Successful Radiofrequency Ablation in Patients With Previous Atrial Fibrillation Results in a Significant Decrease in Left Atrial Size

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Background—The objective of the present study was to evaluate the relation between freedom from atrial fibrillation (AF) and left atrial (LA) size in patients who underwent circumferential pulmonary vein (PV) isolation and LA ablation.

Methods and Results—One hundred five consecutive patients with symptomatic and drug-refractory paroxysmal or persistent AF were included in the present study. The mean age was 52.9 years (range, 27 to 75 years); 74 patients (70%) were male. Paroxysmal AF was present in 52 (49.5%) and persistent AF in 53 (50.5%) patients. Mean AF duration was 6.0 ± 5.1 years in the paroxysmal AF group and 7.6 ± 6.0 years in the persistent AF group. A 3D electroanatomic map of the LA including the PV ostia was constructed with a nonfluoroscopic navigation system (Carto, Biosense Webster). Left- and right-sided PVs were encircled by continuous radiofrequency ablation lines. We performed 128 ablation procedures in 105 patients, ie, 23 redo procedures. The mean long-term follow-up duration was 14.6 ± 4.9 months (range, 6 to 24 months). Sinus rhythm was present in 45 patients (86.5%) in the paroxysmal AF group and in 41 patients (77.3%) in the persistent AF group at the latest follow-up. Six months after ablation, LA dimension in the persistent AF subjects who remained in sinus rhythm decreased from 44.0 ± 5.8 to 40.4 ± 4.5 mm (range, 31 to 51 mm). In contrast, in patients with recurrences of AF, LA dimension increased from 45 ± 6.5 to 49 ± 5.4 mm (range, 32 to 59 mm). In the successfully treated paroxysmal AF group, LA dimension decreased from 40.5 ± 4.4 to 37.5 ± 3.5 mm (P < 0.01).

Conclusions—In radiofrequency ablation of AF using an electroanatomic approach, there is a statistically significant relationship between medium-term procedural success and LA size: persistent sinus rhythm is associated with reduced and recurrent AF with increased LA dimensions. (Circulation. 2005;112:2089-2095.)

Key Words: atrium • catheter ablation • fibrillation

Atrial fibrillation (AF) is the most common arrhythmia, and its incidence likely to rise because of the increasing age of the population.1 In the past decade, surgical and percutaneous catheter-based therapies have been developed.2–14 Haissaguerre et al9 demonstrated that paroxysmal AF can be initiated by rapid ectopic rhythms originating in sleeves of LA myocardium extending around the pulmonary veins (PVs). Segmental ostial catheter ablation has been shown to electrically isolate the PVs from the left atrium (LA) and to cure paroxysmal AF in most patients.9–12 As demonstrated by Pappone et al,13 an alternative to this electrophysiologically guided approach is the circumferential encircling of the PV ostia guided by a 3D electroanatomic navigation system, the so-called electroanatomic approach (EAA). A recent study demonstrated that catheter ablation based on the EAA was more effective than the electrophysiological approach in eliminating paroxysmal AF.14

A relation between atrial tissue mass and AF had been proposed by Garrey15 as early as 1914, and Henry et al16 demonstrated a significant relationship between echocardiographically determined LA size and the development of AF. Kamata et al17 showed that LA size was an independent preditor of sinus rhythm (SR) restoration after the Maze procedure. The aim of our study was to evaluate the relation between freedom from AF and LA size reduction in patients who underwent circumferential PV isolation and LA ablation.

Methods

Study Patients
One hundred five patients with symptomatic paroxysmal or persistent AF underwent radiofrequency (RF) catheter ablation and were enrolled in this study (Table 1). Patients had a mean age of 52 ± 9.5 years (range, 27 to 75 years); 74 patients (70%) were male. Paroxysmal AF was present in 52 patients (49.5%); persistent AF...
was seen in 53 patients (50.5%). Mean AF duration was 6.0 ± 5.1 years in the paroxysmal AF group and 7.6 ± 6.0 years in the persistent AF group. Patients were refractory to 2.7 ± 0.7 antiarrhythmic drugs (range, 2 to 6). At the time of inclusion, 17 patients (16%) were on amiodarone. Hypertension was present in 27 patients (26%); diabetes mellitus was seen in 5 patients (4.8%). The mean LA diameter was 42 ± 5 mm (range, 31 to 59 mm); LA diameter was 40.5 ± 4.4 mm in the paroxysmal group and 44.0 ± 5.8 mm in the persistent group measured by transthoracic echocardiography in the parasternal long-axis (PSLAX) window. The LA diameter in the A-4CH view is summarized in Table 1. The mean left ventricular ejection fraction was 54 ± 4.8%.

