Effect of Catheter Ablation on Progression of Paroxysmal Atrial Fibrillation

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Ablation and Progression of Atrial Fibrillation. ***Objective*****: The objective was to determine the effect of radiofrequency catheter ablation (RFA) on progression of paroxysmal atrial fibrillation (AF).**

Background**: Progression to persistent AF may occur in up to 50% of patients with paroxysmal AF receiving pharmacological therapy. Hypertension, age, prior transient ischemic event, chronic obstructive pulmonary disease, and heart failure (HATCH score) have been identified as independent risk factors for progression of AF.**

Methods**: RFA was performed in 504 patients (mean age: 58 ± 10 years) to eliminate paroxysmal AF. A repeat RFA procedure was performed in 193 patients (38%). Clinical variables predictive of outcome and their relation to progression of AF after RFA were assessed using multivariate analysis.**

Results**: At a mean follow-up of 27 ± 12 months after RFA, 434/504 patients (86%) were in sinus rhythm; 49/504 patients (9.5%) continued to have paroxysmal AF; and 14 (3%) were in atrial flutter. Among the 504 patients, 7 (1.5%) progressed to persistent AF. In patients with recurrent AF after RFA, paroxysmal AF progressed to persistent AF in 7/56 (13%, P < 0.001). The progression rate of AF was 0.6% per year after RFA (P < 0.001 compared to 9% per year reported in pharmacologically treated patients). Age >75 years, duration of AF >10 years and diabetes were independent predictors of progression to persistent AF. The HATCH score was not significantly different between patients with paroxysmal AF who did and did not progress to persistent AF (0.7 ± 0.8 vs 1.0 ± 0.5, P = 0.3).**

Conclusions**: Compared to a historical control group of pharmacologically treated patients with paroxysmal AF, RFA appears to reduce the rate of progression of paroxysmal AF to persistent AF. Age, duration of AF, and diabetes are independent risk factors for progression to persistent AF after RFA.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 9-14, January 2012)*

atrial fibrillation, antiarrhythmic drugs, heart failure, radiofrequency catheter ablation

Introduction

Earlier studies have demonstrated that atrial fibrillation (AF) may progress from paroxysmal to persistent in up to 50% of patients despite pharmacologic therapy.[1-3] Heart failure, advanced age, prior cerebrovascular events, chronic obstructive pulmonary disease (COPD), and hypertension (HATCH score) have been reported as independent predictors of progression of AF in pharmacologically treated patients.[2] However, it is not clear whether radiofrequency catheter ablation (RFA) can prevent progression of paroxysmal AF, and whether HATCH parameters would still be predictive of progression after RFA of AF. Thus, the purpose of this study was to systematically assess the role of RFA on progression of AF in patients with paroxysmal AF and to identify predictors of progression to persistent AF after RFA.

Methods

Study Subjects

A total of 525 consecutive patients with paroxysmal AF who underwent RFA to eliminate AF between January 1, 2006 and December 31, 2008 were enrolled in this study. Despite rigorous efforts, current rhythm status could not be confirmed in 21 patients. Adequate data for analysis were available in 504 of the 525 patients (96%) included in the study. Clinical characteristics and the HATCH score of the patients lost to follow-up and included in the analysis were similar.

Among the 504 patients, there were 338 men and 166 women, and their mean age was 58 ± 10 years. The mean left ventricular ejection fraction and left atrial diameter were 0.58 ± 0.07 and 41 ± 6 mm, respectively. AF was first diagnosed 69 ± 67 months prior to presentation (Table 1). Patients who underwent a prior catheter or surgical ablation procedure for AF were excluded from this study.

Electrophysiologic Study and Radiofrequency Ablation

The study protocol was approved by the Institutional Review Board. An electrophysiologic study and RFA was performed in the fasting state under conscious sedation. All

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antiarrhythmic drugs except amiodarone were discontinued at least 4–5 half-lives before the study. Amiodarone was discontinued 8 weeks earlier. Vascular access was obtained through a femoral vein. A multipolar electrode catheter positioned in the coronary sinus was used for recording electrograms and atrial pacing. After transseptal puncture, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 325–350 seconds. All pulmonary veins (PVs) were mapped with a decapolar ring catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA). An open irrigation, 3.5 mm tip deflectable tip catheter (Thermocool, Biosense Webster) was used for mapping and ablation. Bipolar electrograms were recorded at a band-pass of 30–500 Hz (EPMed Systems, West Berlin, NJ, USA). An electroanatomical mapping system (Carto, Biosense Webster) was used to reconstruct the 3-dimensional geometry of the left atrium and PVs.

