Radiofrequency Catheter Ablation of Chronic Atrial Fibrillation Guided by Complex Electrograms

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Background—Radiofrequency catheter ablation of atrial fibrillation (AF) guided by complex fractionated atrial electrograms has been reported to eliminate AF in a large proportion of patients. However, only a small number of patients with chronic AF have been included in previous studies.

Methods and Results—In 100 patients (mean age, 57±11 years) with chronic AF, radiofrequency ablation was performed to target complex fractionated atrial electrograms at the pulmonary vein ostial and antral areas, various regions of the left atrium, and the coronary sinus until AF terminated or all identified complex fractionated atrial electrograms were eliminated. Ablation sites consisted of ≥1 pulmonary vein in 46% of patients; the left atrial septum, roof, or anterior wall in all; and the coronary sinus in 55%. During 14±7 months of follow-up after a single ablation procedure, 33% of patients were in sinus rhythm without antiarrhythmic drugs, 38% had AF, 17% had both AF and atrial flutter, 9% had persistent atrial flutter, and 3% had paroxysmal AF on antiarrhythmic drugs. A second ablation procedure was performed in 44% of patients. Pulmonary vein tachycardia was found in all patients in both previously targeted and nontargeted pulmonary veins. There were multiple macroreentrant circuits in the majority of patients with atrial flutter. At 13±7 months after the last ablation procedure, 57% of patients were in sinus rhythm without antiarrhythmic drugs, 32% had persistent AF, 6% had paroxysmal AF, and 5% had atrial flutter.

Conclusions—Modest short-term efficacy is achievable with radiofrequency ablation of chronic AF guided by complex fractionated atrial electrograms, but only after a second ablation procedure in >40% of patients. Rapid activity in the pulmonary veins and multiple macroreentrant circuits are common mechanisms of recurrent atrial arrhythmias. (Circulation. 2007;115:2606-2612.)

Key Words: ablation ■ arrhythmia ■ atrium ■ catheter ablation ■ electrophysiology ■ fibrillation

Most all ablation strategies for atrial fibrillation (AF) include pulmonary vein (PV) isolation.1-4 An exception is radiofrequency ablation of complex fractionated atrial electrograms (CFAEs), in which no attempt is made to isolate the PVs. This strategy was evaluated in 64 patients with chronic AF in a single prior study, with a long-term success rate of 77%.5 In that study, CFAEs were ablated in the left atrium, coronary sinus, and right atrium. However, similar efficacy (74% at 1 year) was reported in patients with chronic AF utilizing a strategy of circumferential PV ablation, in which no ablation is performed in the right atrium.6 Therefore, only limited data from a single center are available on the efficacy of targeting CFAEs for chronic AF, and whether or not right atrial ablation is necessary is unclear.

The purpose of the present study was to determine the efficacy of radiofrequency ablation guided by CFAEs in the left atrium and coronary sinus in patients with chronic AF.

Methods

Study Subjects

The subjects of the present study were 100 consecutive patients with chronic AF who underwent radiofrequency ablation of CFAEs in the left atrium and coronary sinus. There were 81 men and 19 women, and their mean age was 57±11 years. The mean left atrial size and left ventricular ejection fraction were 46±6 mm and 0.55±0.08, respectively. Chronic AF was defined as AF that had been present for ≥6 months without intervening spontaneous episodes of sinus rhythm and that required cardioversion for restoration of sinus rhythm. AF had been chronic for 5±6 years before ablation. Structural heart disease was present in 42 patients, consisting of coronary artery disease in 8, a nonischemic cardiomyopathy in 6, and hypertensive heart disease in 35 patients.

Electrophysiological Study

All patients provided informed, written consent before the study. Electrophysiological studies were performed with patients in the fasting state. Treatment with all antiarrhythmic drugs except amiodarone (29 patients) was discontinued at least 4 to 5 half-life periods before the study. A transesophageal echocardiogram was performed.
in all patients before the procedure to rule out intracardiac thrombus. Vascular access was obtained through a femoral vein. A quadripolar catheter was positioned in the coronary sinus for recording electrograms and for atrial pacing. After transeptal catheterization, 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) was sequentially positioned in each PV. An 8-mm-tip, temperature-controlled ablation catheter (Navistar, Biosense Webster) was used for mapping and ablation. Radiofrequency energy was applied at a maximum temperature of 50°C and a maximum power of 35 W around the PV ostia, in the coronary sinus, and along the posterior left atrium and at a maximum temperature of 50°C and a maximum power of 70 W elsewhere in the atrium. Radiofrequency energy was applied for 15 to 45 seconds at each site. Bipolar electrograms were recorded at a bandpass of 30 to 500 Hz (EPMed Systems).

