Follow-Up of Alcohol Septal Ablation for Symptomatic Hypertrophic Obstructive Cardiomyopathy

The Baylor and Medical University of South Carolina Experience 1996 to 2007

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Objectives This study sought to determine the long-term outcome of alcohol septal ablation (ASA).

Background There are inadequate data on the long-term outcome of ASA for symptomatic hypertrophic obstructive cardiomyopathy (HOCM).

Methods Six hundred and twenty-nine patients were enrolled consecutively (1996 to 2007) and 98.4% (n = 619) underwent ASA with 92% follow-up in 2007. Evaluation included deaths, procedural complications, pacemaker requirement, repeat ASA, and myectomy/valve surgery. Follow-up parameters included angina (Canadian Cardiovascular Society score), dyspnea (New York Heart Association functional class), exercise time, and echocardiographic indices (septal thickness, ejection fraction, resting and provoked gradients).

Results Ethanol (2.6 ± 1.0 ml) was injected into 1.3 ± 0.5 septal arteries, inducing a septal infarct. Complications included death 1% (n = 6), permanent pacemaker requirement 8.2% (n = 52), coronary dissection 1.3% (n = 8), and worsening mitral regurgitation 0.3% (n = 2). The mean follow-up was 4.6 ± 2.5 years (range: 3 months to 10.2 years). During follow-up, New York Heart Association functional class decreased from 2.8 ± 0.6 to 1.2 ± 0.5 (p < 0.001); Canadian Cardiovascular Society angina score decreased from 2.1 ± 0.9 to 1.0 ± 0.0 (p < 0.001); and exercise time increased from 4.8 ± 3.3 to 8.2 ± 1.0 (p < 0.001) min. The resting and provoked left ventricular outflow tract gradients decreased progressively (p < 0.001) and remained low during follow-up. The septal thickness decreased from 2.1 ± 0.5 cm to 1.0 ± 0.1 cm (p < 0.001) and the ejection fraction decreased from 68 ± 9% to 62 ± 3% (p < 0.001). The survival estimates at 1, 5, and 8 years were 97%, 92%, and 89%, respectively.

Conclusions The initial benefits of ASA were maintained during follow-up. (J Am Coll Cardiol Intv 2008;1:561–70) © 2008 by the American College of Cardiology Foundation.
Familial hypertrophic cardiomyopathy is a genetic disease with autosomal-dominant inheritance (1–3). Patients with this condition develop myocardial hypertrophy primarily because of mutations of the genes encoding the cardiac sarcomere. Patients with hypertrophic cardiomyopathy that is nonobstructive, although still at risk for cardiovascular events, may remain asymptomatic until late in life (4,5). However, patients with left ventricular outflow tract (LVOT) obstruction, referred to as hypertrophic obstructive cardiomyopathy (HOCM), are often symptomatic, and the severity of obstruction is an important determinant of clinical outcome (6). Resting LVOT obstruction may be present in about one-third of patients. Another one-third of symptomatic patients may not have a significant resting gradient, but develop severe dynamic outflow tract obstruction with provocation (7).

Many strategies have been developed in an attempt to relieve LVOT obstruction produced by the combination of asymmetric septal hypertrophy and systolic anterior motion of the mitral valve (5). Although medical therapy can be effective in relieving symptoms, some patients remain severely symptomatic. Data from randomized trials showed a predominant placebo effect with dual-chamber pacing, and cardiac pacing has found a limited role as a primary therapy for medically refractory HOCM (8,9).

For over 40 years, the standard for treating HOCM has been surgical myectomy, which involves resection of the hypertrophied septal muscle (10,11). Relief of obstruction is noted in >90% of cases, with associated improvement in symptoms and outcomes. The surgical results from tertiary centers with experience have been very good (11), but widespread application is associated with significant morbidity and mortality (12–19). The first description of alcohol septal ablation was by Sigwart (20) in 1995, and this procedure is now an established and readily available percutaneous treatment option with encouraging short- and mid-term results (21–25). However, because the procedure has been performed for just over 10 years, results of a systematic prospective long-term study are lacking. Accordingly, we report the outcome of 629 patients enrolled consecutively (November 1996 to March 2007) and prospectively followed up for symptoms, exercise performance, mortality, and echocardiographic indices.

