Pulmonary Vein Isolation for Paroxysmal and Persistent Atrial Fibrillation

Hakan Oral, MD; Bradley P. Knight, MD; Hiroshi Tada, MD; Mehmet Özaydin, MD; Aman Chugh, MD; Sohail Hassan, MD; Christoph Scharf, MD; Steve W.K. Lai, MD; Radmira Greenstein, MD; Frank Pelosi Jr, MD; S. Adam Strickberger, MD; Fred Morady, MD

Background—The pulmonary veins (PVs) have been demonstrated to often play an important role in generating atrial fibrillation (AF). The purpose of this study was to determine the safety and efficacy of segmental PV isolation in patients with paroxysmal or persistent AF.

Methods and Results—In 70 consecutive patients (mean age, 53±11 years) with paroxysmal (58) or persistent (12) AF, segmental PV isolation guided by ostial PV potentials was performed. The left superior, left inferior, and right superior PVs were targeted for isolation in all patients, and the right inferior PV was isolated in 20 patients. Among the 230 targeted PVs, 217 (94%) were completely isolated, with a mean of 6.5±4.2 minutes of radiofrequency energy applied at a maximum power setting of 35 W. A second PV isolation procedure was performed in 6 patients (9%). At 5 months of follow-up, 70% of patients with paroxysmal and 22% of patients with persistent AF were free from recurrent AF (P<0.001), and 83% of patients with paroxysmal AF were either free of symptomatic AF or had significant improvement. Among various clinical characteristics, only paroxysmal AF was an independent predictor of freedom from recurrence of AF (P<0.05). One patient developed unilateral quadrantopsia after the procedure. There were no other complications.

Conclusions—With a segmental isolation approach that targets at least 3 PVs, a clinically satisfactory result can be achieved in >80% of patients with paroxysmal AF. The clinical efficacy of pulmonary vein isolation is much lower when AF is persistent than when it is paroxysmal. (Circulation. 2002;105:1077-1081.)

Key Words: fibrillation ■ catheter ablation ■ pulmonary vein ■ atrium

The pulmonary veins have been demonstrated to often play an important role in generating atrial fibrillation (AF).1,2 Because of their critical role in AF, a variety of surgical and catheter ablation techniques has been used to isolate the pulmonary veins from the left atrium.3–8 One of the catheter techniques has consisted of applications of radiofrequency energy at segments of the pulmonary vein ostia, guided by pulmonary vein potentials.3 However, in prior studies of segmental pulmonary vein isolation, only the pulmonary veins that were found to generate triggers of AF were isolated, and a large percentage of patients required additional ablation procedures.3,9 Furthermore, there have been limited data on the efficacy of pulmonary vein isolation in patients with persistent AF.5

Anatomic studies have demonstrated that the myocardial sleeves that envelope the pulmonary veins are most prominent at the left superior, left inferior, and right superior pulmonary veins.2,10 Therefore, in the present study, an attempt was made to isolate all 3 of these pulmonary veins during the initial ablation procedure. Our purpose is to describe the safety and efficacy of this approach to the management of AF and to compare the results in patients with paroxysmal and persistent AF.

Methods

Patient Characteristics

The subjects of this prospective study were 70 consecutive patients with paroxysmal or persistent AF who underwent catheter ablation to isolate the pulmonary veins. Their mean age was 53±11 years (range, 27 to 73), and there were 57 men and 13 women. AF was first diagnosed 7.4±7.8 years before referral. The AF was paroxysmal in 58 patients and persistent in 12 patients. AF was considered persistent when it was present for >30 days and when cardioversion was required to restore sinus rhythm. A mean of 2.4±1.2 antiarrhythmic drugs had been ineffective in preventing recurrences of AF before the ablation procedure. Among the 70 patients, 2 had coronary artery disease, 3 had a nonischemic cardiomyopathy, and 65 had no evidence of structural heart disease. The mean left ventricular ejection fraction was 0.55±0.05 (range, 0.35 to 0.60), and the mean left atrial size was 40.3±4.4 mm (range, 30 to 57 mm).

The patients were asked to maintain a log of the number and duration of episodes of symptomatic AF during a period of 2 months before the ablation procedure. There was a mean of 15±12 episodes of AF per month in patients with paroxysmal AF. Six patients with...
recurrent AF after the ablation procedure underwent a second procedure, resulting in a total of 76 procedures.