### Study Protocol

Patients were required to take international normalized ratio–guided oral anticoagulation for at least 4 weeks, followed by subcutaneous fractionated heparin 3 to 5 days before the procedure. Antiarrhythmic drugs, including amiodarone, were not discontinued. Transesophageal echocardiography was performed 1 day before the procedure to exclude LA intracavitary thrombus and to assess interatrial septal anatomy. All catheters were introduced through a femoral vein. A steerable quadripolar 6F electrode catheter was placed in the coronary sinus, and a nonsteerable quadripolar catheter was placed in the right ventricular apex. The LA was approached by a standard transseptal puncture using a Brockenbrough needle and a Precath sheath. Heparin was titrated to maintain an activated clotting time of 250 to 350 seconds. Bipolar and unipolar electrograms were filtered at band-pass settings of 30 to 500 and 0.01 to 775 Hz, respectively, and recorded digitally (Bard EP Systems Inc). In all patients, cardiac enzymes (creatine phosphokinase-MB, troponin T) were determined 16 hours after ablation.

### LA Ablation Procedure

A 3D electroanatomic map of the LA, including the PV ostia, atrial appendage, and mitral valve annulus, was constructed with a quadripolar deflectable navigator catheter (Navistar, Biosense-Webster) and a nonfluoroscopic navigation system (CARTO, Biosense-Webster).18,19 Left- and right-sided PVs (Figure 1) were encircled with continuous RF ablation lines ≥ 1 cm from the ostia of the PVs. Anterior to the left-sided PVs, in the narrow rim of tissue between the PVs and the LA appendage, the ablation line was created as far from the ostia as local anatomy allowed. In addition,
in 42 patients, an ablation line was created from the inferior portion of the left-sided circumferential lesion to the posterior lateral part of the mitral annulus, ie, the LA isthmus line. In some patients, a linear ablation line along the posterior LA was created to connect the right- and left-sided PV encirclings. A right-sided cavitricuspid isthmus ablation was performed in patients with both AF and typical atrial flutter.

RF energy was delivered in a unipolar mode to a cutaneous patch via the distal electrode of the ablation catheter. An 8-mm-tip deflectable catheter (Navistar, Biosense-Webster) or a deflectable catheter with a 3.5-mm irrigated tip with saline cooling of the ablation electrode (Navistar, Biosense-Webster) was used. The RF generator (Stockert, Biosense-Webster) was programmed in the temperature-control mode with power set at 80 W and maximum cutoff catheter tip temperature set at 60°C for the 8-mm catheter. During irrigated-tip ablation (n=32 of the 128 total procedures), normal saline (0.9%) was infused at a rate of 15 to 20 mL/min during RF delivery in the temperature-control mode with power set at 50 W and a temperature cutoff of 50°C. Between RF applications, a flow rate of 2 mL/min was used to maintain catheter cool channel patency. RF lesions were tagged by the CARTO system, and RF current was applied for up to 20 seconds or until the local electrogram amplitude was reduced by >80% or to ≤0.5 mV.

After completion of ablation lines, remapping of the atria was performed during SR or coronary sinus pacing, and a bipolar voltage map was created in and around the area of ablation. The preablation map used as an anatomic starting point. Bipolar electrogram amplitude ≤0.5 mV in the encircled areas was considered proof of adequate ablation. To ensure as complete a line of block as possible, additional RF lesions were applied at sites with a local bipolar electrogram amplitude >0.5 mV.

Postablation Management and Follow-Up

After ablation, patients were hospitalized for at least 24 hours and monitored telemetrically. Low-molecular-weight heparin was given for 1 to 3 days, and acenocoumarol was given for at least 3 months. Antiarrhythmic drugs (class I or III) were continued during the first 3 months and gradually tapered. Holter monitoring was performed at 3-, 6-, and 12-month intervals. All patients visited our outpatient clinic at 3-, 6-, and 12-month intervals. A standard 12-lead ECG was recorded at each outpatient visit. Spiral CT or MRI (MR angiography) of the PVs was performed 3 months after RF ablation to determine atrial size and PV ostial dimensions, respectively.