**Methods**

The investigational protocol was approved by the institutional review boards. All patients provided an informed consent form before participation.

**Recruitment of patients and initial evaluation.** Patients were enrolled consecutively into the alcohol septal ablation study from November 1996 to August 2006 and followed up to March 2007. Criteria for enrollment were the following. First, patients were confirmed to have HOCM and were still symptomatic despite medical therapy. Second, they had resting echocardiogram/Doppler LVOT gradients ≥30 mm Hg at rest or a provoked gradient ≥60 mm Hg induced by Valsalva maneuver or exercise. Initially, dobutamine was used in patients (n = 57) who were unable to exercise, but it has not been used since 2001. Third, obstruction was shown to be at the level of the outflow tract because of contact of the anterior mitral leaflet with the thickened septum. Fourth, the septal thickness was ≥1.6 cm with a septal–posterior wall ratio of ≥1.3:1. A complete history and physical examination were performed before the procedure, along with a 2-dimensional Doppler/echocardiogram with provocation, if indicated.

**Data collection and follow-up procedures.** Patients were evaluated clinically after the procedure, and follow-up was scheduled at 3 months, 1 year, and annually thereafter. Treadmill exercise testing was performed using the Bruce protocol in patients who were able to exercise. In patients in whom the LVOT gradient was induced only with provocation, follow-up gradients were assessed with the same provocation stimulus. Patients enrolled in the study with a significant resting gradient did not undergo provocation before the procedure or in follow-up. Follow-up LVOT gradient in both groups was obtained by echocardiogram Doppler. Left ventricular ejection fraction was assessed by the method of Quinones et al. (26).

**Alcohol septal ablation (ASA) procedure.** Complete details of the now-standard procedure have been reported previously (22). Briefly, a small balloon catheter is placed into an appropriate septal perforator artery, and subsequently absolute alcohol is injected through the central lumen of the inflated balloon, producing a localized area of injury. A number of modifications in the procedure have occurred over time, including the use of contrast echocardiography, softer guide wires, coaxial guiding catheters, a reduced amount of ethanol, a slower injection rate, and smaller and shorter balloons. Acute technical success of the procedure in the catheterization laboratory was defined as a decrease in the LVOT gradient by at least 50% from baseline, determined either by Doppler/echocardiogram or invasive measurements immediately after the procedure.

**Statistical analysis.** Continuous variables are presented as mean ± SD. For continuous variables, serial changes during follow-up were evaluated by repeated-measures ANOVA.
Bonferroni modification was used to assess differences at follow-up. Functional class changes were evaluated using the Wilcoxon signed rank test. A p value ≤ 0.05 was considered statistically significant. Cardiac events occurring within 30 days of the procedure were considered procedure-related.

To determine the survival estimates, traditional Kaplan-Meier estimation was used. All-cause mortality was used for the overall survival analysis. Individuals were either dead (of any cause) or were censored at the last date at which they were known to be alive. For event-free survival related to the outcomes of the initial procedure, individuals had an event (procedural death, surgery, or repeat procedure) or were censored. In this case, death from any cause other than procedural death was treated as a censored event.

**Results**

Six hundred and twenty-nine patients were consecutively enrolled in the study. The mean (SD) of follow-up time (based on overall survival) is 4.59 (2.47) years. The median and interquartile range (25th and 75th percentiles) is 4.49 (2.75, 6.36) years, (range: 3 months to 10.2 years). Patients who could not come for follow-up visits at our centers were contacted by telephone and their functional status was assessed by a questionnaire or per their physician’s evaluation. The Social Security Death Index database and a paid Internet browser were used to track missing patients.

