Freedom From Atrial Tachyarrhythmias After Catheter Ablation of Atrial Fibrillation
A Randomized Comparison Between 2 Current Ablation Strategies

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**Background**—Data on the comparative value of the circumferential pulmonary vein and the segmental pulmonary vein ablation for interventional treatment of atrial fibrillation are limited. We hypothesized that the circumferential pulmonary vein ablation approach was superior to the segmental pulmonary vein ablation approach.

**Methods and Results**—One hundred patients with highly symptomatic atrial fibrillation were randomly assigned to undergo either circumferential (n=50) or segmental pulmonary vein ablation (n=50). Freedom from atrial tachyarrhythmias in a 7-day Holter monitoring at 6 months was the primary end point. Secondary end points were freedom of arrhythmia-related symptoms and a composite of pericardial tamponade, thromboembolic complications, and pulmonary vein stenosis (safety end point). On the basis of the results of the 7-day Holter monitoring at 6 months, 21 patients (42%) after circumferential pulmonary vein ablation and 33 patients (66%) after segmental pulmonary vein ablation (P=0.02) were free of atrial tachyarrhythmia episodes. During the 6-month follow-up period, 27 patients (54%) after circumferential pulmonary vein ablation and 41 patients (82%) after segmental pulmonary vein ablation remained free of arrhythmia-related symptoms (P<0.01). No significant difference was found in the safety end point (6 versus 7 events; P=0.77) in the circumferential versus segmental pulmonary vein ablation group, respectively.

**Conclusions**—This study demonstrates no superiority of the circumferential pulmonary vein ablation over segmental pulmonary vein ablation for treatment of atrial fibrillation in terms of efficacy and safety. *(Circulation. 2005;111:2875-2880.)*

**Key Words:** ablation ■ atrium ■ electrophysiology ■ fibrillation ■ atrial fibrillation

During the past decade, limited success rates of drug treatment1 stimulated an exploration of interventional treatment options for atrial fibrillation.2-5 In most instances, the evaluation of treatment success of the new ablative therapies was based on symptomatic atrial fibrillation recurrences during a follow-up period.1,6,7 It is well known, however, that atrial fibrillation is frequently characterized by a variable spontaneous course and that highly symptomatic and totally silent episodes may be coexisting in the same patient.8 Thus, besides intensive questioning for arrhythmia-related symptoms, long-term monitoring is needed for accurate assessment of the true success rates of new ablative treatment strategies.

We conducted a randomized study comparing the safety and effectiveness of the most commonly used interventional ablation techniques for treatment of paroxysmal and persistent atrial fibrillation: (1) the segmental pulmonary vein ablation approach, which electrically isolates the pulmonary veins from the left atrium by applying discrete lesions at the ostial region of the pulmonary veins.9-12 and (2) the circumferential pulmonary vein ablation approach, in which encircling of all pulmonary veins is performed by creating linear lesions in the left atrial myocardium outside the pulmonary vein ostia.4,13 Limited information exists with regard to the comparative efficacy of these ablation approaches. Thus far, only a single randomized, prospective study comparing both approaches with 40 patients in each treatment arm has been published.14 In this trial, on the basis of patients’ symptoms, the approach of circumferential pulmonary vein ablation appeared to have a greater efficacy than the approach of segmental pulmonary vein ablation.

In contrast to this and other studies, we performed a follow-up focusing not only on arrhythmia-related symptoms but also on 7-day Holter monitoring for objective proof of freedom from arrhythmia.
We hypothesized that the circumferential pulmonary vein ablation approach was superior to the segmental pulmonary vein ablation approach.

Methods

Patients
Highly symptomatic, drug-refractory atrial fibrillation episodes occurring at least twice a month were the inclusion criterion. Exclusion criteria were intracardiac thrombi documented by transesophageal echocardiography, left ventricular ejection fraction <35%, history of myocardial infarction or cardiac surgery in the previous 3 months, and previous ablation procedures for atrial fibrillation. The institutional ethics committee approved the study protocol, and all patients gave written informed consent before recruitment in the study. Between March 2002 and December 2003, 100 patients were randomly assigned according to the randomization code contained in sealed envelopes to undergo either circumferential (50 patients) or segmental (50 patients) radiofrequency pulmonary vein ablation of atrial fibrillation. Because of technical aspects of the procedure, the investigator could not be blinded.