A 3-dimensional reconstruction of the left atrium and PVs was created with an electroanatomic mapping system (Carto, Biosense Webster). To be able to avoid applications of radiofrequency energy over the esophagus, the luminal borders of the esophagus were visualized by barium swallow (E-Z-EM, Canada) and fluoroscopy. Conscious sedation was achieved with midazolam and fentanyl after the barium swallow.

Study Protocol

The study protocol was approved by the institutional review board. All patients presented in AF. Mapping was performed in systematic fashion. CFAEs were defined as electrograms with a cycle length ≤120 ms or shorter than in the coronary sinus (A; mean cycle length 110 ms) or that were fractionated and/or had continuous electric activity (B to F). Abl indicates distal bipolar of the ablation catheter; CS, distal bipolar of the coronary sinus catheter.

Macrocircuits were ablated whenever possible. However, if there were pleomorphic flutters or if the flutter was not stable enough to allow mapping, further ablation was not pursued. Pharmacological cardioversion with ibutilide or electric cardioversion was performed if AF was still present after ablation of all identified CFAEs in the left atrium and coronary sinus. Ibutilide was administered solely for cardioversion and not to facilitate mapping by slowing the cycle length of AF. Reinduction of AF was not attempted. If there was an immediate recurrence of AF, all PVs and the superior vena cava were mapped. Residual CFAEs at these sites were ablated.

Repeat ablation was offered to all patients who had recurrent atrial arrhythmias and was performed in patients who wished to proceed. When an ablation procedure was repeated for recurrent AF during follow-up, the aforementioned ablation strategy was repeated.

Postablation Management

After sheath removal, all patients were treated with intravenous heparin until the next morning. Treatment with warfarin commenced the night of the procedure. Starting 1 day after ablation, low-molecular-weight heparin was used at a dose of 0.5 mg/kg subcutaneously every 12 hours until the international normalized ratio was ≥2.0. Patients were treated for 2 to 3 months with the same antiarrhythmic drugs that had been used before ablation. Aspirin was substituted for warfarin at 3 to 6 months after the ablation procedure if maintenance of sinus rhythm was confirmed, unless there was a history of thromboembolic events or another indication for systemic anticoagulation.

Follow-Up

Patients were seen in an outpatient clinic at 3, 6, and 12 months of follow-up. They were instructed to contact a nurse if symptoms suggestive of an arrhythmia occurred. All patients were provided with a 30-day, auto-trigger event monitor at 6 months after ablation. The mean duration of follow-up was 17±7 months.

Statistical Analysis

Continuous variables are expressed as mean±1 SD. Continuous parameters were compared with the Student t test. Categorical variables were compared by χ² analysis. P<0.05 indicated statistical significance.

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

Targets Sites of Ablation

Among the 100 patients, CFAEs at the ostium or in the antrum of ≥1 PV were targeted for ablation in 90% of patients. The CFAEs were in the antrum of the right-sided PVs in 15 patients (15%), in the antrum of the left-sided PVs in 15 patients (15%), and in the antrum of the right- and left-sided PVs in 14 patients (14%). Ostial CFAEs at ≥1 PV were targeted in 46 patients (46%).

The left atrial sites at which CFAEs were ablated (Figure 2) are shown in the Table. CFAEs within the coronary sinus were ablated in 55 patients (55%). The superior vena cava was targeted in 2 patients because it was the source of an immediate recurrence of AF.

The mean duration of radiofrequency energy application was 36 ± 13 minutes. The mean procedure and fluoroscopy times were 206 ± 43 and 51 ± 16 minutes, respectively.

Termination of AF During Ablation

Among the 100 patients, AF terminated by ablation in 16 patients (16%). Among these 16 patients, AF converted to sinus rhythm in 12 and to atrial flutter in 4 (Figure 3). Among these 4 patients, atrial flutter circuit(s) utilized the roof and mitral isthmus in 2 patients and were pleomorphic in the other 2 patients. In an additional 40 patients, AF converted only after infusion of ibutilide. Among these 40 patients, AF converted to sinus rhythm in 27 and to atrial flutter in 13. In the remaining 44 patients, AF was converted to sinus rhythm by transthoracic cardioversion.