Electrophysiological Procedure
Before the procedure, computerized tomography scan of the heart with 3-dimensional reconstruction was performed in 65 of the 70 patients to define the anatomy of the pulmonary veins. All patients provided written, informed consent. A quadripolar electrode catheter (EP Technologies, Inc) was positioned in the coronary sinus through a femoral vein approach. Transeptal catheterization was performed, and systemic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time of 250 to 350 seconds. Angiograms of the left superior, right superior, and left inferior pulmonary veins were performed in all patients. In 2 patients, the left superior and inferior pulmonary veins were found to have a common ostium. A deflectable, decapolar catheter with a distal ring configuration (Lasso catheter, Biosense Webster) was advanced into the left atrium. A deflectable, quadripolar 7-Fr catheter with 2-5-2-mm interelectrode spacing and a 4-mm distal electrode with an embedded thermistor (EP Technologies, Inc) was inserted into the left atrium either through the same transeptal puncture site or through a second transseptal puncture and was used for ablation. Bipolar and unipolar electrograms were filtered at bandpass settings of 30 to 500 Hz and 0.05 to 200 Hz, respectively, and were recorded digitally (EPMed Systems, Inc, Model EP-3 Clinical Stimulator). Pacing was performed from the coronary sinus or left atrial appendage with a stimulator (EPMed Systems, Inc, Model EP-3 Clinical Stimulator).

Rationale for Pulmonary Vein Isolation
The premature depolarizations that arise within the muscle sleeves of the pulmonary veins often are multifocal and may not be manifest during an electrophysiology procedure.9 Because ablation procedures that have targeted only the pulmonary veins that seem to be arrhythmogenic have been associated with a high recurrence rate of AF,3 at least 3 pulmonary veins were targeted for isolation in this study, regardless of whether they were or were not demonstrated to be arrhythmogenic. Because they are most commonly the veins involved in generating AF,1,2,9 the left superior, left inferior, and right superior pulmonary veins were targeted. Because the right inferior pulmonary vein often is difficult to cannulate with a decapolar ring catheter, and because it has the smallest muscle sleeve,2,10 it was not routinely isolated. However, if feasible, and if pulmonary vein potentials were present at its ostium, the right inferior pulmonary vein also was isolated.

Technique for Pulmonary Vein Isolation
If the patient was in AF, sinus rhythm was restored by transthoracic cardioversion. In 25 of 76 procedures (33%), 1 mg ibutilide or 300 mg amiodarone was administered intravenously to prevent immediate recurrences of AF after cardioversion. The decapolar ring catheter was positioned within a pulmonary vein and gradually withdrawn to within 5 mm of the ostium. Pulmonary vein isolation was performed during sinus rhythm or coronary sinus pacing by delivering radiofrequency energy at ostial sites that had the earliest bipolar potentials or the most rapid intrinsic deflections in the unipolar electrograms.11 Radiofrequency energy was delivered at the pulmonary vein ostium with a target temperature of 52°C and a maximum power output of 30 to 35 W for 30 to 45 seconds (EP Technologies, Inc, Model EPT-1000-TC). Elimination of all ostial pulmonary vein potentials and complete entrance block into the pulmonary vein were considered indicative of complete electrical isolation. After isolation of 3 to 4 pulmonary veins, 20 μg/min dobutamine or 4 μg/min isoproterenol was infused to determine whether any supraventricular arrhythmias were inducible by sympathetic activation and to confirm complete isolation of the pulmonary veins.

All patients were observed in a monitored bed for 24 hours and received intravenous heparin for 24 hours followed by warfarin for 1 to 3 months after the procedure. Low molecular weight heparin was administered for 4 days after discharge.

Antiarrhythmic Drug Therapy
Among the 70 patients, 15 (21%) were treated with a class I (10) or class III (5) antiarrhythmic drug. The reasons for treatment consisted of incomplete isolation of the targeted pulmonary veins, history of persistent AF, or recurrence of AF during the 24-hour observation period after the procedure. If there were no recurrences of AF after 1 month, antiarrhythmic drug therapy was discontinued.

