Echocardiography-Guided Ethanol Septal Reduction for Hypertrophic Obstructive Cardiomyopathy

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Background—Left ventricular outflow tract (LVOT) obstruction is frequently responsible for symptoms in hypertrophic obstructive cardiomyopathy (HOCM). Medical therapy is often not sufficient to control these symptoms, and surgical myotomy-myomectomy is required.

Methods and Results—We enrolled 33 symptomatic patients with HOCM and obstruction (≥40 mm Hg gradient at rest or ≥60 mm Hg dobutamine-provoked). By contrast echocardiography, the bulging septum was localized and infarcted by injection of 2 to 5 mL of absolute ethanol into the septal artery(ies) supplying the hypertrophied area. Baseline echocardiograms with Doppler, myocardial perfusion tomograms, and treadmill exercise or pharmacological testing were compared with those at 6 weeks and 6 months. The mean rise in creatine kinase was 1964±796 U. All patients experienced symptomatic relief; NYHA class decreased from 3.0±0.5 to 0.9±0.6 (P<0.001). Exercise time increased from 286±193 to 421±181 seconds (P=0.03). The resting and dobutamine-provoked gradient decreased from 49±33 and 96±34 mm Hg to 9±19 (P<0.001) and 24±31 mm Hg (P<0.001), respectively. Echocardiograms repeated at 6 weeks after the procedure showed a 28% reduction in septal thickness and 17% reduction in left ventricular mass. Myocardial perfusion imaging showed a “septal amputation pattern,” with scarring in the upper and middle septal areas. Complete heart block developed in 11 patients, who then required permanent pacemaker implantation.

Conclusions—Echocardiography-guided ethanol septal reduction in patients with HOCM is a safe, minimally invasive procedure that provides symptomatic relief with improved hemodynamic and left ventricular parameters. (Circulation. 1998;98:1750-1755.)

Key Words: hypertrophy • cardiomyopathy • ethanol • contrast media • echocardiography

Hypertrophic obstructive cardiomyopathy (HOCM) is a relatively common genetic malformation of the heart, with an estimated prevalence approaching 1 in 500 of the population. As a result of asymmetric septal hypertrophy, left ventricular outflow tract (LVOT) obstruction may develop and may contribute to symptoms such as dyspnea, angina, and syncope. Treatment to relieve the obstruction consists of medications such as β-blockers and calcium channel blockers or surgical myotomy-myomectomy of the septum for patients with refractory symptoms. Although the surgical approach results in resolution of symptoms in most cases, it is associated with significant morbidity and mortality. Dual-chamber pacemakers have been reported to reduce the gradient and improve the symptoms in these patients; however, the results of the currently published studies continue to be inconclusive.

Recently, infusion of ethanol into the septal branches of the left anterior descending coronary artery (LAD) to specifically induce necrosis of the hypertrophied septum has been reported as an ameliorative measure for HOCM. In this study, we report the results of echocardiography-guided, catheter procedure–based ethanol septal reduction in 33 patients with HOCM and severe, refractory symptoms. This therapeutic modality is potentially a new landmark in the treatment of this disease.

Methods

Evaluation

Patients were evaluated by the primary investigator (W.H.S.) before the procedure. Only patients with severe, drug-resistant symptoms of congestive heart failure (NYHA class III or IV), angina (Canadian Cardiovascular Society class III or IV), or syncope were considered. After clinical evaluation, all candidate patients underwent echocardiographic evaluation with Doppler studies. Images were taken with the patient in the left lateral position with a 2.5/3.5-MHz transducer of a Hewlett-Packard Sonos 2000 or an Accuson XP-128 ultrasound system. Parasternal long-axis and short-axis views were acquired first and were followed by the apical views. All enrolled patients had a septal to posterior wall ratio of ≥1.3. With the guidance of color Doppler, LVOT gradient was recorded with continuous-wave Doppler. Care was taken to avoid contamination by any mitral regurgitation jet. Patients with a resting gradient of ≥40 mm Hg were enrolled. When the resting LVOT gradient was <40 mm Hg, intravenous dobutamine was started at 5 μg · kg⁻¹ · min⁻¹ and increased stepwise to a maximum of 40 μg · kg⁻¹ · min⁻¹ as necessary. Patients were enrolled in the study if their dobutamine-provoked gradient was ≥60 mm Hg. Images were recorded on VHS.
videtape for subsequent playback and analysis. Exercise or pharmacological stress with myocardial perfusion was also performed before and at 6 weeks after septal infarction.

