

Safety and Efficacy of Atrial Fibrillation Ablation in Young Patients

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Abstract

Background: Outcome of catheter ablation of atrial fibrillation (AF) in young patients has not been widely reported. This study describes the safety and efficacy of radiofrequency catheter ablation (RFA) for atrial fibrillation in patients forty years or younger.

Methods and Results: Forty consecutive patients who underwent fifty-two RFA procedures for symptomatic, drug-refractory paroxysmal or non-paroxysmal AF were included in the study. The mean (SD) age of the patients at time of initial procedure was 34.1 (5.6) years. Twenty-five (62.5%) patients had paroxysmal AF, 6 (15%) patients had persistent AF, and 9 (22.5%) patients had longstanding persistent AF. Procedural safety and efficacy were assessed based on patient status > 1 year after initial ablation procedure. After a mean (SD) follow-up of 3.8 (2.9) years, 25 (62.5%) patients were free of AF without antiarrhythmic drugs (AAD) and 40 (100%) patients experienced > 95% reduction of AF burden on or off AADs. No major complications or adverse events occurred during the study.

Conclusions: Catheter ablation of AF is a favorable therapeutic option for patients 40 years or younger, resulting in high rates of procedural success with a low risk of major complications.

Introduction

Radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) is a commonly performed procedure for symptomatic patients who are refractory to medical treatment throughout the world. It is notable that the clinical trials that have defined the safety and efficacy of this procedure have been performed to a large extent in patients between the age of 50 and 70 years.¹⁻³ The single procedure success rate of RFA has varied widely from 40% to 70% depending on type and duration of AF, procedural technique, and intensity of

follow-up.¹ Relatively little is known about the outcomes of AF ablation in younger individuals. This study describes the outcomes and complications of AF ablation in young patients (<40 years) at a tertiary care hospital, and also provides a comprehensive review of the literature.

Material and Methods

Patient Population

The patient population included 40 out of 1,173 consecutive patients who underwent radiofrequency (RF) catheter ablation at or before 40 years of age for paroxysmal or non-paroxysmal AF at Johns Hopkins Hospital between January 2002 and July 2012 and who had at least one year of follow up information available. Paroxysmal AF was defined as recurrent (> 2 episodes) AF that terminated spontaneously within 7 days. Non-paroxysmal AF included both persistent and longstanding persistent AF as defined by the 2012 HRS Consensus Document.¹ Each patient provided written informed consent to participate in the ongoing Johns Hopkins AF Ablation Registry.

Ablation Procedure

All patients underwent wide area circumferential RFA as previously

Key Words:

Atrial Fibrillation, Catheter Ablation, Young Adults.

Disclosures:

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described.⁴ Briefly, a double transeptal puncture was performed under fluoroscopic guidance. Pulmonary vein angiograms were then obtained for each of the pulmonary veins. An endocardial map of the left atrium was created with an electroanatomic mapping system (CARTO, Biosense-Webster, Diamond Bar, CA) and superimposed upon the pre-existing CT image of the chamber. Using a circular multipolar electrode mapping catheter (Lasso, Biosense, Diamond Bar, CA, USA), pulmonary vein potentials were evaluated. With routine hemodynamic and electrocardiographic monitoring, a four-millimeter-tipped irrigated ablation catheter (Thermocool, Biosense-Webster, Diamond Bar, CA) was advanced under fluoroscopic guidance to the left atrium. Circumferential lesions were applied surrounding the pulmonary veins. All ablation procedures were performed during sinus rhythm. Patients either presented in sinus rhythm or were cardioverted to sinus rhythm at the start of the procedure. The procedural endpoint was complete isolation of the pulmonary veins with entrance and exit block confirmed by the Lasso catheter. The same procedure was performed for patients undergoing repeat ablation procedures. To prevent short term recurrences of AF, patients continued previously ineffective antiarrhythmic medications for at least three months. The patients were followed in our clinic as detailed below.

