Efficacy of Catheter Ablation in Nonparoxysmal Atrial Fibrillation Patients with Severe Enlarged Left Atrium and Its Impact on Left Atrial Structural Remodeling

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AF Ablation in Patients with Large LA. Introduction: The effect of catheter ablation on severe left atrial enlargement especially in nonparoxysmal atrial fibrillation (NPAF) patients is not well understood. Whether reverse remodelling may occur after ablation has not been evaluated in this setting.

Methods and results: Fifty consecutive patients with left atrial diameter (LAD) ≥50 mm, and LA volume >200 cc undergoing catheter ablation for drug-refractory NPAF were included in this study. Transthoracic echocardiographic measurements were performed at baseline and at 12-months postprocedure. Left ventricular end-diastolic and end-systolic dimensions were indexed by body surface area (LVEDDI, LVESDI). Electroanatomic mapping system (Carto or NavX system) and computed tomography (CT) were used for 3-dimensional reconstruction of the LA. All patients underwent posterior wall isolation and pulmonary vein (PV) antrum and extra PV trigger ablations. Long-term follow-up was monitored by event recordings, 7-day Holter monitors and office visits. The mean age was 65 ± 10 years, 78% male, persistent AF 22 (44%), longstanding AF 28 (56%), LAD diameter 56.9 ± 7.8 mm, left ventricular ejection fraction (LVEF) 53 ± 14 and median AF duration 72 (49–96) months. At 12-month follow-up, 27 patients (54%) remained arrhythmia-free off antiarrhythmic drugs. Significant reduction in LAD at follow-up (≥10% reduction) was observed in 52% (26/50) of the total population and among the 63% (17/27) of recurrence-free patients. Magnitude of LA reduction was identically distributed among the persistent and longstanding persistent AF cohorts (16 ± 12% vs 14 ± 16%, respectively, P = 0.15). A significant 20% improvement in LVEF (from 53 ± 14 to 58 ± 9, P = 0.03) was found in the overall population. Improvement was noted in recurrence-free patients. No significant change in LVEDDI and LVESDI was noted. After adjusting for baseline risk factors in a multivariable model, a reduction in LAD was identified as a strong predictor of long-term success (beta = −11.1, P = 0.013). Preexisting LA scarring was associated with increased LAD (beta = 2.7, P = 0.023). No periprocedural or long-term complications were reported.

Conclusion: Our results show that atrial fibrillation ablation is effective in NPAF patients with severe LA enlargement and is associated with LA reverse remodeling and improvement in LVEF. (J Cardiovasc Electrophysiol, Vol. 24, pp. 1224-1231, November 2013)

atrial fibrillation, catheter ablation, left atrial enlargement, long-lasting persistent atrial fibrillation, pulmonary vein isolation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population and its prevalence increases with age. AF is associated with increased cardiovascular morbidity and mortality, including an increased risk of stroke.1,3 During the past decade, catheter ablation has become an established treatment for symptomatic, drug-refractory AF patients.4 Previous studies have shown the superiority of catheter ablation compared with present antiarrhythmic drug (AAD) therapy in the maintenance of sinus rhythm (SR).5-8 Several ablation techniques have been developed and now patient selection criteria have expanded to a larger number of subjects including those with persistent AF and significantly enlarged
left atrium (LA) and left ventricular (LV) dysfunction.\textsuperscript{9-14} Despite advances in ablation techniques, the success rate of the ablation procedure remains limited in persistent and longstanding persistent AF and repeat ablation is frequently required. Recently, an extensive ablation strategy including nonpulmonary vein (PV) triggers ablation in addition to PV isolation has been proposed to improve outcomes.\textsuperscript{15-17}

The natural history of AF tends to worsen with time. Sustained AF causes several changes in the atrial myocardium and results in electrical, contractile, and structural remodeling.\textsuperscript{18} The changes in electrical activation manifest as a shortening of atrial refractory periods and reduced conduction velocity that promote stabilization of the arrhythmia.\textsuperscript{19} The structural remodeling is characterized by left atrial enlargement, which reflects pathophysiologic processes in the atrium. Loss of atrial contractile function during AF increases atrial remodeling, which has not been studied in this setting.

