Atrial Electroanatomic Remodeling After Circumferential Radiofrequency Pulmonary Vein Ablation

Efficacy of an Anatomic Approach in a Large Cohort of Patients With Atrial Fibrillation

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Background—Circumferential radiofrequency ablation around pulmonary vein (PV) ostia has recently been described as a new anatomic approach for atrial fibrillation (AF).

Methods and Results—We treated 251 consecutive patients with paroxysmal (n=179) or permanent (n=72) AF. Circular PV lesions were deployed transseptally during sinus rhythm (n=124) or AF (n=127) using 3D electroanatomic guidance. Procedures lasted 148±26 minutes. Among 980 lesions surrounding individual PVs (n=956) or 2 ipsilateral veins with close openings or common ostium (n=24), 75% were defined as complete by a bipolar electrogram amplitude <0.1 mV inside the lesion and a delay >30 ms across the line. The amount of low-voltage encircled area was 3594±449 mm², which accounted for 23±9% of the total left atrial (LA) map surface. Major complications (cardiac tamponade) occurred in 2 patients (0.8%). No PV stenoses were detected by transesophageal echocardiography. After 10.4±4.5 months, 152 patients with paroxysmal AF (85%) and 49 with permanent AF (68%) were AF-free. Patients with and without AF recurrence did not differ in age, AF duration, prevalence of heart disease, or ejection fraction, but the LA diameter was significantly higher (P<0.001) in permanent AF patients with recurrence. The proportion of PVs with complete lesions was similar between patients with and without recurrence, but the latter had larger low-voltage encircled areas after radiofrequency (expressed as percent of LA surface area; P<0.001).

Conclusions—Circumferential PV ablation is a safe and effective treatment for AF. Its success is likely due to both PV trigger isolation and electroanatomic remodeling of the area encompassing the PV ostia. (Circulation. 2001;104:2539-2544.)

Key Words: arrhythmia ▪ ablation ▪ fibrillation ▪ mapping

Transcatheter ablation of atrial fibrillation (AF) with radiofrequency (RF) energy has recently been introduced; its target is a modification of the arrhythmogenic substrate, resulting in significant reduction or disappearance of AF.1,2 Linear ablation in the right atrium and/or left atrium (LA) was initially proposed with the purpose of replicating the surgical “maze” procedure.3 Alternatively, selective ablation of arrhythmogenic foci, mainly located within the pulmonary veins (PVs), was reported as an effective treatment for AF.4 Recently, circumferential RF ablation of all 4 PV ostia has been described as a new anatomic approach for AF.5 The present study reports the outcome of this approach in a large cohort of AF patients.

Study Population

We studied 251 consecutive AF patients who underwent circumferential PV ablation between November 1998 and October 2000. The population comprised 179 patients with paroxysmal AF lasting for >1 year who had ≥2 sustained (>1 hour) episodes per week, despite antiarrhythmic therapy with 2.9±1 drugs, and 72 patients with permanent AF for >3 months that was resistant to repeated attempts of pharmacological and electrical cardioversion. Symptom duration ranged from 1 to 28 years (average, 7.9±7.1 years) for patients with paroxysmal AF and from 2 to 28 years (average, 8.5±8.3 years) for those with permanent AF. Most patients were free from structural heart disease; several had previously undergone ablation procedures (Table 1). All patients were on effective oral anticoagulation for >4 weeks. Informed consent was

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2539
Ablation Procedure

RF energy was delivered via the distal electrode of the mapping catheter. Circumferential lines were created with contiguous focal RF lesions at a distance >5 mm from the PV ostia. In most cases, 4 discrete PV orifices were detected, and separate ablation lines were performed around each vein. In some instances, when lateral and/or septal veins had ostia <20 mm apart from each other (13 patients, 5%) or had a common ostium with early branching (3 patients, 1%), or a separately branching PV was identified (8 patients, 3%, always in close proximity to another vein), a single circular line around 2 ipsilateral veins was created. Energy was applied for 15 to 30 s with a maximum temperature setting of 60°C. The target was reduction of the local potential amplitude by 80%.

