Ablation of Persistent Atrial Fibrillation Using Multielectrode Catheters and Duty-Cycled Radiofrequency Energy

Christoph Scharf, MD,* Lucas Boersma, MD,† Wyn Davies, MD,‡ Prapa Kanagaratnam, PtD,‡ Nicholas S. Peters, MD,‡ Vince Paul, MD,§ Edward Rowland, MD,§ Andrew Grace, MD,§ Simon Fynn, MD,∥ Lam Dang, PtID,∥ Hakan Oral, MD,¶ Fred Morady, MD¶ Zurich, Switzerland; Nieuwegein, the Netherlands; London and Cambridge, United Kingdom; and Ann Arbor, Michigan

Objectives
The purpose of this study was to assess the efficacy and safety of a novel, multielectrode, duty-cycled radiofrequency ablation (RFA) system for long-standing persistent atrial fibrillation (AF).

Background
RFA for persistent AF remains a lengthy and challenging procedure.

Methods
In 5 European centers, 50 patients with long-standing persistent AF underwent RFA. A circular pulmonary vein (PV) ablation catheter was used for PV isolation. Complex fractionated atrial electrograms were targeted at the interatrial septum using a multiaarray septal ablation catheter and in the left atrium using a multiaarray ablation catheter.

Results
During a mean total procedure time of 155 ± 40 min, complete PV isolation and complex fractionated atrial electrogram ablation were achieved in all patients. In 50% of patients, redo ablation was performed using the same strategy and technology. There were no device-related adverse events. At 6 months, a 7-day Holter electrocardiogram showed >80% AF reduction in 40 of 50 patients (80%), and 32 of 50 (64%) were off antiarrhythmic drugs. At 20 ± 4 months after the last procedure, 31 of 47 patients (66%) had a >80% reduction in AF burden, with 21 patients (45%) free of AF and off antiarrhythmic drugs.

Conclusions
This initial 50-patient multicenter study demonstrates a 80% short-term and 66% success rate at 20 months, with a low complication rate and a relatively short procedure time in patients with persistent AF using 3 anatomically specific multielectrode ablation catheters and low-energy duty-cycled radiofrequency energy. (J Am Coll Cardiol 2009;54:1450–6) © 2009 by the American College of Cardiology Foundation

Radiofrequency (RF) ablation (RFA) in the left atrium is an established therapy for patients with persistent atrial fibrillation (AF) (1,2). Currently unipolar RF energy usually is applied at power settings of 20 to 50 W with an irrigated-tip ablation catheter. Extensive RF injury can lead to atrioesophageal fistula (3), pulmonary vein (PV) stenosis (4), phrenic nerve paralysis (5), and gastroparesis (6). In persistent AF, a modification of the left atrial substrate by linear ablation (2,7) or by ablation of complex fractionated atrial electrograms (CFAE) (8) is necessary. Techniques, procedure duration, and strategy, as well as outcomes, are operator-dependent (9), and post-ablation left atrial flutters are common (7,10).

To improve efficiency, safety, and efficacy, a novel technology that delivers duty-cycled unipolar and bipolar RF energy at 8 to 10 W through anatomically specific multielectrode catheters has been developed (11). A prior study in patients with paroxysmal AF demonstrated a clinical success rate of 83% using the PV ablation catheter (PVAC) (11). This prospective multicenter trial describes the safety and efficacy of the PVAC and 2 other novel, multielectrode ablation catheters in patients with long-standing persistent AF.
Methods

Study subjects. The study protocol was approved by the local ethics committees at 5 centers in 3 European countries. All patients gave informed consent. Fifty patients with long-standing (≥1 year) persistent AF and with recurrence of AF within 30 days after electrical cardioversion despite treatment with ≥1 Class IC or III antiarrhythmic drug therapy were included (Table 1). There were a mean of 10 ± 5 patients (range 6 to 18) per center. Patients with a prior left atrial ablation, severe structural heart disease, a left atrial diameter >55 mm, and ejection fraction <0.40 were excluded. An intracardiac thrombus was ruled out by transesophageal echocardiography in all patients.

