A Randomized Controlled Trial of the Efficacy and Safety of Electroanatomic Circumferential Pulmonary Vein Ablation Supplemented by Ablation of Complex Fractionated Atrial Electrograms Versus Potential-Guided Pulmonary Vein Antrum Isolation Guided by Intracardiac Ultrasound

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Background—The study was conducted to compare relative safety and efficacy of pulmonary vein antrum isolation (PVAI) using intracardiac echocardiographic guidance and circumferential pulmonary vein ablation (CPVA) for atrial fibrillation (AF) using radiofrequency energy.

Methods and Results—Sixty patients (81% men; 81% paroxysmal; age, 56 ± 8 years) failing 2 ± 1 antiarrhythmic drugs were randomly assigned to undergo CPVA (n = 30) or PVAI (n = 30) at 5 centers between December 2004 and October 2007. CPVA patients had circular lesions placed at least 1 cm outside of the veins. Ipsilateral veins were ablated en block with the end point of disappearance of potentials within the circular lesion. Left atrial roof line and mitral isthmus line were ablated without verification of block. For patients in AF postablation or with AF induced with programmed stimulation, complex fractionated electrograms were mapped and ablated to the end point of AF termination or disappearance of complex fractionated electrograms. PVAI did not include complex fractionated electrogram ablation. Esophageal temperature was monitored and kept within 2°C of baseline or under 39°C. Success was defined as absence of atrial tachyarrhythmias (AF/AT) off antiarrhythmic drugs. There was no difference between CPVA and PVAI regarding to baseline variables, catheter used, duration of the procedure, or RF delivery. Fluoroscopy time was longer with PVAI (54 ± 17 minutes versus 77 ± 18 minutes, P = 0.0001). No significant complications occurred in either arm. PVAI was more likely to achieve control of AF/AT off antiarrhythmic drugs (57% versus 27%, P = 0.02) at 2 ± 1 years of follow-up.

Conclusions—A single PVAI procedure is more likely to result in freedom from AF/AT off antiarrhythmic drugs than CPVA supplemented by complex fractionated electrogram ablation in select patients. (Circ Arrhythmia Electrophysiol. 2009;2:481-487.)

Key Words: atrial fibrillation • catheter ablation • echocardiography • mapping

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia.1 It increases mortality rates, causes considerable disability, impairs quality of life, and is difficult to treat.2–4 It is common in clinical practice to prefer sinus rhythm to AF in many patients largely for symptom relief.

Clinical Perspective on p 487

There is accumulating evidence implicating triggered activity in the pulmonary veins (PV) in initiating AF.5,6 Ablation of such foci of ectopic electric activity has been shown to prevent atrial fibrillation recurrences and in some cases terminate chronic AF.7–11 Early ablation strategies included direct focal mapping and elimination of PV triggers. This was time consuming and resulted in low efficacy at a significant risk of PV stenosis. Two of the mainstream approaches to ablation targeting triggered activity in the PVs in patients with AF include electroanatomically guided circumferential PV ablation using a 3D mapping system (CPVA)9,11 and PV

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antrum isolation using intracardiac echocardiography (ICE) and a circular mapping catheter (PV antrum isolation, PVAI). Another ablation technique that has evolved in the last several years is that of substrate modification, in which atrial regions manifesting complex fractionated electric activity thought to maintain AF are ablated. These strategies boast success, defined as cure of AF, in 60% to 90% of the patients treated, at some risk of hemorrhagic and embolic complications as well as risks of PV stenosis and esophageal fistula to the left atrium late after the procedure, with the cumulative risk of significant complications after the procedure reported at up to 6%.

The potential for significant complications as well as the technical complexity of the procedure has limited penetration of catheter ablation for AF to experienced high-volume centers with most of the evidence to date accumulated from individual center and in some case single-operator registries. To assess performance of several ablation techniques in the real world, we conducted a multicenter, prospective, randomized controlled trial comparing safety and efficacy of electroanatomic circumferential PV ablation and PV isolation guided using a circular mapping catheter and intracardiac echocardiography with adjuvant ablation of complex fractionated activity in patients with refractory or inducible AF after CPVA but not PVAI.

