Clinical Characteristics of Patients With Persistent Atrial Fibrillation Successfully Treated by Left Atrial Ablation

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Background—We sought to characterize patients with persistent atrial fibrillation (AF) who were successfully treated by ablation targeting the left atrium (LA).

Methods and Results—Ninety-three patients (58±10 years, 79 male) undergoing ablation of persistent AF were studied. During the first procedure, ablation was performed in the LA and coronary sinus, consisting of pulmonary vein isolation, linear ablation, and electrogram-based ablation. During follow-up after the first procedure, 35 patients (38%) remained free from tachyarrhythmias, 27 patients (29%) had atrial tachycardia, and 31 patients (33%) had AF. Duration of persistent AF according to medical history and whether AF was terminated by ablation were associated with the outcome (P=0.005, P=0.004, respectively). In multivariate analysis, the duration of persistent AF was the only predictor of freedom from AF (sinus rhythm or atrial tachycardia) (odds ratio, 0.80 for a 1-year increase; 95% confidence interval, 0.67 to 0.95; P=0.01). Of 31 patients in whom AF recurred during follow-up, electrogram-based ablation was performed in the right atrium in 26 patients. Sixteen of those patients (62%) remained free from AF during follow-up. Overall, 82% of patients were free from any tachyarrhythmias at 2-year follow-up after a median of 2 procedures.

Conclusions—Patients with shorter duration of persistent AF were more likely to be free from AF by LA ablation. Right atrial ablation may provide incremental efficacy in patients who are refractory to LA ablation. (Circ Arrhythm Electrophysiol. 2010;3:465-471.)

Key Words: ablation • atrium • fibrillation • tachyarrhythmias

Catheter ablation of atrial tissue aimed at modification of the fibrillatory substrate is commonly added to pulmonary vein (PV) isolation for the treatment of persistent atrial fibrillation (AF). However, the location of the fibrillatory substrate can differ greatly from patient to patient. Stepwise ablation aimed at terminating persistent AF is an ablation strategy that allows individualized treatment and potentially reduces the total amount of atrial tissue damage and procedure duration.1 Importantly, this stepwise ablation strategy is also associated with excellent clinical outcome.

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Mapping of human AF suggests that the left atrium (LA) is the driving chamber of AF.2,3 This has led to targeting of the LA for AF substrate modification. Whether ablation of the right atrium (RA) confers any incremental benefit is a matter of ongoing debate.4–8 For example, it has been reported that biaatrial ablation was required in 10% to 26% of patients to achieve termination of AF with ablation.6,7 However, it is not unusual for sinus rhythm (SR) to be maintained after cardioversion despite failure to achieve termination of AF by ablation. In such patients, biatrial ablation would result in unnecessary atrial tissue damage and longer procedures. It is not known at this time which patients can be successfully treated by modification of the LA substrate versus modification of both LA and RA substrate. The primary goal of our study was to characterize patients who were free from AF after substrate modification in the LA and coronary sinus (CS). A secondary goal was to investigate whether RA ablation produced incremental benefit in patients in whom AF recurred after LA/CS ablation.

Methods

Study Population

Ninety-three patients (58±10 years, 79 male) with drug-refractory symptomatic persistent AF undergoing catheter ablation were studied. Patients had to have had AF continuously for more than 1 month before the ablation to be enrolled. Eighteen patients (20%) had had an electric cardioversion previously. Median duration of the persistent AF was 1 year (1st to 3rd quartile, 0.38 to 4.0 years). Mean LA
were identified, ablation was continued to achieve isolation of the PVs and conduction block of all of the linear lesions were validated less of whether or not AF was terminated by ablation, isolation of the mitral isthmus linear ablation was performed in all patients. Regarding the patients during the procedure. After restoration of SR, cavotricuspid isthmus linear ablation was performed in the LA or RA, an electric cardioversion was performed.

Follow-Up
After the ablation, 100 mg of flecainide and 2.5 to 5.0 mg of bisoprolol were administered for 2 months. After that period, all antiarrhythmic drugs were discontinued. Discovery of persistent or paroxysmal episode of AF/AT continuous for ≥30 seconds after the 2-month blanking period was regarded as a recurrence of tachyarrhythmia, and a repeat procedure was performed.

ECG and 24-hour Holter monitoring were performed monthly beyond the blanking period up to 6 months. After those 6 months, the patients were followed every 3 to 6 months in our outpatient clinic, and an ECG was recorded each time. Patients who had symptoms were provided with a portable ECG monitor (Omron, Kyoto, Japan) for event monitoring for the duration of our study. Asymptomatic patients who had no ECG evidence of AT or AF were categorized as SR, although infrequent occult tachyarrhythmia can never be ruled out.