Echocardiography

Transesophageal echocardiography was performed before ablation and 6 months after ablation in all patients. LA diameter was determined in the PSLAX view. LA medial-lateral size and superior-inferior size were measured in the apical 4-chamber view (A-4CH). Pulsed-wave Doppler flow velocity across the mitral and tricuspid valves was determined. Furthermore, valvular abnormalities, left ventricular wall motion analysis, and left ventricular ejection fraction were assessed.

Statistical Analysis

Continuous variables were expressed as mean±SD. Kaplan-Meier curves were produced to obtain AF-free survival probabilities. The data showed a Gaussian distribution. Arithmetic means were compared through the use of Student’s paired-sample t test. For LA diameter data, repeated-measures ANOVA was used. In case of troponin T, an independent-sample t test was performed. Statistical significance was defined as 2-sided values of P<0.05.

Results

We performed 128 ablation procedures in 105 patients, ie, 23 redo procedures. In all patients, the right and left pulmonary venous ostia were ablated circumferentially. In 72 procedures, an additional ablation line extending from the mitral valve annulus to the junction of the left inferior PV (MV-LIPV) was created. The MV-LIPV ablation line was created in 42 patients with persistent AF and in 30 patients with paroxysmal AF. In 26 patients in the paroxysmal group and 32 patients in the persistent group, an ablation line was created over the posterior LA wall between the right- and left-sided PVs. A right-sided cavitricuspid isthmus ablation was performed in 44 patients who also had a common type of atrial flutter. The mean procedure time was 211±56 minutes (range, 170 to 400 minutes), and the mean fluoroscopy time was 57±25 minutes (range, 30 to 146 minutes). One patient developed reversible coronary spasm during the ablation procedure without further sequelae.

Cardiac Rhythm

Cardiac Rhythm at Discharge

Table 2 summarizes cardiac rhythm at discharge and at the latest follow-up. The ECG at discharge showed SR or AV sequential pacing in 89 patients (85%) and AF in 16 patients (15%). In 101 of 105 patients, antiarrhythmic drugs were continued during the first 3 months after ablation. Forty-two patients were on sotalol, 22 were on amiodaron, 26 were on flecainide, and 11 were on a combination of antiarrhythmic drugs.

Long-Term Follow-Up

Figure 2 shows the RF ablation results. The mean long-term follow-up duration was 14.6±4.9 months (range, 6 to 24 months). In 23 of 105 patients, we performed a second RF ablation procedure as a result of recurrent episodes of AF 3 to 6 months after the first procedure. In the paroxysmal AF group, SR was present in 45 patients (86.5%) at the latest follow-up, whereas in the persistent AF group, SR was present in 41 patients (77%) at the latest follow-up. A Kaplan-Meier curve of AF/patricular flutter–free survival in the paroxysmal and persistent AF patients is shown in Figure 3. During long-term follow-up, 57 of 87 patients (66%) in persistent AF after ablation were free of antiarrhythmic drugs. Twenty patients (23%) with persistent SR after ablation were still on 1 antiarrhythmic drug and 10 patients (12%) were on 2 antiarrhythmic drugs at the latest follow-up. Of these, 5 patients were on amiodaron.

PV stenosis defined as a diameter reduction >50% was not observed in any patient, which is in accordance with previous reports of the EAA.13,18,19 The MV-LIPV ablation line was not associated with a higher success rate in the persistent or paroxysmal AF group. Five of the 6 patients with LA flutter had an MV-LIPV ablation line.

TABLE 2. Cardiac Rhythm at Discharge and Latest Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>After Discharge, n (%)</th>
<th>Latest Follow-Up, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>79 (75)</td>
<td>76 (72.4)</td>
</tr>
<tr>
<td>DDOR pacing</td>
<td>4 (3.8)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>AAR pacing</td>
<td>6 (5.7)</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>WIR pacing with underlying AF</td>
<td>5 (4.8)</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>AF</td>
<td>11 (10.5)</td>
<td>14 (13.3)</td>
</tr>
</tbody>
</table>

DDOR indicates AV sequential rate responsive; AAR, atrium-based rate responsive; and WIR, ventricle-based rate responsive. n=105.
Biochemical Evidence of Debulking
We found that patients with SR at long-term follow-up had a higher troponin T (1.6±0.47 μg/L) determined 16 hours after ablation, whereas patients who remained in AF at long-term follow-up had a significantly lower troponin T (0.87±0.33 μg/L; P<0.01).