Radiofrequency energy was delivered at a maximum power output of 35 W at a flow rate of 30 mL/min and a maximum temperature of 48 °C. The power was reduced to 20–25 W at a flow rate of 17 mL/min, during applications of energy near the PV ostia, in the posterior left atrium, or in the coronary sinus. Antral pulmonary vein isolation (APVI) was performed in all patients and complete electrical isolation was confirmed with a circular multipolar catheter. Ablation of complex fractionated atrial electrograms (CFAEs) and linear ablation were performed at the discretion of the operator.

Postablation Management and Follow-Up

After an overnight hospital stay with electrocardiographic monitoring, all patients were discharged home the next day. All patients were maintained on warfarin ≥3 months after the RFA. When warfarin was discontinued prior to ablation, low molecular weight heparin was used to bridge until the INR was >2.0 after the RFA. The same drug regimen was continued for 8–12 weeks after ablation in patients who were receiving an antiarrhythmic drug before the procedure.

Patients were seen for the follow-up at 3, 6, and 12 months after the ablation procedure. If patients did not have recurrence of AF, they would be contacted by phone or mail once a year for the follow-up. Patients were also asked to call a clinical coordinator if they experienced symptoms suggestive of an arrhythmia. The patients were provided with a 30-day autotrigger event monitor 6 months after ablation and whenever they had symptoms. Rhythm monitoring using an event monitor successfully completed in 80% of the patients. In the remaining patients data were derived from Holter monitors or serial electrocardiograms. The mean duration of follow-up was 25 ± 12 months after the most recent RFA.

A repeat ablation procedure was offered to all patients with recurrent atrial arrhythmias. During repeat ablation, APVI was confirmed and repeated as necessary in all patients. At the discretion of the operator, CFAEs were also targeted and eliminated and/or linear ablation was performed.

Warfarin was discontinued in patients who were confirmed to be in sinus rhythm beyond 3 months after the final ablation procedure if there was no history of thromboembolic events or another indication to continue anticoagulant therapy.

Progression of AF

Progression to persistent AF was defined as paroxysmal AF prior to RFA that became persistent after the RFA. As stated in the Heart Rhythm Society consensus statement, persistent AF was defined as an episode of AF that persisted >7 days or required cardioversion.[4] Patients who were free from recurrent AF (with or without concomitant antiarrhythmic drug therapy) and patients who continued to have paroxysmal AF were considered to have remained free from progression of AF. Patients who had recurrent atrial flutter were not considered to have progression of AF, as atrial flutter is often a manifestation of proarrhythmia secondary to prior ablation lesions and not a natural progression of AF. The HATCH score was determined for each patient.[2] The HATCH acronym stands for hypertension (1 point), age ≥75 years (1 point), transient ischemic attack or stroke (2 points), COPD (1 point), and heart failure (2 points).

Statistical Analysis

Continuous variables were expressed as mean ± SD. Baseline characteristics between patients with and without progression from paroxysmal to persistent AF were compared using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. Duration of AF was compared using the Wilcoxon signed-rank test because data were not normally distributed. Logistic regression analysis was used to evaluate independent predictors for progression to persistent AF. Variables included in the logistic regression model were selected from baseline characteristics with a $P \leq 0.1$ in the univariate analysis. Forward and backward stepwise methods were used to develop the multivariate model. All variables included in the model were tested for interaction. Data analysis was performed with SAS statistical software (version 9.1, SAS Institute Inc., Cary, NC, USA). A two-sided $P < 0.05$ indicated statistical significance.

Results

Clinical Outcome after RFA

During a mean follow-up of 27 ± 12 months after the first RFA, 279 of 504 patients (55%) were in sinus rhythm including 44 of 504 patients (9%) who were receiving an antiarrhythmic drug (7 patients on amiodarone). Among the 504 patients, 179 patients (36%) had recurrent AF, 25 (5%) had atrial flutter, and 21 (4%) had both AF and flutter. A total of 193 patients (38%) underwent ≥2 RFA procedures: 2 procedures in 165, 3 procedures in 22, 4 procedures in 5, and 5 procedures in 1 patient. A mean of 1.5 ± 0.6 procedures was performed per patient.

At 22 ± 13 months after the most recent procedure, 434 patients (86%) remained in sinus rhythm, 49 patients (9.5%) continued to have paroxysmal AF, 7 patients (1.5%) had persistent AF, and 14 patients (3%) had persistent atrial flutter. Sixty-five of 434 patients (15%) in sinus rhythm and 13 of 49 patients (27%) with paroxysmal AF were being treated with an antiarrhythmic drug.