Interventions
Two days before the procedure, oral anticoagulation therapy was replaced by heparin, which was stopped 4 hours before the procedure. Antiarrhythmic drugs were discontinued 5 half-lives before the procedure. Catheter electrodes were inserted with the use of 1 or both femoral veins. The left atrium was accessed by single (circumferential pulmonary vein ablation) or double (segmental pulmonary vein ablation) transseptal puncture or via an open fossa ovalis. Preablation and postablation angiograms of all accessible veins were performed. After placement of electrode catheters within the left atrium, anti-coagulation was started by a bolus administration of 5000 IU heparin, followed by continuous intravenous heparin infusion to maintain an activated clotting time at ~300 seconds. In all patients with ongoing atrial fibrillation, an internal or external cardioversion was performed at the beginning of the ablation procedure. In case of recurrence of sustained atrial fibrillation (>10 minutes) during or at the end of the ablation procedure, sinus rhythm was restored with the use of the same cardioversion techniques.

For circumferential pulmonary vein ablation, the 3-dimensional geometry of the left atrium was reconstructed by the use of an electroanatomic mapping system (CARTO, Biosense Webster Inc) (Figure 1). After each of the pulmonary veins was entered with the ablation catheter, the ostium was identified by pulling the catheter back under fluoroscopic control until the tip entered the cardiac silhouette associated with simultaneous impedance decrease and appearance of atrial potentials. The position of the pulmonary vein was marked with the special features of the CARTO system. Radiofrequency current was applied with the 8-mm tip catheter (40 patients; maximum temperature, 55°C; maximum power, 50 to 70 W) and/or the cooled 4-mm tip (22 patients; maximum temperature, 48°C; maximum power, 35 to 50 W) (both Biosense Webster, Inc) to encircle the left- and right-sided pulmonary veins. Ablation lines consisted of contiguous focal lesions deployed at a distance >5 mm from the pulmonary vein ostia. To prevent left atrial flutter, an additional ablation line was drawn from the circling lesion around the left lower pulmonary vein to the mitral valve annulus. Radiofrequency current was delivered until the end point for ablation, namely, a maximum local bipolar electrogram amplitude reduction by ≥80% or ≤0.1 mV, was reached. The complete isolation of the pulmonary veins was not a target of the procedure.

For segmental pulmonary vein ablation, a circular steerable, decapolar mapping catheter (Lasso, Biosense Webster, Inc) and an irrigated tip ablation catheter (Celsius, Thermo-Cool, Biosense Webster, Inc) were inserted. After the pulmonary vein was entered, the circular mapping catheter was positioned as close to the pulmonary vein ostium as possible (Figure 2). Circular mapping was performed by obtaining 10 bipolar electrograms (1 to 2, 2 to 3, up to 10 to 1 electrode pairs) from the circularly arranged electrodes of the mapping catheter. The selection of the size of the circular mapping catheter was guided by angiographically estimated size of the pulmonary veins. Each vein was mapped circumferentially to document typical sharp local pulmonary vein potentials during steady state coronary sinus pacing (left pulmonary veins) or sinus rhythm (right pulmonary veins). Pulmonary vein isolation was performed by applying radiofrequency current at the ostial sites showing the earliest bipolar pulmonary vein potentials during sinus or paced rhythms, as previously described. Radiofrequency current was applied with the maximum temperature set at 48°C and the power set at 30 to 35 W. Disappearance or dissociation of the distal local pulmonary vein potentials during sinus or paced rhythm throughout the ostial circumference was considered a criterion for an effective electric isolation of the pulmonary vein from the left atrium.

Postablation Management
Patients remained hospitalized under continuous rhythm monitoring for at least 3 days after the ablation procedure. Heparin infusion was continued until the international normalized ratio was ≥2. No antiarrhythmic drugs were prescribed at discharge. If no recurrence of atrial fibrillation was detected within the first 3 to 6 months, coumadin was discontinued. A reablation procedure, with the use of the same technique as the first ablation, was offered to the patient in case of a symptomatic atrial fibrillation recurrence beyond the third month after the ablation procedure.