Remapping Procedure

After completion of ablation, the pre-RF anatomic map was used to acquire new points, with the purpose of comparing pre-RF and post-RF maps. Lesion completeness was defined according to the following criteria: (1) Low peak-to-peak bipolar potentials (<0.1 mV) inside the lesion (Figure 1) and (2) a LAT delay >30 ms between contiguous points lying in the same axial plane across the line (Figure 2).

To quantify the ablated area (Figure 3), custom-designed software was applied to the standard CARTO reference frame. For calculating the low-voltage encircled area, all points inside and around the lesion are carefully reviewed to verify that none has a bipolar amplitude ≥0.1 mV, then the outermost points with an amplitude <0.1 mV are selected and tagged and the software calculates the surface area (in mm²) of the 3D reconstruction inside the marked region. The LA surface area outside the lesion is then automatically determined. For all points in the PV ostial areas, bipolar and unipolar signal amplitudes were highly correlated (r=0.87, P<0.001), suggesting the limited influence of different tip-tissue contact and orientation of the catheter. Measurements were performed off-line by 2 independent operators who had no knowledge of clinical and outcome data. Both interobserver and intraobserver variability, expressed as the mean±SD difference between the measurements, were acceptable with a mean difference <5%. The average of 3 measurements was used for analysis.

Postablation Management

After ablation, all patients were placed on anticoagulant therapy (warfarin) and observed with telemetry monitoring for 24 to 48 hours. Among paroxysmal AF patients, 140 (78%) were discharged without antiarrhythmic drugs, and 39 (22%) received drugs (10 received propafenone, 13 flecainide, 3 amiodarone, and 13 sotalol) because they manifested atrial arrhythmias (extrasystoles, tachycardia, or AF) during the 2 days after ablation. For permanent AF patients who had resistant and long-lasting arrhythmia, we thought that antiarrhythmic drugs could improve the likelihood of modifying atrial electrical remodeling and maintaining sinus rhythm. Therefore, such patients were discharged with 1 drug that, in the past, seemed to be well tolerated although unable to prevent AF. In all patients, antiarrhythmics and anticoagulant treatment were discontinued after 3 months in the absence of AF recurrence, unless other risk factors were present. Other medications, including digitals, β-blockers and calcium antagonists, were prescribed when indicated.

Follow-up consisted of outpatient visits with serial echocardiograms and Holter monitoring performed at discharge, monthly for ≥3 months, and on symptom recurrence. The procedure was considered successful if no recurrences of AF lasting >30 s were present during postdischarge follow-up. Transesophageal echocardiography was performed within 3 days and 1 to 3 months after ablation to assess potential PV narrowing.

Sympathovagal Balance Analysis

Sympathovagal balance was assessed in 39 patients with paroxysmal AF by time- and frequency-domain analysis of heart rate variability, as measured from 24-hour Holter recordings obtained before RF and at discharge. Commercially available software was used to analyze the root mean square difference of successive RR intervals (RMSSD) and the percentage of adjacent RR intervals that differed by >50 ms (pNN50). Power spectral analysis was performed by a fast Fourier transform algorithm, producing a spectrum for the 0.01- to 0.1-Hz

### TABLE 1. Clinical Characteristics of the 251 Study Patients

<table>
<thead>
<tr>
<th>Risk factors, n (%)</th>
<th>Paroxysmal AF (n=179)</th>
<th>Permanent AF (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>38 (21)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Smoke</td>
<td>31 (17)</td>
<td>30 (42)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>27 (15)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>153 (85)</td>
<td>61 (85)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>11 (6)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>6 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>2 (1)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Other arrhythmias, n (%)</td>
<td>44 (24)</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Previous ablation, n (%)</td>
<td>39 (22)</td>
<td>20 (28)</td>
</tr>
<tr>
<td>Linear RA ablation</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Linear LA ablation</td>
<td>46 (26)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Conus/IVS/tricuspid annulus</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Circumferential PV ablation</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>AV node modulation</td>
<td>2 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