Repeat Ablation
If patients were in SR, atrial burst pacing was performed to induce AF or AT. In patients with spontaneous or induced AF, resolation of the PVs and ablation of the remaining complex electrograms in the LA/CS were performed first. If AF continued after the LA ablation, electrogram-based ablation was performed in the RA. To avoid injury to the sinus node and AV node, the high posterolateral wall of the RA and the right anterosuperior to the tricuspid annulus were not ablated. The procedural end point was termination of AF and restoration of SR as in the first procedure. If AF continued after ablation of all sites displaying complex electrograms in the both atria, an electric cardioversion was performed.

In patients with AT, ablation was performed for all of the ATs that were inducible by atrial burst pacing. A CARTO system was used for mapping the ATs, as previously described.9 The procedural end point was noninducibility of ATs.

Statistical Analysis
The data are presented as mean±standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed variables. Continuous variables grouped by the outcome of the first ablation were compared using 1-way ANOVA if normally distributed or Kruskal-Wallis test if skewed. Continuous variables grouped by the overall outcome were compared using independent-samples Student t test if normally distributed or Wilcoxon rank-sum test if skewed. A comparison of proportions was performed by a χ² test. For comparison of AF cycle length between before and after ablation, the paired Student t test was used. Multiple logistic regression analysis was used to identify the predictors of elimination of AF and freedom from tachyarrhythmias after the first ablation. Receiver-operator characteristic curves were used to determine the duration of persistent AF that provided the best sensitivity and specificity for elimination of AF after the first ablation. Freedom from tachyarrhythmias was analyzed by the Kaplan–Meier method. A value of P<0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS 15.0.

Results
First Procedure
The PVs were isolated in all 93 patients, with RF duration of 42±13 minutes. AF terminated in 2 patients (2%) during the PV isolation. The remaining 91 patients (98%) underwent electrogram-based ablation in the LA and CS, with RF
Takahashi et al LA Ablation for Persistent AF

Table 1. Clinical, Echocardiographic, and Electrophysiologic Variables Grouped by Outcome of the First Procedure

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Freedom From Arrhythmias (35 Patients)</th>
<th>Recurrence of AT (27 Patients)</th>
<th>Recurrence of AF (31 Patients)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59±9</td>
<td>58±10</td>
<td>59±10</td>
<td>0.9</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>30 (86)</td>
<td>22 (81)</td>
<td>27 (87)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>11 (31)</td>
<td>12 (46)</td>
<td>13 (42)</td>
<td>0.5</td>
</tr>
<tr>
<td>Median duration of persistent AF at enrollment, y, 1st to 3rd quartile</td>
<td>0.6 (0.25–1.2)</td>
<td>1.2 (0.5–4)</td>
<td>3 (0.5–7)</td>
<td>0.005</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>43±6</td>
<td>46±5</td>
<td>44±5</td>
<td>0.09</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>59±11</td>
<td>58±12</td>
<td>63±8</td>
<td>0.13</td>
</tr>
<tr>
<td>AF termination by ablation, n (%)</td>
<td>16 (46)</td>
<td>6 (22)</td>
<td>3 (10)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

AF cycle length in LA

| Baseline, ms, n=93 | 143±13 | 140±15 | 137±15 | 0.26 |
| Precardioversion, ms, n=68 | 165±18 | 163±25 | 159±19 | 0.6   |
| Increase, ms, n=68 | 24±15  | 25±24  | 20±13  | 0.6   |

AF cycle length in RA

| Baseline, ms, n=93 | 145±15 | 145±20 | 139±15 | 0.3   |
| Precardioversion, ms, n=68 | 150±17 | 152±25 | 149±23 | 0.9   |
| Increase, ms, n=68 | 10±13  | 11±16  | 8±7    | 0.7   |

duration of 29±12 minutes. Linear ablation at the LA roof and mitral isthmus was performed in 81 (87%) and 79 (85%) patients with RF duration of 8±3 and 14±7 minutes, respectively. Complete conduction block was achieved in 56 (69%) and 48 (61%) patients for the roof line and mitral isthmus line, respectively. SVC isolation was performed in 7 patients (8%), and complete isolation was achieved in all with RF duration of 8±4 minutes. The total procedure duration was 250±51 minutes.

