Noninducibility of Atrial Fibrillation as an End Point of Left Atrial Circumferential Ablation for Paroxysmal Atrial Fibrillation
A Randomized Study

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Background—An anatomic approach of left atrial radiofrequency circumferential ablation (LACA) to encircle the pulmonary veins is often effective in eliminating paroxysmal atrial fibrillation (AF). However, no electrophysiological end points other than voltage abatement and/or conduction slowing or block across ablation lines have been used. It has been unclear whether noninducibility of AF is a clinically useful end point.

Methods and Results—In 100 patients with paroxysmal AF (mean age, 55±10 years), LACA to encircle the left- and right-sided pulmonary veins was performed during AF, with additional ablation lines in the posterior left atrium and mitral isthmus, with an 8-mm-tip catheter. After completion of this lesion set, sinus rhythm was present, and AF lasting >60 seconds was not inducible in 40 patients (40%; group 1). The 60 patients in whom AF was still present or who still had inducible AF were randomly assigned to no further ablation (group 2; 30 patients) or to additional ablation lines along the left atrial septum, roof, and/or anterior wall where there were fractionated electrograms (group 3; 30 patients). In group 3, AF was rendered noninducible in 27 of 30 patients (90%). At a 6-month follow-up, 67% of patients in group 2 were free of AF without drug therapy compared with 86% of patients in group 3. (P=0.05, log-rank test). Left atrial flutter occurred in 17% and 27% of patients in each group, respectively (P=0.3).

Conclusions—After LACA in patients with paroxysmal AF, AF usually can be rendered noninducible by additional ablation at sites of fractionated electrograms. Noninducibility of AF attained by additional electrogram-guided left atrial ablation may be associated with a better midterm clinical outcome than when AF is still inducible after LACA alone.

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Key Words: atrial fibrillation ■ atrium ■ catheter ablation

A n anatomic approach to left atrial ablation that includes circumferential ablation lines around the left- and right-sided pulmonary veins (PVs) has been demonstrated to often eliminate paroxysmal atrial fibrillation (AF).1–3 To date, the only electrophysiological end points used in this approach have been voltage abatement and conduction slowing or block across the ablation lines.1,3–5 The acute effects of left atrial circumferential ablation (LACA) on the inducibility of AF have not been described, and whether the noninducibility of AF is a clinically useful end point during LACA is unknown. The primary hypotheses of this study were that it is possible to render paroxysmal AF noninducible by left atrial catheter ablation and that this improves clinical outcome after LACA in patients with paroxysmal AF.

Methods

Study Subjects
The subjects of this study consisted of 100 patients in whom AF was inducible by atrial pacing in the baseline state who underwent LACA for symptomatic, drug-resistant, paroxysmal AF. There were 80 men and 20 women; mean age of the patients was 55±10 years. AF was first diagnosed 7±6 years before LACA. The patients experienced a mean of 9±11 episodes of AF per month. Mean left ventricular ejection fraction was 0.57±0.09, and mean left atrial diameter was 43±6 mm.

Electrophysiological Study
All patients provided written informed consent. An electrophysiological study was performed in subjects in the postabsorptive fasting state. All antiarrhythmic medications, except for amiodarone in 9 patients, were discontinued 4 to 5 half-lives before the procedure. Conscious sedation was achieved with fentanyl and midazolam. Vascular access was obtained through a femoral vein. A quadripolar catheter (EP Technologies) was positioned within the coronary sinus. After the transseptal puncture, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 275 to 350 seconds. A temperature-controlled 8-mm-tip quadripolar catheter (Navistar, Biosense-Webster) was advanced into the left atrium and used for mapping and ablation.
Bipolar electrograms were recorded and stored digitally at a band pass of 30 to 500 Hz (EPMed Systems). Atrial pacing was performed within the coronary sinus with a stimulator (EPMed Systems, Clinical Stimulator model EP-3) at 10 mA and with a pulse width of 2 ms. In patients who were in sinus rhythm at the beginning of the procedure, AF was induced by rapid atrial pacing. The stimulation protocol used to induce AF consisted of 5 attempts at atrial pacing at the shortest cycle length resulting in 1:1 atrial capture for $\approx 15$ seconds. AF was considered inducible only if its duration was $>1$ minute.

