Clinical Significance of Early Recurrences of Atrial Fibrillation After Pulmonary Vein Isolation

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

Ann Arbor, Michigan

OBJECTIVES
The purposes of this study were to describe the prevalence of early recurrences of atrial fibrillation (ERAF) that occur within two weeks after pulmonary vein (PV) isolation, and to determine whether ERAF is predictive of long-term outcome after PV isolation.

BACKGROUND
Atrial fibrillation (AF) sometimes recurs within days after PV isolation and may prompt an early repeat intervention. Segmental PV isolation was performed using radiofrequency energy in 110 consecutive patients (mean age 53 ± 11 years) with paroxysmal (93 patients) or persistent (17 patients) AF. Three to four PVs were targeted for isolation in all patients. Pulmonary vein isolation was complete in 338 of the 358 PVs that were targeted (94%).

METHODS
METHODS
Segmental PV isolation was performed using radiofrequency energy in 110 consecutive patients (mean age 53 ± 11 years) with paroxysmal (93 patients) or persistent (17 patients) AF. Three to four PVs were targeted for isolation in all patients. Pulmonary vein isolation was complete in 338 of the 358 PVs that were targeted (94%).

RESULTS
Early recurrences of AF occurred in 39 of 110 patients (35%) at a mean of 3.7 ± 3.5 days after the procedure. The prevalence of ERAF was similar in patients with paroxysmal and persistent AF (33% and 47%, respectively, p = 0.4). Beyond the first two weeks, at 208 ± 125 days of follow-up, 60 of the 71 patients without ERAF (85%) and 12 of the 39 patients with ERAF (31%) were free of recurrent AF in the absence of antiarrhythmic drug therapy (p < 0.001).

CONCLUSIONS
Early recurrences of AF occur in approximately 35% of patients within two weeks after isolation of three to four PVs, and are associated with a lower long-term success rate than in patients without ERAF. However, approximately 30% of patients with ERAF have no further symptomatic AF during long-term follow-up. Therefore, temporary antiarrhythmic drug therapy may be more appropriate than early repeat ablation in patients with ERAF. (J Am Coll Cardiol 2002;40:100–4) © 2002 by the American College of Cardiology Foundation

Isolation of the pulmonary veins (PVs) to eliminate paroxysmal or persistent atrial fibrillation (AF) has been performed using a variety of catheter ablation techniques (1–4). Recurrences of AF after PV isolation have been reported in up to 40% of patients (1), and may prompt an early repeat ablation procedure (5). However, the long-term clinical significance of an early recurrence of atrial fibrillation (ERAF) after PV isolation has not been well defined. The purposes of this study were to describe the prevalence of ERAF within two weeks after PV isolation and to determine whether ERAF is predictive of long-term outcome.

METHODS
Patient characteristics. Pulmonary vein isolation was performed in 110 consecutive patients with symptomatic paroxysmal or persistent AF. The clinical characteristics of these patients are described in Table 1. For the purposes of our study, we have defined persistent AF as an episode of AF that lasted for more than 30 days and required cardioversion to restore sinus rhythm. All patients were asked to maintain a log of the episodes of symptomatic AF before and after the ablation procedure. Seventy of the 110 patients were included in a prior study that described the clinical results of PV isolation (4).

PV isolation. All patients provided written informed consent. After trans-septal catheterization, systemic anticoagulation was achieved with intravenous heparin titrated to maintain an activated clotting time of 250 to 350 s. Selective venograms of the left superior, left inferior and right superior PVs were performed. A decapolar catheter with a distal ring configuration (Lasso Catheter, Biosense Webster, Diamond Bar, California) sequentially was positioned within 5 mm of the ostium of each PV. A deflectable quadrupolar electrode catheter (EP Technologies, Inc., San Jose, California) was positioned in the coronary sinus. Ablation was performed using a deflectable quadrupolar 7F catheter that had 2–5–2 mm interelectrode spacing and a 4-mm distal electrode with an embedded thermistor (EP Technologies, Inc.). Electrograms were recorded digitally (EPMed Systems, Inc., Mount Arlington, New Jersey) and were filtered at bandpass settings of 30 to 500 Hz for bipolar recordings and 0.05 to 200 Hz for unipolar recordings.

Pulmonary vein isolation was performed by delivering radiofrequency (RF) energy at a maximum temperature of 52°C and a maximum power of 30 to 35 W for 30 to 60 s at ostial sites that had the earliest bipolar PV potentials and/or the most rapid intrinsic deflections in the unipolar...
PV potentials (4,6). Isolation of the left superior, left inferior and right superior PVs was attempted in all patients. In 28 patients, isolation of the right inferior PV also was attempted. Elimination of all PV potentials and entrance block into the PV were considered indicative of complete electrical isolation.

**Postablation follow-up.** After the procedure, all patients were observed in a telemetry unit for 24 h and were anticoagulated with warfarin for 6 to 12 weeks. The patients were seen in an outpatient clinic four to six weeks after the procedure and three to four months thereafter. No patient was lost to follow-up.