Overall, AF was terminated by ablation in 25 patients (27%), and the remaining 68 patients (73%) were all successfully electrically cardioverted. Of the 25 patients with AF termination by ablation, AF was converted into AT in 17 patients (68%) and directly into SR in the remaining 8 patients. SR was restored by ablation of the subsequent ATs in 11 patients and electric cardioversion was required in 6 patients. In the 68 patients requiring cardioversion for termination of AF, ablation had significantly increased the AF cycle length relative to baseline in both atria (LA, 138±14 ms to 161±20 ms, P<0.0001; RA, 140±16 ms to 149±19 ms, P<0.0001). The postablation AF cycle length was also significantly longer in the LA than in the RA (P<0.0001).

During mean follow-up after the first 1.8±0.7 years (range, 0.6 to 2.9 years), 35 of 93 patients (38%) remained in SR, 27 (29%) were found to have AT, and 31 (33%) had recurrence of AF (paroxysmal, 7; persistent, 24). A follow-up period was 1.8±0.6, 2.0±0.6, and 1.7±0.7 years in patients with SR, AT, and AF, respectively. AF was eliminated (SR or AT alone) in 62 of 93 patients (67%). Of the subset of 68 patients who had required electric cardioversion for termination of AF, 28 patients (41%) had AF and the remaining 40 patients (59%) were free from AF (SR, 19 [28%]; AT, 21 [31%]). In Table 1, clinical, echocardiographic, and electrophysiological variables are summarized according to the 3 outcomes (SR, AT, and AF) after the first procedure. As shown, age, sex, left ventricular ejection fraction, and AF cycle lengths were not different between the outcomes. Two parameters were statistically different between outcomes, the duration of persistent AF (P=0.005) at time of enrollment, and whether AF termination had required electric cardioversion (P=0.004). Patients in whom AF recurred had a longer duration of persistent AF (median 3 years) and a larger percentage of them (90%) had required electric cardioversion for AF termination. Multiple logistic regression analysis demonstrated that the duration of persistent AF was the only predictor of elimination of AF (SR or AT) after the first ablation (odds ratio, 0.80 for a 1-year increase; 95% confidence interval, 0.67 to 0.95; P=0.01). The optimal cutoff value of the duration of persistent AF was 1.9 years according to receiver-operator characteristic curve analysis. Figure 1 shows the duration of persistent AF grouped by outcome. Sensitivity, specificity, positive predictive value and negative predictive value with this cut-off value and AF termination by ablation for elimination of AF are shown in Table 2. When freedom from both AF and AT (as opposed to freedom from AF) was regarded as the outcome of interest, multiple logistic regression analysis again found the duration of persistent AF to be the only predictor (odds ratio, 0.73 for a 1-year increase; 95% confidence interval; 0.57 to 0.95, P=0.02).

Repeat Ablation for AF

Twenty-eight of the 31 patients who had recurrence of AF (paroxysmal, 7; persistent, 21) during follow-up underwent a second procedure (Figure 2). Reisolation of the PVs was required and performed in 18 patients, with RF duration of 9±4 minutes. Electrogram-based ablation in the LA or CS was performed in 25 patients (89%), with RF duration of 16±12 minutes.
Reisolation of the PVs terminated AF in 1 patient (4%) and the LA/CS ablation terminated AF in 1 patient (4%). In the 26 patients whose AF was not terminated by LA/CS ablation, electrogram-based ablation was performed in the RA with RF duration of 21 minutes. AF terminated during RA ablation in 5 patients (18%). The total procedural duration was 221 minutes.

The baseline LA cycle length was significantly longer than the RA cycle length (151 ms versus 138 ms, \( P = 0.001 \)). Reisolation of the PVs and electrogram-based ablation in the LA/CS increased the LA cycle length to 157 ms (without an increase in the RA cycle length (140 ms, \( P = 0.36 \)). Excluding the 5 patients in whom the RA ablation had terminated AF, ablation in the RA significantly increased RA cycle length (143 ms to 156 ms, \( P < 0.0001 \)) but not LA cycle length (158 ms to 160 ms, \( P = 0.35 \)).

Over follow-up in the 26 patients who had received RA ablation, 6 remained in SR (23%), 10 were found to have AT (38%), and 10 (38%) had AF (paroxysmal, 4; persistent, 6). The remaining 2 (4%) originated from the RA, and both were focal ATs arising from the RA septum. Of the 20 macroreentries, 18 (90%) were associated with conduction gaps in prior linear lesions. Over follow-up of these patients, 18 patients (66%) remained in SR, 8 (30%) had a recurrence of AT, and 1 (4%) had paroxysmal AF. Five of those 8 patients with AT and the 1 patient with AF underwent a third procedure (Figure 2).