**LACA Procedure**

LACA was performed as described previously. Briefly, a left atrial shell was constructed with an electroanatomic mapping system (CARTO, Biosense-Webster). LACA was performed to encircle the left- and right-sided PVs 1 to 2 cm from their ostia, with additional lines in the posterior left atrium between the 2 encircling lesions and in mitral isthmus. Radiofrequency energy was delivered at a maximum power output of 70 W and a target temperature of 55°C for 20 to 40 seconds at each ablation site. When there was a $>80\%$ decrease in the local electrogram amplitude or when energy had already been applied for 40 seconds, the catheter was moved to the next site. After completion of the encircling lesions, additional applications of radiofrequency energy were delivered within the circles at sites where the local electrogram amplitude was $<0.2$ mV.

**Study Protocol**

The study protocol was approved by the Institutional Review Board. After completion of LACA, sinus rhythm was present and AF was no longer inducible in 40 patients (group 1). Patients in whom AF had not terminated or in whom AF lasting $>1$ minute was still inducible were randomly assigned to either no further ablation (group 2) or additional left atrial ablation aimed at rendering the AF noninducible (group 3). Additional ablation consisted of ablation lines created along the left atrial septum, roof, posterior mitral annulus, and/or anterior wall on the basis of the presence of fractionated or rapid atrial activity (Figures 1 and 2). Additional ablation was continued until AF terminated and became noninducible with the stimulation protocol described above. The presence of conduction block across the ablation lines was not assessed. There were no significant differences in the clinical characteristics of the patients in the 3 groups (the Table).

If AF had not terminated or if AF still was inducible after 60 minutes of additional ablation, sinus rhythm was restored by pharmacological or transthoracic cardioversion.

**Postablation Management**

After the ablation procedure, patients were treated with intravenous heparin and observed in an inpatient monitored bed overnight. They were discharged from hospital the day after ablation and were treated with low-molecular-weight heparin for 5 days and warfarin for 3 months. All patients were treated with a class I or III antiarrhythmic drug for 8 to 12 weeks after the procedure.

**Follow-Up**

The patients were seen in an outpatient clinic 3 months after the procedure and every 6 months thereafter. In addition, a dedicated nurse-practitioner contacted each patient every 4 weeks after the procedure for follow-up. Patients were instructed to call the nurse-
practitioner whenever they experienced symptoms suggestive of AF, in which case an event recorder was used to document the rhythm at the time of symptoms.

No patient was lost to follow-up. The mean duration of follow-up was 8.11 months. Because early recurrences of AF or atrial flutter within the first weeks after the ablation may be transient, a blanking period of 6 weeks after ablation was applied.

Statistical Analysis
Continuous variables are expressed as mean±SD and were compared by a Student t test. Categorical variables were compared by χ² analysis or with Fisher exact test when appropriate. Freedom from recurrent AF was determined by Kaplan-Meier analysis with the log-rank test. A value of P<0.05 indicated statistical significance.

Results
Termination of AF and Inducibility After LACA
The initial LACA lesion set was accomplished with a mean of 43±10 minutes of radiofrequency energy, a mean fluoroscopy duration of 36±11 minutes, and a mean procedure time of 169±40 minutes.

AF terminated in 54 of the 100 patients (54%) during the initial LACA lesion set. In these 54 patients, AF converted to sinus rhythm in 38, to atypical atrial flutter in 11, and to typical atrial flutter in 1. With the standardized atrial stimulation protocol, AF lasting >1 minute was inducible in 14 of these patients and was no longer inducible in 40 patients (40%; group 1). Among the 14 patients who still had inducible AF and the 46 patients who remained in AF after LACA, 30 were randomly assigned to no further ablation (group 2), and 30 were randomly assigned to additional left atrial ablation (group 3).

Additional Ablation in Group 3
In the 30 patients in group 3, an additional left atrial ablation line was created along the roof in 14 patients, the anterior wall in 21 patients, the septum in 23 patients, and the posterior mitral annulus in 7 patients. There was 1 additional left atrial ablation line in 6 patients, 2 lines in 9 patients, 3 lines in 11 patients, and 4 lines in 4 patients. The mean number of additional minutes of radiofrequency energy used to create these lines was 14±12; mean additional procedure time was 25±15 minutes.

After additional left atrial ablation, AF terminated in 27 of the 30 patients (90%) and became no longer inducible (Figure 3). In the other 3 patients in group 3, AF either did not convert or was still inducible after additional ablation.