AV indicates atrioventricular; IVC, inferior vena cava.
frequency band. Low-frequency power (0.04 to 0.15 Hz) and high-frequency power (0.15 to 0.4 Hz) spectra were obtained, and the low/high frequency ratio was calculated.6

Statistics
Dichotomous variables were compared using $\chi^2$ with Yates’ correction. Continuous measures are expressed as mean±SD and were compared with a $t$ test for paired or unpaired data, as appropriate. Statistical significance was inferred at $P<0.05$.

Results
Feasibility and Safety
Lesions were deployed during sinus rhythm in 124 patients (49%) and during AF in the remaining 127 (51%). Among the latter, sinus rhythm was acutely restored during RF application in 31 (24%) and by direct current shock in the remaining 96. Total procedure duration was 148±26 minutes, with a fluoroscopy time of 28±17 minutes, a mapping time of 57±8 minutes, and an ablation time of 54±12 minutes for delivering 92±16 RF pulses.

RF application around PV orifices did not result in intolerable pain or severe cough. Transient advanced or complete AV block or systolic hypotension ($<90$ mm Hg) occurred in 30 patients (12%) during RF delivery, particularly around the superolateral PV (19 patients). In these patients, no bradycardias were recorded during subsequent telemetry monitoring. There were 2 cases (0.8%) of cardiac tamponade requiring pericardiocentesis, and 2 cases of minor pericardial effusion managed medically. No thromboembolic episode occurred.

Among 980 lesions performed around individual PVs ($n=956$) or 2 ipsilateral veins with close openings or common ostium ($n=24$), 75% were defined as complete by post-RF remapping. By quantitative voltage map analysis, the low-voltage encircled area ranged from 2941 to 4231 mm$^2$ (average, 3594±449 mm$^2$), which accounted for 23.9% of the total LA surface area. Interestingly, the amplitude reduction occurred not only within the area encompassed by the circular line, but also outside the line.

By off-line local electrogram analysis from 124 pre-RF maps during atrial pacing, PV potentials preceded by far-field atrial activity were detected in 401/1146 near-ostial points (35%). This pattern was mostly observed in superior PVs (superolateral, $n=99$ [80%]; superoseptal, $n=82$ [67%]) and less frequently in inferior veins (inferoseptal, $n=25$ [20%]; inferolateral, $n=61$ [49%]). In post-RF maps, PV potentials were not recorded in any of the complete lesions, although they were found in 106 of 270 incomplete lesions.

Clinical Outcome
After a follow-up of 10.4±4.5 months (range, 3 to 27 months), freedom from AF was 80% overall (201 of 251 patients, including 13 on antiarrhythmic drugs), 85% for paroxysmal AF (152 of 179 patients, including 35 discharged on paroxysmal AF (152 of 179 patients, including 35 discharged on antiarrhythmic drugs, 31 of whom discontinued their

Figure 1. Voltage maps of the LA, posteroanterior view (left, before ablation; right, after ablation) depicting peak-to-peak bipolar electrogram amplitude. Red represents lowest voltage and purple, highest voltage. Postablation areas within and around the ablation lines show a marked voltage reduction. SL indicates superolateral; SS, superoseptal; IS, inferoseptal; and IL, inferolateral.

Figure 2. Solid activation maps of the LA during coronary sinus pacing, posteroanterior view (left, before ablation; right, after ablation). Color-coding represents activation times, with red expressing earliest and purple, latest activation. After ablation, the sudden transition from green to blue in the ablated areas represents markedly delayed activation, which occasionally involves the LA appendage, as in the given example. SL indicates superolateral; SS, superoseptal; IS, inferoseptal; and IL, inferolateral.
medication at 3 months), and 68% for permanent AF (49 of 72 patients, including 40 no longer on drugs). Among 23 permanent AF patients with recurrence, 15 developed a paroxysmal AF type responsive to drugs.