Methods

Between December 2004 and October 2007, 60 patients with paroxysmal and persistent AF who were thought to warrant ablation were randomly assigned to CPVA using the CARTO XP (Biosense Webster, Diamond Bar, Calif) system or PVAI guided by intracardiac echocardiography and a circular mapping catheter. To correct for physician preference in the use of an irrigated catheter or an 8-mm catheter, the patients were further randomly assigned to ablation using one or the other (Celsius DS, Navistar DS, Celsius ThermoCool, Navistar ThermoCool, Biosense Webster, Diamond Bar, Calif). Patients were systemically anticoagulated for a period of at least 3 weeks before ablation regardless of their CHADS2 risk score.

Inclusion Criteria

Inclusion criteria included (1) any patient with paroxysmal recurrent or persistent atrial fibrillation, who was thought to warrant ablation; (2) continuous anticoagulation for at least 3 weeks before the experimental study; (3) an INR >2 or a transesophageal echocardiogram negative for left atrial thrombus or spontaneous echocardiographic contrast on the day of the procedure in patients presenting for ablation in sustained AF of longer than 24 hours' duration; and (4) ability and willingness to give written informed consent to participate in the trial.

Exclusion Criteria

Exclusion criteria included (1) inadequate anticoagulation as defined in the inclusion criteria; (2) chronic atrial fibrillation; and (3) significant underlying pulmonary disease.

CARTO-Guided CPVA

The technique of circumferential PV ablation using a nonfluoroscopic mapping system has been described elsewhere. In brief, the ablation catheter was advanced into the left atrium (LA) via a transseptal puncture. Once in the LA, 3D electroanatomic maps of the LA were constructed by sequential acquisition of points in 3D space with or without integration of preacquired CT or MRI images. The catheter was placed 2 to 4 cm into each PV and slowly pulled back. Along pullback, multiple locations were recorded to tag the vein. PV ostia were identified by fluoroscopic visualization of the catheter tip entering the cardiac silhouette with simultaneous impedance decrease and appearance of atrial potentials. LA ablation was performed 1 to 2 cm from the PV ostia to encircle the left- and right-sided PVs for ≥20 seconds at each site and until the maximum local electrogram amplitude decreased by ≥75% or to <0.1 mV. Ablation lines connecting right and left PVs across the LA roof and extending the lesion to the mitral annulus were allowed at the investigator discretion. After completion of the circular lesions around the left- and the right-sided PVs, the area within the ablation lines was explored with the ablation catheter, and radiofrequency energy could be applied at sites that had a local electrogram amplitude >0.1 mV. Use of a circular mapping catheter was not permitted in the CPVA group, and the completeness of conduction block across the ablation lines was not assessed. In patients still in AF at the end of the procedure, the LA was explored for areas manifesting complex fractionated atrial electrograms (CFAEs) which were targeted for ablation. In patients who were in sinus rhythm at the end of the procedure, AF induction was attempted using distal coronary sinus pacing at the shortest 1:1 atrial capture rate for 15 seconds at a time, up to 5 times in a row at 30-second intervals between attempts, and, if AF was still inducible, the LA was explored for areas manifesting CFAEs, which were targeted for ablation. CFAEs were defined as follows: (1) fractionated electrograms composed of 2 deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period; and (2) atrial electrograms with a very short cycle length (120 ms) averaged over a 10-second recording period. The end points during radiofrequency ablation of high-frequency potential areas included either complete elimination of the areas with these potentials or conversion of AF to normal sinus rhythm. No further induction of AF took place if sinus rhythm was achieved with CFAE ablation.

In patients ablated using the 8-mm-tip catheter, radiofrequency energy was delivered at a target temperature of 55°C and a maximum power of 60 W apart from the posterior wall of the LA, where peak temperature of 50°C and peak power of 45 W was used. Patients were randomly assigned to the use of the irrigated tip catheter, radiofrequency energy was delivered at a target temperature of 40°C and a maximum power of 50 W apart from the posterior wall of the LA, where peak temperature of 40°C and peak power of 35 W were used. Ablation sites were tagged on the 3D map of the left atrium. At tagged sites, radiofrequency energy was applied for ≥20 seconds and until the maximum local electrogram amplitude decreased by ≥75% or to <0.1 mV.

