Implantable Cardioverter-Defibrillator Therapy for Primary Prevention of Sudden Death After Alcohol Septal Ablation of Hypertrophic Cardiomyopathy

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Objectives
The purpose of this study was to examine the effects of alcohol septal ablation (ASA) on ventricular arrhythmias among patients with obstructive hypertrophic cardiomyopathy (HCM), as measured by appropriate implantable cardioverter-defibrillator (ICD) discharges.

Background
Alcohol septal ablation is an effective therapy for patients with symptomatic HCM. However, concern has been raised that ASA may be proarrhythmic secondary to the iatrogenic scar created during the procedure. The impact of ASA on ventricular arrhythmias has not been well described.

Methods
This prospective study included 123 consecutive patients with obstructive HCM who underwent ASA and had an ICD implanted for primary prevention of sudden cardiac death (SCD). The ICDs were implanted based on commonly accepted risk factors for SCD in the HCM population. Data from ICD interrogations during routine follow-up were collected.

Results
Nine appropriate ICD shocks were recorded over a mean follow-up of 2.9 years in the cohort, which had a mean of 1.5 ± 0.9 risk factors for SCD. Using Kaplan-Meier survival analysis, the estimated annual event rate was 2.8% over 3-year follow-up. There were no significant differences in the incidence of risk factors between patients who did and did not receive appropriate shocks.

Conclusions
The annual rate of appropriate ICD discharges after ASA is low and less than that reported previously for primary prevention of SCD in HCM. This suggests that ASA is not proarrhythmic. Traditional SCD risk factors did not predict ICD shocks in this cohort. (J Am Coll Cardiol 2008;52:1718–23) © 2008 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is associated with significant morbidity, and it is one of the leading causes of sudden death under the age of 35 years (1–6). Traditionally, surgical myectomy is used to relieve outflow tract obstruction and improve symptoms in this population (7–12). More recently, alcohol septal ablation (ASA) has become an increasingly common nonsurgical treatment for obstructive HCM. This procedure results in an iatrogenic myocardial infarction, which in turn decreases septal thickness and systolic anterior motion (SAM) of the mitral valve, reducing resting and provocative left ventricular outflow tract (LVOT) gradients (13–18). It is an effective treatment for the symptoms of obstruction, resulting in decreased angina, reduced heart failure symptoms, and improved exercise tolerance (18).

Despite the clear benefit of ASA on the symptoms associated with HCM, the effects of this procedure on the arrhythmia substrate for sudden death remain controversial. On one hand, the septal myocardial infarction could be a substrate for ventricular tachyarrhythmias and increase the incidence of sudden death (19). On the other hand, the remodeling that occurs after ASA with reductions of outflow tract gradient and septal thickness could reduce the risk of sudden death (20). Despite this controversy, there are no large studies evaluating the risk of life-threatening arrhythmias or sudden death in HCM after ASA. Accordingly, the present study was a prospective long-term evaluation of implantable cardioverter-defibrillator (ICD) therapy after ASA.

Methods
Patient eligibility. This study included 123 consecutive patients undergoing ASA for symptomatic HCM who had

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an ICD for primary prevention of sudden cardiac death (SCD) at either the Medical University of South Carolina or Baylor College of Medicine. The criteria for selection of patients for ASA were reported previously (16). All patients signed a written informed consent form, and this study was approved by the local institutional review boards.

The ICDs were implanted for the primary prevention of SCD based on commonly accepted risk factors. These risk factors included: 1) a family history of SCD in a first-degree relative; 2) a history of syncope or near-syncope not explained by other mechanisms; 3) an abnormal blood pressure response during exercise treadmill test (a failure to increase systolic blood pressure by >20 mm Hg during peak exercise using a Bruce protocol); and 4) marked septal hypertrophy (septal thickness ≥3 cm). The decision for ICD implantation was left to the clinical discretion of the primary physician. Patients were excluded from the study if they had a history of SCD, sustained ventricular arrhythmias (before study enrollment), or appropriate ICD therapy before their ASA. To minimize the risk of selection bias, only those patients with an ICD implanted before ASA or during the procedural hospitalization were included.

ASA procedure. The details of the ablation procedure have been described in previous reports. Briefly, the septal arterial branches supplying the septal bulge were identified with the assistance of contrast echocardiography. Between 1 and 3 ml ethanol was used in each septal branch. Gradients across the LVOT were measured before and after ethanol injection, and initial success was defined as a decrease in LVOT gradient at rest by >50% as measured by Doppler echocardiography or catheter immediately after the procedure. Additional septal branches were targeted if initial success was not achieved. A temporary pacemaker in the right ventricular apex was used in all patients who did not have a permanent pacemaker or ICD, and was removed if there was no evidence of high-grade atrioventricular (AV) block after ASA. If high-grade AV block did occur, the temporary pacemaker remained in place until baseline conduction returned or a permanent pacemaker was implanted. Of note, ICD implantation was only performed if patients were at risk for sudden death by clinical criteria as described above, not for the treatment of heart block. The ICD programming was left to the discretion of the implanting physician, but in general only shock therapy was used to treat ventricular tachyarrhythmias and not antitachycardia pacing.