Inducibility of AF and Freedom From Recurrent AF
At 6 months, 85% of patients who did not have inducible AF after the initial LACA lesion set (group 1) were free of AF. Among the randomized patients, 67% in group 2 compared with 86% in group 3 were free of AF (P=0.05, log-rank test; Figure 4).

Among the 70 patients who did not have inducible AF after LACA or who had additional left atrial ablation after LACA, 85% were free of recurrent AF in the absence of antiarrhythmic drug therapy at 6 months of follow-up. Among the remaining patients who still had spontaneous or inducible AF, 67% were free of recurrent AF in the absence of antiarrhythmic drug therapy (P=0.02, log-rank test).

Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=40)</th>
<th>Group 2 (n=30)</th>
<th>Group 3 (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±10</td>
<td>55±11</td>
<td>56±9</td>
<td>0.8</td>
</tr>
<tr>
<td>Gender, M/F</td>
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<td>24/6</td>
<td>26/4</td>
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<td>Duration of AF, y</td>
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<td>7±5</td>
<td>6±4</td>
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</tr>
<tr>
<td>LA diameter, mm</td>
<td>43±7</td>
<td>43±7</td>
<td>44±6</td>
<td>0.9</td>
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<tr>
<td>LVEF</td>
<td>0.53±0.13</td>
<td>0.59±0.04</td>
<td>0.58±0.07</td>
<td>0.2</td>
</tr>
</tbody>
</table>

LA indicates left atrial; LVEF, left ventricular ejection fraction. Data are mean±SD when appropriate. Probability values refer to comparisons among the 3 groups. There were no significant differences between groups 2 and 3.

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Figure 3. Inducibility of AF before and after ablation. Shown are surface ECG leads I, II, III, V₁, and V₅ and intracardiac electrograms recorded from ablation catheter positioned in left atrium and coronary sinus. After LACA, persistent AF was still inducible by rapid atrial pacing from coronary sinus (A). After additional left atrial ablation, persistent AF was no longer inducible (B). Abbreviations as in Figure 1.
Clinical efficacy of PV isolation were found to depend on the termination and noninducibility of AF after PV isolation and the probability of AF terminated and became noninducible in those who underwent LACA. In prior studies, the probability of AF terminating and becoming noninducible was 27% who underwent LACA plus additional ablation, (19%) who underwent only LACA and in 8 of the 30 patients who underwent segmental ostial ablation (dotted line, group 3). Among randomized patients, patients in group 3 had more favorable outcome than patients in group 2 (P=0.05, log-rank test). The x axis represents duration of follow-up starting from day of ablation. If patient had recurrence within blanking period and continued to have recurrent AF afterward, earliest time of recurrence (even if it was within blanking period) was displayed.

Complications
Persistent left atrial flutter occurred in 13 of the 70 patients (19%) who underwent only LACA and in 8 of the 30 patients (27%) who underwent LACA plus additional ablation (P=0.4). Among these 21 patients, 6 who had persistent left atrial flutter underwent a successful ablation procedure to eliminate flutter. In the remaining patients, left atrial flutter resolved within 6 months after the ablation. None of the patients in this study underwent a repeat ablation procedure for AF.

Discussion
Main Findings
This study demonstrate that (1) LACA renders AF noninducible by rapid atrial pacing in 40% of patients with paroxysmal AF; 2) with additional left atrial ablation lines, the percentage of patients in whom AF is rendered noninducible increases to 90%; and 3) rendering AF noninducible by additional left atrial ablation after LACA is associated with a better clinical efficacy than when AF is still inducible after LACA.

These findings demonstrate that noninducibility of AF achieved by additional left atrial substrate modification may be a clinically useful end point of ablation in patients with paroxysmal AF who have undergone LACA.

Effect of LACA on AF Inducibility
AF terminated and became noninducible in 40% of patients who underwent LACA. In prior studies, the probability of termination and noninducibility of AF after PV isolation and the clinical efficacy of PV isolation were found to depend on the prevalence of PV tachycardias. However, the efficacy of LACA is independent of the presence of PV tachycardias.

Furthermore, although the PVs are encircled when LACA is performed, this often does not completely isolate the PVs, and the clinical efficacy of LACA does not depend on the number of PVs that are completely isolated. These observations suggest that elimination of PV tachycardias is not a major mechanism by which LACA renders AF noninducible.