Progression to Persistent AF

Among the 504 patients in this study, AF progressed to persistent in 7 patients (1.5%) after RFA. Progression to persistent AF occurred in 7 of the 56 patients (13%) in whom RFA was not effective in eliminating paroxysmal AF ($P < 0.001$).

The incidence of AF progression after RFA was 0.6% per year (Fig. 1). In comparison, the rate of progression of AF

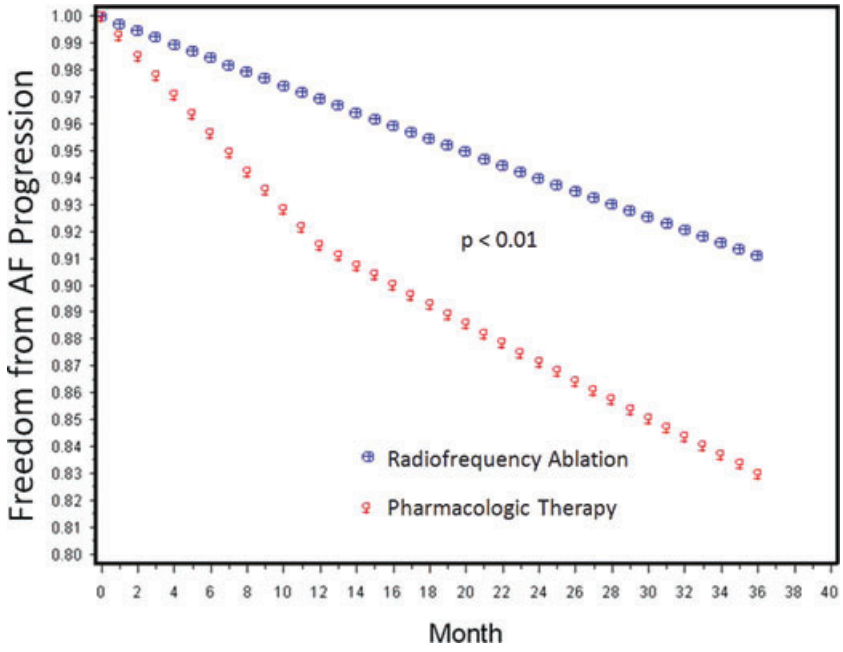

Figure 1. *Rate of AF progression. The probability of AF progression was 0.6% per year after RFA in this study (blue line) versus 8.6% in the first year with slow but steady progression to 24.7% in 5 years in patients treated pharmacologically (red line).*[3]

has been reported as 9% during the first year and 25% after 5 years in pharmacologically treated patients with paroxysmal AF ($P < 0.01$ compared to progression of AF after RFA).[3]

Predictors of Progression of AF

On univariate analysis, patients who developed persistent AF were older (71 ± 5 vs 58 ± 10 years, $P < 0.01$) and were more likely to have diabetes (43% vs 11%, $P = 0.03$) than patients without AF progression (Table 1). On multivariate logistic regression analysis, age >75 years (OR = 26, ±95% CI: 4–200, $P < 0.01$), AF duration >10 years (OR = 6.8, ±95% CI: 1.4–33.3, $P = 0.02$) and diabetes (OR = 8.1, ±95% CI: 1.5–43.5, $P = 0.01$) were independent predictors of progression to persistent AF after RFA (Table 2).

HATCH Score

The mean HATCH score was 0.7 ± 0.8. The mean HATCH score was similar among patients whose AF progressed (1 ± 0.6) and did not progress to persistent AF (0.7 ± 0.8, $P = 0.3$). The HATCH score was ≥2 in 53 of 477 patients (11%) without AF progression and in 1 of 7 patients (14%) with progression to persistent AF ($P = 0.57$).

$CHADS_2$ Score

The mean $CHADS_2$ score was 0.8 ± 0.8. The mean $CHADS_2$ score was higher among patients with progression to persistent AF (1.4 ± 0.5) than without AF progression (0.8 ± 0.8, $P = 0.04$). The $CHADS_2$ score was ≥2 in 78/477 patients (16%) without AF progression and in 3 of 7 patients (43%) with progression to persistent AF ($P = 0.1$). Although, the $CHADS_2$ score was a univariate predictor (OR = 1.93, 95% CI = 1.00–3.72, $P = 0.05$), on multivariate analysis the $CHADS_2$ score was not predictive of progression to persistent AF after RFA.