In patients who were discharged without antiarrhythmic drug therapy and had recurrent AF, antiarrhythmic drug therapy was initiated unless the patient was satisfied with the extent of symptomatic improvement or elected to undergo a repeat ablation procedure.

Follow-Up
The patients were seen in an outpatient clinic 4 to 6 weeks and 3 to 4 months after the ablation procedure. All patients were asked to keep a log of the duration and frequency of their symptoms. All patients who reported symptoms were given an event monitor to document the cause of symptoms. To look for pulmonary vein stenosis, computerized tomography scanning of the pulmonary veins was repeated 2 to 4 months after the ablation procedure. The mean duration of follow-up was 150±85 days. No patients were lost to follow-up.

For the purpose of categorizing the clinical outcome after pulmonary vein isolation, freedom from AF was defined as the absence of symptomatic AF in association with no antiarrhythmic drug therapy. Improvement in AF was defined as a ≥90% reduction in the frequency of symptomatic episodes of AF in the absence of antiarrhythmic drug therapy or during treatment with an antiarrhythmic drug that had been ineffective before the ablation procedure.

Statistical Analysis
Continuous variables are expressed as mean±SD. Continuous variables were compared by Student’s t test. Differences among groups of continuous variables were determined by analysis of variance, and post-hoc analyses were performed with the Newman-Keuls test. Categorical variables were compared by χ² analysis or with Fisher’s exact test. A Kaplan-Meier analysis with the log-rank test was used to determine the probability of freedom from recurrent AF and the probability of improvement in AF after pulmonary vein isolation. A Cox multivariate regression analysis was performed to determine the clinical predictors of freedom from symptomatic AF. P<0.05 was considered statistically significant.

Results
Pulmonary Vein Isolation
Electrical isolation was complete in 64 of the 70 left superior (94%), 68 of the 70 right superior (97%), 65 of the 70 left inferior (93%), and 20 of the 20 right inferior pulmonary veins in which isolation was attempted (100%, Figure 1). There were no significant differences in the efficacy of the isolation procedure among the 4 pulmonary veins. All of the targeted PVs were completely isolated in 59 of the 70 patients (84%).

Procedural Aspects
There was a significant decrease in the total procedure and fluoroscopy times as the experience with the procedure increased. During the first 10 procedures, the mean total procedure and fluoroscopy times were 277±59 and 148±34 minutes, respectively, whereas during the last 10 procedures, the mean total procedure and fluoroscopy times were 204±34 (P<0.01) and 64±12 minutes (P<0.001), respectively.

The mean duration of radiofrequency energy applications needed to achieve isolation was 7.5±4.1 minute for the left superior pulmonary vein, 7.9±4.4 minutes for the right
superior pulmonary vein, 5.2 ± 3.3 minutes for the left inferior pulmonary vein, and 1.8 ± 1.4 minutes for the right inferior pulmonary vein. Compared with the other 3 pulmonary veins, shorter applications of radiofrequency energy were necessary to isolate the right inferior pulmonary vein (P < 0.001).

To achieve complete electrical isolation, radiofrequency energy was applied at 21% to 59% of the circumference of the ostia (Figure 2). The segments of the ostia that required ablation were smaller in the inferior pulmonary veins than in the superior pulmonary veins (P < 0.001, Figure 2).

Repeat Ablation Procedures
Six patients underwent a repeat ablation procedure 81 ± 54 days (range, 30 to 180 days) after the first procedure. In each patient, there was recovery of conduction in a pulmonary vein that had been previously isolated. No additional arrhythmogenic foci were identified in any of these patients. Three of the 6 patients who had a repeat procedure had paroxysmal AF, and the other 3 patients had persistent AF. All of the 6 patients had complete isolation of all of the targeted pulmonary veins after the second procedure. Each of the 3 patients with persistent AF and none of the patients with paroxysmal AF had recurrent AF after the second ablation procedure (P < 0.01). AF recurred at a median of 4 days (range, 1 to 19 days) after the second procedure.

Recurrence of AF After Pulmonary Vein Isolation in Patients With Paroxysmal AF
By 148 ± 87 days of follow-up, recurrent AF had occurred in 17 of 58 patients (29%) with paroxysmal AF. AF recurred at a median of 6 days (range, 1 to 45 days) after the procedure. By Kaplan-Meier analysis, the percentage of patients who were free of symptomatic AF at 5 months of follow-up was 70% (Figure 3). At 5 months of follow-up, 83% of patients with paroxysmal AF were either free of symptomatic AF or markedly improved (Figure 4).