Of the 629 patients enrolled in the study, 579 (92%) patients had follow-up data in 2007. Data for 50 of 629 patients (8%) were not available for 2007. Six of these 50 patients were foreign nationals. The other 44 patients were not represented as dead in the U.S. Social Security Death Index database. Thirty-two patients without 2007 follow-up had at least 1 follow-up visit at 16 ± 14 (mean ± SD) months and a New York Heart Association (NYHA) functional class of 1.44 ± 0.7 (mean ± SD) when seen. Only 18 (2.9%) patients were completely lost to follow-up after their ASA procedure. Attempted alcohol septal ablation was unsuccessful in 10 patients. Four patients opted out of follow-up, 25 patients underwent subsequent myectomy (includes 6 patients in whom ASA was not done), 11 patients had aortic or mitral valve surgery, and 51 patients died.

**Baseline characteristics.** Baseline characteristics are shown in Table 1. The ASA procedure was performed with acute success in 619 patients (98.4%) (Table 2). The mean age of patients in the study was 53.9 ± 15 years (range: 13 to 90 years). The youngest patient was a 13-year-old Caucasian male patient with NYHA functional class III symptoms who had recently suffered cardiac arrest and was implanted with an implantable cardioverter-deﬁbrillator (ICD) and refused surgery. There were 311 (49.5%) female patients. Most patients were receiving multiple medications for HOCM. There were 98 (15.6%) patients who had a prior pacemaker or ICD, and 6 had a prior myectomy. Five hundred and three patients (80%) had a mean resting gradient of 77 ± 31 mm Hg. There were 126 (20%) patients with no significant resting gradient, but a mean provoked gradient of 74 ± 33 mm Hg. Overall 1.3 ± 0.5 septal arteries were injected with 2.6 ± 1.0 ml ethanol per patient. The mean value of peak creatine kinase was 1,243 ± 713 units/l. Most patients experienced burning chest discomfort during alcohol injection despite pre-medication with meperidine or fentanyl and midazolam. No patient had sustained ventricular ﬁbrillation during alcohol injection.

**In-hospital complications of the procedure.** The major complications of the procedure included death in 6 patients (1%)
(Table 3), coronary dissection in 8 patients (1.3%), and complete heart block requiring permanent pacemaker implantation in 52 patients (8.2%). Two patients (0.3%) required mitral valve replacement.

**Coronary dissections.** The procedure was complicated by coronary dissections in 8 patients. One patient had a spiral dissection complicated by ventricular fibrillation and arrest, which eventually led to the patient’s death during surgery. Another LAD dissection occurred before alcohol injection and was referred directly to surgery. Five of the remaining dissections were treated successfully by coronary stents, and the other was left alone with no deleterious consequences on follow-up. One of the dissections was noted 10 days after the procedure, when the patient had a repeat cardiac catheterization for chest pain and was stented uneventfully. The incidence of dissection was disproportionately higher in women (7 female, 1 male). As a result of these dissections, the procedure was modified by using coaxial guide catheters and soft-tip guide wires. Since then, no dissection has occurred in the last 400 patients.

**Permanent pacemaker implantation.** Permanent pacing was needed in 52 patients after ASA for high-grade atrioventricular (AV) block or complete heart block. The incidence of high-grade AV block necessitating permanent pacemaker implantation in the initial 50 patients was 28%. The incidence of AV block decreased significantly after the procedure was modified by slower injection of smaller amounts of ethanol per septal perforator artery and the use of myocardial contrast echocardiography. In the subsequent 579 patients, the pacemaker requirement rate was 6.5%, yielding a net rate of permanent AV sequential pacing of 8.2% in the entire cohort of 629 patients. Excluding patients with a pre-existing pacemaker or ICD, the new pacemaker requirement attributable to high-grade AV block was 9.7%.

**Mitral valve replacement.** Periprocedural mitral regurgitation occurred in 2 patients who required mitral valve replacement. This was thought to be because of subendocardial ischemia during guide catheter manipulation.

**Follow-up results, 1996 to 2007. EFFECT OF ALCOHOL SEPTAL ABLATION ON SYMPTOMS AND EXERCISE PERFORMANCE.** All patients were symptomatic at presentation, with a mean baseline NYHA score of 2.8 ± 0.6 for dyspnea. Significant improvement in the NYHA functional class was seen at 3 months (NYHA score 1.4 ± 0.6), after which the initial benefit was maintained (Fig. 1). After 5 years, >86% (n = 121) of patients available for evaluation were in NYHA functional class 1.