Technique of duty-cycled bipolar/unipolar RFA. The Ablation Frontiers Cardiac Ablation System (Ablation Frontiers, Inc., Carlsbad, California) has 3 different multi-electrode catheters capable of simultaneous mapping and ablation. The PVAC is a 9-F, decapolar, over-the-wire, deflectable catheter with a 25-mm diameter spiral array at the distal end (Fig. 1). The multiarray septal catheter (MASC) contains 6 paired electrodes on 3 arms (Fig. 2). Once deployed into the left atrium, this catheter can ablate CFAEs by pulling back toward the septum. The multiarray ablation catheter (MAAC) has 4 arms, each with 1 pair of electrodes, and is used for mapping and ablation in the left atrium (Fig. 3). No other catheters were used for ablation in these patients.

The catheters are connected to a multichannel, duty-cycled RF generator (GENius, Ablation Frontiers, Carlsbad, California) capable of delivering independently powered unipolar/bipolar energy to any combination of paired electrodes in temperature-controlled mode (Fig. 4). Unipolar energy (to an external pad electrode) and bipolar energy (between adjacent, paired electrodes) is titrated up to a set target temperature of 60°C with maximum output of 8 to 10 W in 5 pre-defined energy settings (modes): bipolar, unipolar, and 3 ratios (1:1, 2:1, and 4:1) of bipolar-to-unipolar energy. Energy delivery was 1 min per application, and the mode setting is selected according to desired lesion depth to minimize the risk of collateral injury based on prior experimental studies (12). For example, on the posterior wall, a 4:1 ratio of bipolar-to-unipolar energy was routinely used to avoid esophageal injury.

Electrophysiologic study. After femoral venous access and transeptal puncture, a single 10.5-F sheath was inserted into the left atrium, and heparin was administered to maintain an activated clotting time (ACT) >300 s. The PVs were isolated with the PVAC catheter by 60-s applications of 4:1 bipolar/unipolar duty-cycled RF energy. Bidirectional steering was used for large PV diameters or left common PV anatomy.

Septal ablation with the MASC catheter and left atrial wall with the MAAC catheter was performed using a 1:1 bipolar/unipolar ratio or 4:1 bipolar/unipolar ratio at the posterior wall. The criteria and end points for CFAE ablation were left to the operator’s discretion. However, conversion to sinus rhythm was not a goal or end point of CFAE ablation. All 3 multielectrode ablation catheters were used in all patients in the first procedure and in redo procedures.

After electrical cardioversion, ablation with the PVAC was continued to eliminate all PV potentials at the PV ostium. The technique and sequence of the 3 procedure steps were similar in redo ablations. Procedure times were defined as the duration of the entire procedure, from femoral access to removal of the sheaths. Oral anticoagulation was bridged with low-molecular-weight heparin, and unfractionated heparin was used during the procedure to maintain an ACT >300 s.

Follow-up. Oral anticoagulation was recommended for 6 months. Follow-up visits were at 1, 2, 4, 6, and 20 ± 4 months after the last ablation procedure (18 ± 4 months [range 10 to 25 months] after the last cardioversion). Quality of life was assessed at baseline and 6 months of follow-up with the SF-36 Quality of Life questionnaire (Quality Metrics, Lincoln, Rhode Island) and a symptom severity score (1). Antiarrhythmic drug therapy was left to the discretion of the investigator. Cardioversion and/or repeat ablation was recommended for recurrent AF, preferably within the first 3 months after the procedure. One additional procedure using the same catheters and ablation strategy as in the initial procedure was allowed, which reset the 6-month end point evaluation.

Computed tomography (CT) or magnetic resonance imaging (MRI) of the heart and transthoracic echocardiogram were obtained at baseline and 6 months after the last ablation procedure. A 7-day continuous electrocardiogram (ECG) recording was routinely performed 6 months after the last procedure and was interpreted at a core laboratory by blinded investigators. Recurrence of AF was defined as any atrial tachyrhythmia lasting >30 s.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients Characteristics (n = 50)</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Duration of atrial fibrillation (yrs)</td>
<td>3 ± 3 (range 1-17)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.54 ± 0.09</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>46 ± 5</td>
</tr>
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</table>

Data are shown as mean ± SD.
The pulmonary vein ablation catheter (PVAC) is a decapolar, circular, over-the-wire mapping and ablation catheter designed for pulmonary vein (PV) isolation. Stability is provided by the guiding wire advanced into the pulmonary vein (PV), whereas the catheter itself is positioned at different aspects of the PV antrum for mapping and ablation. Note the noise created by the phasing of radiofrequency (RF) energy through the ablation electrodes and the marked circumferential electrogram voltage reduction after 1 min of RF ablation. CS = decapolar coronary sinus electrode with proximal and distal pairs.