ICE-Guided PVAI

The technique of ICE-guided PV antrum isolation has been previously described. In brief, a 10F, 64-element, phased-array ultrasound catheter (Siemens AG Inc, Mountain View, Calif) was positioned in the middle of the right atrium via a left femoral access. This catheter remained in the right atrium for the duration of the entire procedure to guide the transseptal punctures, define the PV anatomy, and monitor for microbubble formation during radiofrequency ablation in patients treated using an 8-mm-tip catheter. Two independent transseptal punctures were performed. Each puncture was guided by ICE and by fluoroscopy. The LA was then instrumented with a decapolar Lasso circular mapping catheter (Biosense Webster Inc, Diamond Bar, Calif) and an ablation catheter. The Lasso was sequentially positioned along each segment of the antral circumference to look for PV potentials. PV potentials identified during mapping of the antrum with the Lasso catheter were then targeted for ablation.

As the Lasso catheter was moved from the ostial portion of the antrum out and from one segment of the LA-antral interface to the next, ablation was performed at the poles that demonstrated PV potentials. The ablation catheter was moved to the target pole on the Lasso. Ablation artifact on the recording from a specific Lasso pole confirmed contact between the ablation catheter and the Lasso. The use of 3D mapping systems was not permitted in patients with PV antrum isolation.
In patients randomly assigned to the 8-mm-tip catheter, RF energy was initially set at 30 W and 55°C. Power was titrated up in 5-W increments every 5 seconds while monitoring for microbubble formation on ICE until the level of delivered energy was sufficient to eliminate PV potentials or microbubbles were seen. If any were seen, the power was titrated down by 5 W every 5 seconds until no bubbles were seen. If a brisk shower of bubbles was detected, radiofrequency energy delivery was immediately terminated. In patients randomly assigned to the irrigated tip catheter, power was titrated using a similar protocol to that applied to the CPVA patients. Each lesion was delivered over 30 to 50 seconds. The catheter was then moved to the next adjacent position on the Lasso until the entire segment has been isolated.

After ablating all segments of a PV antrum, the Lasso was used to remap the PV-LA interface to confirm the absence of any PV potentials. The Lasso was then advanced into the tube of the PV to confirm absence of PV potentials there, representing entrance block into the vein.

Ablation strategy in either arm of the study did not differ between patients with paroxysmal and persistent AF. All operators were required to have more than 2 years’ experience with AF ablation at more than 50 cases performed per year. Before enrollment, the operators have had to perform at least 15 CPVA and at least 15 PVAI procedures with at least 5 of each proctored by an expert ablator. All operators have had extensive experience with the use of the CARTO system and intracardiac echocardiography.

**Anticoagulation and Antiarrhythmic Drug Therapy**

All antiarrhythmic drugs were held 5 half-lives before ablation. Amiodarone was discontinued at least 3 months before ablation. An intravenous heparin bolus of 8000 U was given after the transseptal puncture in the group randomly assigned to the CPVA approach. In the PVAI group, a 10,000-unit bolus was given before the first transseptal puncture, with another 3000 to 5000 units given after the second transseptal puncture at investigator’s discretion. Intravenous heparin infusion was adjusted to activated clotting time of 350 to 400 seconds. Each patient received 10 mg of intravenous protamine on withdrawal of the catheters into the right atrium. Further protamine was given to bring activated clotting time below 250 seconds for removal of the intravenous sheaths.

Esophageal temperature was monitored in all patients, with temperature cutoff of 39°C or a rise of 2°C from baseline at the ablation site used to terminate radiofrequency delivery at any one site.