Discussion

Main Findings

This study demonstrates that (1) the rate of progression of paroxysmal AF to persistent AF is low after RFA; (2) the HATCH score, previously described to be predictive of AF progression in pharmacologically treated patients, does not appear to predict progression of AF after RFA in this study. However, it should be noted that the mean HATCH score was low in this study; (3) age, duration of AF, and diabetes are independent predictors of progression of AF after RFA.

These findings suggest that RFA reduces the rate of progression of paroxysmal AF compared to historical cohorts of pharmacologically treated patients. It appears that age, duration of AF, and diabetes have profibrillatory effects that promote progression to persistent AF after failed RFA of paroxysmal AF.

Progression of AF

Progression of AF from paroxysmal to persistent is most likely due to the development of an electroanatomical substrate capable of perpetuating AF.[5-7] A number of variables have been implicated in structural and electrophysiologic remodeling of the atria. An increase in the duration and frequency of episodes of AF by itself was demonstrated to promote remodeling in a goat model of AF.[7]

Aging is associated with an increase in the prevalence of AF.[8] Fibrosis appears to play a key role in promoting perpetuation of AF in the aging heart and in patients with structural heart disease.[9] AF *per se* may also facilitate atrial fibrosis.[9] Atrial fibrosis may result in an increase in nonuniform anisotropy and local conduction heterogeneity which perpetuate AF.[10] It is not clear whether other factors such as a change in the autonomic tone and innervation of the heart also play a role in age-related progression of AF.

In earlier studies, advanced age, left atrial enlargement, and cardiomyopathy were reported to be predictors of AF progression in patients receiving pharmacological therapy.[2,3,11,12] Atrial dilatation may promote perpetuation of

Table 1
Baseline Characteristics

	Number AF Progression N = 483	Progression to Persistent AF N = 7	P
Age (years)	58 ± 10	71 ± 5	< 0.01
Gender (male/female)	323/160	4/3	0.7
AF duration (months)	67 ± 63	168 ± 169	0.1
Weight (kg)	92 ± 20	87 ± 19	0.5
BMI (kg/m^2)	29 ± 6	30 ± 5	0.7
Hypertension	231 (48%)	5 (71%)	0.3
Coronary artery disease	50 (10%)	1 (14%)	0.5
Diabetes mellitus	52 (11%)	3 (43%)	0.03
COPD	11 (2%)	0	1.0
Thyroid disease	68 (14%)	2 (29%)	0.1
CVA	36 (8%)	0	1.0
Left atrial size (mm)	41 ± 6	42 ± 7	0.6
LV EF	0.58 ± 0.07	0.55 ± 0.08	0.3
HATCH score	0.7 ± 0.8	1 ± 0.6	0.3
$CHADS_2$ score	0.7 ± 0.8	1.4 ± 0.5	0.04

Data are shown as mean±SD. Percentages are shown in parentheses. BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular event; LV EF; left ventricular ejection fraction.

AF through a variety of mechanisms most notably due to an ability to accommodate longer and multiple wavelengths of potential reentrant circuits.[10]

Radiofrequency Catheter Ablation and Progression of AF

Progression of AF has been reported in up to 50% of patients with paroxysmal AF receiving pharmacological therapy.[1-3] It is not clear how often sinus rhythm was maintained in these patients as no specific predefined attempt was made to systematically pursue a rhythm control strategy. However, based on a number of studies that demonstrated only modest efficacy of antiarrhythmic drug therapy in maintaining sinus rhythm, it is unlikely that sinus rhythm was maintained in the majority of patients even when a rhythm control strategy was attempted.

RFA has been effective in maintaining sinus rhythm, particularly in patients with paroxysmal AF. Because RFA is unlikely to modify the aging process or eliminate electroanatomical abnormalities associated with structural heart disease, effective maintenance of sinus rhythm may have been the key factor that reduced the rate of progression of AF. Furthermore, during RFA of paroxysmal AF, typical targets are intermittent PV tachycardias and triggers originating from other thoracic veins. Extensive substrate modification is usually not performed. Therefore, it appears that early and effective elimination of primarily PV drivers is sufficient to decrease the rate of progression of AF despite continued evolution and progression of an atrial substrate capable of maintaining sinus rhythm. Of note is that paroxysmal AF progressed to persistent in 13% of the patients in whom RFA was not effective in controlling AF in this study, similar to the progression rate reported in an earlier study of patients who received pharmacological therapy for rate or rhythm control.[2]

Similar to the findings of earlier studies, age was an independent predictor of AF progression after RFA in this study.[2,3] However, unlike earlier studies, the 2 other independent predictors of progression of AF after RFA were the duration of AF prior to RFA and diabetes. A long duration of AF has long been recognized to promote electroanatomical remodeling of the atria and is likely to contribute to perpetuation of AF.[7] In several studies, longer duration of AF has been associated with a less favorable clinical outcome after RFA of AF. Therefore, earlier RFA of AF may be more effective in preventing progression of AF than a late intervention after atrial remodeling has already started.

