Randomized Evaluation of Right Atrial Ablation After Left Atrial Ablation of Complex Fractionated Atrial Electrograms for Long-Lasting Persistent Atrial Fibrillation

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Background—With electrogram-guided radiofrequency ablation (RFA) of long-lasting persistent atrial fibrillation (AF), the best results have been reported when complex fractionated electrograms (CFAEs) in both the left (LA) and right (RA) atria were targeted. However, many studies have reported excellent outcomes from RFA of long-lasting persistent AF with the use of other ablation strategies that were limited to the LA. The incremental value of RFA of RA CFAEs is yet to be defined.

Methods and Results—In 85 patients with long-lasting persistent AF (age=59±10 years), RFA was directed at CFAEs in the LA and coronary sinus until AF terminated (19) or all identified LA CFAEs were eliminated. Sixty-six patients who remained in AF were randomly assigned to cardioversion and no further RFA (n=33) or to RFA of RA CFAEs (n=33). RA sites consisted of the crista terminalis (69%), septum (38%), superior vena cava (28%), coronary sinus ostium (22%), and the base of the appendage (31%). AF terminated in 1 (3%) of 33 patients during RA RFA. At 17±6 months after a single ablation procedure, 74% of the patients in whom AF terminated during LA RFA were in sinus rhythm. Rates of freedom from AF were similar in the patients randomized to no RFA in the RA (24%) and those randomized to RFA of RA CFAEs (30%, P=0.8). The ablation procedure was repeated in 26 patients (31%) for AF (n=22) or atrial flutter (n=4). At 16±7 months after the final procedure, 89% of the patients in whom AF terminated during LA RFA were in sinus rhythm. Among the randomized patients, the proportion of patients who remained in sinus rhythm was similar in patients who did not undergo RFA of RA CFAEs (52%) and those who did (58%, P=0.6).

Conclusion—After RFA of CFAEs in the LA and coronary sinus, ablation of CFAEs in the RA provides little or no increment in efficacy among patients with long-lasting persistent AF. (Circ Arrhythmia Electrophysiol. 2008;1:6-13.)

Key Words: atrial fibrillation ▪ catheter ablation ▪ arrhythmias, cardiac ▪ heart atria
There were 74 men and 11 women, and their mean age was 59±10 years (range 36 to 79 years). The mean left atrial size and left ventricular ejection fraction were 46±7 mm and 0.53±0.10, respectively. AF had been first diagnosed 4±5 years before presentation and had been persistent for 4±3 years before ablation (range 0.5 to 10 years). Structural heart disease was present in 38 (45%) of the patients, with coronary artery disease in 7 (8%), a dilated cardiomyopathy in 6 (7%), hypertensive heart disease in 33 (39%), and valvular heart disease in 3 (4%).

Electrophysiological Study

All patients provided informed written consent. The electrophysiological studies were performed in the postabsorptive state. All antiarrhythmic drugs except amiodarone were discontinued at least 4 to 5 half-lives before the study. Among the 85 patients, 26 (31%) were receiving amiodarone at the time of catheter ablation. Vascular access was obtained through a femoral vein. A quadripolar catheter was positioned in the coronary sinus and was used for recording and atrial pacing. After the transseptal puncture, systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 300 to 350 seconds. A decapolar ring catheter (Lasso, Biosense Webster, Diamond Bar, Calif) was positioned sequentially within the pulmonary veins (PVs). An open-irrigation, 3.5-mm-tip deflectable catheter (Thermocool, Biosense Webster) was used for mapping and ablation. Bipolar electrograms were recorded at a band pass of 30 to 500 Hz (EPMedSystems, West Berlin, NJ).

A 3D depiction of the left atrium and PVs was constructed with an electroanatomic mapping system (Carto, Biosense Webster). To avoid applications of radiofrequency energy near the esophagus, the esophagus was visualized by barium swallow.6 Conscious sedation was achieved with midazolam and fentanyl after the barium swallow.

Radiofrequency energy was applied at a maximum power output of 35 W at a flow rate of 30 mL/min and a maximum temperature of 45°C. When ablation was performed near the PV ostia, in the PV antrum, and radiofrequency ablation (RFA) was not performed at sites where proximity to the phrenic nerve was identified by pacing at 20 mA, and radiofrequency ablation (RFA) was not performed at sites where phrenic nerve capture was noted. CFAEs at the right atrial septum, ostium of the superior vena cava were ablated. Proximity to the phrenic nerve was identified by pacing at 20 mA, and radiofrequency ablation (RFA) was not performed at sites where phrenic nerve capture was noted. CFAEs at the right atrial septum, ostium of the coronary sinus, crista terminalis, base of the right atrial appendage, and anterior and posterior right atrial walls then were identified and ablated. The end point of CFAE ablation in the right atrium was conversion of AF to sinus rhythm or atrial flutter or ablation of all identified CFAEs. Sinus rhythm was restored by pharmacological cardioversion with ibutilide (if the left ventricular ejection fraction was >0.30) or transthoracic cardioversion in patients who remained in AF.