**Follow-Up and Outcomes**

Patients were discharged home the day after ablation. All patients were discharged on oral anticoagulation with warfarin. After 3 months, anticoagulation was stopped unless patients had recurrence of AF, or if more than 50% narrowing of the treated PV could be demonstrated by spiral CT performed 3 months after ablation, or if any thromboembolic risk factors were present. Patients with a CHADS2 score of 2 or greater were encouraged to continue oral anticoagulation indefinitely. Antiarrhythmic medications in patients taking these before ablation were continued for the first 2 months after ablation. Investigators were discouraged to use amiodarone after ablation.

Patients were followed at 3 months after the ablation with a spiral CT of the chest. Significant PV stenosis was defined as 50% or more narrowing of the treated PV on follow-up spiral CT.

Recurrence of AF was assessed by a 24-hour Holter at 1, 3, 6, and 12 months and a 12-lead ECG at each clinical visit. Additional ambulatory monitoring with a loop event recorder or a Holter monitor was encouraged in the presence of symptoms. Any episode of AF longer than 30 seconds was considered a recurrence. Recurrences within the first 2 months after ablation were considered to fall within a blanking period and were analyzed separately. Quality-of-life measures (SF-36) were collected at baseline and again at 6 months after the intervention.

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PVAI</th>
<th>CPVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Men</td>
<td>24 (80)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54±7</td>
<td>57±9</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>25 (83)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>5 (17)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>SHD or CVSx</td>
<td>5 (17)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Mean duration of AF, y</td>
<td>8±8</td>
<td>7±6</td>
</tr>
<tr>
<td>No. of episodes/mo</td>
<td>14±16</td>
<td>8±9</td>
</tr>
<tr>
<td>LA size, mm</td>
<td>38±9</td>
<td>38±12</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0)</td>
<td>3 (10) (1 type 1, 2 type 2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (27)</td>
<td>10 (33)</td>
</tr>
<tr>
<td>NYHA class ≥2</td>
<td>2 (6)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>2 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CHADS–2 score</td>
<td>0 18 (60)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>1 9 (30)</td>
<td>8 (27)</td>
<td></td>
</tr>
<tr>
<td>2 3 (10)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>3 0 (0)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>No. of failed AAD</td>
<td>1.6±1.0</td>
<td>1.6±0.8</td>
</tr>
<tr>
<td>Failed amiodarone</td>
<td>7 (23)</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. SHD indicates structural heart disease; CVSx, cardiovascular surgery; AAD, antiarrhythmic drugs; NYHA, New York Heart Association; CVA, cardiovascular accident; TIA, transient ischemic attack.

The study was approved by institutional review committees at each of the participating institutions, and the subjects gave informed consent before enrollment into the study.

### Statistical Analysis

Baseline and procedural variables were compared using t tests and χ² tests. The proportion of patients developing AF or organized LA tachycardia recurrence and PV stenosis in the CPVA and PVAI groups were prespecified as the primary efficacy and safety outcomes and were compared using survival analysis (log-rank test).

Change in the quality-of-life measures from baseline was assessed using paired t tests within each treatment group. Analysis of covariance was used to compare the change in the quality-of-life measures between treatment groups. Differences were considered significant at P<0.05. All continuous variables were expressed as mean±SD. Analysis was carried out using SAS 9.0 statistical software package.

### Sample Size Calculation

This was a pilot study with planned enrollment of 50 patients per arm (CPVA versus PVAI), for a total of 100 patients enrolled at 4 to 5 enrolling centers. At 2-tailed significance level <0.05 this would provide 80% power to tell the difference between 88% and 62% success of the procedure and 80% power to tell the difference between 1% and 20% risk of PV stenosis using binomial distribution Fisher exact test. Given the small trial size, randomized assignment to an 8-mm-tip versus irrigated tip catheter would not test the difference in outcomes between these catheters as a primary outcome but rather control for use of the 2 most commonly used catheter types. An interim analysis was planned after the first 50 patients enrolled in the study achieved 1-year follow-up. Study termination was planned at that point if the difference in outcomes between treatment arms exceeded 25% or greater, with a statistical significance for the difference at 0.05.
Results

There was no difference between CPVA and PVAI with respect to the baseline variables apart from history of diabetes (Table 1). Patients were generally young and had paroxysmal AF refractory to medical therapy with little structural heart disease.