Procedure

Informed consent was obtained from each patient before enrollment in the study, according to a protocol approved by the institutional review board at Baylor College of Medicine. On the day of the study, a baseline ECG was performed. Blood was collected for creatine kinase (CK) enzyme and MB isoforms both before and at 4-hour intervals up to 36 hours after the procedure. The total CK and the CK-MB activity were assayed according to a method developed at our institution.8 All patients underwent coronary angiography. Patients with significant coronary artery disease (>50% stenosis in the LAD) were excluded. A temporary pacemaker was placed in the apex of the right ventricle in all except 7 patients who already had a permanent dual-chamber pacemaker in place. A multipurpose catheter was advanced through the aortic valve into the apex of the left ventricle, and the intraventricular gradient was measured by the pull-back technique (Figure 1). An 8F guiding catheter was then engaged in the ostium of the left main coronary artery. Initial angiography was done to localize the origin of the septal arteries (Figure 2). All patients were then sedated with benzodiazepines and analgesics. A 2.0×10.0-mm balloon catheter was introduced over a 0.014-in standard wire into the septal perforator and inflated. With the balloon inflated, the LVOT gradient was measured by Doppler echocardiography, as previously described in the text. Contrast (Omnipaque, Winthrop) was injected through the balloon lumen to delineate the area supplied by the septal branch and to ensure that balloon inflation prevented spillage into the LAD (Figure 2). The procedure was modified after the 10th patient: for contrast echocardiography, 1.5 mL Albunex (Mallinckrodt) diluted in an equal volume of saline was injected to delineate the area to be infarcted (Figure 3). Depending on the septal artery size and the septal thickness, 2 to 5 mL of absolute ethanol was instilled through the lumen of the inflated balloon catheter and left in place for 5 minutes. Ethanol injections were given as a bolus in the first 17 patients; however, the technique was later modified, and in the remainder of the patients, ethanol was injected at 1 mL/min. After balloon deflation and removal, angiography was performed to confirm the patency of the LAD and the occlusion of the target septal branch. Measurement of the LVOT gradient was again performed by echocardiography. Other septal branches were injected in a similar manner if the gradient did not decrease to <16 mm Hg with the first ablation. A 6F multipurpose catheter was then advanced to the left ventricle to measure the final residual gradient (Figure 1). The temporary pacemaker was sutured in place. Patients were observed in the coronary care unit for at least 24 hours. The pacemaker lead was then removed, and if there was no high-degree atrioventricular (AV) block, the patients were transferred to an ECG telemetry unit for the remainder of their stay (usually 24 hours).

Patients were examined by the principal investigator at 6 weeks (33 patients) and 6 months (11 patients). Echocardiographic evaluation with Doppler and dobutamine provocation and myocardial perfusion tomography with treadmill exercise or pharmacological stress were also done with the previously described methods.

Data Analysis

Echocardiographic Studies

The left ventricular minor dimension (D) was measured in the parasternal long-axis view at both end diastole and end systole. The long-axis dimension (L) was taken from the apical views. For both measurements, care was taken to avoid beats with foreshortening of the left ventricle. End-diastolic volume was calculated from the equation $EDV = (3.42 \times D \times L) - 6$, which has been previously validated in our laboratory,4 and the ejection fraction was derived with the multiple-diameter method.10 Basal septal and posterior wall thicknesses were also measured from the parasternal views, and the left ventricular mass was calculated with the area-length method.11 LVOT gradient was derived with the modified Bernoulli equation: $gradient = 4V^2$, where V is the maximum velocity recorded in the LVOT.12

Radionuclide Imaging

Stress myocardial single photon emission CT (SPECT) was performed according to previously described methods at our institution.13 Quantification of myocardial perfusion defect size was performed with computer-generated polar maps. The raw polar maps for each patient were compared with a corresponding normal data bank to determine the size of the left ventricular perfusion defect and the extent of scar and ischemia. Myocardial SPECT images were quantitatively and qualitatively interpreted by an expert nuclear cardiologist. Abnormal myocardial tomograms were defined by visually abnormal slices in the short-axis, horizontal long-axis, or
vertical long-axis views, and ≥3% focal perfusion defect on polar maps was compared with normal data banks.