Follow-up

Patients were seen in our outpatient clinic for their first follow-up visit three months after their procedure. The follow-up visit consisted of a detailed history, physical examination, and a 12-lead electrocardiogram. Antiarrhythmic drugs were discontinued in patients who were free of symptomatic or asymptomatic AF. Subsequently, patients were followed at Johns Hopkins or by a referring physician on a regular basis and ECGs were obtained at each visit regardless of symptoms. Follow-up telephone calls were conducted for all patients at 3, 6, 9, and 12 months, and then at 12-month intervals.

If symptoms suggestive of an arrhythmia occurred, patients were asked to undergo 24-hour Holter monitoring or 30-day event monitoring depending on frequency of their symptoms. Antiarrhythmic drug therapy was continued or restarted in patients who experienced recurrent AF more than 3 months after the ablation procedure. If patients remained symptomatic more than 3 months

after the ablation procedure despite being restarted on antiarrhythmic drug treatment, a clinically indicated second procedure was offered to the patient.

Outcome Assessment

Recurrent AF was defined based on the 2012 HRS Consensus Document as symptomatic or asymptomatic AF, atrial tachycardia, or atrial flutter of 30 seconds duration or longer after a 3-month blanking period.¹

Procedural success was based on patient status > 1 year after initial ablation and categorized as a complete success, a clinical success, or a failure. Complete success was defined in accordance with the 2012 HRS Consensus Document as the absence of AF or other atrial tachycardias while off antiarrhythmic drug therapy after a 3-month blanking period.¹ Clinical success included rare episodes of AF defined as < 6 AF episodes over the follow-up year that terminated either spontaneously and/or with a single cardioversion and/or a >95% reduction in AF burden when monitoring was compared before and after ablation.⁵ If neither endpoint was achieved, the ablation procedure was considered a failure.

Major complications and adverse events were defined as those that were life-threatening, resulted in permanent harm, required intervention, or significantly prolonged hospitalization.¹

Statistical Analysis

Descriptive statistics were estimated as mean \pm standard deviation for continuous variables and percentages for categorical variables. Means were compared with Student's t-test using STATA, StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp, LP. A p-value of <0.05 was considered statistically significant.

Results

Of the 40 patients who met the inclusion criteria, 32 patients were male (75%) and the mean age was 34.1 \pm 5.6 years. Shown in Figure 1 is the distribution of patients' ages stratified base on whether the patient had paroxysmal or non-paroxysmal AF. AF was paroxysmal in 25 (62.5%) patients. There was no statistical difference between

Table 2: Comparison of patient characteristics associated with complete vs. clinical success only for RFA

	Complete Success (n = 25)	Clinical Success only (n = 15)	P-value
Age; mean (SD)	33.8 (5.1)	34.7 (6.3)	.62
Caucasian (n, %)	19 (76%)	11 (73%)	.86
Male	18 (72%)	14 (93%)	.11
Paroxysmal	19 (76%)	6 (40%)	.02
BMI mean (SD)	28.4 (3.9)	31.0 (5.6)	.10
AF_Duration (yrs) median (range)	2 (0.5 - 26)	5 (0.5 - 20)	.74
LVEF mean (SD)	56.4 (7.3)	54.3 (6.8)	.41
CHADS2 median (range)	0 (0 - 3)	0 (0 - 3)	.81
Hypertension; n (%)	5 (20%)	2 (13.3%)	.59
Structural heart disease; n (%)	0 (0%)	1 (6.7%)	.33

Results from a clinical case series of patients, \leq 40 years old, who underwent radiofrequency catheter ablation for symptomatic atrial fibrillation refractory to medication at a tertiary care hospital in United States. Complete success refers to freedom from AF without the use of antiarrhythmic drugs after a 3-month blanking period and clinical success refers to rare episodes of AF defined as < 6 AF episodes over the follow-up year that terminated either spontaneously and/or with a single cardioversion and/or a >95% reduction in AF burden.