Postablation Management and Follow-Up

After venous sheath removal, all patients were treated with intravenous heparin until the next morning, during an overnight hospital stay. Patients were discharged taking warfarin and using low-molecular-weight heparin until the international normalized ratio was >2.0. Patients who had been taking a rhythm-control drug before ablation continued with the same drug therapy for 8 to 12 weeks after the procedure. Patients were seen in an outpatient clinic 3 months after the ablation procedure and every 3 to 6 months afterward. Patients were advised to call a clinical coordinator if they developed symptoms suggestive of an arrhythmia. Cardioversion was performed in 29 (34%) of 85 patients who had recurrent AF or atrial tachyarrhythmias within 3 months after the ablation. All antiarrhythmic drugs were discontinued within 8 to 12 weeks after ablation in patients who remained in sinus rhythm. At 6 months after ablation, monitoring was performed with an autotriggered event recorder for 30 days to identify asymptomatic AF. Unless
the patient had a history of stroke or a transient ischemic episode, anticoagulation with warfarin was discontinued at 6 months after ablation if there was no evidence of symptomatic or asymptomatic AF. A repeat ablation procedure was offered to all patients with recurrent atrial tachyarrhythmias beyond 12 weeks after ablation, and 26 of the 53 patients with recurrent atrial arrhythmias underwent repeat ablation. During redo procedures, CFAEs in the PVs, left atrium, and coronary sinus again were targeted. The mean duration of follow-up was 16.7 months after the final ablation procedure.

Statistical Analysis
Continuous variables are expressed as mean±SD and were compared by the Student t test or by ANOVA. Categorical variables were compared by χ² analysis or with the Fisher exact test where appropriate. P<0.05 indicated statistical significance.

The primary end point of the study was freedom from symptomatic and asymptomatic AF or other atrial tachyarrhythmias in the absence of antiarrhythmic drug therapy after a single ablation procedure. Any episode of atrial tachyarrhythmia that lasted ≥30 seconds and occurred beyond 12 weeks after the ablation was considered to be a recurrence. On the basis of the findings of 2 prior studies of CFAE ablation that did and did not include right atrial ablation in patients with long-lasting persistent AF, it was estimated that 33 patients would be needed to detect a 30% difference in efficacy between the 2 randomization arms of the study at a power of 0.80 and 1-tailed α=0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Left Atrial RFA
A mean of 44±24 left atrial sites that harbored CFAEs were ablated during left atrial ablation (Figure 2). CFAEs within the coronary sinus were also ablated in 22 of 85 patients. The locations of the CFAEs that were ablated are shown in Table 1. The mean duration of radiofrequency energy application in the left atrium and coronary sinus was 42±12 minutes. The mean fluoroscopy and procedure times were 57±21 and 198±74 minutes, respectively.

Among the 85 patients, AF converted to sinus rhythm in 8 (9%) and to atrial tachycardia/flutter in 11 (13%) during left atrial RFA. The flutter circuits used the cavotricuspid isthmus in 3 patients, coronary sinus in 1, left atrial roof in 1, and mitral isthmus in 3. One patient had a right atrial double-loop flutter that used the cavotricuspsid isthmus and the septum. Four patients had ≥2 flutter circuits. One patient had a focal tachycardia that arose at the ostium of the left superior PV.

Randomization
AF persisted in 66 (78%) of 85 patients after ablation of CFAEs in the left atrium and coronary sinus (Figure 3). These patients were randomly assigned to undergo no additional ablation (n=33) or to undergo ablation of right atrial CFAEs (n=33). There were no significant differences between the 2 groups of patients in clinical or echocardiographic variables (Table 2) or in the number of left atrial CFAEs ablated or the mean duration of left atrial radiofrequency energy applications (Table 3).