**Third Ablation**

Nineteen patients (20%) underwent a third procedure (6 patients for AF and 13 for AT). A total of 15 ATs were mapped, and all originated from the LA or CS except for 1 arising from the SVC (macroreentry, 6; focal AT, 8; localized reentry, 1). Of the 6 patients undergoing ablation for AF (paroxysmal, 5; persistent, 1), AF was terminated by electrogram-based ablation in the LA and RA in 2 patients and 1 patient, respectively. Over the follow-up period, 16 patients (84%) remained arrhythmia-free, 1 patient (5%) had paroxysmal AT, and 2 (11%) had AF (paroxysmal, 1; persistent, 1; Figure 2).

**Overall Clinical Outcome**

Overall, a median of 2 procedures were performed, and the follow-up period from their last procedure was 1.3 years. From the Kaplan–Meier curve, freedom from any symptomatic tachyarrhythmias was estimated as 82% at both 1 and 2 years follow-up (Figure 3). Of the 77 tachyarrhythmia-free patients, 5 were on antiarrhythmic drugs (amiodarone in 1, flecainide in 4). Of the 16 patients (17%) in whom tachyarrhythmias recurred, 5

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**Table 2. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value With Duration of Persistent AF ≥1.9 Years and AF Termination by Ablation for Elimination of AF**

<table>
<thead>
<tr>
<th>Duration of persistent AF ≥1.9 y</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF termination by ablation</td>
<td>36% (29 to 39)</td>
<td>90% (78 to 97)</td>
<td>88% (73 to 96)</td>
<td>41% (36 to 44)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent 95% confidence intervals.
had paroxysmal AT or AF, 2 had persistent AT, and 9 (10%) had persistent AF. Three of the 5 patients with paroxysmal AT or AF were on antiarrhythmic drugs (amiodarone in 1, flecainide in 2). Of the variables studied, recurrence of AF after the first procedure was the only variable associated with an overall failure of maintenance of SR (P=0.0002) (Table 3). Duration of persistent AF had a tendency (P=0.10) to be longer in patients whose tachyarrhythmias recurred.

Adverse Events
Adverse events occurred in 2 patients (2%). One patient had a stroke during the first procedure, and the neurological deficits (left arm weakness) disappeared 1 month after the procedure. The other patient had a pericardial effusion 1 day after the first ablation, which required percutaneous drainage. No other adverse events (including phrenic nerve injury) occurred in any patients during the follow-up period.

Discussion
Compared with recurrence of AT, recurrence of AF after ablation is associated with failure of maintenance of SR. Therefore, the first goal of our study was to identify the characteristics of persistent AF that could be eliminated by a single (LA-based) ablation. We determined that the number of years that patients had been documented to have persistent AF at the time of study enrollment (first procedure) was significantly shorter in patients whose AF was eliminated by LA ablation (SR or AT), compared with those who had a recurrence of AF. AF termination by ablation was the other parameter significantly associated with successful outcome, consistent with other reports, but this was not a predictor in multivariate analysis. For prediction of elimination of AF by LA ablation, sensitivity and negative predictive values of a 1.9-year cutoff for persistent AF duration were better than that of AF termination by ablation.

The second goal was determination of the benefits of right-sided ablation. Sixty-two of our 93 study patients (67%) were freed from AF by the LA ablation protocol, which was performed first, although 27 of the 62 patients (44%) required a repeat ablation for ATs. Of the 26 patients who received RA ablation during a second ablation, a further 16 patients (62% of 26) were free of AF. These results indicate the obvious merit of RA electrogram-based ablation.

Procedural End Point in the Catheter Ablation of Persistent AF
Mapping studies of persistent AF suggest that focal activities emanate from the PVs and posterior LA during ongoing AF. The posterior LA involving the PVs was initially considered to be the dominant fibrillatory substrate. However, the limited efficacy of ablation targeting the posterior LA indicates that the fibrillatory substrate is also present outside of the posterior LA. Catheter ablation using electrogram-based ablation techniques enables us to terminate persistent AF, demonstrating that the sites critical for maintaining AF are present not only in the PVs but also in other areas such as the CS, LA appendage, or interatrial septum. Furthermore, ablation aimed at termination of AF improves clinical outcome. However, the predictive value of electrogram characteristics associated with termination of AF is modest. Localization of the critical fibrillatory substrate remains challenging, and mapping and ablation of complex electrograms in both atria require considerable time. In fact, the procedural end point for electrogram-based ablation is time in many centers. Even if ablation fails to terminate persistent AF, ablation can prevent recurrence of AF in many patients. This is reflected in the poor sensitivity and negative predictive value of AF termination by ablation for prediction of freedom from AF (Table 2). Considering efforts for AF termination by ablation, this fact is discouraging indeed. The present study suggests that ablation of all areas displaying electrogram of interest in the LA/CS could be an alternative end point of procedures in patients with a short duration of persistent AF, if ablation failed to terminate AF.