After the procedure, 39 of the 110 patients (35%) were treated for one month with a class I (23 patients) or III (16 patients) antiarrhythmic drug. These patients were treated because of an incomplete isolation of the targeted PVs, a history of persistent AF or a recurrence of AF during the 24-h observation period after the procedure.

Patients who reported symptoms suggestive of recurrent AF during follow-up were provided with an event recorder to document the cause of the symptoms. Any episode of AF that recurred within two weeks after the AF isolation procedure was defined as an ERAF. Patients with ERAF who were not already receiving antiarrhythmic medications were treated with a class I or III antiarrhythmic drug and/or a beta-blocker or calcium channel blocker, unless the patient felt that treatment was not necessary. Antiarrhythmic drug therapy was discontinued in all patients who had no further episodes of symptomatic AF after one month.

**Statistical analysis.** Continuous variables are expressed as mean ± SD and were compared using Student t test. Categorical variables were compared by chi-square analysis. A Kaplan-Meier analysis was used to determine the probability of freedom from recurrent AF during follow-up. A Cox multivariate regression analysis was performed to determine the clinical predictors of ERAF. A value of p < 0.05 was considered significant.

**RESULTS**

**PV isolation.** Complete electrical isolation was achieved in 103 of 110 left superior PVs (94%), 104 of 110 right superior PVs (95%), 103 of 110 left inferior PVs (94%) and 28 of 28 targeted right inferior PVs (100%). Overall, PV isolation was complete in 338 of the 358 PVs that were targeted (94%). In 93 of the 110 patients (85%), all targeted PVs were completely isolated electrically. The mean duration of RF energy application was 6.4 ± 4.2 min per PV.

**Recurrences of AF.** During 208 ± 125 days of follow-up, symptomatic AF recurred in 50 of the 110 patients (45%) after the ablation procedure. The first recurrent episode occurred within two weeks of the procedure in 39 of 110 patients (35%), between two weeks and one month after the procedure in 8 of 110 patients (7%) and between one and two months after the procedure in 3 of 110 patients (3%) (Fig. 1).

The mean time to ERAF was 3.7 ± 3.5 days (range 1 to 14 days). Among the 39 patients with ERAF, the first recurrence of AF occurred within 24 h of the procedure in 33% and within one week of the procedure in 90% (Fig. 2).

Early recurrence of AF occurred in 23 of the 71 patients (32%) who were discharged from the hospital without antiarrhythmic drug therapy, and in 16 of the 39 patients (41%) who were discharged with antiarrhythmic drug therapy after the PV isolation procedure (p = 0.4).

**Recurrence of AF in patients with paroxysmal and persistent AF.** Early recurrence of AF occurred in 31 of 93 patients (33%) with paroxysmal AF and in 8 of 17 patients (47%) with persistent AF (p = 0.3). The mean times to ERAF were 3.5 ± 3.6 days and 4.6 ± 3.0 days in patients with paroxysmal and persistent AF, respectively (p = 0.4).

At 208 ± 125 days of follow-up, 38 of the 110 patients (35%) had recurrent episodes of AF beyond the first two weeks after the PV isolation procedure. Among the 93 patients with paroxysmal AF, 67 (72%) were free from recurrent episodes of symptomatic AF in the absence of...
antiarrhythmic drug therapy, compared with only 5 of the 17 patients (30%) with persistent AF (p = 0.001).

**Frequency of symptomatic episodes of AF before and after PV isolation.** Six of the 39 patients with ERAF (15%) reported an increase in the frequency of symptomatic episodes of AF in the first two weeks after the PV isolation procedure. In these patients, the mean number of episodes of symptomatic AF was 9 ± 7 in the two weeks before the ablation procedure, compared with 15 ± 9 in the two weeks after the ablation procedure (p < 0.01). The other 24 patients with ERAF reported either no change in the frequency of episodes (15 patients), or a decrease from a mean of 10 ± 7 episodes before the procedure to a mean of 2 ± 1 episode after the procedure (p < 0.001).

**Time to resolution of ERAF.** In patients who had ERAF but were free from recurrent episodes of AF during long-term follow-up, the mean time to resolution of symptomatic episodes of AF was 20 ± 11 days (range 1 to 30 days).

**Predictors of ERAF.** Among the variables of age, gender, duration of AF, frequency of AF, presence of structural heart disease, left ventricular ejection fraction (LVEF), left atrial size, whether the AF was paroxysmal or persistent, whether all targeted PVs were completely isolated or not and total duration of RF energy application, there were no independent predictors of ERAF.

**Long-term outcome in patients with and without ERAF.** During long-term follow-up of the 39 of 110 patients who had ERAF, 12 (31%) remained free from recurrent episodes of AF without antiarrhythmic drug therapy. In comparison, among the 71 patients who did not have ERAF, 60 (85%) remained free from recurrent episodes of AF without antiarrhythmic drug therapy (p < 0.001) (Fig. 3).

