ORIGINAL ARTICLE

Incidence of Atrial Fibrillation following Alcohol Septal Ablation for Hypertrophic Cardiomyopathy

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Background: Patients with hypertrophic cardiomyopathy (HCM) are at a fourfold to sixfold higher risk of developing atrial fibrillation (AF) compared to the general population, though incidence rates among patients undergoing alcohol septal ablation (ASA) are not well characterized. The purpose of this study was to evaluate atrial fibrillation incidence following ASA.

Methods: We studied 132 consecutive HCM patients without comorbid AF that underwent 154 ASA procedures. The incidence of AF in follow-up was assessed through chart abstraction including electrocardiography. Survival free of AF was estimated using Kaplan-Meier methodology.

Results: Over a mean follow-up of 3.6 ± 2.7 years (maximum 11.3 years), 10 (7.6%) patients developed new-onset AF. Of those who developed AF, both resting and provoked left ventricular outflow tract (LVOT) gradients had improved significantly (difference –79.78 mm Hg, $P \leq 0.005$). Severity of mitral regurgitation improved in 7 (70%) patients. Survival free of AF was estimated to be 99.1%, 93.7%, and 91.7% at 1, 3, and 5 years.

Conclusions: Despite relieving LVOT obstruction and improving mitral regurgitation severity via ASA, new-onset AF remained a common complication of hypertrophic cardiomyopathy.

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Alcohol septal ablation (ASA) is an alternative to surgical myectomy for treatment of symptomatic hypertrophic cardiomyopathy (HCM) that provides long-term resolution of left ventricular outflow tract (LVOT) obstruction, improves functional status, and prolongs longevity similar to that expected after surgical myectomy.[1,2] Nevertheless, patients with HCM are at a fourfold to sixfold higher risk of developing atrial fibrillation (AF), with a prevalence of 20% and an incidence of 3% per year.[3–6] AF confers increased risk of all-cause mortality, including that due to heart failure and thromboembolic events and is associated with worsened exercise capacity and symptoms impacting quality of life.[3,4,6] Despite multiple cohort studies of patients undergoing ASA for symptomatic HCM,[1,2,7–27] none has reported on the incidence of AF. We evaluated the incidence of AF following ASA for symptomatic HCM.

METHODS

We studied consecutive patients with symptomatic HCM without known comorbid AF prior to undergoing ASA from 2002 to 2011 at both the University of Colorado Hospital and the Denver

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Veterans Affairs Medical Center. Indications for ASA included persistent symptoms (New York Heart Association [NYHA] class II–IV) despite optimal medical therapy, significant resting or provoked LVOT gradients, and coronary anatomy amenable for proximal septal ablation. No patients had had prior surgical myectomy. The Colorado Multiple Institutional Review Board approved this analysis.

Procedure and Measurements

Prior to undergoing the ASA procedure all patients had a baseline transthoracic echocardiogram that demonstrated a normal left ventricular ejection fraction (>55%), as measured by the biplane method of discs.[28] Additional echocardiographic indices included left atrial (LA) linear dimension, interventricular septal wall thickness, resting and provokable LVOT gradients, assessment of systolic anterior motion (SAM) of the mitral leaflet, and grading of the severity of mitral regurgitation.

The septal ablation procedure was performed in standard fashion as previously described.[9] Patients were evaluated postprocedure to assess functional status (NYHA class), clinical symptoms, medication regimen, and echocardiographic indices. Routine follow-up was performed postprocedure and then annually or as clinically indicated.

Our primary outcome was the incidence of AF assessed through systematic chart review and inspection of 12-lead electrocardiograms. Ambulatory telemetric monitoring was not performed routinely in asymptomatic individuals. Comprehensive two-dimensional and Doppler echocardiography included evaluation of septal wall thickness, left ventricular ejection fraction, LA linear dimension, presence or absence of SAM, mitral regurgitation severity, as well as both resting and provoked LVOT gradients.