Outcome After a Single Ablation Procedure

During a mean follow-up of 14 ± 7 months after a single ablation procedure, 33 of the 100 patients were in sinus rhythm in the absence of antiarrhythmic drug therapy, 38 had persistent AF, 17 had persistent AF with periods of atrial flutter, 9 had atrial flutter, and 3 had paroxysmal AF with antiarrhythmic drug therapy.

Repeat Ablation

Among the 100 patients, repeat ablation was performed in 44 patients at a mean of 9 ± 5 months after the first procedure. A second ablation was performed to eliminate recurrent AF in 27 patients (61%), atrial flutter in 8 (18%), and both AF and atrial flutter in 9 (21%) of the 44 patients. A third ablation procedure was performed in 4 of the 100 patients, for recurrent AF in 1 patient and atrial flutter in 3 patients.

During the repeat ablation procedures, CFAEs were identified and ablated in ≥1 of the previously targeted (n=29) and previously untargeted (n=78) PVs in all patients with recurrent AF. Additional left atrial CFAEs were ablated in all patients, and CFAEs in the coronary sinus were ablated in 5 patients.

In 7 of 19 patients (37%) who underwent a repeat ablation procedure for atrial flutter, there was only 1 macroreentrant circuit that utilized the cavotricuspid isthmus in 3, mitral isthmus in 3, and left atrial roof in 1 patient. Among the remaining 12 patients (63%), 4 had 3 to 6 macroreentrant circuits that had a critical isthmus in the mitral isthmus, coronary sinus, left atrial roof, and/or the anterior or posterior left atrial wall (Figure 4). In 2 patients, in addition to macroreentry, there was a focal tachycardia originating in the coronary sinus or right middle PV.

Freedom From AF and Atrial Flutter

At a mean follow-up of 13 ± 7 months after the final ablation procedure, 57 of the 100 patients were in sinus rhythm in the absence of antiarrhythmic drug therapy, 32 patients had persistent AF, 6 patients had paroxysmal AF (with antiarrhythmic drug therapy in 2), and 5 had atrial flutter.

Among the 19 patients who underwent repeat ablation for atrial flutter, 11 (58%) were in sinus rhythm, 3 (16%) had persistent AF, 3 (16%) had recurrent atrial flutter, and 2 (10%) had paroxysmal episodes of AF.

Conversion of AF to sinus rhythm or atrial tachycardia/flutter during ablation, with or without ibutilide infusion, was not predictive of freedom from recurrent AF.

### Sites Where CFAEs Were Ablated

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrium</td>
<td></td>
</tr>
<tr>
<td>Anterior wall</td>
<td>91</td>
</tr>
<tr>
<td>PV antrum or ostium</td>
<td>90</td>
</tr>
<tr>
<td>Septum</td>
<td>75</td>
</tr>
<tr>
<td>Roof</td>
<td>64</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>41</td>
</tr>
<tr>
<td>Mitral isthmus</td>
<td>21</td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>55</td>
</tr>
</tbody>
</table>

**Figure 2.** Example of radiofrequency ablation guided by CFAEs. Shown are anteroposterior (A) and posteroanterior (B) projections of a 3-dimensional electroanatomic depiction of the left atrium (LA). Red tags indicate ablation sites. The pink tags indicate the course of the esophagus along the posterior left atrial wall. LS indicates left superior; RS, right superior; LI, left inferior; and RI, right inferior.
Complications
A total of 148 ablation procedures were performed in the 100 patients in the present study. Pericardial tamponade occurred in 2 patients and was managed successfully by pericardiocentesis. Another patient had a transient ischemic attack that resolved within hours after the procedure. There were no late thromboembolic events in any patient, including the 35 patients in whom anticoagulation with warfarin was discontinued.

