group as well as those of other HOCM patients with a significant degree of dyspnea, and corroborate the subjective NYHA assessments.

Implications. For patients with HOCM who remain symptomatic despite optimal medications, reduction of LVOT obstruction by surgery or NSRT is beneficial. NSRT and surgery appear to be equally effective in reducing obstruction, and in improving symptoms and exercise tolerance. Also, in our patient cohort these benefits were associated with a preserved ejection fraction. Although initially the incidence of heart block was higher after NSRT, the incidence of heart block after NSRT has been significantly lower (8.6%) since we modified our technique. Obviously, even in experienced centers both procedures carry mortality and morbidity risks varying from minor complications to death and, therefore, can only be justified in the very select group of highly symptomatic HOCM patients.

Although the long-term safety and efficacy of surgical myectomy are known, and the effects of NSRT at one year are similar to those of surgery, there is currently a paucity of data to assess the outcome of NSRT beyond one year (22,23). Our study both provides the base and exposes the need for prospective randomized trials aimed at assessing this nonmedical approach for the treatment of refractory HOCM.

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Reprint requests and correspondence: Dr. Sherif F. Nagueh, 6550 Fannin Street, SM-1246, Houston, Texas 77030-2717. E-mail: sherifn@bcm.tmc.edu.

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