The multiarray septal catheter (MASC) has 3 arms with 4 electrodes each on the backside and is applied by pullback through the transseptal puncture to the left atrial septum. The electrodes have cooling fins to prevent heating during 1:1 unipolar/bipolar duty-cycled RF delivery. Note the noise created by the phasing of RF energy through the ablation electrodes and the marked electrogram voltage reduction after 1 min of RF ablation. Abbreviations as in Figure 1.
Study end points. The primary efficacy end point was an 80% reduction in AF burden on the 7-day ECG recording at 6 months, with or without antiarrhythmic drug treatment. The primary safety end point consisted of serious adverse events related to the device technology, including PV stenosis. Secondary efficacy end points were improvements in echocardiographic and quality-of-life parameters.

Statistics. Continuous variables are presented as mean ± SD and were compared using a paired t test or the Wilcoxon signed-rank test for nonparametric variables. A value of p < 0.05 indicated statistical significance.

Results

RFA. The total procedure and fluoroscopy durations were 155 ± 40 min and 55 ± 35 min, respectively. PV ablation took 32 ± 12 min with the PVAC, followed by septal ablation with the MASC for 8 ± 3 min and left atrial ablation for 13 ± 5 min using the MAAC. One patient converted to sinus rhythm during ablation; the others were cardioverted. PV isolation was confirmed in all patients.

Due to recurrent AF, 25 of 50 patients (50%) underwent repeat ablation 124 ± 50 days after the first procedure. Three patients refused a second procedure and were counted as single-procedure failures. During the second ablation procedure, a similar ablation strategy was employed. The mean procedure time for the redo procedures was 146 ± 53 min. Because ablation was started during AF, the extent of PV reconnection could not be quantified. Electrical cardioversion was used to restore sinus rhythm in all redo procedures. Ablation time with each of the 3 catheters was shorter in the second than in the first procedure: 26 ± 11 min versus 32 ± 12 min for the PVAC (p < 0.05), 5.4 ± 3.5 min versus 8 ± 3 min for the MASC (p < 0.005), and 9.8 ± 5.7 min versus 13 ± 5 min for the MAAC (p < 0.05).

Left atrial flutter/atrial tachycardia. Conversion to atrial tachycardia/flutter was not observed during any procedure. During follow-up, 2 patients developed a left atrial tachycardia/flutter, with a centrifugal activation pattern at the lower septum and right inferior PV in 1 patient and within the left atrial appendage in the other patient. Both patients underwent successful ablation with a conventional 3-dimensional mapping system during a third procedure, and both patients remained in sinus rhythm thereafter. These patients were counted as 6-month efficacy failures but were documented to have stable sinus rhythm at late follow-up. No macro-re-entrant left atrial flutter occurred during follow-up.
Adverse events. All adverse events were recorded and reviewed by an independent Data and Safety Monitoring Board. There were 4 serious procedural complications: groin hematoma in 1 patient, arteriovenous fistula requiring surgical repair in 1 patient, cardiac tamponade from the transseptal puncture in 1 patient, and a prolonged reversible ischemic neurologic event manifesting as ataxia and confirmed by an MRI scan in 1 patient. During this procedure, the ACT was maintained above 300 s, and no char or thrombus was noted on the catheters. The neurologic deficit resolved within 2 weeks. Because this event may have been caused by an air embolus, the sheaths were routinely flushed in all patients thereafter.