Table 1. Left Atrial Sites at Which CFAEs Were Ablated in All Patients

<table>
<thead>
<tr>
<th>Percentage of Patients</th>
<th>(n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial site</td>
<td></td>
</tr>
<tr>
<td>PV antrum or ostium</td>
<td>100</td>
</tr>
<tr>
<td>Anterior wall</td>
<td>82</td>
</tr>
<tr>
<td>Roof</td>
<td>77</td>
</tr>
<tr>
<td>Septum</td>
<td>76</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>46</td>
</tr>
<tr>
<td>Mitral isthmus</td>
<td>31</td>
</tr>
<tr>
<td>Posterior annulus</td>
<td>29</td>
</tr>
<tr>
<td>Base of left atrial appendage</td>
<td>28</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>27</td>
</tr>
</tbody>
</table>
Ablation of Right Atrial CFAEs

A mean of 19/1006 14 CFAEs were ablated in the right atrium (Figure 4). The locations of right atrial CFAEs that were ablated are shown in Table 4. The mean duration of radiofrequency energy application in the right atrium was 6.4/1006 4.4 minutes. The mean procedure and fluoroscopy durations for ablation in the right atrium were 25.2/1006 13.6 and 6.9/1006 4.2 minutes, respectively.

AF converted to atypical atrial flutter in 1 (3%) of 33 patients during ablation of right atrial CFAEs. In the remaining 32 patients, sinus rhythm was restored by ibutilide infusion or transthoracic cardioversion.

Primary End Point

At a mean follow-up of 17/1006 6 months after a single ablation procedure, among the 33 patients who were randomized to no further ablation, 8 (24%) were in sinus rhythm without antiarrhythmic drug therapy, 20 (61%) had persistent AF, and 5 (15%) had paroxysmal AF. Among the 33 patients randomized to ablation of right atrial CFAEs, 10 (30%) were in sinus rhythm without antiarrhythmic drug therapy, 19 (58%) had persistent AF, 2 (6%) had atrial flutter, and 2 (6%) had paroxysmal AF (P=0.8 between the 2 randomization groups; Figure 3). Among the 19 patients whose AF converted to sinus rhythm or atrial flutter during ablation of left atrial CFAEs and who therefore were not randomized, 14 (74%) were in sinus rhythm without antiarrhythmic drug therapy, 4 (21%) had recurrent AF, and 1 (5%) had atrial flutter.

In the overall group of 85 patients, AF converted to sinus rhythm or atrial flutter during ablation of left atrial with or without right atrial CFAEs in 20 patients. At 17/1006 6 months after a single procedure, 14 (70%) of these 20 patients were free of atrial tachyarrhythmias in the absence of antiarrhythmic drug therapy. Among the 65 patients whose AF did not convert during ablation, a significantly lower proportion (18

<table>
<thead>
<tr>
<th>Table 2. Clinical Characteristics</th>
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<tbody>
<tr>
<td>AF Terminated During Left Atrial RFA</td>
</tr>
<tr>
<td>n=19</td>
</tr>
<tr>
<td>n=33</td>
</tr>
<tr>
<td>n=33</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex (male/female), n</td>
</tr>
<tr>
<td>Duration of AF, y</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
</tr>
<tr>
<td>Amiodarone before RFA</td>
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</tbody>
</table>

Data are shown as mean±SD or n (%).
of 65, or 28%) were free of atrial tachyarrhythmias (P = 0.001).

Repeat Ablation Procedures
Repeat ablation procedures were performed in 26 patients (31%) at a mean of 10 ± 3 months after the first procedure. The second procedure was performed because of recurrent AF in 22 patients and atrial flutter in 4. A third ablation procedure was performed in 3 patients 8 ± 4 months after the second procedure, for recurrent AF in 2 patients and for atrial flutter in 1 patient.

During the repeat ablation procedures, CFAEs were identified near 1 or more PVs in all patients and were ablated by ostial and/or antral applications of radiofrequency energy. There were ≥2 flutter circuits in all of the patients who had a repeat ablation procedure for atrial flutter. The flutter circuit used the roof of the left atrium in 1 patient, the posterior left atrium in 1 patient, and the septum in 2 patients. One patient had cavotricuspid isthmus–dependent atrial flutter. One patient had focal atrial tachycardia that originated at the crista terminalis.

At a mean of 16 ± 7 months after the last ablation procedure, among the 19 patients who had termination of AF during left atrial ablation, 17 (89%) were in sinus rhythm without antiarrhythmic drug therapy, and 2 (11%) had recurrent AF. Among the 33 patients randomized to no further ablation after left atrial RFA, 17 (52%) were in sinus rhythm without antiarrhythmic drug therapy, 8 (24%) had recurrent AF, 3 (9%) had atrial flutter, and 5 (15%) had paroxysmal AF. Among the 33 patients randomized to right atrial ablation, 19 (58%) were in sinus rhythm without antiarrhythmic drug therapy, 8 (24%) had recurrent AF, 3 (9%) had atrial flutter, and 3 (9%) had paroxysmal AF (P = 0.6 between the 2 randomization groups).