Methods

Study Population

Fifty consecutive patients with symptomatic, drug-refractory, nonparoxysmal AF (persistent and longstanding persistent AF) and LAD $\geq$ 50 mm undergoing radiofrequency catheter ablation were included in this study. All patients underwent standard TTE at baseline and at 12 months postprocedure. Left atrial remodeling was analyzed on the structural level and based on the left atrial diameter. All patients underwent PV antrum and posterior wall isolation and extra PV trigger ablations. LA scarring was detected by a circular mapping catheter and by voltage mapping. The long-term outcome was monitored by event recordings, 7-day Holters and office visits. Data were collected in the AF database and was analyzed.

ACCF/AHA/HRS guidelines and the Venice Chart Consensus Statement\textsuperscript{4,34} define persistent AF as sustained episodes beyond 7 days, necessitating pharmacological or electrical cardioversion and longstanding persistent AF as continuous AF for more than 1 year.

Before procedures, all patients signed an informed written consent.

Ablation Procedure

All patients discontinued AADs at least 5 half-lives before their ablation procedure, while amiodarone was discontinued 4–6 months earlier. Transesophageal echocardiography was performed to exclude any atrial thrombi 48 hours before ablation. The details of our strategy of PV isolation (PVI) have previously been described.\textsuperscript{35} In brief, a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) and a 3.5 mm open-irrigated tip catheter (TermoCool, Biosense Webster) were used to record electrical activity and to ablate the PV antrum. The ablation was extended to the entire posterior wall, to the coronary sinus (CS) and to the left side of the septum to abolish all electrograms. Intracardiac echocardiography (ICE) was also used to guide transseptal punctures and to define the anatomy of the PVs. An esophageal probe was placed to monitor temperature and power during the procedure. Radiofrequency energy output was between 40 and 45 W with a maximum catheter tip temperature of 41 °C. At each site, radiofrequency energy was applied for 20 seconds. The maximum power was limited to 35 W when energy was delivered within the CS, and was interrupted if the esophageal temperature probe reached 39 °C. Three-dimensional (3D) reconstruction of the LA was created with the use of the CARTO system (Biosense Webster) or the NavX system (St. Jude Medical, St. Paul, MN, USA).

The endpoint of the procedure was the local elimination of all PV potential along the antra or inside the PVs. The antrum includes the entire posterior wall and extends anteriorly to the right PVs along the left septum. The superior vena cava (SVC) along the right atrium/SVC junction was also ablated if mapping revealed PV-like potentials. High output (30 mA) pacing was performed to exclude phrenic nerve capture.

During ablation, the categories of AF consisted of conversion to SR, organization into a regular atrial tachyarrhythmia (AT) with a similar cycle length in both atria and CS, or persistence of AF that required cardioversion. When AF organized into an AT, the latter arrhythmia was mapped and ablated.

CFAE ablation also was performed in the LA and CS. CFAEs were defined based on the following criteria: (1) atrial electrograms with 2 deflections or more or with fractionated baseline complexes with continuous activity over a 10-second recording time or (2) atrial electrograms with a cycle length of 120 milliseconds over a 10-second recording time.

The ablation catheter was required to be in a stable position when recording these electrograms.\textsuperscript{35} These areas were identified in the LA and the CS and were ablated to abolish the fractionated atrial electrograms. LA scarring was detectable by a circular mapping catheter, and by voltage mapping.\textsuperscript{36} Scarring was defined as an area with a bipolar voltage amplitude $<0.05$ mV. The area of scarred segments of the LA was expressed as a percentage of the total LA surface area using visual inspection. Three categories of LA scarring were identified based on percentage of scarred area: mild $<20\%$, moderate 20–60%, and severe $>60\%$.

Postablation Management and Follow-Up

After ablation all patients were discharged on warfarin with a target international normalized ratio between 2 and 3. Anticoagulation therapy was continued for at least 6 months. Previously ineffective AADs were also continued, except amiodarone. Patients visited the outpatient clinic at 3–, 6–
9-, and 12-month intervals. A 7-day Holter monitor was utilized every 3 months during the 12-month follow-up.

Procedural success was defined as the absence of AT/AF recurrence or atrial flutter after a blanking period of 3 months during the follow-up period.34 Thus, arrhythmia recurrence was defined as any AT, lasting ≥30 seconds, recorded after the blanking period with Holter monitoring, or when patient symptoms coincided with an arrhythmia that was documented by an event recorder, or 7-day Holter monitor.