The CCS angina score at baseline was 2.1 ± 0.9, which improved to 1.2 ± 0.5 at 3 months, and remained fairly stable thereafter. Before ASA, 29% of patients were angina-free compared with 87% at 3 months and >92% (n = 121) at 5 years and thereafter.

Objectively, the treadmill exercise duration increased progressively from 4.9 ± 3.4 min at baseline to 7.5 ± 1.0 min for those tested at years 1 to 5.

**EFFECT OF ALCOHOL SEPTAL ABLATION ON LVOT GRADIENT.** A resting gradient ≥30 mm Hg was present in 503 patients at baseline (Fig. 2). The mean resting gradient at baseline was 77 ± 31 mm Hg, which decreased to 26 ± 27 mm Hg at 3 months, 20 ± 24 mm Hg at 1 year, and
continued to decline yearly and was <10 mm Hg in those tested after 5 years.

There were 126 symptomatic patients with a resting gradient <30 mm Hg, but with a significant provoked gradient. The baseline-provoked gradient of 74 ± 33 mm Hg decreased after ASA to 37 ± 34 mm Hg at 3 months, 32 ± 30 mm Hg at 1 year, and remained <10 mm Hg in those tested after 5 years.

**EFFECT OF ALCOHOL ABLATION ON SEPTAL THICKNESS AND VENTRICULAR FUNCTION.** Basal septal thickness measured at the site of the ablation decreased significantly from 2.1 ± 0.5 cm to 1.6 ± 0.4 cm at 3 months, and 1.5 ± 0.4 cm at 1 year (Fig. 3). Thereafter, the mean septal thickness at the site of ablation showed a gradual thinning over the follow-up period. Despite significant thinning of the septum in some patients, no ventricular septal defects or aneurysms were noted during the follow-up period.

Average left ventricular ejection fraction was 68 ± 9% at baseline, and decreased to 65 ± 9% at 3 months, but remained mostly in the 60% to 65% range throughout the follow-up period (Fig. 4). Congestive heart failure caused by systolic dysfunction was not observed. Congestive heart failure during follow-up was attributable to diastolic dysfunction.

**Repeat ASA and other procedures.** A total of 91 repeat ASA procedures were needed in 81 patients (14%) for persistence or recurrence of symptoms, along with dynamic obstruction. An ASA was performed 4 times in 1 patient, 3 times in 4 patients, and twice in 76 patients. Success was related to the availability of additional target septal perforator arteries that were amenable for ablation. Most patients with repeat procedures had a successful reduction of the gradient and relief of symptoms throughout follow-up (94% success rate).

Twenty-five patients (includes 6 patients in whom the ASA was aborted) with persistent symptoms and residual gradients underwent surgical myectomy. In addition, 7 patients underwent aortic valve replacement, and 4 undergone mitral valve replacement during follow-up. Four patients had worsening mitral regurgitation during follow-up (2 of these 4 patients had worsening mitral regurgitation periprocedurally). The other 2 patients developed flail mitral leaflets on longer follow-up requiring surgery. The remaining 3 patients underwent surgery elsewhere and the cause of the mitral regurgitation is unknown. Two patients developed severe calcific aortic stenosis at >5-year follow up, and were referred by us for valve replacement. The other valve surgeries were recommended by the referring cardiologist, and were performed at the referring institution or at another center. There were 8 post-operative deaths.

**Mortality.** There were 51 deaths over this 10-year follow-up period (Table 4). There were 24 deaths of cardiac origin, 21
noncardiac deaths, and 6 deaths attributable to unknown causes. The mean age at death was 67 ± 14 years (range: 27 to 88 years). At the time of death, 6 patients (12%) were <50 years old, and 27 patients (53%) were >70 years old.