ICD follow-up. The patient follow-up period began immediately after ASA and ICD implantation. The ICD data were collected during routine follow-up visits (every 3 to 6 months). The ICD shocks were verified by 2 investigators, and deemed appropriate if they treated an episode of ventricular tachycardia (VT) or ventricular fibrillation (VF). Dual-chamber stored electrograms were available in all patients to facilitate the interpretation of events. For survival analysis, follow-up was censured at the time of first appropriate ICD therapy. Inappropriate therapies (attributable to rapidly conducted atrial fibrillation, sinus tachycardia, or other causes) were noted, but were not an end point in this study.

Statistical methods. Data are expressed as a mean ± SD. Continuous variables were compared using the Student t test, whereas categorical variables were analyzed using the Fisher exact test. Survival analysis for shock-free survival was performed using the Kaplan-Meier method. A p value ≤0.05 was considered statistically significant. Survival analysis and statistical calculations were performed using the GraphPad Prism software package (GraphPad Software, Inc., San Diego, California).

Results

Data from all 123 consecutive subjects with HCM undergoing ASA were collected and available for analysis. Ten patients (8.1%) had at least 1 repeat ASA, and 1 had a total of 3 septal ablation procedures. The ICD implantation was performed after the ASA procedure in 87 patients (70.7%), whereas the remaining 36 patients underwent implantation before the initial procedure (802 ± 853 days). All patients received dual-chamber devices (right atrium, right ventricular apex) to allow for atrial based pacing, if needed.

Baseline characteristics. Table 1 compares the baseline characteristics of the patients in this study who underwent ASA and had an ICD implanted for primary prevention with a similar cohort of consecutive patients who underwent ASA at the Medical University of South Carolina but did not receive ICDs. The baseline characteristics and data from the ASA procedures for the study population are summarized in Table 2. The mean age of the ICD cohort was 48 ± 15 years, and 81 patients (66%) were male. The subjects had

| Table 1. Comparison of Baseline Characteristics in Patients Who Underwent ASA and Received an ICD for Primary Prevention With a Non-ICD Cohort |
|----------------|----------------|------------------|-----------------|------------------|
| Non-ICD Cohort (n = 284) | ICD Cohort (n = 123) | p Value |
| Age (yrs) | 53 ± 16 | 48 ± 15 | 0.003 |
| Gender (male/female) | 146/138 | 81/42 | 0.009 |
| Resting gradient before ASA (mm Hg) | 66 ± 37 | 61 ± 36 | 0.237 |
| Resting gradient after ASA (mm Hg) | 7 ± 12 | 14 ± 11 | <0.001 |
| Septal thickness (cm) | 2.1 ± 0.5 | 2.2 ± 0.5 | 0.079 |
| Risk factors for SCD | 1.1 ± 0.9 | 1.9 ± 0.9 | <0.001 |

Values are mean ± SD.

ASA = alcohol septal ablation; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.
a mean septal thickness of 2.2 ± 0.5 cm and 1.5 ± 0.9 traditional risk factors for SCD.

**ICD shocks.** The combined total follow-up from this study was 363 patient-years, with a mean follow-up of 2.9 ± 2.2 years. Appropriate ICD discharges for ventricular arrhythmias occurred in 9 patients over this period. Two patients (22%) had rapid, monomorphic VT as the rhythm that triggered ICD discharge, whereas the remainder had polymorphic VT or VF. There were no statistically significant differences in the baseline characteristics of the group who did and did not have appropriate ICD shocks (Table 3). Moreover, the presence of multiple risk factors also did not predict appropriate ICD shocks (3 of 9 vs. 56 of 114, p = 0.49). However, the group who did receive shocks had a lower resting LVOT gradient both immediately after ASA and at 3- to 12-month follow-up. Using Kaplan-Meier survival analysis, the estimated event rate was 2.8% annually. Figure 1 illustrates the shock-free survival curve of this cohort.

**Discussion**

This is the first large study to evaluate the long-term risk of ventricular tachyarrhythmias, as measured by appropriate ICD shocks, in a high-risk cohort after ASA. The primary findings are that sustained ventricular arrhythmias are uncommon after ASA given the low rate of appropriate ICD shocks in this population. The shock-free survival rate of 90% at 3 years compares favorably with other studies of HCM, suggesting that the ASA procedure does not increase the risk of ventricular tachyarrhythmias.