Echocardiography

Two-dimensional TTE (2D-TTE) was performed before the ablation procedure and 12 months after ablation in all patients. The investigators were blinded to the study outcomes. The standard echocardiographic parameters were obtained on the basis of the American Society of Echocardiography (ASE) guidelines.37 LA diameter was measured at end-systole from the parasternal long-axis view (PSLAX). The image of the LV was defined in the parasternal long-axis, apical 2-chamber (A-2CH), and 4-chamber views (A-4CH), including LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), intraventricular septum (IVS), and posterior wall (LVPW). Then, left ventricular ejection fraction was assessed. Left ventricular end-diastolic and end-systolic diameters were indexed by body surface area (LVEDDI, LVESDI).

Primary outcomes included changes in LA diameter from baseline, before catheter ablation, to the end of the 12-month follow-up period. Total changes in LA size were analyzed separately to assess the effects of catheter ablation in patients with AF recurrence compared to patients free of AF. Changes in LV ejection fraction were analyzed in a similar way.

Statistical Analysis

Continuous data are described as mean ± standard deviation (SD) and as counts and percent if categorical. Paired t-tests were used to compare echocardiographic parameters at baseline and at 12-month follow-up periods. A multivariate general linear model was used for identifying significant predictors of LAD improvement (Cox regression was used for identifying predictors of AF recurrence) while controlling for clinically relevant covariates (age, gender, type of AF, baseline LVEF). Potential confounders were entered into the model based on known or expected clinical relevance, regardless of their statistical significance. All tests were 2-sided and a P-value <0.05 was considered statistically significant. Analyses were performed using (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Fifty consecutive patients with nonparoxysmal AF undergoing catheter ablation for AF presenting with large LA (diameter ≥50 mm) were included in the study. Most patients were male (78%), and the mean age was 65 ± 10 years. Patients with nonparoxysmal AF consisted of 22 (44%) persistent and 28 (56%) longstanding persistent AF. The reported median AF duration was 72 (49–96) months. The baseline LAD was 59.6 ± 7.8 mm and the LVEF was 53 ± 14%. The overall prevalence of hypertension was 64%, coronary artery disease 28%, and diabetes 18%. The baseline clinical characteristics and echocardiographic parameters are presented in Table 1.

Among the 20 (40%) who had preexistent LA scarring detected during LA mapping, the majority 12 (60%) had moderate scarring, while severe and mild scarring was seen in 6 (30%) and 2 (10%) patients, respectively. There were no differences between the baseline characteristics of patients with and without scarring.

Procedural Outcome

Acute procedural success was achieved in all 50 (100%) patients and all patients were in SR at the end of the procedure. AF terminated to SR or organized to a left atrial arrhythmia in 29 patients (58% of the cases). Among the 21 (42%) patients who had persistence of arrhythmia at the end of the procedure, SR was achieved by cardioversion.

The radiofrequency time was 72 ± 28 minutes and the fluoroscopy time was 85 ± 34 minutes. The mean procedure duration was 172 ± 65 minutes, presented in Table 1.

At the 12-month follow-up the success rate was 54% after a single procedure. Of the 50 patients, 27 patients remained in SR without AADs, while 23 patients presented with recurrent atrial flutter or tachycardia (19 patients) or atrial fibrillation (4 patients). The postablation 7-day Holter of these 23 patients showed no paroxysmal arrhythmia, while their recurrent AT persisted for the entire recording period.

No statistical correlation between success rate at follow-up and termination during ablation was found (P = 0.1). A stratified analysis showed that success rate was not significantly different across AF types; 13 (59%) with persistent AF and 14 (50%) with longstanding persistent AF were successful.
arrhythmia-free at the end of the follow-up period (log-rank $P = 0.49$).

During the 12-month follow-up period no periprocedural or long-term complications were reported.

**Change in LA Diameter and LVEF at Follow-Up**

Overall a significant change of LAD ($\Delta$LAD) was observed at the 12-month assessment; a $\geq 10\%$ reduction in LA size from baseline was noted in 26 of 50 (52\%) patients (from $56.9 \pm 7.8$ to $47.9 \pm 8.8$ mm, $P < 0.001$) and 17 of 27 (63\%) of those who were recurrence-free (from $57.6 \pm 9.5$ to $45.5 \pm 8.3$ mm, $P < 0.001$). Compared to patients with recurrence, a trend toward higher LAD reduction was observed in the recurrence-free patients ($\Delta$LAD $-11.8$ mm vs $-5.2$ mm, $P = 0.08$). Individual patient level change in LAD stratified by recurrence status is displayed in Figure 1. $\Delta$LAD was identically distributed across AF types ($16 \pm 12\%$) showed reduction in persistent AF versus $14 \pm 16\%$ in longstanding persistent population ($P = 0.15$).