Discussion

Main Findings
In the present study, radiofrequency ablation of left atrial and coronary sinus CFAEs resulted in maintenance of sinus
rhythm in 57% of patients with chronic AF. However, to attain this success rate, a second ablation procedure was necessary in 44% of patients. CFAEs in or near the PVs were commonly present during repeat ablation procedures. Macroreentrant atrial flutter occurred after ablation in ~25% of patients, and multiple macroreentrant circuits were common in these patients. Conversion of AF to sinus rhythm during ablation of CFAEs occurred in only a small proportion of patients and was not predictive of the long-term clinical outcome.

Significance of CFAEs
The modest efficacy attained in this study despite extensive ablation of left atrial and coronary sinus CFAEs suggests either that CFAEs do not accurately identify sites that are critical to the maintenance of chronic AF or that ablation of CFAEs is not sufficient to eliminate the driving mechanisms of chronic AF in a large proportion of patients. There are multiple potential mechanisms for CFAEs. A previous study that utilized intraoperative epicardial mapping of the atrium demonstrated that CFAEs may indicate sites of slow conduction, wavefront collision, or anchor points for reentrant circuits.11 Such sites may be critical in the multiple wavelet hypothesis.12 Recent optical mapping studies in ex vivo and simulation models provided evidence that high-frequency sources, ie, rotors, play a role in the genesis of AF.13–15 During centrifugal propagation of the wavefront from the core of a rotor, wave break and fibrillatory conduction may occur, resulting in CFAEs.16 However, the presence of rotors during AF in the human atrium have yet to be demonstrated. Vagal innervation shortens the atrial effective refractory period, thereby facilitating the formation of CFAEs, and it has been proposed that CFAEs indicate sites of ganglionated plexi.17 CFAE might also occur at sites where different myocardial fiber orientations overlap or at sites of anisotropic conduction.18–21 It is important to note that ablation of CFAEs that result from anisotropic conduction, fibrillatory conduction, or wave break would be unlikely to be of any value in eliminating chronic AF. A prior study demonstrated that CFAEs often appeared shortly after a decrease in AF cycle length, suggesting that they may be a passive phenomenon.22 Therefore, an important question that remains to be answered is the sensitivity and specificity of CFAEs in identifying sites critical to the perpetuation of chronic AF.

Importance of PVs
Previous studies have demonstrated the importance of PV tachycardias in the maintenance of AF.23,24 Of note is that PV tachycardias (ie, CFAEs near or in a PV) were identified in all patients who underwent a second ablation procedure. In some cases, previously ablated PV fascicles had recovered conduction.25,26 However, the sources of tachycardia were also PVs or PV fascicles that had not been targeted during the first ablation procedure. This indicates that CFAEs near PVs may not be consistently present on a day-to-day basis. This points out a major limitation of the CFAE ablation strategy and provides a strong argument in favor of routine isolation of all PVs, regardless of whether or not CFAEs are seen near or in the PVs.

Termination of AF
In a previous study, AF converted to sinus rhythm during ablation of CFAEs in 62% of patients with chronic AF without administration of an antiarrhythmic drug.5 In contrast, in the present study, AF converted to sinus rhythm or atrial flutter during ablation of CFAEs (in the absence of ibutilide) in only 16% of patients. There are at least 2 possible reasons for this discrepancy, as follows: (1) CFAEs in the right atrium were ablated in the previous study but not in the present study. Although the distribution of CFAEs was not specifically described in patients with chronic AF, CFAEs along the septum were ablated in ~90% of the overall study group. Whether this was the left atrial or right atrial septum was not specified; however, it was indicated that the septum was the most frequently targeted right atrial site. Additional right atrial ablation sites included the proximal coronary sinus and its ostium in 32 patients, cavotricuspid isthmus in 17, inferolateral aspect of the right atrium in 5, and superior vena cava in 2 patients. (2) An unspecified number of patients in the previous study were being treated with an antiarrhythmic drug at the time of the ablation procedure.

In a study that incorporated ablation of CFAEs into a stepwise approach for ablation of persistent AF, conversion to sinus rhythm occurred during ablation in 87% of patients.6 However, in that study, empirical isolation of all PVs was routinely performed, and a variety of left atrial linear lesions often was necessary for termination of AF. Furthermore, one third of the patients were being treated with amiodarone, which may have facilitated mapping and conversion. Unlike the previous study,7 right atrial ablation was performed in only 3 patients (5%).4 There was no relationship between the acute termination of AF during ablation and long-term freedom from recurrent AF in this study. This confirms the results of prior studies in patients with chronic AF that demonstrated a clinically successful outcome despite the need for pharmacological or electric cardioversion after ablation.5,27,28 Potential explanations include progressive lesion matura tion after ablation and/or elimination of the triggers that initiate AF.