**Mechanisms of ventricular arrhythmias after ASA.** Patients with HCM are at increased risk of developing ventricular arrhythmias, most frequently complex premature ventricular complexes, couplets, and NSVT (27–29). Stable, sustained monomorphic VT is rarely observed among patients with HCM. Polymorphic VT and/or VF are the most common sustained ventricular arrhythmias in this population (28). It is speculated that these disorganized rhythms may predominate secondary to the myocardial fiber disarray that occurs on a histological level in HCM (30,31). Addi-
tionally, some investigators have suggested that LVOT obstruction itself is an independent risk factor for SCD and appropriate ICD discharges (32). It has been postulated that an iatrogenic scar could create a substrate for re-entry after ASA (5,19); however, unlike scar caused by ischemic myocardial infarction secondary to coronary artery disease, scar secondary to ethanol infusion via a septal artery may be less arrhythmogenic for several reasons. First, histological findings show less pronounced infiltration of connective tissue into the infarcted myocardium (21). Second, the size of the infarct is generally small: <10% of myocardial mass as measured by cardiac magnetic resonance imaging (33). The size of myocardial scar using nuclear perfusion imaging has been shown to be a significant predictor of inducibility of VT/VF at electrophysiology study (34). Third, ASA leads to regression of left ventricular hypertrophy (LVH) (20) and reduction in the LVOT gradient (13–18), which may have a beneficial effect given that the risk of SCD in HCM increases with the magnitude of LVH (35) as well as the degree of LVOT obstruction (32). Fourth, the patients undergoing ASA from this and other studies generally have no associated coronary artery disease, which can be a cause of VT/VF (13–17). Finally, LV ejection fraction is perhaps the most important factor in determining risk for developing VT/VF after myocardial infarction, and ASA does not result in a significant reduction of LV function, as assessed using multiple modalities (18,21,32,33,36,37).

**ICD shocks and ventricular arrhythmias post-myectomy.** In a recently published report of 125 patients with obstructive HCM who underwent ICD implantation (38), the group who underwent surgical septal myectomy (n = 56) had over 10-fold fewer appropriate ICD discharges compared with the nonmyectomy cohort (0.24% vs. 4.3% annually, respectively, p = 0.004). The investigators of this report speculate that this lower event rate may be attributable to a decrease in LVH, as well as to a decrease in microvascular dysfunction resulting from the decrease in LVOT obstruction and associated improvements in regional myocardial perfusion. Although this cohort included patients who underwent implantation for both primary as well as secondary prevention of SCD, their findings are consistent with those in our cohort; that is, the reduction in LVH and LVOT gradient associated with septal reduction procedures may offset any proarrhythmic effects from an iatrogenic scar created during these procedures. Additionally, the fact that the ICD discharge rate in the post-myectomy group was lower than that of the ASA group in this study may suggest that the types of scars created by these 2 procedures are fundamentally different. Finally, assuming that the risk factor profile in the post-myectomy cohort is similar to the cohort in this study, surgical myectomy may be more effective than ASA in reducing ventricular arrhythmias and ICD shocks; however, direct comparison of these cohorts is uncontrolled and retrospective observation that needs to be confirmed with further studies such as a randomized, prospective study to draw any definitive conclusions.

**ICD shocks and ventricular arrhythmias post-ASA.** There are few data regarding the incidence of ventricular arrhythmias beyond the immediate post-procedural period after ASA. In one series of 39 patients, programmed ventricular stimulation was performed before and 2 weeks after ASA; 60% of these patients had a repeat electrophysiology study at 7 months post-procedure as well (21). These investigators showed that there was actually a nonsignificant decrease in inducibility of VT/VF after the procedure. Additionally, the event-free survival in this group was 100% over a 15-month follow-up period. In a series of 50 patients who underwent ASA (21), 2 patients developed VF in the immediate post-procedure setting, but no patients developed sustained ventricular arrhythmias after 48 h out from their procedure. In another study, 9 patients who underwent ASA were followed up with serial Holter monitors at 3, 7, and 90 days after their intervention (23), and no ventricular arrhythmias were found with the exception of isolated premature ventricular complexes. A 1-year follow-up of 50 patients who underwent ASA reported NSVT in 5 patients within 24 h of their procedure and 1 episode of witnessed cardiac arrest with documented VF in a patient who later survived to ICD implantation (18). Finally, a small study published by Lawrenz et al. (22) reported an 8% annual appropriate ICD event rate in 15 post-ASA patients over a follow-up period of approximately 3.5 years. This study, however, included a significant number of patients with ICD implantation for secondary prevention, with a history of VT/VF and/or SCD prior to ASA; the event rate in the primary prevention group was lower than in the secondary prevention group (5% vs. 10%, respectively).