The older patients had significant comorbidities. There were 6 procedure-related deaths, of which 2 were dissection-related and 1 was caused by an acute ventricular septal defect. One patient died because of retroperitoneal

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**Figure 2. Resting and Provoked LVOT Gradients During Follow-Up After ASA**

There is a marked reduction in both resting and provoked left ventricular outflow tract (LVOT) gradients at 3 months after alcohol septal ablation (ASA). There is further reduction of gradients until 5 years, and this improvement persisted during follow-up. BL = baseline.

**Figure 3. Septal Thickness During Follow-Up After ASA**

There was marked reduction of septal thickness at 3 months after alcohol septal ablation and further gradual reduction during follow-up. Abbreviations as in Figure 1.
bleeding. There were 2 deaths at 10 days, 1 because of an arrhythmia and the other because of late inferior wall and right ventricular infarction caused by a right coronary artery clot.

Of the 629 individuals, 611 had sufficient follow-up information regarding overall survival and could be included in the Kaplan-Meier analysis (Fig. 5) (18 patients were not available for follow-up after the ASA procedure). The 1-year survival estimate (95% confidence interval [CI]) for all-cause mortality is 0.97 (95% CI: 0.95 to 0.98). After the 1-year mark, 565 individuals were still at risk of death and were being followed up in the study. The 5-year survival estimate is 0.92 (95% CI: 0.90 to 0.94), with 272 individuals still at risk for death. At the 8-year time point, the survival estimate is 0.89 (95% CI: 0.86 to 0.92), with 130 individuals at risk. The last event occurred at 8.36 years, so no further survival estimates are reported.

**Figure 4. Ejection Fraction During Follow-Up After ASA**

The ejection fraction, which was hyperdynamic at baseline, declined gradually but remained in normal range during follow-up. Abbreviations as in Figure 1.

**Table 4. Mortality Data (51 Deaths)**

<table>
<thead>
<tr>
<th>Cardiac Deaths (n = 24)</th>
<th>Noncardiac Deaths (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure related, n = 6</td>
<td>Lung disease, n = 7</td>
</tr>
<tr>
<td>Post-operative, n = 8</td>
<td>Infection and sepsis, n = 4</td>
</tr>
<tr>
<td>CHF (EF &gt;60%), n = 3</td>
<td>Cancer, n = 3</td>
</tr>
<tr>
<td>SCD, n = 7</td>
<td>CVA, n = 4</td>
</tr>
<tr>
<td>Other causes, n = 3</td>
<td></td>
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</tbody>
</table>

There were 6 deaths with unknown causes.

CHF = congestive heart failure; CVA = cerebrovascular accident; EF = ejection fraction; SCD = sudden cardiac death.

**Figure 5. Kaplan-Meier All-Cause Mortality**

The 1-year survival estimate for all-cause mortality is 0.97 (95% confidence interval [CI]: 0.95 to 0.98). After the 1-year mark, 565 individuals were still at risk for death and were being followed up in the study. The 5-year survival estimate is 0.92 (95% CI: 0.90 to 0.94), with 272 individuals still at risk for death. At the 8-year time point, the survival estimate is 0.89 (95% CI: 0.86 to 0.92), with 130 individuals at risk. Pts = patients.
Event-free survival. Event-free survival, freedom from procedural death, cardiac surgery, and repeat alcohol septal ablation procedure are shown in the Kaplan-Meier curve (Fig. 6). Six hundred and twenty-seven subjects were included in the analysis of event-free survival. Procedural deaths, repeat procedures, and surgeries (myectomy, mitral/aortic valve surgery) were all included as events in this analysis. Deaths from causes other than procedural deaths were censored at the time of death. Of the 627 individuals in this analysis, 113 had an event. The 1-year survival estimate and 95% confidence interval (CI) is 0.88 (95% CI: 0.85 to 0.91), with 509 patients at risk at the 1-year time point. The 5-year survival estimate and confidence interval is 0.80 (95% CI: 0.77 to 0.83), with 249 patients at risk.