During follow-up, 1 patient developed pain and fever associated with pericardial and pleural effusions at 2 months. Symptoms resolved after a pericardial drain was placed. Ultimately the patient underwent a second ablation, and sinus rhythm was present 6 months later. A second patient was admitted for heart failure secondary to rapidly conducting recurrent AF and was managed with rate control medications. On follow-up CT/MRI scans, there was no evidence of PV stenosis in any patient.

Efficacy. At a mean follow up of $6.3 \pm 0.9$ months after the second procedure, a continuous ECG was recorded for $6.7 \pm 0.8$ days in all 50 patients (Table 2). Sinus rhythm was present in 8 of 8 patients receiving antiarrhythmic drug therapy with amiodarone ($n = 5$), sotalol ($n = 2$), and flecainide ($n = 1$). None of the 5 patients with self-converting AF were receiving an antiarrhythmic drug. The mean left ventricular ejection fraction increased from $0.55 \pm 0.09$ to $0.60 \pm 0.09$ ($p < 0.005$), and the mean left atrial diameter decreased from $46 \pm 6$ mm to $43 \pm 6$ mm ($p < 0.001$). Among successfully treated patients, left atrial diameter decreased by $4 \pm 1$ mm ($46 \pm 6$ mm vs. $42 \pm 6$ mm; $p < 0.001$), whereas in the 10 patients with continued AF, the left atrial diameter did not change significantly ($46 \pm 8$ mm vs. $47 \pm 6$ mm).

Long-term efficacy was assessed in 47 patients at $20 \pm 4$ months after the last ablation and $18 \pm 4$ months (range 10 to 25 months) after the last cardioversion (Table 2). In the remaining 3 patients, a 12-lead ECG at late follow-up showed sinus rhythm in 1 patient and AF in 2 patients.

**Table 2 Primary Efficacy End Point on 7-Day Continuous Holter ECG**

<table>
<thead>
<tr>
<th>Primary Efficacy End Point (n = 50)</th>
<th>Latest Follow-up (n = 47)*</th>
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</thead>
<tbody>
<tr>
<td><strong>Duration of follow-up (months)</strong></td>
<td>6.3 ± 0.9</td>
</tr>
<tr>
<td><strong>AF reduction ≥ 80%</strong></td>
<td>40 (80%)</td>
</tr>
<tr>
<td><strong>Free of AF</strong></td>
<td>35 (70%)</td>
</tr>
<tr>
<td><strong>Free of AF off AAD</strong></td>
<td>27 (54%)</td>
</tr>
<tr>
<td><strong>AF reduction ≥ 80% off AAD</strong></td>
<td>32 (64%)</td>
</tr>
</tbody>
</table>

AF recurrence was defined as any atrial tachyarrhythmia longer than 30 s on continuous 7-day ECG.

*These patients were not available for 7-day ECG beyond 12 months. 2 of them showed AF and a sinus rhythm on a 12-lead ECG. During long-term follow-up, an additional 2 patients were in sinus rhythm after an additional flutter ablation using 3-dimensional mapping.

**Improved in symptoms.** Among the 40 subjects who maintained sinus rhythm at 6 months, the prevalence of fatigue decreased from 92% to 43%, shortness of breath from 78% to 29%, light-headedness from 68% to 31%, and exercise intolerance from 92% to 41%. There were no changes in these symptoms among the patients with recurrent AF.

An SF-36 V2 Health Screening Survey (Quality Metrics, Lincoln, Rhode Island) was completed at all follow-up visits. Raw scores were calculated into component scores for physical (PCS) and mental (MCS) health. On a scale of 1 to 100, baseline measurements for PCS and MCS averaged 48 ± 7 and 49 ± 4, respectively. Patients meeting the efficacy end point demonstrated an improvement in PCS to 54 ± 5 ($p < 0.05$) and MCS to 55 ± 6 ($p < 0.05$), whereas there was no significance in decreased component scores of those with recurrent AF (PCS: 45 ± 7 and MCS: 47 ± 8 [$p = NS$]).

**Discussion**

This is the first study using duty-cycled RF with multielectrode ablation in patients with long-standing persistent AF. The efficacy of 80% at 6 months and 66% at 20 months compares favorably with conventional RF (1,13), and a procedure time of approximately 2.5 h was relatively short. Furthermore, the incidence of post-ablation atrial flutter/tachycardia was low (4%). Preliminary results from studies using the same technology are similar (14,15), and a clinical efficacy of ~85% has been demonstrated in patients with paroxysmal AF (11).