Follow-Up
After discharge, patients were scheduled for repeated visits in the arrhythmia clinic at 1, 3, and 6 months after the first ablation. At each of these visits, intensive questioning for arrhythmia-related symptoms (fatigue, dizziness, and nausea) since the last follow-up visit was performed, especially for those that the patient had experienced before ablation. At the 6-month follow-up visit, 7-day Holter monitoring was performed.

Multislice CT of the pulmonary vein was obtained before and 3 months after the ablation procedure for evaluation of the pulmonary vein anatomy and for detection of radiofrequency ablation-induced pulmonary vein stenosis.

Study End Points and Definitions
The primary end point of the study was freedom from atrial tachyarrhythmias (of ≥30-second duration) including atrial fibrilla-
tion and atypical atrial flutter documented by 7-day Holter monitoring performed at the 6-month follow-up.

Two secondary study end points were chosen. The first was freedom from arrhythmia-related symptoms during the 6-month follow-up. Because early recurrences of atrial tachyarrhythmias within the first month after ablation may be a transient phenomenon, this time interval was excluded from analysis. Second, a composite of peri procedural pericardial tamponade, thromboembolic complications, and pulmonary vein stenosis with ≥50% lumen loss (main vessel or first branching) was defined as a safety end point. Both the analysis of Holter recordings and the evaluation of the clinical outcome were performed by medical personnel unaware of the randomly assigned treatment.

Statistical Analysis
The number of patients included in the study was determined on the basis of the estimation of the sample size needed to identify a significant difference in the primary end point of the study. On the basis of previous studies, we assumed a relative risk reduction of 66% after circumferential compared with segmental pulmonary vein ablation.13,16 A sample size of 100 patients (50 patients per group) was required to ensure the detection of the difference between the groups with a 2-sided α value of 0.05 and a power of 90%.

All analyses were done on the basis of the intention-to-treat principle, i.e., the analyses were based on all randomized patients, as randomized. Data are presented as mean ± SD, median (25th, 75th percentiles), counts, or proportions (percentages). Differences in the continuous variables were checked for statistical significance by the use of t test if the data were normally distributed or Wilcoxon test for the data that did not follow a normal distribution. The normality of distribution was assessed with the 1-sample Kolmogorov-Smirnov test. Categorical data were compared by the χ² test or Fisher exact test when expected cell values were <5. Kaplan-Meier method was used to estimate arrhythmia-symptom–free survival. Differences in the arrhythmia-symptom–free survival were assessed by the log-rank test. A 2-sided P<0.05 was considered to indicate statistical significance.

Results
Baseline Characteristics
The clinical characteristics of patients in both groups are shown in Table 1. All patients had drug-refractory atrial fibrillation, with 10 (median) atrial fibrillation episodes per month despite the use of 2 (median) antiarrhythmic drugs.

Procedural Characteristics
The mean total procedure times were 284±86 minutes for circumferential pulmonary vein ablation and 256±72 minutes for segmental pulmonary vein ablation (P=0.02). The mean fluoroscopy times were 45±21 minutes for circumferential pulmonary vein ablation and 72±26 minutes for segmental pulmonary vein ablation (P<0.01). Total ablation time was 72±19 minutes for the circumferential pulmonary vein ablation approach and 52±30 minutes for the segmental pulmonary vein ablation approach (P<0.001).

Efficacy Analysis
All patients completed the 6-month follow-up, and no patient died during this period. During the 6-month follow-up, 27 patients (54%) after circumferential pulmonary vein ablation and 41 patients (82%) after segmental pulmonary vein ablation (P<0.01) were free of arrhythmia-related symptoms (Figure 3). A reablation procedure was performed between 3 and 6 months after randomization in 12 symptomatic patients of the circumferential pulmonary vein ablation group and in 8 symptomatic patients of the segmental pulmonary vein ablation group (P=0.31).