Distribution of the Fibrillatory Substrate
It is well known that the distribution of the fibrillatory substrate is related to the clinical presentation of AF, whether
it is paroxysmal or persistent AF. The present study suggests that the distribution of the fibrillatory substrate greatly differs even among patients with persistent AF, depending on the duration of persistent AF. The perpetuation of AF causes electric and structural remodeling. In addition to these changes, the present data suggest that the fibrillatory substrate progressively extends from the LA to RA over time, because LA ablation was more effective in patients with shorter duration of AF and additional RA ablation was required in patients with longer duration of AF. Although it has been reported that duration of persistent AF is associated with the clinical outcome of catheter ablation, the present study provides new insights into the relation between duration of persistent AF and extent of fibrillatory substrate. The arrhythmogenicity of the PV is associated with its histological and electrophysiological characteristics, and atrial stretch. These underlying factors may also contribute to the progression of the fibrillatory substrate in the LA.

### Atrial Tachycardias Occurring After Ablation of Persistent AF

ATs are common tachyarrhythmias occurring after ablation of persistent AF. In the present study, the patients presenting with ATs after the first procedure had a longer duration of persistent AF than those free from any tachyarrhythmias. This may suggest that the mechanisms of the ATs act as a part of the fibrillatory substrate. It is also possible that extended ablation within the atria is creating a substrate for the ATs, contributing to the high recurrence rate of AT in our study. The creation of linear lesions with complete conduction block reduces the occurrence of ATs, but ablation techniques to prevent focal ATs or localized reentry have not been developed. ATs are more amenable to ablation than AF; thus, it appears that the occurrence of ATs is a tolerable outcome after the first procedure. If the ablation converts AF into ATs during the procedure, ablation of the subsequent ATs can prevent the occurrence of ATs and improve clinical outcome. This is one of advantages of catheter ablation aimed at procedural termination of AF.

### Limitations

Our study was conducted with an 8-mm-tip catheter, because an irrigated-tip catheter was not available in Japan during the study period. This is a major limitation considering the increasing use of irrigated-tip catheters for AF ablation at present and may explain the lower success rates in this study. Use of an irrigated-tip catheter may have been helpful for prevention of conduction recovery and produced a better clinical outcome. The present study suggests that patients with a long duration of persistent AF are more likely to benefit from biatrial ablation. To investigate the superiority of biatrial ablation over LA ablation, a randomized study is warranted. In the repeat ablation procedures for recurrent AF, many patients underwent ablation of the LA also. Thus, the efficacy of the repeat ablation was not attributable to ablation of the RA alone. However, the baseline AF cycle length in the repeat ablation was significantly shorter in the RA than in the LA, and the RA ablation terminated AF or increased RA cycle length. This suggests that the fibrillatory drivers were present in the RA in patients in whom the first ablation failed to eliminate AF.

### Conclusion

Patients free from AF after the LA/CS ablation were characterized as having a shorter duration of persistent AF. Thus, biatrial ablation aimed at termination of AF may result in unnecessary procedural duration and tissue damage in patients with a short duration of persistent AF. In contrast, the efficacy of RA ablation in patients with recurrent AF may suggest that the RA also must be targeted in some patients, particularly in those with a long duration of persistent AF.

### Disclosures

None.

### References


**CLINICAL PERSPECTIVE**

Development of ablation techniques and technologies now enables us to maintain sinus rhythm even in patients with persistent atrial fibrillation (AF). However, the ablation targets required in an individual patient have not been fully investigated. Previous data suggest a dominant role for the left atrium (LA) in maintenance of AF over the right atrium (RA). Therefore, the LA, including the pulmonary veins, has been the primary target in most centers. Efficacy of RA ablation is still controversial. In the present study, the LA was ablated in the first ablation and the RA was targeted in a repeat ablation only if AF recurred. Duration of persistent AF was the only predictor of elimination of AF by LA ablation. The repeat ablation, in which the RA was targeted, eliminated AF in 62% of patients. These results suggest that the distribution of the fibrillatory substrate greatly differs among patients with persistent AF, depending on the duration of persistent AF, and that the fibrillatory substrate progressively extends from the LA to the RA over time. Biatrial ablation may improve clinical outcome in patients with a long duration of persistent AF, although a randomized, prospective study is needed to investigate the superiority of biatrial ablation over LA ablation.
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