However, the results did not show significant differences in preablation parameters of LAD and LVEF nor at 12 months after ablation between patients with preexisting scarring and without scarring. In patients with preexisting scarring, an $18 \pm 10\%$ reduction in LAD was observed in those with mild/moderate scarring compared to $16 \pm 10\%$ in patients with severe scarring ($P = 0.691$). There were no statistically significant differences between the 2 categories.

A substantial $20 \pm 6\%$ improvement in LVEF was reported in the overall population (baseline $53 \pm 14$ to $58 \pm 9$ mm, at 12 months, $P = 0.03$). Long-term procedure success was associated with a larger improvement ($P = 0.034$). No significant change in LVEDD and LVESD was noted (Table 2).

### Multivariable Analysis: Predictor of $\Delta$LAD and Arrhythmia Recurrence

A multivariate linear model analysis was performed using GLM procedure and predictors of LAD change were
assessed. After adjusting for important covariates such as age, gender, type of AF, and baseline LVEF, ablation success was found to be a significant predictor of LAD reduction (beta = −11.1, P = 0.003), whereas preexisting LA scarring was associated with an increase in LAD (beta = 2.7, P = 0.02). Cox regression was performed to identify predictors of AF recurrence. No significant association was observed between the predictors and the outcome, both at univariate level (Table 3) and after adjusting for the covariates.

Discussion

Main Findings

This is the first prospective clinical study where persistent and longstanding persistent AF patients with markedly enlarged LA were ablated for AF. Moreover, this study provides evidence of LA remodeling after catheter ablation in this setting.

Our finding has demonstrated that extensive catheter ablation is effective in nonparoxysmal AF patients with severe LA enlargement. The outcome is comparable to previous studies in chronic AF patients where the LA was less dilated. Furthermore, we observed LA reverse remodeling in more than half of the total population after 12 months of follow-up.

Clinical Outcome

Catheter ablation for persistent and longstanding persistent AF remains challenging and has a lower success rate than paroxysmal AF. PV isolation alone is an ineffective approach in most patients with longstanding persistent AF.5 However, PV electrical isolation remains a cornerstone of treatment for persistent AF patients, but additional targets aimed at further AF substrate modification are required. This suggests that the underlying mechanism is different between paroxysmal and persistent groups.15–17

In earlier studies, Pappone et al. demonstrated 68% success in patients with permanent AF using a single ablation procedure and after 10-month follow-up. Similarly, Oral et al. presented 74% success in persistent AF patients after a 1-year follow-up.11,38 In a systematic review published by Brook et al., it was found that a single procedure with substrate ablation techniques for persistent and/or longstanding persistent AF are comparable and resulted in a mean success rate of 47%.17

In our study, the success rate was 54%, indicating that extensive PV isolation of the antrum and posterior wall, associated with non-PV trigger ablation, resulted in more than half of the patients remaining in SR at a 12-month follow-up. Our data is comparable to recently published data by Parikh et al., reporting a 52% success rate in the persistent AF group at 14 months.25 Furthermore, McCready et al. obtained a 32% success rate in the persistent AF group at 13 months with a single ablation using a similar ablation approach to ours. The success rate increased to 64% with 1.5 ablations.26

However, there was an important difference between our study and the aforementioned studies. In this study, we involved only patients who had more than 50 mm LA diameter whereas in previous series the LA diameter was either 40 mm or less, or patients had an average LA size of 47 mm.39 This is much less than the LA size of our study, where the mean dimension was 56.9 ± 7.8 mm.

Furthermore, our group included predominately longstanding persistent AF, which is considered a more challenging group of patients.

Changes in LA

Persistent AF causes structural changes in the LA.18 LA remodeling is an adaptive response of the cardiomyocytes against different stressors.40 The magnitude of structural change could reflect the duration of the external agents such as AF and ischemia, or volume and pressure overload of the atria. It is known that LA dilatation is a hallmark of LA structural remodeling.18,41

Earlier studies demonstrated reversal of LA remodeling after catheter ablation of AF.11,32,38 Similar to these studies, Beukema et al. reported significant reduction in LAD in patients with SR compared to an increase in LAD in patients with AF recurrence after ablation at 14 months follow-up (from 44 to 40 mm in persistent AF).27 Tops et al. also reported a significant decrease in LA size and volume in patients with successful ablation within the first 3 months.28 Importantly, some reports described significant reduction in the LA dimension not only in patients who remained in SR during the follow-up, but also with AF recurrence.29–31 Reant et al. found a significant decrease in LA size in AF free patients (11%) at 1-year follow-up. In addition, patients with arrhythmia recurrence positive changes in LA and LV remodeling were also observed.11,29