The primary end point analysis based on the results of 7-day Holter monitoring at the 6-month follow-up showed that 21 patients (42%) after circumferential and 33 patients (66%) after segmental pulmonary vein ablation were in sinus rhythm (P=0.02). Of the 54 patients with sinus rhythm in the

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
<th>Circumferential Pulmonary Vein Ablation (n=50)</th>
<th>Segmental Pulmonary Vein Ablation (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>28/22</td>
<td>36/14</td>
<td>0.71</td>
</tr>
<tr>
<td>Age, y</td>
<td>59 (52–64)</td>
<td>61 (54–65)</td>
<td>0.84</td>
</tr>
<tr>
<td>Duration of atrial fibrillation, y</td>
<td>5 (3–7)</td>
<td>4 (2–7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>43</td>
<td>46</td>
<td>0.38</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
<td>7</td>
<td>4</td>
<td>0.38</td>
</tr>
<tr>
<td>Atrial fibrillation episodes per month</td>
<td>10 (4–27)</td>
<td>10 (5–21)</td>
<td>0.97</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>27</td>
<td>30</td>
<td>0.54</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>47 (41–50)</td>
<td>46 (40–49)</td>
<td>0.60</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>64 (61–72)</td>
<td>62 (57–68)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are number of patients or median (interquartile range).
7-day Holter monitoring, 10 patients (4 patients in the circumferential and 6 patients in the segmental pulmonary vein ablation group) had a second ablation procedure 90 to 121 days after the initial procedure.

We found that 8 of 29 patients (28%) in the circumferential pulmonary vein ablation group and 8 of 17 patients (47%) in the segmental pulmonary vein ablation group with documented recurrence of atrial tachyarrhythmia were free of arrhythmia symptoms during the 6-month follow-up.

Atypical atrial flutter was observed in 9 patients after circumferential pulmonary vein ablation and in 1 patient after segmental pulmonary vein ablation ($P=0.01$).

Safety Analysis

The composite end point of periprocedural pericardial tamponade, thromboembolic complications, and pulmonary vein stenosis was encountered in 6 patients (12%) of the circumferential pulmonary vein ablation group and in 7 patients (14%) of the segmental pulmonary vein ablation group ($P=0.77$).

A detailed list of procedure-related complications is shown in Table 2. Mild pericardial effusion (3 to 8 mm) was observed in 22 patients in the circumferential pulmonary vein ablation group versus 5 patients in the segmental pulmonary vein ablation group ($P<0.01$). This did not lead to cardiac tamponade in any of the patients, and percutaneous drainage was never needed.

Thromboembolic complications occurred as transient ischemic attacks in 2 patients after circumferential pulmonary vein ablation and in 1 patient after segmental pulmonary vein ablation. One stroke with a persistent sensorimotor defect was noted in a patient after circumferential pulmonary vein ablation.

Pulmonary vein stenosis occurred after both ablation strategies (Table 2). However, it was more frequent after segmental pulmonary vein ablation (6 patients with 7 affected pulmonary veins versus 3 patients with 3 affected pulmonary veins after circumferential pulmonary vein ablation). An occlusion of a side branch of the left inferior pulmonary vein was noted in 2 patients, 1 in each ablation group. None of the patients with pulmonary vein stenosis was symptomatic during follow-up.

Discussion

Multiple lines of evidence suggest that the posterior wall of the left atrium plays a crucial role in atrial fibrillation by providing the arrhythmogenic substrate for atrial fibrillation maintenance. The initiating triggers, however, seem to originate frequently from the pulmonary veins. On the basis of these findings, 2 main ablation concepts for interventional treatment of atrial fibrillation have been developed during the past several years: (1) the segmental pulmonary vein ablation, which by inserting limited ablation lesions at the ostial pulmonary vein region has the potential to cure atrial fibrillation by an electric isolation of the pulmonary veins from the left atrium, and (2) the circumferential pulmonary vein ablation.
pulmonary vein ablation, which rather modifies the arrhythmogenic substrate for atrial fibrillation maintenance by creation of circular lesions in the left atrium around the pulmonary vein ostia. It potentially attenuates vagal innervation, thus reducing vagal reflexes that are believed to trigger atrial fibrillation.\textsuperscript{21} Using the technique of segmental pulmonary vein ablation, Haissaguerre et al\textsuperscript{16} reported that only 56\% of 70 treated patients remained free of arrhythmia-related symptoms after a single ablation procedure. The percentage of patients free of arrhythmia-related symptoms improved to 73\% for a follow-up period of 4 months, with 41 patients having undergone a repeated ablation procedure. In a series of 70 consecutive patients who underwent segmental pulmonary vein ablation, Oral et al\textsuperscript{14} reported that 83\% of patients with paroxysmal or persistent atrial fibrillation remained free of arrhythmia or had significant improvement at 5 months of follow-up.