After the first 50 patients completed 1-year follow-up in the study, outcome analysis showed a 26% higher likelihood of arrhythmia recurrence among patients treated using the CPVA approach ($P=0.01$). At this point, a decision to allow a further 10 patients to complete the study was made with the provision that if the difference in outcomes between the 2 approaches is sustained, study enrollment would terminate.

Procedural characteristics are illustrated in Table 2. The study was controlled for the catheter used during ablation. Procedure time with either approach was similar, with less use of fluoroscopy in the CPVA arm of the study. Baseline and procedural characteristics were similar for the 8-mm-tip and the irrigated tip catheters for the entire group of patients and within each of the study arms. The use of the irrigated tip versus the 8-mm-tip catheter for CPVA but not PVAI was associated with a higher rate of early recurrences within the 2-month blanking period (13 [87%] versus 7 [47%] patients, $P<0.03$). Mitral isthmus and left atrial roof lines were ablated in 23 of 30 (77%) patients randomly assigned to CPVA. CFAE were ablated in 9 of 30 (30%) patients randomly assigned to CPVA.

After 2±1 years of follow-up, PVAI was more likely to achieve control of AF or organized LA tachycardia off antiarrhythmic medications (57% versus 27%, $P=0.02$) during the follow-up period. This finding was further supported by survival analysis (Table 3, Figure 1). Among patients who had an AF recurrence in the CPVA arm, 12 (40%) recurred in paroxysmal AF, 4 (1%) recurred in persistent AF, and 11 (37%) recurred in an organized LA tachycardia (Figure 2). Three patients (10%) who were originally in paroxysmal AF recurred in persistent AF, and 3 patients (10%) who started out with persistent AF recurred in paroxysmal AF. Among patients randomly assigned to PVAI, 11 (37%) recurred in paroxysmal AF, 2 (1%) recurred in persistent AF, and 4 (1%) recurred in an organized LA tachycardia (Figure 2). One of the patients who recurred in persistent AF had paroxysmal and 1 had persistent AF before ablation. One of the patients with persistent AF before to ablation recurred in paroxysmal AF. The difference in the rate of recurrence due to regular LA tachyarrhythmia between CPVA and PVAI arms of the study was significant ($P<0.04$).

Table 2. Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PVAI</th>
<th>CPVA</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irrigated tip</td>
<td>14 (47)</td>
<td>15 (50)</td>
<td></td>
</tr>
<tr>
<td>8-mm tip</td>
<td>16 (53)</td>
<td>15 (50)</td>
<td></td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>$220\pm52$</td>
<td>$220\pm47$</td>
<td>0.98</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>$77\pm18$</td>
<td>$54\pm17$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in LA, min</td>
<td>$157\pm37$</td>
<td>$174\pm41$</td>
<td>0.13</td>
</tr>
<tr>
<td>Radiofrequency delivery time, min</td>
<td>$67\pm20$</td>
<td>$69\pm21$</td>
<td>0.81</td>
</tr>
<tr>
<td>Mitral isthmus line</td>
<td>NA</td>
<td>23 (77)</td>
<td></td>
</tr>
<tr>
<td>LA roof line</td>
<td>NA</td>
<td>23 (77)</td>
<td></td>
</tr>
<tr>
<td>CFAE ablation</td>
<td>NA</td>
<td>9 (30)</td>
<td></td>
</tr>
<tr>
<td>Concurrent AFL ablation</td>
<td>8 (27)</td>
<td>6 (20)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. AFL indicates right-sided cavo-tricuspid isthmus atrial flutter; NA, not applicable.

Table 3. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>PVAI</th>
<th>CPVA</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrences &lt;2 mo</td>
<td>12 (40%)</td>
<td>20 (67%)</td>
<td>0.07</td>
</tr>
<tr>
<td>No arrhythmia* &gt;2 mo off AAD</td>
<td>17 (57%)</td>
<td>8 (27%)</td>
<td>0.02</td>
</tr>
<tr>
<td>No arrhythmia* &gt;2 mo on AAD</td>
<td>24 (80%)</td>
<td>18 (60%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Months to first recurrence (outside blanking period)</td>
<td>$9\pm5$</td>
<td>$6\pm4$</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. AAD indicates antiarrhythmic drugs.