**Predictors of long-term freedom from recurrent AF.** Among the variables of age, gender, duration of AF, presence of structural heart disease, LVEF, left atrial size, whether AF was paroxysmal or persistent, the number of completely isolated PVs and ERAF, the absence of ERAF (p < 0.01) and a history of paroxysmal AF (p = 0.01) were the only independent predictors of freedom from recurrent AF.

**Long-term freedom from recurrent AF in patients with ERAF.** Within the group of patients with ERAF, among the variables of age, gender, presence of structural heart disease, LVEF, duration of AF, whether the AF was paroxysmal or persistent, the number of PVs completely isolated, total duration RF energy application and time to recurrence of AF, only a history of persistent AF was an independent predictor of recurrent AF (p < 0.05).

**DISCUSSION**

**Main findings.** The results of this study demonstrate that ERAF are common after segmental PV isolation, occurring in approximately 35% of patients with paroxysmal or persistent AF. Some patients with ERAF experienced a transient increase in the frequency of episodes of AF. Patients who had ERAF were significantly less likely to have long-term freedom from recurrent AF than were patients without ERAF. Nevertheless, approximately 30% of patients with ERAF were free from recurrent episodes of symptomatic AF in the absence of antiarrhythmic drug therapy during long-term follow-up. There were no clinical or technique-related predictors of ERAF after PV isolation. However, a history of persistent AF was an independent predictor of recurrent episodes of AF among the patients who had ERAF.

The eventually successful clinical outcome in approximately one-third of patients with ERAF after PV isolation suggests that recurrent AF may be a transient phenomenon and not necessarily an indicator of long-term recurrences of AF.
ERAF after PV isolation. Early recurrence of AF was defined in this study as any recurrence of AF that occurred within two weeks after the PV isolation procedure. Our purpose was to identify how often recurrent AF after PV isolation is a transient phenomenon, caused either by a delayed therapeutic effect or a transient stimulatory effect of the RF energy applications. Because acute inflammatory changes due to RF energy resolve and well-demarcated areas of necrosis form by two weeks after RF ablation procedures (7–9), a two-week cutoff for ERAF was used in this study. Although recurrent episodes of AF that are due to incomplete PV isolation, to recovery of conduction in a previously isolated PV or to arrhythmogenic foci outside the PVs also may occur within two weeks of PV isolation, these causes of ERAF would be expected to result in recurrent AF throughout the follow-up period, not just within the first two weeks after ablation.

Among the majority of patients in whom recurrent AF was a transient phenomenon, the mechanism of the transient AF cannot be defined. However, approximately 15% of patients who had ERAF in this study had a transient increase in the frequency of symptomatic episodes of AF shortly after the PV isolation procedure. In these patients, it is likely that ERAF was caused by a transient stimulatory effect of RF energy. It may be that the inflammatory response that develops after thermal injury transiently aggravates the arrhythmogenic activity of the PVs (10,11). Several studies have reported an association between inflammation and AF (12–15). Moreover, postoperative AF, which occurs transiently in ~33% of patients after open-heart surgery, also could be triggered by an inflammatory response within the atria (16–18).

Among patients who undergo RF catheter ablation of an accessory pathway and have an unsuccessful acute outcome, approximately 15% no longer have accessory pathway conduction during long-term follow-up (19). A delayed therapeutic effect of RF energy may be attributable to growth of the ablation lesion in the first few days after the procedure (20). Therefore, it is possible that some patients in this study no longer had recurrent AF after the first two weeks of follow-up because of a delayed therapeutic effect of RF ablation. However, among the majority of patients in this study in whom recurrent AF was a transient phenomenon, the mechanism of the transient AF cannot be defined.

Study limitations. A limitation of this study is that recurrent episodes of AF after discharge from the hospital were quantitated on the basis of symptoms reported by the patients. Although the many episodes of ERAF that occurred within 24 h after ablation and were documented by continuous telemetric monitoring were always associated with symptoms, it is possible that asymptomatic episodes of AF may have been unrecognized after discharge from the hospital. However, all patients had symptomatic AF before the ablation procedure, and symptomatic episodes of AF were confirmed with an event recorder.

Clinical implications. In conclusion, in approximately 30% of patients who experience recurrent episodes of AF within two weeks after segmental ostial ablation to isolate the PVs, the AF may be a transient phenomenon that eventually resolves and may be caused by acute stimulatory effects of RF energy or may be a delayed therapeutic effect of RF ablation. In some centers, patients are monitored for several days after PV isolation, and an early repeat ablation is attempted if ERAF occurs (5). However, because AF often does not recur long-term in patients who have had ERAF, a brief course of antiarrhythmic drug therapy may be more appropriate than an early repeat ablation procedure.

Acknowledgments

We are grateful to Dr. Michel Haissaguerre and his colleagues for introducing us to the technique of segmental ostial ablation. We also thank Marcy Yackish, MS, NP, for her contributions in clinical follow-up of the patients.

Reprint requests and correspondence: Dr. Hakan Oral, Cardiology, B1F245, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109-0022. E-mail: oralh@umich.edu.

REFERENCES