Pappone et al\textsuperscript{13} performed circumferential pulmonary vein ablation under the guidance of an electroanatomical mapping system in a larger series of 251 patients with atrial fibrillation. These authors reported that 85\% of patients with paroxysmal or persistent atrial fibrillation and 68\% of patients with permanent atrial fibrillation remained free of arrhythmia-related symptoms during a follow-up of 6 to 12 months. A recent randomized study by Oral et al\textsuperscript{14} comparing both techniques in 80 patients concluded that circumferential pulmonary vein ablation is more effective than segmental pulmonary vein ablation in patients with paroxysmal atrial fibrillation. In that study, at the 6-month follow-up, only 67\% of patients who underwent segmental pulmonary vein ablation but 88\% of patients after circumferential pulmonary vein ablation were free of symptomatic atrial fibrillation recurrences or had significant improvement of arrhythmia-related symptoms without repeated ablation procedures. Although our study followed a very similar ablation protocol, the findings of the 2 studies differ significantly.

With regard to overall efficacy, our data for circumferential pulmonary vein ablation are less favorable than those achieved in the study of Oral et al.\textsuperscript{14} Three study aspects may offer an explanation for these discrepancies. First, 57\% of patients in our trial but only 4 of 80 patients in the study of Oral et al\textsuperscript{14} had structural heart disease. Second, in agreement with the initial description of the method,\textsuperscript{5,13} we did not draw a posterior ablation line between the 2 encircling lines around the left and right pulmonary veins. This was also due to safety concerns related to the close neighborhood of the esophagus.\textsuperscript{23} Third and probably more important, we used 7-day Holter monitoring to detect atrial tachyarrhythmia episodes for follow-up, whereas only the symptomatic atrial fibrillation episodes were accounted for in the study of Oral et al.\textsuperscript{14}

We found that 28%/47\% of patients in the circumferential/segmental pulmonary vein ablation group with documented recurrence of atrial tachyarrhythmia were free of arrhythmia symptoms during the 6-month follow-up, respectively. Our findings coincide with other studies that reported asymptomatic episodes in >50\% of patients with documented atrial fibrillation episodes\textsuperscript{24,25} but are in contrast to recently published data of Pappone et al.\textsuperscript{21} Furthermore, our data show that clinical trials that rely only on symptomatic episodes of atrial fibrillation considerably overestimate the efficacy of interventional treatment strategies. It is well known that atrial fibrillation at first appearance might present as a highly symptomatic arrhythmia. An unknown percentage of patients remains highly symptomatic for years, whereas others become increasingly asymptomatic, particularly when atrial fibrillation adopts a chronic course.\textsuperscript{3} However, not only the high percentage of asymptomatic atrial fibrillation episodes hampers the assessment of interventional treatment strategies of atrial fibrillation but also the variable natural course of atrial fibrillation.\textsuperscript{8}

In our study both ablation techniques were associated with the occurrence of moderate to severe but always asymptomatic pulmonary vein stenosis during follow-up. The rate was higher with segmental pulmonary vein ablation, as assessed by spiral CT. These findings are in accordance with other studies that have reported development of pulmonary vein stenosis after pulmonary vein ablation.\textsuperscript{26,27} Although pulmonary vein stenosis was asymptomatic in our series, this study warrants caution and advocates proper screening to detect pulmonary vein stenosis after both segmental and circumferential pulmonary vein ablation.

In conclusion, this study shows no superiority of circumferential pulmonary vein ablation over segmental pulmonary vein ablation for treatment of atrial fibrillation. Before making the choice between the 2 techniques, we should consider that symptomatic atypical atrial flutter is observed more frequently with the circumferential pulmonary vein ablation approach and that pulmonary vein stenosis occurs more often after segmental pulmonary vein ablation.

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Disclosure

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References


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