Recurrence of AF After Pulmonary Vein Isolation in Patients With Persistent AF
AF recurred in 9 of 12 patients (75%) with persistent AF by a mean follow-up of 156 ± 79 days. AF recurred at a median of 6 days (range, 1 to 60 days) after the procedure. By Kaplan-Meier analysis, the percentage of patients who were free of symptomatic AF at 5 months of follow-up was 22% (Figure 3). At 5 months of follow-up, 29% of patients with persistent AF were either free of symptomatic AF or markedly improved (Figure 4).

Clinical Predictors of Freedom From Recurrence of AF
A multivariate analysis of clinical variables, including age, sex, structural heart disease, left atrial size, duration of AF, and paroxysmal versus persistent AF, demonstrated that the only independent clinical predictor of recurrent AF after
Main Findings
The results of this study demonstrate that the efficacy of empiric isolation of the left superior, right superior, and left inferior pulmonary veins by segmental ostial applications of conventional radiofrequency energy, with or without isolation of the right inferior pulmonary vein, is strongly dependent on whether the AF is paroxysmal or persistent. The procedure resulted in resolution or marked improvement of symptoms in \( \approx 85\% \) of patients with paroxysmal AF, compared with only \( 29\% \) of patients with persistent AF. A clinically satisfactory outcome required a second ablation procedure in only \( 9\% \) of patients. The risk of the procedure was low, with a thromboembolic complication occurring in \( 1.4\% \) of patients and with no instances of symptomatic pulmonary vein stenosis or other symptomatic complications.

Segmental Pulmonary Vein Isolation
As reported previously, \( >90\% \) of PVs were electrically disconnected from the left atrium by targeting only certain segments of the ostial circumference, as guided by pulmonary vein potentials. The results confirm that there are isolated fascicles that travel from the left atrium into the muscle sleeves that surround the pulmonary veins and that radiofrequency ablation of these fascicles, as opposed to circumferential ablation at the ostium, is sufficient to isolate the veins.

The inability to isolate a small percentage of pulmonary veins may have been attributable to anatomic variations in the geometry of the ostia that limited the optimal recording of pulmonary vein potentials with the decapolar ring catheter. In addition, it is possible that some of the fascicles were too thick to be ablated with conventional radiofrequency energy limited to 35 W. This would explain why a saline-irrigated ablation catheter, which creates deeper lesions than a conventional ablation catheter, was needed to isolate \( \approx 10\% \) of pulmonary veins in a prior study. In the present study, it is possible that a higher percentage of pulmonary veins could have been isolated if the power of the radiofrequency energy applications had not been limited to 35 W. However, a conservative approach to ablation was favored to minimize the risk of pulmonary vein stenosis.

Complications
One patient developed a unilateral quadrantopsia 3 hours after the ablation procedure, despite a continuous infusion of heparin. A neuro-ophthalmologic examination was consistent with a retinal artery embolus. In 2 other patients, 25% to 30% narrowing of the left superior or inferior pulmonary vein was detected by computerized tomography scan 2 to 3 months after the ablation procedure. These patients were asymptomatic.

Discussion
Paroxysmal Versus Persistent AF
In the present study, the efficacy of pulmonary vein isolation in patients with persistent AF was only \( 29\% \). This is consistent with a previous study in which pulmonary vein isolation was performed intraoperatively under direct visualization in patients with chronic AF, with restoration of sinus rhythm in only \( \approx 33\% \) of patients. These results suggest that the pulmonary veins play a less critical role in generating AF once the AF has become persistent. It is possible that the electrophysiological and anatomic remodeling that occurs during persistent AF often allows the atria to continue fibrillating independent of the pulmonary veins. Therefore, it may be preferable to intervene with catheter ablation before paroxysmal AF progresses to persistent AF.

In contrast to the findings of the present study, another study reported that pulmonary vein isolation was equally effective in patients with paroxysmal and persistent AF, with

Figure 4. Improvement in AF after pulmonary vein isolation in patients with paroxysmal (solid line) and persistent (dashed line) AF (\( P < 0.001 \)). Improvement in AF was defined as a \( \geq 90\% \) reduction in the frequency of symptomatic episodes of AF in the absence of antiarrhythmic drug therapy or during treatment with an antiarrhythmic drug that had been ineffective before the ablation procedure.