It is likely that LACA eliminates the inducibility of AF by modifying the left atrial substrate. Compartmentalization of the left atrium and/or elimination of rotors may have contributed to making AF noninducible after LACA. In addition, LACA may have indirectly altered the left atrial substrate in some patients by vagal denervation.

Effects of Additional Left Atrial Ablation
In the patients in this study who underwent additional left atrial ablation because they still had spontaneous or inducible AF after LACA, placement of the ablation lines was based on the presence of fractionated and continuous or rapid atrial electrograms. The rationale for this approach is based on both experimental and clinical studies. A relatively short cycle length may indicate the presence of a driver, analogous to the frequency gradient from the drivers/rotors to the rest of the atria observed in experimental models of AF. Fractionated and continuous electrical activity may indicate the presence of slow conduction or the pivot point of a reentry circuit. Furthermore, fractionated electrograms may reflect a short local effective refractory period resulting from vagal innervation, and ablation of these sites may have contributed to vagal denervation. Regardless of the underlying mechanisms, a clinical study demonstrated that AF can often be eliminated by catheter ablation that targets atrial sites where there is rapid or fractionated electrograms.

In this study, additional left atrial ablation lines through areas of fractionated or rapid atrial activity increased the noninducibility of AF from 40% to 90%. However, it is unclear whether the effect of the additional left atrial ablation lines was additive to or independent of the effects of LACA. Also unclear is whether the additional ablation lines would have had the same effect on the inducibility of AF had they not transversed regions of fractionated or rapid atrial electrograms.

Noninducibility of AF as an End Point of Ablation
A prior study demonstrated that the inducibility of AF immediately after segmental ostial ablation to isolate the PVs was associated with a higher probability of recurrent AF during follow-up. This observation suggests that the presence of a left atrial substrate capable of maintaining AF may be responsible for recurrent episodes of AF after PV isolation by segmental ostial ablation. In the present study, additional left atrial ablation guided by local electrograms rendered AF noninducible and resulted in improved clinical efficacy. These findings are consistent with the multifactorial nature of AF. In a prior study, LACA, which may have several potential mechanisms of action, was found to be more effective than PV isolation by segmental ostial ablation, which eliminates only the PV-dependent mechanisms. Likewise, the clinical efficacy of left atrial ablation that rendered AF noninducible after LACA was incremental to that of LACA alone, probably because residual mechanisms of AF
that were still present after LACA were eliminated by additional electrogram-guided left atrial ablation. The ability to still induce an arrhythmia after catheter ablation generally predicts that the arrhythmia will recur clinically. However, ~67% of patients who still had inducible AF after the ablation procedure also remained free of recurrent AF. It is possible that lesion maturation and scar formation, along with atrial remodeling, augment the therapeutic effect of LACA over time, explaining why the inducibility of AF shortly after LACA may not necessarily preclude a long-term beneficial outcome. It also is possible that LACA eliminates premature depolarizations that trigger AF so that AF no longer occurs clinically even though it is still inducible when the trigger is supplied by pacing.

Study Limitations
A limitation of this study is that the evaluation of clinical efficacy was based on symptoms, and there were no systematic attempts to rule out asymptomatic recurrences of AF. However, because of the randomized study design, asymptomatic recurrences are unlikely to have been a confounding variable. Moreover, a prior study showed that asymptomatic recurrences of AF in patients with symptomatic paroxysmal AF are rare in patients who become asymptomatic after ablation.18

Because only patients with paroxysmal AF were included in this study, the results cannot be applied to patients with chronic AF. Furthermore, the findings of the study may be specific to the particular lesion set used and may not apply to other lesion sets.

Clinical Implications
To date, LACA for paroxysmal AF has stood apart from most other types of ablation procedures in that a clear-cut electrophysiological end point has not been used. The only end point of ablation used in most studies has been voltage abatement, and although one study suggested that complete block across the ablation lines was a useful electrophysiological end point,4 this was not confirmed in 2 other studies.5,12 The only end point has not been used. The only end point of ablation used in most studies has been voltage abatement, and although one study suggested that complete block across the ablation lines was a useful electrophysiological end point,4 this was not confirmed in 2 other studies.5,12

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Disclosure
Drs Morady and Oral have served as consultants to Biosense-Webster.

References
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