These results are consistent with our findings in patients with severe LA enlargement, which were not included in previous series. In our study, all patients demonstrated a significant reduction in LA size (≥10%) year follow-up, but most of them were without AF recurrence and the magnitude of reduction was higher in this group. In addition, LVEF improvement was observed in the total population. The explanation is likely multifactorial, but it is possible that extensive catheter ablation may decrease the AF burden even though there may be long-term recurrence.

Of note, the change in LA diameters did not show any important differences between the persistent and the longstanding persistent AF groups. It seems that persistent arrhythmias in either group cause similar structural changes with time and could lead to similar clinical manifestations such as tachycardia-induced atrial cardiomyopathy.41

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99 (0.95–1.03)</td>
<td>0.73</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.1 (0.43–2.79)</td>
<td>0.84</td>
</tr>
<tr>
<td>AF type (longstanding persistent)</td>
<td>1.5 (0.64–3.42)</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI</td>
<td>1.06 (0.92–1.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.03 (0.44–2.39)</td>
<td>0.94</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.02 (0.71–1.41)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.2 (0.67–2.63)</td>
<td>0.67</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.18 (0.75–2.18)</td>
<td>0.77</td>
</tr>
<tr>
<td>LVEDD</td>
<td>1.08 (0.57–2.05)</td>
<td>0.81</td>
</tr>
<tr>
<td>LVESD</td>
<td>1.02 (0.59–1.76)</td>
<td>0.95</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.3 (0.84–1.76)</td>
<td>0.68</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.86 (0.95–1.45)</td>
<td>0.57</td>
</tr>
<tr>
<td>LVPWd thickness</td>
<td>1.31 (0.64–1.87)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

LVEDD = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVPWd = left ventricular posterior wall thickness at end diastole.
Therefore, the type of persistent AF did not directly influence the reduction of LA dilatation associated with the procedural outcome.

Furthermore, LA scarring is an important intraprocedural predictor that impacts on procedural outcomes. LA scarring is representative of the tissue pathology underlying AF. AF is associated with diffuse LA fibrosis and a reduction in endocardial voltage. Persistent AF is more likely to be associated with cardiac heart disease, which further increases atrial fibrosis. Verma et al. reported that preexisting scarring is an independent factor of AF recurrence and Wylie et al. found that the reduction of LA size and systolic function are strongly correlated with the volume of LA scarring. The correlation between scar identified by 3D mapping system and poorer outcome following AF ablation when limited to PV isolation alone was first reported by Verma et al.

Recent data further suggested that LA fibrosis (scar) detected by MRI is independently associated with stroke events and predicts ablation outcome in AF patients.

We found in our study that preexisting scarring was associated with increased LAD by multivariate analysis. However, patients with LA scarring did not show significant differences in the decrease of LAD compared to patients without scarring at 12 months. In this series, patients in the severe scar category were few (6/20) and most of them had moderate scarring that did not have a strong influence on the changes in LA dimension in a markedly enlarged atrium. Importantly, ablation success was found to be a significant predictor of LAD reduction by multivariate analysis. Many studies demonstrated that LA size is a strong predictor of AF recurrence after ablation and cardioversion. Therefore, it is important to know whether catheter ablation is useful in treating nonparoxysmal AF patients with markedly enlarged atria.

Study Limitation

We obtained the measurement of LA size by 2D-TTE from M-mode dimension, which is normally used in everyday clinical practice. However, ASE has recommended quantification of LA size from apical 4-chamber view, which is more accurate. In this study, LA scar was defined based on the amplitude of atrial electrogram. Using MRI to determine LA scar and to evaluate LAV could be another option, but this data was not available in all the patients.

Conclusions

Our results show that atrial fibrillation ablation is effective in nonparoxysmal AF patients with severe LA enlargement, and is associated with LA reverse remodeling and improves LV EF. Our results are promising and may encourage other electrophysiologists to treat this group of patients with ablation. Many conditions are associated with LA remodeling and the mechanisms underlying atrial remodeling and reverse remodeling are not yet clear. Further research is required to develop our understanding.

References


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