Statistical Analysis
Continuous data are presented as mean±SD. For continuous variables, changes from before to after the procedure were evaluated by paired Student’s t test. A value of P≤0.05 was considered statistically significant. The correlation coefficient was used to evaluate the correlations between the left ventricular mass reduction and LVOT reduction and also the relation between the volume of ethanol injected and the peak CK released. All measurements performed comparing preprocedure and postprocedure studies were done in a blinded fashion.

Results
Baseline Characteristics
The baseline characteristics of the enrolled patients (16 women and 17 men) are reported below. The mean age was 52±15 years (range, 32 to 83 years). Three patients had class IV CHF symptoms, 25 patients had class III symptoms, and 5 patients had class II symptoms. Twenty-eight, 23, and 18 patients reported severe dyspnea, angina, and presyncope/syncope, respectively. All patients were on ≥2 medications, which included β-blockers (29 patients), calcium antagonists (24 patients), or antiarrhythmic drugs such as sotalol, amiodarone, and disopyramide (10 patients). Seven patients had a permanent pacemaker placed before enrollment in the study, and 1 patient had an implantable defibrillator for inducible ventricular tachycardia.

Effect of Septal Reduction on Symptoms
All patients reported a significant improvement in symptoms before hospital discharge. The mean duration of stay in the hospital was 3.6±1.7 days. At 6 weeks, 22 patients had NYHA class I symptoms, 5 patients had NYHA class II symptoms, and 6 patients were completely asymptomatic. The mean NYHA class decreased from 3.0±0.5 to 0.9±0.6 (P<0.001) at 6 weeks. All patients reported subjective improvement in exercise tolerance. Only 7 patients continued to take medications on follow-up. At 6 months, 5 of 11 patients were completely asymptomatic, and the rest had class I symptoms.

Twenty-three patients were able and agreed to undergo a baseline treadmill exercise test (Bruce protocol). The mean exercise time in this selected group of patients was 286±193 seconds. At 6 weeks, the mean exercise time increased in the same group of patients to 422±181 seconds (P=0.03).

ECG Findings
Twenty-five patients had baseline left ventricular hypertrophy, 9 patients had right bundle-branch block (RBBB), 5 patients had left bundle-branch block (LBBB), and 4 patients had left-axis deviation. Eleven patients (33%) developed complete heart block, with junctional or ventricular escape rhythms requiring permanent pacemaker implantation after the procedure. Six (55%) of these had a baseline RBBB (n=3) or LBBB (n=3) in the initial 12-lead ECG. Two patients developed ST-segment elevation in leads V1 and V2 in the setting of acquired RBBB after alcohol injection that persisted for ≈24 hours. Of the patients who did not require pacing, 8 had new RBBB, and 3 developed left anterior fascicular block.

Plasma CK Profile Due to Septal Injury
The number of arteries injected with ethanol per patient was 1.7±0.4. The mean volume of ethanol injected per patient was 4.2±1.6 mL. The mean peak CK rise was modified 1964±796 U (range, 599 to 4230 U). The mean time to peak CK rise was 9.4±4.6 hours. The peak CK rise correlated with the volume of ethanol injected (r=0.59, P=0.04).

Effects of Septal Reduction on Hemodynamics
The resting LVOT gradient measured by Doppler echocardiography was reduced (29 patients) or abolished (4 patients) in all patients immediately after the procedure. The resting gradient decreased from 49±33 to 12±12 mm Hg (P<0.001) after the procedure (similar results were obtained by catheter pullback immediately after the procedure) and 9±19 mm Hg (P<0.001) at 6 weeks. In 14 patients with a minimal residual gradient immediately after the procedure, the gradient was no longer present at 6 weeks. Six-month follow-up in 11 patients showed a resting residual gradient of only 3±11 mm Hg. No differences were noted in baseline or follow-up LVOT gradients measured in patients who had a pacemaker in place before the procedure, those who required permanent pacing for complete heart block after the procedure, and those without pacemakers.