Complications
After 114 ablation procedures in 85 patients, 1 patient who underwent only left atrial ablation developed pericarditis that did not require an intervention.

Discussion
Main Findings
The main finding of the present study is that ablation of right atrial CFAEs does not significantly improve the results of ablation of CFAEs in the left atrium and coronary sinus in patients with long-lasting persistent AF. Therefore, although drivers of long-lasting persistent AF occasionally may arise in the right atrium, ablation of right atrial CFAEs on a routine basis is unlikely to enhance the success rate of CFAE ablation in the left atrium and coronary sinus.

An incidental but important finding of the study is that the acute conversion of AF to sinus rhythm or atrial flutter during ablation of CFAEs was associated with a markedly higher long-term success rate than when AF was still present after CFAE ablation. As has been reported to be the case with the stepwise approach to the ablation of long-lasting persistent AF,11,12 this finding suggests that the acute conversion of AF by CFAE ablation reflects the elimination of the critical drivers of AF. On the other hand,
when AF is still present, it may be more likely that at least some of the critical drivers of AF are still present, which would result in a higher incidence of recurrent AF after ablation.

**Right Atrial CFAEs**

Common sites for CFAEs in the right atrium include the ostia of superior vena cava and the coronary sinus, the septum, and the crista terminalis. Focal tachycardias that originate in the superior vena cava, coronary sinus, and crista terminalis may give rise to CFAEs. Reentrant circuits that utilize conduction gaps along the crista terminalis may play a role in the perpetuation of AF and could be another source of CFAEs.

The right atrium has a complex histological structure, with overlapping myocardial fibers along the interatrial septum, crista terminalis, and cavotricuspid isthmus that may facilitate anisotropic conduction, thereby creating CFAEs during AF. Because there is a frequency gradient from the left atrium to the right atrium during AF, the breakthrough of activated wave fronts with fibrillatory conduction is likely to occur at the interatrial septum, which would also create CFAEs. Therefore, CFAEs in the right atrium may often represent tissue heterogeneity, anisotropic conduction, and wave break with fibrillatory conduction instead of sites that are critical for the maintenance of AF. This may explain the very low (3%) conversion rate of AF during ablation of right atrial CFAEs.

**End Points for Ablation of Long-Lasting Persistent AF**

Compared with paroxysmal AF, long-lasting persistent AF is more difficult to convert to sinus rhythm by RFA. Furthermore, an ablation end point of noninducibility is feasible and predictive of outcomes after ablation of paroxysmal AF. In contrast, in long-lasting persistent AF, if sinus rhythm is achieved acutely by ablation, AF almost always is acutely reinducible by rapid pacing, probably because of the electrical and structural remodeling associated with long-lasting persistent AF. Therefore, the use of noninducibility as an end point for ablation of long-lasting persistent AF is not feasible.

The acute conversion of AF may be a spontaneous event related to abatement in the activity of critical drivers. In the case of long-lasting persistent AF, the acute conversion of AF during ablation presumably indicates successful ablation of the critical drivers that were maintaining the AF. Although not all prior studies have shown a relationship between the acute response to ablation of long-lasting persistent AF and the long-term clinical outcome, it seems plausible to conclude that critical drivers are more likely to still be present when long-lasting persistent AF does not terminate acutely in response to ablation.

**Prior Studies**

In a prior study, CFAEs were targeted in the left atrium, coronary sinus, and right atrium. Unlike the present study, AF terminated in 60% of patients with long-lasting persistent AF, and 77% of patients remained in sinus rhythm without antiarrhythmic drug therapy. Because there was no control group of patients who did not undergo ablation of right atrial CFAEs, and because the sites at which CFAE ablation terminated AF were not described, the incremental value of ablating the right atrial CFAEs was unclear.

A recent study utilized a stepwise approach to ablation in 60 patients with long-lasting persistent AF, with one of the steps consisting of ablation of CFAEs in the right atrium. Overall, AF was terminated by ablation in 87% of the patients; however, termination occurred during ablation within the right atrium in only 2 patients (3%). Consistent with the results of the present study, in the vast majority of patients, the ablation sites that resulted in acute termination of AF were in the left atrium and coronary sinus.