Atrial Flutter
Proarrhythmia in the form of atrial tachycardia or flutter often is related to gaps in a line of block created by linear ablation in the left atrium and has been reported to occur in ~20% of patients after radiofrequency ablation of AF.6,28–30 Because linear lesions are not created when CFAEs are targeted, proarrhythmia might be expected, at least in theory, to be less common than when radiofrequency energy applications are contiguous. Nevertheless, macroreentrant atrial flutters occurred during follow-up in a sizeable percentage of patients and often were multiple. The findings suggest that macroreentrant atrial flutters are as common after ablation of CFAEs as when other ablation strategies are used. It is possible that flutter circuits are
created in regions where there are clusters of noncontiguous ablation lesions. In addition, it is possible that “de-fragmentation” by ablation of CFAEs eliminates fibrillatory conduction and uncoveres underlying reentrant circuits in the left atrium.31,32

Limitations
A limitation of this study is that CFAEs were identified simply by visual inspection and not by spectral analysis or automated signal analysis algorithms. It is possible that a rigorous quantitative analysis of CFAEs would have resulted in more precise identification of suitable ablation sites. However, in the prior study that achieved an efficacy of 77% in patients with chronic AF, CFAEs also were identified only by visual inspection.5 Another limitation of this study is that ablation of CFAEs was not compared in randomized fashion to Ablation Frontiers, Inc. The other authors report no conflicts.

Drs Oral and Morady are founders and stockholders of Ablation Frontiers, Inc. Drs Oral et al Ablation for Chronic Atrial Fibrillation 2611

Conclusions
In conclusion, the strategy of ablationing CFAEs in the left atrium and coronary sinus in patients with chronic AF often requires a second ablation procedure to achieve a relatively modest short-term success rate of 57%. The findings during repeat procedures strongly suggest that the failure to isolate the PVs is a major limitation of this ablation strategy. It is likely that the efficacy of CFAE ablation for chronic AF would be enhanced by routine isolation of all PVs. However, a fairly high efficacy of ̄75% already has been reported in patients with chronic AF with techniques such as PV antral isolation,33 wide-area circumferential ablation to isolate the PVs,3 and circumferential PV ablation.6 Therefore, whether ablation of CFAEs has incremental value when added to one of these other ablation strategies is unclear and remains to be determined.

Disclosures
Drs Oral and Morady are founders and stockholders of Ablation Frontiers, Inc. Drs Oral and Morady have also served as consultants to Ablation Frontiers, Inc. The other authors report no conflicts.

References
CLINICAL PERSPECTIVE

Ablation strategies to eliminate atrial fibrillation (AF) almost always involve isolation of the pulmonary veins (PVs). However, in a recent single-center study, ablation of complex fractionated atrial electrograms (CFAEs) in both atria and in the coronary sinus has been reported to eliminate AF in 77% of patients with chronic AF. In the present study, the efficacy of radiofrequency catheter ablation guided by CFAEs in the left atrium and coronary sinus was assessed in 100 patients with chronic AF. Radiofrequency catheter ablation was performed to target CFAEs at the PV ostial and antral areas, various regions of the left atrium, and the coronary sinus until AF terminated or all identified CFAEs were eliminated. During 14±7 months of follow-up after a single ablation procedure, 33% of patients were in sinus rhythm without antiarrhythmic drugs. A repeat ablation procedure was performed in 44% of patients for recurrent AF and/or atrial flutter. PV tachycardias in previously targeted and nontargeted PVs were found in all patients. There were multiple macroreentrant circuits in the majority of patients with atrial flutter. At 13±7 months after the last ablation procedure, 57% of patients were in sinus rhythm without antiarrhythmic drugs, 32% had persistent AF, 6% had paroxysmal AF, and 5% had atrial flutter. The findings of the present study suggest that radiofrequency catheter ablation of chronic AF guided by CFAE results in modest short-term efficacy. However, repeat ablation may be necessary in >40% of patients to eliminate recurrences of AF due to PV tachycardias or atrial flutter utilizing multiple macroreentrant circuits.
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