The baseline dobutamine-provoked gradient was 96±34 mm Hg. It decreased to 24±31 mm Hg at 6 weeks (n=33) and 40±43 mm Hg (n=11) at 6 months (P<0.001 for both). All patients showed a reduction of the dobutamine-provoked gradient.

Effect of Septal Reduction on Left Ventricular Parameters
The left ventricular ejection fraction did not decrease after septal reduction (Table). Basal septal thickness decreased by 28% (2.1±0.7 to 1.5±0.6 cm, P<0.001) at 6 weeks, accompanied by a 17% reduction in left ventricular mass (271±75 to 224±72 g, P<0.001). As expected, the posterior wall thickness was unchanged. Figure 4 shows a parasternal long-axis view of the left ventricle showing the reduction in septal thickness at 6 weeks. These findings correlated with an increase in end-diastolic left ventricular diameter as measured in the short axis (4.1±0.3 versus 4.5±0.5 cm, P<0.01) and
end-diastolic volumes (118±17 versus 129±23 mL, P<0.001), suggesting a ventricular remodeling effect. The reduction in left ventricular mass correlated with the reduction in LVOT gradient (r=0.49, P<0.01). Six-month follow-up showed persistence of these findings in 11 patients studied to date.

Quantitative Assessment of Septal Reduction by SPECT
At 6 weeks, 29 patients had a follow-up stress (exercise, n=23; pharmacological, n=6) myocardial perfusion SPECT. All patients had a fixed perfusion defect. These defects involved the upper or the upper and middle septal area. Perfusion defects were characterized by the unique appearance of “septal amputation,” as a result of sharp demarcation between normally and abnormally perfused myocardium. The tracer reduction in the perfusion defect was moderate to severe in 17 patients and mild in 12 patients. The extent of the perfusion defect, measured by computerized polar plots, involved 10±6% of the left ventricular mass (range, 3% to 16%). Figure 5 demonstrates an example of a new septal scar 6 weeks after the procedure.

Untoward Effects of Ethanol
All patients had transient chest pain with multiple premature ventricular beats during alcohol injection. Only 3 patients had persistent chest pain that required multiple injections of ethanol.

Figure 4. Parasternal long-axis view of left ventricle showing reduction of septal thickness after ethanol septal infarction. Septal basal thickness decreased from 2.1 cm (left) to 1.2 cm at 6 weeks (right). PW indicates posterior wall; other abbreviations as in Figure 3.

Figure 5. Myocardial perfusion SPECT showing normal perfusion at baseline (top panels in A, B, and C). A fixed defect developed after procedure, localized to upper and middle septal areas, as shown in short axis (A), horizontal long axis (B), and polar map (C) during both exercise (middle) and rest (bottom).
analgesics. One patient had a 3-beat run of ventricular tachycardia. Complete heart block occurred immediately with alcohol injection and persisted for 3 days after the procedure in 11 patients, who then required implantation of permanent pacemakers. Eight of these cases occurred in the first 17 patients before we modified our technique, using contrast echocardiography to delineate the hypertrophied area and also injecting ethanol at a slower rate, as mentioned in the Methods section. Three patients had transient heart block that resolved within 24 hours. Only 8 patients continue to be pacemaker-dependent at 6 weeks. No patient died during the procedure or to date.