Furthermore, in a surgical series of 105 patients with long-lasting persistent AF, intraoperative ablation was performed during concomitant cardiac surgery. Intraoperative ablation was limited to the left atrium in 57 patients and was bialtral in 48 patients. At a mean follow-up of 11 months, there was no significant difference in efficacy between the left atrial procedure and the bialtral procedure. These results are consistent with the findings of the present study and provide further evidence for the dominance of the left atrium and coronary sinus over the right atrium as important sites for ablation of long-lasting persistent AF.

In a recent randomized study, left atrial ablation was compared with bialtral ablation in 80 patients with persistent or permanent AF. Circumferential PV ablation was performed in all patients. Right atrial ablation consisted of intercaval septal and posterior right atrial lines and isolation of the superior vena cava. In contrast to the findings of the present study and prior studies, AF terminated acutely much more often with bialtral ablation (85%) than with left atrial ablation (24%); however, the ablation sites that resulted in termination of AF were not specified. Furthermore, only 17% of patients in the left atrial group were free of recurrent AF without antiarrhythmic drug therapy at 14 months, which is a much lower success rate than in other studies that have used circumferential PV ablation. This suggests that circumferential PV ablation may have been performed in suboptimal fashion.

**Study Limitations**

A limitation of the present study is that CFAEs were identified by visual inspection, not by automated signal...
analysis. It is possible that formal signal-analysis techniques would have more accurately identified CFAE potentials.

Another limitation is that the study was underpowered to detect a small benefit of right atrial ablation; however, the sample size would have to be substantially larger to detect a small effect of right atrial ablation. For example, detection of a 10% improvement in efficacy with 85% power would have required 443 patients in each of the 2 arms of the study.

A third limitation is that with higher-density mapping, it may have been possible to identify residual drivers. A fourth limitation is that a second autotriggered event monitor could not be provided to all asymptomatic patients beyond the initial assessment at 6 months after ablation primarily because of compliance and insurance issues; however, rhythm was assessed periodically by electrocardiography and symptomatic assessment in these patients.

Lastly, the total amount of RFA in the right atrium was considerably less than in the left atrium. It is possible that additional ablation in the right atrium would have augmented the incremental value of right atrial ablation.

Conclusions

It is clear that the superior vena cava or reentry through gaps in the crista terminalis occasionally may be sources of AF, particularly paroxysmal AF, and the results of the present study are not contradictory with this. Nevertheless, the findings suggest that the indiscriminate ablation of right atrial CFAEs in patients with long-lasting persistent AF is unlikely to enhance the overall efficacy of ablation of CFAE sites in the left atrium and coronary sinus. It appears likely that CFAEs in the right atrium may often be nonspecific markers of discontinuous conduction instead of reliable indicators of sites that play a critical role in the generation of long-lasting persistent AF. It may be that adjunctive right atrial ablation is most appropriate in patients with long-lasting persistent AF who have clearly identifiable drivers that arise in the right atrium; however, the best techniques for identifying the patients with long-lasting persistent AF who will benefit from right atrial ablation are unclear and remain to be established.

Disclosures

Drs Oral and Morady are founders and equity owners of Ablation Frontiers, Inc. Dr Oral has received research grants from St. Jude Medical and Boston Scientific. The remaining authors report no conflicts.

References

**CLINICAL PERSPECTIVE**

Complex fractionated atrial electrograms (CFAEs) have been targeted to eliminate atrial fibrillation (AF). Although the best outcomes have been reported after ablation of CFAEs in both the left and right atria, excellent results have also been achieved after catheter or surgical ablation of AF limited to the left atrium. The purpose of the present study was to determine the incremental role of ablation of CFAEs in the right atrium after catheter ablation of CFAEs in the left atrium and coronary sinus in patients with long-lasting persistent AF. In this study, 85 consecutive patients with long-lasting persistent AF first underwent ablation of CFAEs in the left atrium and coronary sinus until AF terminated (n=19) or all identified left atrial CFAEs were eliminated. Subsequently, 66 patients who remained in AF were randomized to undergo cardioversion and no further ablation (n=33) or ablation of right atrial CFAEs. At a mean of 17 months after a single ablation procedure, 74% of the patients in whom AF terminated during left atrial ablation were in sinus rhythm. Rates of freedom from AF were similar in the patients who received no further ablation (24%) and those who underwent ablation of right atrial CFAEs (30%). Although triggers and drivers that originate from the right atrium or superior vena cava may occasionally be the source of AF, indiscriminate routine ablation of CFAEs in the right atrium provides little or no additional benefit in improving efficacy among patients with long-lasting persistent AF.
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