Table 1: Baseline Characteristics of Young Patients who Underwent RFA for Symptomatic, drug-refractory AF

Age; mean (SD)	34.1 (5.6)
Caucasian; n (%)	30 (75%)
Male; n (%)	32 (80%)
Paroxysmal AF; n (%)	25 (62.5%)
Persistent AF; n (%)	6 (15%)
Longstanding persistent AF; n (%)	9 (22.5%)
BMI; mean (SD)	29.4 (4.7)
AF duration (yrs); median (range)	2.5 (0.5 - 26)
LVEF; mean (SD)	55.5 (7.0)
CHADS2; median (range)	0 (0 - 3)
Hypertension; n (%)	7 (17.5%)
Structural heart disease; n (%)	1 (2.5%)

RFA = Radio Frequency Ablation, AF = Atrial Fibrillation, SD = Standard Deviation, yrs = years, LVEF = Left Ventricular Ejection Fraction, CHADS2 score refers to risk stratification score for stroke among patients with AF.

the ages of patients with paroxysmal or non-paroxysmal AF ($p=0.13$). The mean body mass index and left ventricular ejection fraction was 29.4 ± 4.7 and $55.5 \pm 7\%$, respectively. Additionally, the median AF duration time, defined as the time between first documented episode of AF and initial ablation procedure, was 2.5 years (range 0.5 – 26 years). The clinical characteristics of these patients are summarized in Table 1.

At the time of ablation procedure, 11 (27.5%) patients were being treated with Class I antiarrhythmic medications including flecainide (54.5%), disopyramide (18.1%), propafenone (18.1%), and quinidine (9.1%). Additionally, 17 (42.5%) patients were receiving Class III agents, including amiodarone (47.1%), sotalol (41.1%), dronedarone (5.9%), and dofetilide (5.9%). Prior to ablation procedure, 15 (37.5%) patients were being treated with oral anticoagulation therapy. Following their ablation procedure, all patients were administered oral anticoagulation for at least two months.

RFA for AF was acutely successful in all patients, as defined by complete isolation of all PVs. The average total procedure time for initial procedures were 263.1 ± 68.6 minutes, respectively. Among the 40 patients, no major complications or adverse events occurred peri-procedurally.

During a mean (SD) follow-up duration of 3.8 (2.9) years, clinical success was seen in 100% of patients after one or more AF ablation procedures. Of the 40 patients included in the study, 30 (75%) patients underwent one procedure, 8 (20%) patients underwent two procedures, and 2 (5%) patients underwent three procedures. At the time of last follow-up, 25 (62.5%) patients were free of AF while off of antiarrhythmic drug therapy and met the criteria for complete success. The remaining 15 (37.5%) patients had clinical success and continued antiarrhythmic drug therapy and/or experienced at least a 95% reduction in AF burden. Of the 25 patients who achieved complete success, 20 (80%) patients met criteria after a single pulmonary vein isolation procedure, 3 (12%) patients underwent two procedures, and 2 (8%) patients underwent three procedures. Additionally, among the patients with complete success, 19

(76%) patients had paroxysmal AF and 6 (40%) had persistent or longstanding persistent AF prior to ablation.

There was no significant difference in age, race, gender, BMI, AF duration, left ventricular ejection fraction, and CHADS₂ score between patients who had complete success and those who had clinical success following catheter ablation of AF (Table 2). However, patients with paroxysmal AF were significantly more likely to achieve complete success compared to patients with non-paroxysmal AF (Table 2, $p = 0.02$).

Discussion

The results of this study demonstrate that RFA in young patients (<40 years of age) with drug refractory AF is effective and safe. Clinical success was achieved in all patients after one or more ablation procedures.

In an early study published in 2004, Nanthakumar et al. presented electrophysiological findings and outcomes of RFA for symptomatic, lone AF in 9 adolescents between the ages of 8 and 19.⁶ During a mean (SD) follow-up of 35 (22) months,⁷ (77.8%) patients were arrhythmia free without medications, while 2 (22.2%) patients required medication to achieve AF control.⁶ Since publication of this first study, two subsequent studies examined the outcomes of AF ablation in young patients (defined as those < 45 years), and compared AF ablation outcomes and complications of these patients to patients > 45 years.^{5,7} In the first study, Leong-Sit et al. reported an 87% rate of AF control at 32 months in 232 patients undergoing AF ablation before the age of 45.⁵ AF control was defined as no AF episodes on any AADs, no AF episodes off AADs, or <6 AF episodes over the follow-up year.⁵ Of the 232 young patients, 71% of patients had paroxysmal AF; however, the mean or median age of this cohort was not reported. In a similar study, Chun et al. described the procedural outcomes and complications of AF ablation in 593 patients < 45 years from the German Nationwide Ablation Registry.⁷ The median age of the young cohort in this registry was 41 years (range 38 – 44 years) and 68.9% of these patients had paroxysmal AF.⁷ At a follow-