Discussion

HOCM is a complex disease with diverse genetic, morphological, functional, and clinical manifestations. Hypertrophy, the hallmark of this disease, usually develops after puberty; although in most patients, hypertrophy is initially restricted to the septum, it often progresses with age to involve the whole ventricle. LVOT obstruction due to the enlarged septum occurs in 20% to 30% of patients, and it stimulates more hypertrophy, resulting in angina, dyspnea, syncope, and sudden death. A considerable number of patients continue to be symptomatic despite maximal drug therapy, and ventricular septal myotomy-myomectomy is usually recommended for these patients. Surgery reduces or eliminates the obstruction in most individuals, and the effects are long-lasting. Major complications of surgery include complete heart block, ventricular septal defect, severe aortic insufficiency, and death. The reported postoperative mortality as a result of this operation varies from 1% in young patients to 17% in patients >65 years old, especially in the presence of coronary artery disease or other concomitant surgical procedures. Recently, dual-chamber pacing has been reported to result in a substantial decrease in the LVOT gradient, with symptomatic improvement. However, randomized studies suggest that a placebo effect may play an important role in the short-term symptomatic improvement reported by patients. The idea of inducing a septal infarction by catheter techniques was suggested by the observations that systolic and diastolic myocardial function of selected areas of the left ventricle can be suppressed by balloon occlusion of the supplying artery during coronary angioplasty and that intracavitary pressure gradients in HOCM decrease significantly when the first septal artery is temporarily occluded by an angioplasty balloon catheter.

In this study, we evaluated the effect of echocardiography-guided, catheter-based ethanol septal reduction in 33 patients with symptomatic HOCM. Echocardiography provided a uniform method to measure the gradient before, during, and after the procedure. In addition, selective injections of alcohol into the septal artery before ethanol therapy provided direct echocardiographic visualization and localization of the area to be infarcted and allowed precise selection of the correct septal branch(es) with the greatest blood supply to the hypertrophied septal segment. This approach resulted in limiting both the number of arteries injected and the volume of ethanol used per patient without compromising the efficacy of our therapy.

Patients had marked resolution of their symptoms at discharge and on follow-up at 6 weeks and 6 months (11 patients). Associated with symptomatic improvement, we observed a major reduction in the LVOT gradient at rest and after dobutamine provocation coupled with a significant improvement in duration of exercise. These results are extremely encouraging; however, one cannot rule out a possible placebo effect, because we did not have a placebo treatment arm for comparison.

Our study demonstrates for the first time that ethanol septal reduction results in significant left ventricular changes that explain the symptomatic improvement and the reduction of the pressure gradients. Using echocardiographic measurements, we found a 28% reduction in septal thickness and an associated 17% reduction in left ventricular mass (as determined by the area-length method, which erroneously assumes the presence of uniform ventricular hypertrophy in patients with HOCM). These changes resulted in ventricular remodeling, with an increase in the left ventricular end-diastolic minor diameter measured in the parasternal views and a similar increase in end-diastolic volume.

Using nuclear studies, we demonstrated that the induced infarct resulted in a scar localized to the upper and middle septal areas, as planned, with no residual ischemia. The defect size was small and was sharply localized to the septal regions. This finding is consistent with the concept that it is important to localize the particular septal branch that serves the area of the septum responsible for the obstruction. This localization was greatly facilitated by use of contrast echocardiography to identify the segment of the septum supplied by the catheterized septal artery.

In this study, a surprisingly high percentage of our patients initially had persistent heart block for >3 days after the procedure, requiring placement of permanent pacemakers. Seggewiss et al reported this complication 10 minutes to 5 days after the procedure in 12 of 24 of their patients. Complete heart block persisted in only 4 of their patients. In comparison, Knight et al reported only transient complete heart block in 4 of their 18 patients, and none required permanent pacemaker placement. One possible explanation for the initial high incidence of this complication could be that our patients had more conduction abnormalities at baseline, and they may have progressed to complete heart block more readily by the ethanol-induced infarct. In addition, a more extensive infarct may have resulted in damaging the vital blood supply to the septal branches supplying the bundle of His and/or the bundle branches. However, after modifying our technique by using contrast echocardiography and injecting alcohol at a slower rate (1 mL/min) into the septal arteries, we achieved the same reduction in LVOT gradient with less AV block. Interestingly, we found that permanent dual-chamber pacing does not confer any additional therapeutic effects to ethanol septal reduction, especially if complete ablation could be achieved.

Conclusions

In summary, ethanol septal reduction is a minimally invasive procedure that provides patients with immediate symptomatic and hemodynamic relief. Follow-up data available on all
patients at the time of this writing show persistence of these results, with septal thinning and increased diastolic dimensions. There are no intermediate-term complications, such as septal wall perforations, worsening ejection fraction, or ventricular arrhythmias. However, it is not yet known whether this new therapeutic modality will change the natural history of patients with HOCM.

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