Discussion

This report represents the largest number of patients enrolled consecutively as candidates for ASA. The procedure was feasible in most patients. Complications of the procedure included primarily complete heart block and coronary dissections. Importantly, procedural modifications markedly reduced coronary dissections, and reduced the incidence of complete heart block to <10%. Alcohol septal ablation resulted in significant clinical and hemodynamic improvement in the vast majority. The LVOT gradient, both resting and provoked, was markedly reduced at 3 months and continued to decrease during the 10-year period. The LVOT gradient reduction was accompanied by a significant reduction in dyspnea and angina, as well as improvement in exercise tolerance, all of which were sustained throughout the follow-up period.

Feasibility. There were 10 cases of procedure failure, 4 were caused by coronary dissections, all of which occurred early, and since the modification of the procedure with coaxial guide catheters and soft guide wires, none have occurred. Two early procedures that were aborted for technical reasons could probably have been performed now because of smaller balloons and operator experience.

Repeat ASA. There were 91 repeat procedures in 81 patients. The reasons for this 14% incidence of repeat procedures are several. First, because this cohort starts with the beginning of the alcohol ablation experience, it is in part related to the steep learning curve. Second, the determinants of acute success in the laboratory are at best inexact and therefore may not always predict long-term success. More importantly, we were successful in most (94%) of the repeat procedures.

Mortality. During this 10-year follow-up period, there were 51 deaths, of which 24 were cardiac deaths. Six deaths were procedure-related, and 7 were sudden cardiac deaths. Postoperative deaths accounted for 8 patients (of 36 patients who had myectomy/mitral valve/aortic valve surgery). These 8 patients were elderly women (mean age 67.5 ± 13.9 years) with significant comorbidities. Only 2 of these patients who underwent valve replacement or myectomy surgery died under our care post-operatively.

There were 3 deaths of congestive heart failure. None of the heart failure deaths were caused by systolic dysfunction. A number of elderly patients had significant comorbidities and died of noncardiac causes or unknown causes.

Comparison with surgical myectomy. There is ongoing controversy regarding the outcome and efficacy of ASA as compared with myectomy for the treatment of symptomatic HOCM (27,28). Several nonrandomized retrospective reports have been published (29–33), but there are no prospective, randomized trials of the 2 procedures. Concern has been expressed that the septal scar resulting from ASA would create a milieu for the generation of malignant ventricular arrhythmias and resultant sudden cardiac death (34). Yet, the low incidence of known sudden cardiac death during the follow-up period seems to negate these concerns. However, it is to be noted that 8% (n = 50) of patients were lost to final follow-up in 2007. It is reassuring that 44 of these patients who were U.S. nationals were not represented as dead in the Social Security death index database.

The 1-year (97%), 5-year (92%) and 8-year (89%) survival are similar to the survival after surgical myectomy from Toronto General Hospital (35) (n = 338), and Mayo Clinic.
(36) (n = 289), which was 98%, 95% to 96%, and 83% at 1, 5, and 10 years, respectively. The surgical series had a longer follow-up duration (Toronto General Hospital: 7.7 ± 5.7 years, Mayo Clinic: 5.8 ± 4 years) compared with 4.6 ± 2.5 years in this alcohol septal ablation cohort. This patient cohort was older (53.9 ± 15 years) than the Toronto General Hospital (47 ± 14 years) or Mayo Clinic (45.3 ± 19 years) cohorts, yet the long-term survival was similar.

We (37) and others (38) have shown that the relief of LVOT obstruction with ASA is associated with a significant regression of left ventricular hypertrophy. Because the extent of hypertrophy (5) in HOCM as well as LVOT obstruction (6) has been shown to be independent risk factors for cardiac death, it is possible that regression of hypertrophy and gradient reduction more than offset the putative risk attributable to the localized septal infarction.

Study limitations. This is a prospective, nonrandomized study that is limited by the lack of a control/comparison group and a paucity of objective follow-up data after 5 years. Also, dobutamine provocation, used initially, is no longer used because of a lack of specificity. The wide geographic distribution of patients within the U.S. and abroad made it difficult to get some patients to return for follow-up at our center, which could have affected the outcomes.

Conclusions

The present study shows that ASA is a safe and efficacious treatment for symptomatic HOCM. An ASA can be performed in most patients with a high success rate. This report shows that successful alcohol ablation results in a sustained clinical and hemodynamic improvement.

Acknowledgments

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