LA Dimension
Baseline LA dimension in the total study group was 42.1±5.4 mm (range, 31 to 59 mm) in the PSLAX view and 62±8.1 and 43±6.5 mm in the A-4CH view. The baseline LA dimension in the persistent AF group was 44.0±5.8 mm (range, 32 to 59 mm) in the PSLAX view and 64±8.6 mm (range, 50 to 95 mm) and 47±6.7 mm (range, 30 to 63 mm) in the A-4CH view. The baseline LA diameter in the paroxysmal AF group was 40.5±4.4 mm (range, 31 to 49 mm) in the PSLAX view and 59±7.9 mm (range, 45 to 78 mm) and 44±6.1 mm (range, 28 to 54 mm) in the A-4CH view. Baseline PSLAX LA diameter in the persistent AF group was larger compared with paroxysmal AF patients (P=0.0021). The difference in the A-4CH view was not calculated because this view lacks the reproducibility of the PSLAX. In the paroxysmal group, there was no difference in LA size before circumferential ostial pulmonary vein isolation when measured in SR or AF (40.6±4.7 versus 41.1±5.7 mm; P>0.05). In the persistent group, there was a difference in LA size before circumferential ostial pulmonary vein isolation when measured during SR or AF (44.4±5.8 versus 47.6±4.7 mm; P=0.04). Figures 4 and 5 show the changes in LA dimension measured in the PSLAX view 6 months after ablation. The Data Supplement Figures I and II (found at http://circ.ahajournals.org/cgi/content/full/112/14/2089/DC1) show the changes in LA dimension measured with the A-4CH view 6 months after ablation. The decrease in LA size of successfully ablated patients is statistically significant (P<0.01) regardless of whether the preablation measurement was during SR or AF.

The x-y plots in Figures 4 and 5 illustrate the changes in LA dimension measured with the PSLAX view 6 months after ablation. Data Supplement Figures I and II show the changes in LA dimension measured with the A-4CH view 6 months after ablation.
in LA dimension measured with the A-4CH view 6 months after ablation. The LA dimension in the persistent AF group who remained in SR decreased from 44.0±5.8 to 40±4.5 mm (range, 31 to 51 mm; P<0.01) in the PSLAX view and from 64±8.6 and 47±6.7 to 59±7.8 and 43±6.5 mm in the A-4CH view (P<0.01), whereas in patients with recurrences of AF during follow-up, LA dimension increased significantly from 45±6.5 to 49±5.4 mm (range, 32 to 59 mm; P=0.001) in PSLAX and from 69±7.6 and 49±6.5 to 75±8.2 and 53±6.5 mm (P<0.01) in the A-4CH view. In the persistent AF group, the difference in LA diameter before ablation versus 6 months after ablation was statistically significant (P=0.001). In the paroxysmal AF group, the LA dimension decreased from 40.5±4.4 to 37.5±3.5 mm (P<0.01) in PSLAX and from 59±7.9 and 44±6.1 to 54±7.1 and 41±5.9 mm (P<0.01) in A-4CH. In contrast to the persistent AF group patients, there was no increase in LA dimension in the paroxysmal AF group with recurrent AF after ablation (SR, 40.1±4.4; AF, 40.7±5.8 mm; P>0.05).

Discussion

Main Findings

We describe the long-term results of 128 procedures in a cohort of 105 highly symptomatic patients with paroxysmal or persistent AF resistant to class I and III antiarrhythmic drugs who underwent circumferential ostial RF ablation of the PVs. The outcome is comparable to previous reports by Pappone et al,13,18,19 and Oral et al,14 but we found that in patients with persistent SR after ablation, LA dimension decreased significantly and that in patients with persistent or permanent AF after ablation, LA size increased significantly. To the best of our knowledge, this is the first catheter ablation study to report a statistically significant relationship between LA size and medium-term procedural success: Recurrent AF was associated with larger LA dimensions. There is increasing experimental and clinical evidence that atrial size is a marker of vulnerability for AF, with increased size associated with this arrhythmia.
Garrey\textsuperscript{15} proposed in 1914 that the persistence of AF was directly proportional to the size of the tissue mass. Moe's\textsuperscript{20} multiple wavelet hypothesis, which was experimentally proven by Allessie et al.,\textsuperscript{21} proposes that a critical number of wandering wavelets is needed for perpetuation of AF, and one may speculate that an enlarged atrium would be able to accommodate more circulating wave fronts, thereby stabilizing AF. Kamata et al.\textsuperscript{17} and Chen et al.\textsuperscript{22} showed that LA size reduction and right atrial and LA size reduction were independent predictors of stable SR after the surgical Maze procedure in patients with structural heart disease.