Patients with and without AF recurrence are compared in Table 2. Subgroups did not differ in age, AF duration, presence of heart disease, or ejection fraction, but LA diameter was significantly greater \( P<0.001 \) in permanent AF patients with unsuccessful ablation.

During follow-up, all patients without AF recurrence showed preserved and/or improved LA contraction, assessed by mitral inflow Doppler tracings, and a significant \( P<0.05 \) reduction in LA size versus pre-RF. Transesophageal echocardiography showed no high-velocity turbulence near the ostia that suggested PV stenosis in any of the patients.7

The percentage of PVs with complete lesions was similar between patients with and without recurrence. In paroxysmal patients without recurrence, the postablation low-voltage encircled area was larger \( P<0.001 \), encompassing 32% of the total LA surface area compared with only 21% in those with recurrence. This finding was related in part to a greater extent of the low-voltage area outside the lesions \( P=0.01 \). In permanent AF patients without recurrence, the extent of encircled area and the percent of low-voltage area outside the lesions trended toward significantly higher values than in patients with recurrence \( P=0.07 \) and 0.06, respectively), and the amount of post-RF low-voltage area was significantly higher when related to the overall LA surface area (29% versus 13%, \( P<0.001 \)).

Heart Rate Variability Analysis

Compared with pre-RF values (Table 3), time-domain measures primarily modulated by parasympathetic tone (pNN50, RMSSD) were significantly increased after ablation, and frequency-domain analysis suggested decreased sympathetic activity with increased high frequency power and decreased low/high frequency ratio.

Discussion

This study describes the outcome of a new ablation technique aimed at curing AF in a large patient population. An anatomic approach targeting the areas around the PV ostia was selected on the basis of experimental data and human surgical observations, as well as our initial experience in a group of 26 patients, supporting the dominance of the LA and the PV regions for triggering and maintaining AF.

The feasibility of our approach and procedure duration were improved compared with the technique originally described. In fact, ablation during AF was performed using a simple anatomic map that is less time-consuming than a complete cycle-length map, which we initially acquired to assess AF electrogram types. Furthermore, we previously used a maximum RF application over 60 s, a standard approach for ablation procedures, whereas in the present study, shorter pulses of 15 to 30 s obtained the target voltage reduction in the thin venous portions of the LA. An advantage of our technique is that the lesion can be tailored to the varying PV-LA junction features, unlike novel circumferential ablation catheters with a prefixed size and design, which are difficult to accommodate in ostia with larger diameters, eccentric shapes, or a complex proximal PV branching pattern.

Despite the rewarding success rates obtained in different studies that seem to call for a broader clinical application of PV ablation, concerns still exist about the possibility of serious complications, such as cerebrovascular accidents, PV stenosis, cardiac tamponade, and damage to extracardiac structures, such as bronchioles, the right pulmonary artery, and lung tissue. In our large cohort, only 0.8% of the patients experienced major complications (cardiac tamponade). By performing ablation outside the PV ostium and carefully avoiding RF application at points where a definite atrial potential was not recorded, we did not produce PV stenosis, in keeping with other ablation studies that deployed the lesions in the proximal portion of the vein. In this and other studies, the risk of thromboembolic events was virtually absent after appropriate patient screening and prophylactic treatment.

The present study confirmed the high success rate (80%) of circumferential PV ablation in a large cohort of patients with both paroxysmal and permanent AF. Although most patients were free from structural heart disease, good clinical results were achieved even in some subjects suffering from mitral stenosis, mitral valve prolapse, cardiomyopathy, and coronary heart disease. We observed no significant relationship...
Circumferential PV ablation may affect AF initiation and/or maintenance by preventing the egress of impulses arising from arrhythmogenic PVs. However, an evaluation of electroanatomic maps detects a delay of PV activation but does not validate PV isolation, as demonstrated by the abolition of PV spike potentials. Instead, we found a delay of PV activation. Nevertheless, the absence of discrete electrical activity inside the lesion may be a surrogate for effective atriovenous disconnection, as substantiated by our finding of no PV potentials in any of the complete lesions. However, isolation of PV foci may not be the sole mechanism responsible for the AF cure, as suggested by our finding of no significant relationship between lesion completeness and clinical outcome.