Although diabetes is recognized as a risk factor for thromboembolic events, the role of diabetes in the pathophysiology of AF has not been well established. An earlier epidemiologic study suggested a higher risk of AF in patients with metabolic syndrome.[13] In addition to obesity, hypertension, and low-HDL levels, impaired fasting glucose levels were also an independent risk factor for AF.[13] In another study, diabetes was one of the predictors of progression of AF after RFA in selected patients with AF.[14] In a transgenic mouse model, a reduction in phosphoinositide 3-kinase activity, as frequently observed during impaired glucose tolerance and insulin resistance, was associated with a higher probability of developing AF.[15] In an *in vitro* study, hypertonicity, occurring during hyperglycemic states, was found to increase the frequency of depolarizations in PV myocytes.[16] Diabetes is also associated with microvascular disease, which could facilitate atrial fibrosis.[17] Furthermore, autonomic dysregulation secondary to diabetes may also play a role in the genesis AF.

Table 2
Multivariate Predictors of Progression to Persistent AF

	OR	± 95% CI	P
Age >75 years	26	4–200	<0.01
AF duration ≥10 years	6.8	1.4–33.3	0.02
Diabetes mellitus	8.1	1.5–43.5	0.01

Prior Studies

In an earlier study, the HATCH scoring system was proposed to predict the risk of progression of AF in patients receiving pharmacological therapy.[2] In patients with a HATCH score of ≥6, AF progressed in ∼50% after 1 year, whereas the rate of progression was 6% in patients with a HATCH score of 0. The mean HATCH score was lower and the range

of HATCH scores was also narrower in this study than in the earlier report. In this study, RFA reduced the rate of progression to 1.5% in a cohort of patients whose mean HATCH score was <2. Unlike in the earlier study, hypertension, prior cerebrovascular events, chronic obstructive pulmonary disease, and heart failure were not independent predictors of progression of AF after RFA in this study. However, in addition to age, duration of AF and diabetes were independent predictors.

In the Canadian Registry of Atrial Fibrillation (CARAF) study, the rate of progression of AF was ∼9% during the first year and 25% over a 5-year follow-up. Age, cardiomyopathy, left atrial dilatation, significant aortic stenosis or mitral regurgitation, and a slower heart rate at presentation were independent predictors of progression of AF. However, the role of RFA or any other active intervention for rhythm control on the rate of progression was not assessed in that study.

In another study, selected patients who presented to the hospital with a first documented episode of AF were followed for 5 years.[14] Age, heart failure, and diabetes were identified as predictors of progression. RFA was performed in only 11 of the 56 patients in the study and there was no recurrence of AF in any of the 11 patients after ablation. This study systematically investigated the role of RFA on progression of AF in 504 consecutive patients who underwent ablation to eliminate paroxysmal AF. Moreover, the effect of RFA was also analyzed in the context of recently proposed risk factors for progression of AF in patients treated pharmacologically.

Limitations

A limitation of this study is that there was no randomized control group and comparisons were made to historical cohorts of patients. Another limitation is that patients referred for RFA may have had fewer comorbidities than patients treated pharmacologically in earlier studies. Therefore, the progression rate of AF may have been lower in this study than reported previously. Nevertheless, when comparisons were made after adjustment of baseline comorbidites and HATCH score, RFA still appeared to reduce the rate of progression in this study.

Despite our effort to obtain a 30-day autotrigger event monitor at 6 months after ablation in all patients, there were some patients who did not receive the event monitor. Therefore, asymptomatic AF episodes could have been missed in these patients and the actual recurrence rate of atrial arrhythmias could have been higher.

The confidence intervals of predictors of progression to persistent to AF are very wide. This diverse range of effect sizes is probably due to a small number of patients who progressed to persistent AF.

It would have been helpful to determine the relationship between residual arrhythmia burden after RFA and rate of progression of AF. However, arrhythmia burden was not systematically analyzed in this study.

Clinical Implications

The findings of this study suggest that RFA may substantially reduce the rate of progression of AF and should be considered early in treatment of patients with AF. Furthermore, patients who are less likely to benefit from a rhythm control strategy using pharmacological therapy may still benefit from RFA to prevent progression of AF.

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