Statistical Analysis

Incident AF-free survival was evaluated by censoring patients at the date of newly diagnosed AF or last known follow-up. Survival estimates were determined with traditional Kaplan-Meier estimation.[29] For a small subset of patients who underwent additional ASA procedures, our time to event analysis is based on the first procedure. Continuous variables are presented as mean ± standard deviation. Longitudinal changes of continuous variables were assessed using either a paired or unpaired 2-tailed Student's t test. Mann-Whitney U testing was used to assess both categorical and longitudinal changes of rank order variables. For all assessments, a P value ≤ 0.05 was deemed statistically significant. Statistical analysis was performed using R: A Language and Environment for Statistical Computing, version 3.1.3 (Vienna, Austria).[29,30]

RESULTS

Of the 145 consecutive patients with HCM, 13 were excluded because of preexisting AF. The remaining 132 patients with HCM and without comorbid AF underwent 154 ASA procedures. Immediately following the procedure, resting and provoked LVOT gradients decreased to ≤30 mm Hg in 118 (91%) patients (of 130 with complete data). Prior to the procedure, all patients had symptoms attributable to LVOT obstruction with a mean NYHA class of 2.9 ± 0.4, which on follow-up improved significantly to 1.3 ± 0.5 (change = −1.6, P < 0.001). We previously described the complications and longitudinal echocardiographic indices that persisted after the ASA procedure[17,31], but we reanalyzed these same parameters for this subset of patients who did not have AF at baseline.

The mean follow-up time to last known clinical assessment was 3.6 ± 2.7 years (maximum 11.3 years) and was available for 130 (98%) patients. Of the 129 patients with echocardiographic follow-up, 125 (98%) had preserved (>55%) left ventricular ejection fraction. Serial echocardiography revealed persistent improvement in LVOT obstruction gradients and no significant change in LA linear dimension (41 ± 7 mm vs 42 ± 7 mm, P = 0.13) in the overall study cohort.

During this period 10 (7.6%) patients developed AF. Characteristics of the study population at baseline for those who remained free of AF and those who later developed AF are outlined in Table 1. Patients who went on to have AF were older (64.8 ± 16.9 years vs 56.4 ± 15.3 years, respectively) but had the same NYHA functional class (2.9) at baseline. LVEF remained preserved in all but one patient who developed AF. Eight patients experienced paroxysmal AF, while two patients developed persistent AF. Three of the eight patients with paroxysmal AF (38%) were treated with antiarrhythmic drugs. No patients underwent

Table 1. Characteristics of Patient Population at Baseline (n = 132)

	Survival Free of Atrial Fibrillation (n = 122)		Incident Atrial Fibrillation (n = 10)		
	Mean (n)	SD (%)	Mean (n)	SD (%)	P value
Age (years)	56.4	±15.3	64.8	±16.9	0.158
Women	60	49%	5	50%	0.963
Prior stroke	7	6%	1	10%	0.686
Hypertension	58	48%	4	40%	0.666
Diabetes mellitus	9	7%	1	10%	0.804
Coronary artery disease	50	42%	5	50%	0.654
Chronic kidney disease	5	4%	2	20%	0.267
Family history of sudden cardiac death	13	11%	2	20%	0.168
Syncope	36	30%	2	20%	0.510
NYHA functional class	2.9	± 0.4	2.9	± 0.3	–
Medications					
Beta-blocker	89	75%	8	80%	0.716
Calcium channel blocker	57	48%	3	30%	0.286
Angiotensin converting enzyme inhibitor	19	16%	1	10%	0.583
Disopyramide	9	8%	1	10%	0.818
Amiodarone	1	1%	1	10%	0.385

Values are expressed as either mean ± standard deviation (SD) or number (n) and percentage (%). NYHA = New York Heart Association; – = not enough observations for comparison.

pulmonary vein isolation or left atrial catheter ablation, though one individual required atrioventricular node ablation. The mean CHA_2DS_2Vasc score among patients with incident AF was 2.3 ± 1.2. Despite therapeutic anticoagulation in all patients, a thromboembolic stroke occurred in one during follow-up.

Regarding the outcome of ASA among those who later developed AF, both resting and provoked LVOT gradients had improved significantly ($P \leq 0.005$) and the severity of mitral regurgitation had improved in 7 (70%) of these patients (Figs. 1A and B). LA linear dimension appeared to improve in the group of patients with AF, but this was not significantly different from those without AF (difference –6.6 mm, $P = 0.09$) as shown in Figure 1C. Survival free of AF was estimated to be 99.1%, 93.7%, and 91.7% at 1, 3, and 5 years (Fig. 2).