\*Arrhythmia was defined as AF or organized LA tachycardia.

Figure 1. Survival free of AF or organized atrial tachyarrhythmia without an antiarrhythmic agent (probability value for the log-rank test). Kaplan-Meier survival analysis of freedom from AF or organized LA tachycardia without an antiarrhythmic agent after the 3-month “blanking period.” Dashed line represents outcomes among patients randomly assigned to the PV antrum isolation approach. Solid line represents outcomes among those randomly assigned to the circumferential PV ablation approach.

Figure 2. Distribution of recurrences after CPVA and PVAI.
Table 4. Quality-of-Life Outcomes

<table>
<thead>
<tr>
<th>Scale</th>
<th>PVAI Baseline</th>
<th>PVAI Follow-Up</th>
<th>P Value*</th>
<th>CPVA Baseline</th>
<th>CPVA Follow-Up</th>
<th>P Value*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>70 (25)</td>
<td>79 (22)</td>
<td>0.11</td>
<td>66 (24)</td>
<td>67 (34)</td>
<td>0.84</td>
<td>0.29</td>
</tr>
<tr>
<td>Role physical</td>
<td>37 (42)</td>
<td>62 (43)</td>
<td>0.07</td>
<td>50 (41)</td>
<td>60 (44)</td>
<td>0.42</td>
<td>0.73</td>
</tr>
<tr>
<td>Role emotional</td>
<td>55 (46)</td>
<td>67 (43)</td>
<td>0.44</td>
<td>61 (46)</td>
<td>69 (45)</td>
<td>0.45</td>
<td>0.95</td>
</tr>
<tr>
<td>Energy</td>
<td>44 (15)</td>
<td>59 (18)</td>
<td>0.002</td>
<td>52 (23)</td>
<td>53 (22)</td>
<td>0.74</td>
<td>0.07</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>70 (15)</td>
<td>70 (16)</td>
<td>0.71</td>
<td>66 (20)</td>
<td>68 (22)</td>
<td>0.79</td>
<td>0.83</td>
</tr>
<tr>
<td>Social function</td>
<td>60 (24)</td>
<td>75 (25)</td>
<td>0.09</td>
<td>72 (30)</td>
<td>68 (34)</td>
<td>0.65</td>
<td>0.32</td>
</tr>
<tr>
<td>Pain</td>
<td>81 (20)</td>
<td>82 (18)</td>
<td>0.88</td>
<td>71 (30)</td>
<td>74 (25)</td>
<td>0.61</td>
<td>0.48</td>
</tr>
<tr>
<td>General health</td>
<td>70 (18)</td>
<td>65 (18)</td>
<td>0.29</td>
<td>65 (17)</td>
<td>63 (21)</td>
<td>0.64</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).
* t test with repeated measures.
† Analysis of covariance.

Table 4 illustrates the quality-of-life measures among the patients in the study, separating these into baseline and follow-up, 6 months after the ablation procedure. Although there was a trend for improvement across multiple areas including physical function, physical and emotional roles, and social function among the PVAI patients, only the change in energy levels reached statistical significance, at $P=0.02$. Only a trend toward improvement in the physical and emotional roles was seen among the CPVA patients. Comparing the 2 groups, a trend to greater improvement in the energy levels was seen among PVAI patients compared with their CPVA counterparts ($P=0.07$).

Complications

One of the patients randomly assigned to PVAI had an intraprocedural pericardial effusion that was drained in the electrophysiology laboratory. No patient had PV stenosis in excess of 20%. There were no thromboembolic events or strokes. One of the patients was started on amiodarone after an early recurrence and continued it until 9 months after ablation. Although this patient had no further AF recurrences during this period, the outcome was classified as ablation failure, based on study definitions.