In our cohort, 9 of 123 patients with an ICD implanted for primary prevention of SCD had appropriate ICD shocks over an average follow-up of almost 3 years. This represented an overall appropriate ICD discharge rate of 2.8% per year, which is lower than previous reports in patients who underwent ASA (22) and is similar to that reported in the HCM population who received an ICD for primary prophylaxis based on SCD risk factors (27,28,39). In one of these reports, patients with familial HCM accompanied by LVOT obstruction had a 1.5% rate of SCD annually (37), whereas another study reported a 5% annual appropriate ICD discharge rate in HCM patients with ICDs for primary prevention of SCD (28). In a recently published study with over 500 patients with HCM who underwent ICD implantation for both primary and secondary prevention, the overall appropriate ICD intervention rate was 5.5%/year (27). In this study, the primary prevention group (n = 383, 76%) had at an appropriate intervention rate of 3.6%/year over 5 years.

The presence of individual or multiple traditional risk factors for SCD in the HCM population were not associated with an increased rate of appropriate ICD shocks in our study; however, given the low number of events in this
cohort, this observation must be interpreted with caution. Similarly, in the recent report of Maron et al. (27) of a large cohort of HCM patients, no individual risk factor was associated with an increased incidence of appropriate ICD therapy and the presence of multiple risk factors did not predict a higher risk of shock.

Interestingly, the patients in this study who received appropriate ICD shocks post-ASA did have a significantly lower LVOT gradient at 3 months post-procedure. This is not easily explained, and implies that a reduction in LVOT gradient is not solely responsible for the potential antiarrhythmic effects of nonsurgical septal reduction. In fact, it could suggest that the scar created post-ASA may be proarrhythmic, but this iatrogenic proarrhythmic effect is outweighed by a multitude of more beneficial factors, including reducing septal size, ventricular remodeling, and decreasing LVOT gradient.

**Monomorphic VT after ASA.** Several case reports of sustained monomorphic VT have been published after ASA for symptomatic HCM (24–26), including 1 patient in this study (26). All 3 reports occurred within 3 weeks of the ASA procedure. None of these patients had a history of VT/VF or significant CAD, and none of the 3 had any significant arrhythmias within 48 h post-procedure. In 2 of the cases (25,26), slow VT was reported (approximately 150 beats/min) with an exit location near the ventricular septum. Although the spontaneous VT morphology reported by Simon et al. (26) was more consistent with an apical free wall exit point, a subsequent electrophysiology study resulted in an inducible monomorphic VT (285 beats/min) with a basal septal exit point, more consistent with an ASA-induced scar location. Clearly these reports indicate that there is a small incidence of proarrhythmia for VT after this procedure.

In the present study, 2 of 9 patients with appropriate shocks had monomorphic VT as the cause of their ICD shock. Overall, these episodes represent only 1.6% of the entire cohort, confirming that monomorphic VT is a rare occurrence post-ASA and that scar-mediated re-entry may not be a significant long-term complication of this procedure. Presumably the small early proarrhythmic effect of ASA is more than offset by the long-term antiarrhythmic effect of this procedure, resulting in a low cumulative incidence of ICD shocks.

**Study limitations.** This study should be interpreted in light of certain methodological limitations. All of the patients in this study underwent ASA for symptomatic obstructive HCM; thus, our results cannot be generalized to the overall HCM population. Additionally, we did not have a control group of patients with ICDs for primary prevention of SCD who did not undergo ASA to compare event rates, so we can only compare our event rates with historical registry and previously published data. We did attempt to compare a cohort who underwent ASA and did not receive ICDs to the cohort in this study, but as expected, there were certain significant differences between them; namely, the group who received ICDs were perceived to be at higher risk for SCD (i.e., younger, thicker septums, more risk factors for SCD). As noted previously, the low numbers of appropriate ICD shocks preclude robust analysis of the factors that may predict or contribute to these events. Finally, data regarding inducibility of VT/VF prior to ASA were not available for most patients in this study, although the predictive value of electrophysiology testing in this population is controversial.

**Conclusions**

In summary, the annual rate of appropriate ICD discharges after ASA is low and less than that reported previously for primary prevention of SCD in a similar population. In fact, as suggested by previous studies, ASA may reduce VT/VF by relieving outflow tract obstruction and promoting reverse remodeling. Although scar-mediated re-entry can occur after iatrogenic infarct, it seems to be a rare complication of this procedure and more than offset by the beneficial effects of remodeling in the long term. Finally, traditional SCD risk factors did not predict appropriate ICD shocks in this cohort.

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