TABLE 3. Changes in Indexes of Heart Rate Variability After Circumferential PV Ablation

<table>
<thead>
<tr>
<th></th>
<th>Before Ablation</th>
<th>After Ablation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMSSD, ms</td>
<td>22.2±6.72</td>
<td>27.4±5.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>5.2±1.8</td>
<td>7.1±3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HF power, ms</td>
<td>291±34</td>
<td>336±31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>3.46±0.51</td>
<td>2.87±0.67</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

HF indicates high frequency; LF, low frequency.
Importantly, the only predictive criterion for a successful ablation seems to be the amount of post-RF low-voltage encircled area. Furthermore, the phenomenon of the reduction of voltage amplitude outside the ablation line seems to be a discriminating factor. It is, therefore, likely that ablation, when effective, results in a profound atrial electroanatomic remodeling involving, to some extent, the LA posterior wall to the point that the substrate for AF is no longer present. This contention is substantiated by our observation of permanent AF termination with RF delivery at PV ostia and also by the improvement in LA size and transport function during follow-up, which allowed us to safely discontinue anticoagulation. The critical role of the area surrounding the PV ostia in AF has been demonstrated by several studies showing that the majority of organized atrial electrical activity arises from the PV regions and LA posterior wall.1,5,8,9 Ablation targeting these sites is able to interrupt connections between the sleeves of myocardial fibers in the PVs and the atrial myocardium, making unsuitable reentry pathways, destroying focal driving rotors (“mother waves”) responsible for AF maintenance, and/or exerting a denervation effect.1,5,9,13 Regarding the denervation effect, we detected a postablation shift of sympathovagal balance toward parasympathetic predominance, suggesting the stimulation and/or destruction of endocardial nerve terminals. This effect is probably also involved in the genesis of inhibitory cardiovascular reflexes during ablation, which was observed in 12% of our patients. Circumferential PV ablation could result in damage to structures involved in autonomic regulation, such as Marshall’s ligament, whose interruption prevents isoproterenol-induced AF in dogs.13 Hsieh et al.14 in a group of 30 paroxysmal AF patients undergoing focal PV ablation, reported postablation enhanced sympathetic activity, namely, heart rate variability changes opposite to those detected after circumferential PV ablation. Therefore, our technique most likely produced local denervation rather than autonomic stimulation, and this effect could contribute to the suppression of AF.

This study has some limitations. Definition of the true PV ostium using CARTO alone may be difficult due to the varying 3D vein morphology. Detection of a common ostium or very close openings of 2 ipsilateral veins does not affect our approach, but missing a separately branching PV could have occurred in some patients, although this pattern is infrequent according to anatomic findings.15

Given the anatomic nature of our approach, no investigation was made on right atrial or LA electrical activity. Therefore, possible foci or reentry circuits from non-PV areas could have contributed to the failure of the procedure in some cases. Moreover, a substantial proportion of patients were on drugs for 3 months after ablation, so the early effect of ablation cannot be assessed with certainty. Patients, however, were so highly symptomatic, despite medical treatment before ablation, that the disappearance or dramatic reduction of the arrhythmia cannot be attributed to antiarrhythmic therapy alone.

In conclusion, this study suggests that circumferential PV ablation is a safe and effective treatment for AF, regardless of the underlying mechanism of the arrhythmia. Because effective PV isolation is not crucial to achieve favorable clinical outcomes, the efficacy of our anatomic approach is likely due to both PV trigger isolation and electroanatomic remodeling of the area encompassing the PV ostia.

Acknowledgments

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References

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