DISCUSSION

AF contributes to the exacerbation of symptoms and the development of heart failure in patients with HCM.[5] It has been shown that increased LA afterload in HCM corresponds well with LV diastolic dysfunction[32] and that septal reduction therapy improves the severity of mitral regurgitation.[7,11,17,18,20,21,25,33] While septal reduction therapy including ASA is not primarily performed to reduce subsequent AF burden in HCM, the favorable anatomic correction leading to reduced mitral regurgitation and decreased LA afterload—as demonstrated in our study—might reasonably be expected to lead to a corresponding decrease in the AF. Table S1 summarizes previous literature documenting that most patients with HCM have enlarged LA linear dimension at baseline or prior to septal reduction therapy

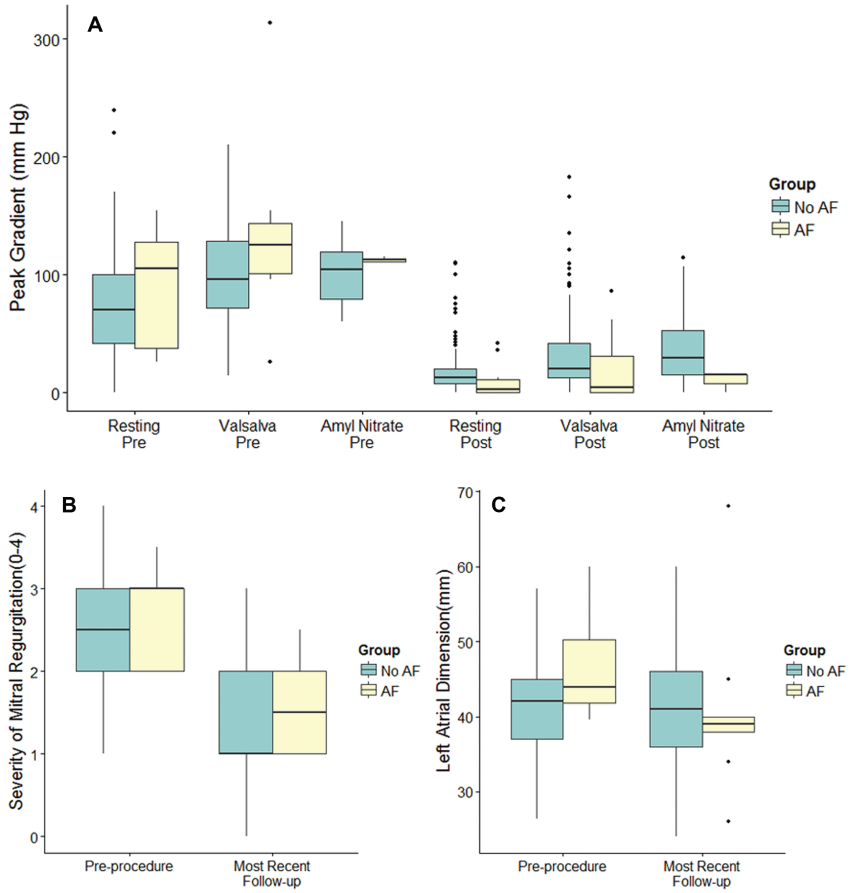

Figure 1. (A) Peak left ventricular outflow tract gradients at baseline and postprocedure in hypertrophic cardiomyopathy patients with and without incident atrial fibrillation (yellow and green fill respectively). Graphical depictions of inter-quartile range (IQR, 25th–75th percentiles; box), median (horizontal line), and outliers (>1.5*IQR; points). Between groups comparisons were not statistically significant with the exception of with amyl nitrate (0.047 and 0.014 pre = and post = respectively). (B) Severity of Mitral regurgitation on a semi-quantitative scale of 0–4 (none = 0, trace = 1, mild = 2, moderate = 3, and severe = 4) at baseline and at most recent follow-up in hypertrophic cardiomyopathy patients with and without incident atrial fibrillation (yellow and green fill respectively). Graphical depictions of interquartile range (IQR, 25th–75th percentiles; box), median (horizontal line), and outliers (>1.5*IQR; points). Whiskers extend to 1.5 times the IQR. Between groups comparisons were not statistically significant. (C) Left atrial linear dimension at baseline and at most recent follow-up in HCM patients with and without incident atrial fibrillation (yellow and green fill, respectively). Graphical depictions of interquartile range (IQR, 25th to 75th percentiles), median (horizontal line), and outliers (>1.5*IQR; points). Whiskers extend to 1.5 times the IQR. Between groups comparisons were not statistically significant.

and confirms our findings that while there is improvement in the severity of MR, LA linear dimension is not substantially reduced.