**Safety.** Duty-cycled bipolar/unipolar RF delivery at low energy levels of 3 to 8 W per electrode may be helpful for preventing complications created by extensive thermal injury. Although several serious adverse events were noted in this study, none were judged by the Data and Safety Monitoring Board to be directly related to the ablation technology. The lone neurological event could have resulted from the 10.5-F sheath, as described with standard technology (9). The absence of char with these nonirrigated catheters may be attributable to the phasing between bipolar and unipolar RF, a slow ramp-up algorithm for temperature-controlled ablation, and passive cooling through a unique electrode design.

There was no evidence of PV stenosis or atrioesophageal fistula in this study on follow-up MRI/CT scans. A prior study with this technology in patients with paroxysmal AF also demonstrated a good safety profile (11).

**Efficacy.** Ablation of long-standing persistent AF with a linear approach (7,16), point-by-point ablation of CFAE (8), or extensive stepwise ablation until conversion (2,7) remains challenging. The results have varied widely, even among very experienced centers (1,7,8,16).

Our results compare favorably with those of single-center studies (6-month success rate 80%, 20 months 66%) and were achieved by 8 different electrophysiologists at 5 cen-
ters, suggesting that the ablation strategy is easily adoptable. The relatively high redo rate of 50% might be explained by the study protocol, which encouraged repeat ablation within 3 months. Three months may have been too short to allow maximal lesion maturation and atrial remodeling. The clinical results translated into a significant decrease in left atrial diameter of 4 mm within the first 6 months after ablation \( p < 0.001 \). Of note is that 11% of patients who previously had persistent AF for >1 year had self-converting AF without antiarrhythmic drug treatment during follow-up.

A long-term success rate of 66% after 20 ± 4 months in long-standing persistent AF is reasonable. The 7-day continuous ECG recording is comparable to that of transtelephonic ECG transmissions as a follow-up tool (17).

Quality of life. The increase in quality of life by 6 points in successfully treated patients is similar to the results obtained in studies of patients with paroxysmal AF (18,19). A placebo effect of ablation was not present, because nonresponders did not improve. An improvement of ≥5 points has been considered to be clinically meaningful (20).

Study limitations. The main limitations of this study are the relatively small sample size and the absence of a control group. A randomized study with this technology is underway and will better define the efficacy of these novel catheters in accordance with published guidelines. Although the embolic neurologic event and the cardiac tamponade that occurred in this study were not considered to be directly related to the study devices, this possibility cannot be excluded, and larger studies are necessary to address safety.

The extent of PV reconnection was not quantified during redo procedures. After conventional ablation, PV reconnection is found in the majority of patients with AF (21) or atrial tachycardia (22) and even in patients in sinus rhythm (23). It would be expected that a substantial proportion of patients with recurrent AF in this study would have had reconnection. In addition, the specific sites at which CFAEs were ablated were not specified in this study because no 3-dimensional electroanatomical mapping systems were used.

A possible limitation of the ablation technology used in this study is the cost of 3 anatomically specific ablation catheters. However, the cost for conventional AF ablation using a 3-dimensional mapping system includes reference patches, a multipolar ring catheter, and an irrigated ablation catheter. The cost of conventional ablation guided by a 3-dimensional mapping system may fall into a similar range or be less than the costs of the catheters used in this study.

Conclusions

This initial 50-patient multicenter study demonstrates that a good success rate, a low complication rate, and a relatively short procedure time are achievable in patients with persistent AF using 3 anatomically specific multielectrode ablation catheters and duty-cycled RF energy. Additional studies in a larger number of patients monitored for 7 to 10 days at a time at 6, 12, 18, and 24 months of follow-up are necessary to validate the results of this initial study.

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Reprint requests and correspondence: Dr. Christoph Scharf, Cardiovascular Center, Clinic Im Park, Seestrasse 220, 8027 Zurich, Switzerland. E-mail: christoph.scharf@gmail.com.
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