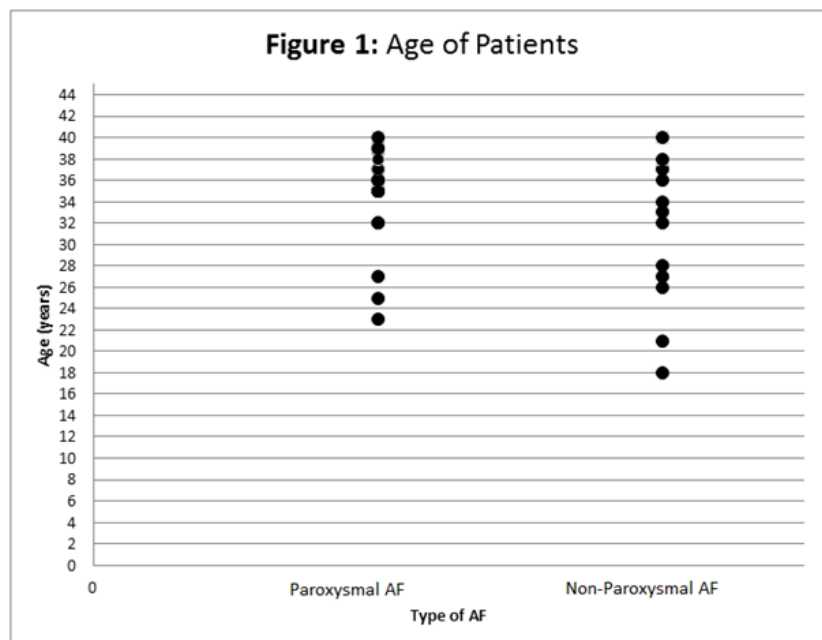


Figure 1: Distribution of patients' ages stratified base on whether the patient had paroxysmal or non-paroxysmal AF.

Table 3: Characteristics of Prior Studies

Author	Number of patients (n)	Age (years)	Paroxysmal AF (% of study sample)	Follow-up (in months)	Complete Success (% of study sample)	Clinical Success (% of study sample)
Nanthakumar et al. ⁶	9	15.9±3.3 (mean (SD))	66.7%	35	77.8%	100%
Leong-Sit et al. ⁷	232	< 45	71%	32	76%	87%
Chun et al. ⁵	593	41 (median)	68.9%	12		79.3%
Dewire et al. (current study)	40	34.1 ± 5.6 (mean(SD))	62.5%	45.6	62.5%	100%

up of 12 months, arrhythmia recurrence was reported in 40.1% of patients.⁷ No major complications occurred in patients <45 years in the three studies.⁵⁻⁷

The results of the present study confirm and extend the findings of these prior studies evaluating young patient cohorts undergoing catheter ablation for AF (Table 3). We observed clinical success in 100% of patients and complete success in 62.5% of patients with no major complications at the end of follow-up. To increase comparability of procedural efficacy in our study to that of Leong-Sit et al., we included the criteria for AF control in our definition of clinical success. Additionally, to facilitate interpretation of our results in the context of most previously published literature of AF ablation, we used the 2012 HRS Expert Consensus Guidelines' definitions for reporting outcomes and complications of AF catheter ablation. Additionally, to gain insight into the impact of catheter ablation on a novel cohort, we defined young adulthood as < 40 years of age. At time of ablation, the mean age of the patients in our cohort was 34.1 years, and all patients were between 18 and 40 years of age (Figure 1). Comparatively, the young patients included in the cohort of Nanthakumar et al. were between 8 and 19 years, and young patients included in the registry of Chen et al. were between 38 and 45 years. The specific ages, mean age, or age range of the young patients in the study of Leong-Sit et al. were not reported. In the present study one patient was between 8 and 19 years and 12 patients were between 38 and 40 years. Twenty-seven (67.5%) of our patients were of an age that was not included in these previous two studies.