Relationship Between Number of Isolated Pulmonary Veins and Clinical Outcome
AF recurred in 7 of 11 patients (64%) who had complete isolation of 1 to 2 pulmonary veins and in 19 of 59 patients (32%) who had complete isolation of 3 to 4 pulmonary veins (\( P < 0.05 \)).

Figure 4. Improvement in AF after pulmonary vein isolation in patients with paroxysmal (solid line) and persistent (dashed line) AF (\( P < 0.001 \)). Improvement in AF was defined as a \( \geq 90\% \) reduction in the frequency of symptomatic episodes of AF in the absence of antiarrhythmic drug therapy or during treatment with an antiarrhythmic drug that had been ineffective before the ablation procedure.
than the pulmonary veins in only 5% to 15% of patients.

Reasons for Recurrence of AF
A recurrence of AF after pulmonary vein isolation may be caused either by the failure to permanently isolate a pulmonary vein or by the presence of critical foci outside of the pulmonary veins. In the small group of patients in this study who underwent a second procedure, incomplete isolation of a previously isolated pulmonary vein always was found. This, along with the fact that arrhythmogenic foci outside of the pulmonary veins were never identified, suggests that recovery of conduction through inadequately ablated muscle fascicles in the muscle sleeves surrounding the pulmonary veins may be the most common reason for recurrent AF after pulmonary vein isolation, at least among patients with paroxysmal AF. This is consistent with prior studies\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) that have demonstrated that the foci that trigger paroxysmal AF arise from areas other than the pulmonary veins in only 5% to 15% of patients.

Limitations
A limitation of this study is that there were only 12 patients with persistent AF. Because it became clear early in the study that the isolation procedure was much less effective for persistent than for paroxysmal AF, the enrollment of patients with persistent AF was intentionally restricted. Because of the small sample size, no attempt was made to distinguish persistent from chronic or permanent AF, and whether the duration of persistent AF affects the response to pulmonary vein isolation could not be determined.

Because >90% of the patients in this study had idiopathic AF, it is not known whether the techniques used in this study would yield similar results in patients with structural heart disease.

Another limitation is that the clinical efficacy of pulmonary vein isolation was based on symptoms reported by the patients. Whenever a patient reported symptoms suggestive of recurrent AF, documentation of the arrhythmia was obtained with an event recorder. However, ambulatory monitoring was not routinely performed in patients who reported having no symptoms during follow-up. Therefore, asymptomatic episodes of AF may have been missed. However, because all of the patients in this study had symptomatic AF before ablation, the absence of symptomatic AF after the ablation procedure was considered an acceptable clinical end point.

In this study, the pulmonary veins were evaluated for stenosis only at 2 to 4 months after the ablation procedure. Long-term reevaluation may be needed to rule out late stenosis.

A final limitation of this study is that only 9% patients with recurrent AF elected to undergo a second ablation procedure. Therefore, the reasons for recurrent AF could not be identified in most patients.

Conclusions
More than 90% of pulmonary veins can be electrically isolated from the left atrium by conventional applications of radiofrequency energy along segments of the ostia, guided by pulmonary vein potentials. Generally, 3 or 4 pulmonary veins can be isolated in <4 hours without creating pulmonary vein stenosis and with a low risk of other serious complications. A satisfactory clinical outcome, consisting of either complete resolution or marked improvement in symptoms, can be achieved in ≈85% of patients with paroxysmal AF. When 3 to 4 pulmonary veins are isolated, a satisfactory clinical outcome can be achieved in most patients with a single procedure and without the need for antiarrhythmic drug therapy.

In contrast to paroxysmal AF, persistent AF usually is not eliminated by pulmonary vein isolation. This suggests that intervention with pulmonary vein isolation in patients with drug-refractory paroxysmal AF should not be postponed until the AF becomes persistent. Once AF has become persistent, it is likely that pulmonary vein isolation will have to be supplemented by some other type of ablation procedure directed at the atrial myocardium. The ideal catheter ablation strategy for persistent AF remains to be determined.

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