Discussion

This study compared long-term outcomes of catheter ablation for patients with paroxysmal and persistent AF refractory to antiarrhythmic drugs using the PV antrum isolation approach guided by ICE and a circular mapping catheter versus a 3D mapping–guided technique without ensuring PV isolation, supplemented by ablation of complex fractionated atrial electrograms. The patients enrolled into either group had similar baseline clinical parameters. Each procedure took close to 4 hours to complete, with 3D mapping associated with a shorter fluoroscopy exposure time.

Patients randomly assigned to ablation using the PV antrum isolation approach were significantly more likely to achieve and maintain sinus rhythm compared with patients treated using the circumferential PV ablation technique supplemented by CFAE ablation in select patients. These patients showed a trend to improvement across the spectrum of the quality-of-life domains, with a somewhat greater change from baseline in energy levels compared with patients randomly assigned to CPVA. Although patients randomly assigned to CPVA were somewhat more likely than patients treated with PVAI to have an AF recurrence, most of the difference in recurrence rates was driven by a significantly higher rate of recurrence in an organized LA tachyarrhythmia. Although the difference may be secondary to linear lesions and CFAE ablation in the CPVA arm, it is probably multifactorial and underscores our limited ability to verify the permanence of the delivered lesions at the time of ablation because no conduction gaps in the lines were seen as validated by the ablation catheter, suggesting that (1) contact between catheter and tissue may have been inconsistent because of inherent differential deformation of the left atrium, (2) the ablation catheter may not be an adequate tool to check for gaps, and (3) linear lesions are destined to fail regardless of whether block is established at the time of the procedure because of formation of linear or bifurcated gaps in recovery, whereas during a PVAI using a roving Lasso approach, energy delivery at any site displaying PV potentials within the area of interest would be more likely to generate overlapping lesions and recover with no gaps or with angulated gaps.

Similar success rates have been previously reported with electroanatomically guided circumferential ablation and with circular mapping and ICE-guided PV antrum isolation approach. Most of the data are based on large single-center registries. Two published studies compared circumferential PV ablation with the PV isolation approach in a randomized fashion. In one study, patients ablated using the electroanatomical technique were treated with an 8-mm-tip as opposed to the 4-mm-tip catheter used in the other group. The circular mapping catheter was not guided by ICE, and the lesions were delivered to achieve ostial rather than more proximal isolation of the veins, later shown to be less effective by other investigators. Furthermore, energies used to create ablation lesions in patients treated using circular mapping were far lower than those used in the electroanatomically guided ablation group. Only short-term results were reported, and there was no consistent method for tracking PV stenoses beyond symptomatic patient follow-up. These factors may have favored the group treated with electroanatomically guided isolation and disadvantaged the
other group in this study. A randomized study from another center demonstrated superiority of the PV isolation approach.24 There is growing awareness that PV isolation is important in improving AF ablation outcomes and should serve as the basis for any adjunct ablative approach.25 Our study, in which both lesion sets were delivered proximally, further supports this strategy.

Apart from shedding further light on the question of importance of PV isolation, this study illustrates outcomes expected for catheter ablation of AF outside of the large dedicated AF ablation centers in a multicenter/multioperator environment. The success rates demonstrated in either group are substantially lower than those historically published for either approach, probably more closely representing clinical practice in the real world. Some of the variables accounting for the difference in outcomes between this and previously published studies may include looking at the success of a single ablation rather than the success of an ablation strategy, which may include several procedures. A very strict definition of recurrence was used with any recurrence of AF or an organized LA tachyarrhythmia after ablation (beyond the blanking period) considered failure. All centers in our study perform local AF follow-up without reliance on the peripheral centers for recurrence information. With no patient lost to follow-up, this may have been responsible for a greater number of arrhythmia events coming to light.

The study inclusion criteria allowed enrollment of patients with paroxysmal and persistent AF. The numbers of patients in either group are distributed evenly between study arms, as illustrated in Table 1. Although the study does not have enough power to better assess whether one or the other ablation strategy is more effective in paroxysmal or persistent patients, the results stand in a group of patients composed of a mix of approximately 80% paroxysmal and 20% persistent AF. This is a typical distribution of AF patients ablated at the Canadian centers, making results of this study more generalizable.