We found that despite favorable alterations in echocardiographic structure—reduced septal hypertrophy—and function—reduced LVOT gradients and mitral regurgitation—as well as improved patient symptoms, the incidence of AF in this cohort of patients with HCM after undergoing ASA mirrored that reported in studies of HCM

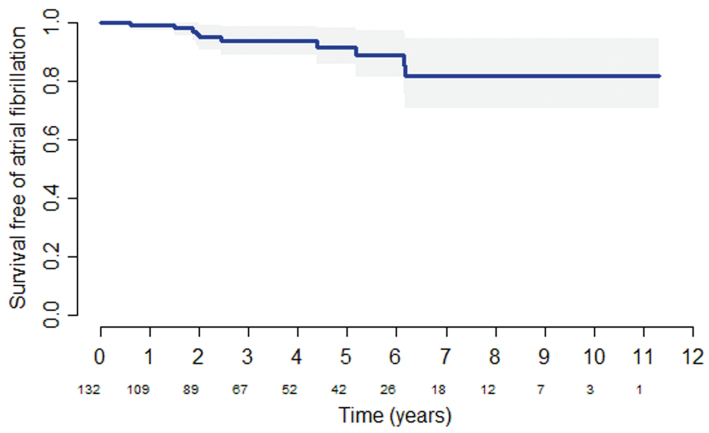

Figure 2. Incidence of atrial fibrillation after alcohol septal ablation. Bands represent 95% confidence interval of survival estimates. Number of patients at risk appears below x-axis.

populations that did not undergo ASA. In a meta-analysis of 22 cohort studies (6413 patients) investigating AF in HCM as either a primary or secondary outcome, Guttmann et al. found the overall AF incidence to be 3.08% per year; however, very few patients had undergone ASA (n: 27; 0.42%).[4] To our knowledge, ours is the first HCM cohort study to report the incidence of AF after ASA and demonstrates remarkable consistency in the incidence of AF when compared with previous cohorts of more general HCM populations.

Several groups have reported clinical and echocardiographic covariates associated with AF incidence in the HCM population. In their study of a general HCM cohort, Losi et al. found LA dysfunction, defined by LA fractional shortening ≤ 16% and LA linear dimension ≥45 mm were strongly associated with the development of AF. Similarly, Olivotto et al. found that increased LA linear dimension was strongly associated with subsequent AF.[3,5] This was corroborated in the largest single-center study of HCM where multiple echocardiographic parameters were significantly correlated with the prevalence of AF, including higher LA volume index, LV posterior wall thickness, medial E/e′ ratio, and shorter mitral E-wave deceleration time, a marker of restrictive physiology.[6] Surprisingly, this same study also found that patients with obstructive physiology defined by a rest LVOT peak gradient of >30 mm Hg or a provoked LVOT peak gradient of >50 mm Hg were less likely to develop AF.[6] More recently, LA percent ejection fraction has been shown to reliably identify patients with HCM at risk for development of AF.[34] Yet others found that the LA wall in HCM patients with AF was not thicker than that of matched patients without structural heart disease, suggesting that overt atrial fibrosis and hypertrophy do not contribute to the incidence of AF.[35]

We surmise that the symptoms that prompt consideration for performing ASA may indicate that the condition has progressed sufficiently to irreversibly alter the structure and function of the LA. Alternatively, the underlying cardiomyopathy might also impact the atria independent of its influence on LV diastolic dysfunction and mitral regurgitation. In fact the coexistence of ventricular and atrial myopathy can be as high as 36–45%, but, as currently measured, this has not yet been shown to have a direct association with AF.[5]

We acknowledge a number of limitations to the current analysis. This was a retrospective, nonrandomized, cohort study without a contemporaneous control group. All assessments were performed on a clinical basis rather than stipulated by protocol. Although the timing of assessments was not identical for all patients, this reflects real world experience with generalizability to the broader HCM population. Because routine surveillance ambulatory telemetry monitoring was not performed, incidence rates may be underestimated due to lower ascertainment of asymptomatic paroxysmal AF. In addition, atrial linear dimensions were utilized in the current study, though increasingly left atrial volumes indexed for body surface area are used in practice and research settings.[28] Only

1 patient in our study developed AF complicated by an embolic stroke. A larger cohort of patients would be needed to assess whether stroke risk is modulated by ASA in HCM patients with AF. Finally, our sample size of incident AF patients precludes the use of multiple regression analysis to assess for covariates that reliably predict arrhythmia incidence.

We conclude that after relieving LVOT obstruction and improving mitral regurgitation severity via ASA, incident AF remained a common complication of hypertrophic cardiomyopathy. Significant decreases in LA size were not observed in our cohort. Atrial remodeling, fibrosis, or factors other than effective LA afterload may contribute to the high incidence of AF in this HCM population. Further studies should be done to compare the incidence of AF in cohorts of patients who do not all undergo septal reduction therapy such as ASA.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web site:

Table S1. Alcohol septal ablation for hypertrophic cardiomyopathy cohort studies.