An important finding in our study was that the extent of troponin T increase 16 hours after ablation was correlated with the medium-term arrhythmia-free outcome. Previous studies have demonstrated that the extent of myocardial damage incurred by RF ablations can be quantified by using cardiospecific biochemical markers such as troponin T.\textsuperscript{23,24} In the present study, the patients with persistent SR had significantly higher troponin T levels compared with patients who had recurrent AF after ablation, suggesting that "biochemical proof" of atrial debulking may play a role in the persistence of SR after catheter ablation of AF. Therefore, electric mass reduction could be considered an integral part of the EAA and may play an important role in its success.

Medium-Term Decrease in LA Size

Remodeling of the AF substrate appears to play an important role in the medium-term, and probably long-term, success. The mechanism of medium-term reversion of LA dilation after ablation in patients who maintain SR has not been delineated yet. Recent studies have demonstrated that during atrial fibrillation upregulation and downregulation of tissue-specific metalloproteinas\textsuperscript{25,26} cause extracellular matrix remodeling. Allessie et al.\textsuperscript{27} showed that the reduction in atrial contractility during AF may enhance atrial dilatation. In a Langendorff-perfused rabbit heart model, it was shown that dilatation of the atria was a major determinant for the vulnerability of AF and closely related to shortening of the atrial effective refractory period.\textsuperscript{28} Kalifa et al.\textsuperscript{29} elegantly showed in an experimental setup that the sources of rapid atrial activation during stretch-related AF were located in the PV-LA junction and that spatiotemporal organization correlated with intra-atrial pressure.

Previous studies\textsuperscript{30,31} in patients who underwent serial electrical cardioversions showed that restoration of SR reverts the process of LA and right atrial enlargement. A study of atrial function 0.6 to 4.2 years (median, 2.86 years) after surgical linear endocardial RF ablation showed that atrial size decreased in patients in whom SR was restored but increased in those in whom AF persisted, despite preoperative LA size being similar in both groups.\textsuperscript{32} From these experimental and clinical studies, it appears that LA size and size reduction are important markers for clinical success, and our data corroborate these findings.

Limitations of the EAA

Currently, there are no well-defined acute postprocedural electrophysiological parameters that predict long-term success. Lesion completeness, as assessed by peak-to-peak bipolar electrograms <0.1 mV inside the encircled areas, a delay of >30 ms across the ablation line, and pacing maneuvers, bears no significant relation with freedom from AF during follow-up.\textsuperscript{19,33} However, the postablation low-voltage area was larger in patients without AF recurrence compared with patients with AF recurrence during follow-up.\textsuperscript{19} Troponin T may act as a biochemical marker for the extent of electrical mass reduction by RF ablation, and this study finds troponin T concentration 16 hours after ablation to be correlated to procedural midterm success. This finding is in conjunction with the postablation low-voltage area being higher in patients without AF recurrence.

The definition of success poses a problem and is in need of revision. Unless the patient has a pacemaker, the burden of atrial arrhythmia cannot be determined reliably. Silent AF is a well-appreciated phenomenon, and patient history cannot always be trusted. Currently, the best we can do is to equip the patient with an event recorder and to record quality-of-life questionnaires.

Remaining Issues

Some unresolved issues remain. For example, does catheter ablation of AF prolong life? Until now, only 1 nonrandomized study has shown a significant decrease in all-cause mortality in patients who underwent catheter ablation compared with medically treated patients.\textsuperscript{34} No randomized studies demonstrate substantial prognostic benefit from PV isolation.

The question of whether these ablation procedures cure patients of AF or delay the onset of permanent AF remains unanswered. This study showed decreased LA size to be associated with midterm procedural success. We hypothesize that earlier treatment with catheter-based therapies may yield better results by preventing atrial dilatation. Earlier efforts to prevent atrial dilatation might reduce AF.

References


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