Thankfully, no significant complications beyond a single pericardial effusion drained in the electrophysiology laboratory were seen in either treatment group in our study despite a rigorous follow-up protocol that included routine postablation CT to rule out PV stenosis and damage to collateral structures, suggesting that AF ablation is a relatively safe procedure even outside of the large centers.

In reality, patients treated with catheter ablation for AF may be offered a procedure guided by 3D mapping, circular mapping catheter, and real-time ICE. The fact that we limited the use of ICE and the circular mapping catheter to the PV isolation group is both a limitation and a strength of the study, closely following clinical practice at the outset of the trial in 2004. This limitation underscores the difficulty in conducting a clinical trial for AF ablation outside of a large center in the context of a rapidly evolving ablation approach. It may be reasonable to suggest that the 3 techniques combined might deliver a better efficacy and safety profile. This remains to be determined in future studies.

Limitations

This was a relatively small study, with patients distributed across multiple centers. Furthermore, only a small number of proctored cases were required from each operator before enrolling patients into the study. On the other hand, all operators in the study were otherwise experienced electrophysiologists with years of experience in AF ablation and 3D mapping, and the number of required proctored cases was similar between the treatment arms.

Routine arrhythmia induction was not specified in the study apart from CPVA patients who were in sinus rhythm at the end of the procedure. It is possible that if reinduction was indeed a part of the protocol, some organized LA arrhythmias could have been induced and mapped, possibly affecting the outcome of this study. Whether or not single-catheter CPVA followed by routine arrhythmia induction, mapping, and ablation of all resultant organized arrhythmias is superior to CPVA alone may need to be studied further.

Conclusion

A single PV antrum isolation procedure may be more likely to result in freedom from AF or organized LA tachycardia off antiarrhythmic drugs than circumferential PV ablation supplemented by ablation of CFAE in select patients.

Disclosures

Drs Khaykin, Verma, and Skanes have served on advisory boards for Biosense Webster. This trial predates trial registration requirements.

References


**CLINICAL PERSPECTIVE**

Two of the mainstream approaches to ablation in patients with atrial fibrillation include circumferential pulmonary vein ablation guided by 3D imaging and pulmonary vein antrum isolation using circular mapping alone or in combination with intracardiac echocardiography. Both strategies boast success, defined as cure of atrial fibrillation, in 60% to 90% of the patients treated, with some risk of hemorrhagic, embolic, and other complications. Although 3D electroanatomic imaging–guided pulmonary vein ablation is a clinically attractive procedure, until recently, only 1 center was able to consistently demonstrate an acceptable efficacy and safety profile with this technique. Pulmonary vein antrum isolation guided by circular mapping, on the other hand, may have a better-defined procedural end point. Unlike the static images of the left atrium provided by most 3D mapping systems, intracardiac echocardiography provides real-time imaging of the pulmonary vein ostia and catheter position, adding an extra level of comfort to the procedure both in terms of identification of the anatomic substrate and avoidance of complications. Accordingly, the objective of this multicenter, multiprovider, randomized, controlled trial was to compare safety and efficacy of electroanatomic circumferential pulmonary vein ablation and pulmonary vein antrum isolation guided using a circular mapping catheter and intracardiac echocardiography with adjuvant ablation of complex fractionated activity in patients with refractory or inducible atrial fibrillation after circumferential pulmonary vein ablation but not pulmonary vein antrum isolation. We found a significant difference in outcomes after a single ablation procedure with more than double the rate of arrhythmia recurrence in patients treated with circumferential pulmonary vein ablation.
A Randomized Controlled Trial of the Efficacy and Safety of Electroanatomic Circumferential Pulmonary Vein Ablation Supplemented by Ablation of Complex Fractionated Atrial Electrograms Versus Potential-Guided Pulmonary Vein Antrum Isolation Guided by Intracardiac Ultrasound

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