The two major limitations of our study are the observational nature of the data and the limited number of patients included in analysis.

The results of our study, combined with those of the previously reported trials, support the safety and effectiveness of RFA in young individuals below the age of 40 years. As a single-center retrospective study, the findings provide useful insight into the role of catheter ablation in young patients, but cannot provide the conclusions of randomized trials. In our clinical experience, few patients (3.4%) are diagnosed with and undergo catheter ablation for AF before the age of 40. A similarly small percentage (8%) of young patients with AF was found in the German registry as well. Of note, the majority of young patients in the German registry were between 40 years and 45 years.⁷ Additionally, the lack of published studies on the procedural efficacy and complication rate of catheter ablation in the age range of the studied cohort may suggest the rarity of AF in young patients.

Conclusions:

In conclusion, the high efficacy and low rates of complications in our study, which are consistent with prior reports, support the argument that catheter ablation of AF should be considered an appropriate treatment option in patients less than 40 years of age. To the extent that all patients in our study had previously failed a trial

of one or more antiarrhythmic agents, these findings cannot be used to support catheter ablation as first line therapy, but rather support the notion that, if AF cannot be controlled on a well-tolerated medication, catheter ablation is a reasonable next step.

References:

1. Calkins H, Kuck KH, Cappato R, Brugada J, Camm J, Chen SA, Crijns H, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the heart rhythm society (HRS) task force on catheter and surgical ablation of atrial fibrillation. developed in partnership with the european heart rhythm association (EHRA), a registered branch of the european society of cardiology (ESC) and the european cardiac arrhythmia society (ECAS); and in collaboration with the american college of cardiology (ACC), american heart association (AHA), the asia pacific heart rhythm society (APHRS), and the society of thoracic surgeons (STS). endorsed by the governing bodies of the american college of cardiology foundation, the american heart association, the european cardiac arrhythmia society, the european heart rhythm association, the society of thoracic surgeons, the asia pacific heart rhythm society, and the heart rhythm society. *Heart Rhythm*. 2012;9(4):632-696.e21.
2. Calkins H, Reynolds MR, Spector P, Sondhi, M, Xu Y, Martin A, Williams C, et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: Two systematic literature reviews and meta-analyses. *Circulation: Arrhythmia and Electrophysiology*. 2009;2(4):349-361.
3. Bonanno C, Paccanaro M, Vecchia L, Ometto R, Fontanelli A. Efficacy and safety of catheter ablation versus antiarrhythmic drugs for atrial fibrillation: A meta-analysis of randomized trials. *Journal of Cardiovascular Medicine*. 2010;11:408-418.
4. CHEEMA A, DONG J, DALAL D, Vasamreddy C, Marine J, Henrikson C, Spragg D, et al. Long-term safety and efficacy of circumferential ablation with pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2006;17(10):1080-1085.
5. Leong-Sit P, Zado E, Callans DJ, Garcia F, Lin D, Dixit S, Bala R, et al. Efficacy and risk of atrial fibrillation ablation before 45 years of age. *Circulation: Arrhythmia and Electrophysiology*. 2010;3(5):452-457.
6. Nanthakumar K, Lau YR, Plumb VJ, Epstein AE, Kay GN. Electrophysiological findings in adolescents with atrial fibrillation who have structurally normal hearts. *Circulation*. 2004;110(2):117-123.
7. Chun KRJ, SCHMIDT B, Kuck KH, Andresen D, Willems S, Spitzer S, Hoffman E, et al. Catheter ablation of atrial fibrillation in the young: Insights from the german ablation registry. *Clin Res Cardiol*. 2013;102:459-468.