Long-Term Outcome After Successful Catheter Ablation of Atrial Fibrillation

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Background—Pulmonary vein isolation (PVI) is increasingly used for treatment of atrial fibrillation (AF), but few reports exist regarding long-term success. We determined 5-year outcomes of PVI among patients with freedom from AF off antiarrhythmic drugs (AAD) for 1 year after PVI.

Methods and Results—Consecutive patients with paroxysmal or persistent AF who underwent PVI at the University of Pennsylvania from 2000 to 2003 and were free from AF 1 year after ablation were included. Proximal isolation of PVs and non-PV triggers of AF was performed. Long-term ablation success, defined as freedom from AF off AAD after a single ablation procedure, was determined. All patients had transtelephonic monitoring at 3 to 6 months and 12 months and at least yearly contact thereafter. One hundred twenty-three patients were free of AF without AAD at 1 year. AF freedom off AAD was 85% at 3 years and 71% at 5 years, with an approximate 7% per year late recurrence rate after the first year. Patients with recurrent AF ≥5 years after index PVI were older, had larger left atrial size, more AF triggers and more likely had persistent AF. In multivariate analysis, persistent AF (odds ratio, 2.8; 95% confidence interval, 1.4 to 5.7, \( P=0.005 \)) and age (odds ratio, 1.1; 95% confidence interval, 1.0 to 1.1, \( P=0.036 \)) independently predicted long-term AF recurrence.

Conclusions—Among patients with paroxysmal or persistent AF and AF freedom 1 year after segmental PVI, the majority (71%) remained free of AF for up to 5 years, with an approximate late recurrence rate of 7% per year. Continued vigilance for recurrent AF after PV isolation is warranted, particularly in patients with persistent AF. (Circ Arrhythm Electrophysiol. 2010;3:237-242.)

Key Words: atrial fibrillation ■ catheter ablation ■ pulmonary vein isolation outcome

Pulmonary vein isolation (PVI) is increasingly used to treat atrial fibrillation (AF). Since the initial description by Haissaguerre\(^1\) in 1998, the procedure has evolved from ablation of focal AF triggers inside the pulmonary veins to wide area circumferential PV isolation. In 2001, our group began using the technique of proximal isolation of arrhythmogenic PVs guided by a circular mapping catheter.\(^2\) We later showed, in a prospective randomized study, that this technique was equivalent to empirical isolation of all PVs.\(^3\)

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Short-term (6 months to 1 year) outcome after PVI has varied depending on the center, technique, and patient population.\(^4\)\(^-\)\(^7\) However, few reports of long-term outcome have been reported.\(^3\)\(^-\)\(^8\)\(^-\)\(^17\) Detailed long-term outcome is often difficult to ascertain because patients often undergo multiple procedures and some may remain on antiarrhythmic drugs. In addition, many centers do not continue to follow patients >1 year after a successful ablation to determine whether late recurrences occur. Our group has had a consistent approach for patients undergoing AF ablation as well as a prospective database collecting outcome after AF ablation. Now that patients have been followed for ≥5 years after ablation, this provides a unique opportunity to obtain long term follow-up after AF ablation. We sought to evaluate long-term outcome after PV isolation in patients who had an initially successful AF ablation.

Methods

Study Population
Consecutive patients who underwent segmental PVI of arrhythmogenic PVs at the University of Pennsylvania Health System from 2001 to 2003 for either paroxysmal or persistent AF and who were free from AF without antiarrhythmic drugs (AAD) 1 year after ablation were included in the present study. Patients who had undergone focal ablation or segmental PVI before the index proce-
Ablation Strategy
Ablation was performed by 6 different operators at the University of Pennsylvania. Patients were brought to the electrophysiology laboratory in a fasting state and off AADs for at least 5 half-lives, except for amiodarone, which was stopped at least 2 weeks before the procedure. Our ablation protocol has been previously described.\textsuperscript{18} To summarize, 2 decapolar catheters with 5-mm electrodes and 2-mm interelectrode spacing were placed in the coronary sinus and posterior right atrium. A phased-array diagnostic ultrasound catheter (5.5 to 10 MHz, 10F, AcuNav, Siemens Medical, Mountain View, Calif) was advanced to the level of the fossa ovalis in the right atrium and manipulated to adequately image all PVs and to record peak flow velocity at the ostium of each vein. The left atrium was accessed through 2 transseptal punctures, and 10-pole, 20-mm Lasso ( Biosense Webster, Inc, Diamond Bar, Calif) and 4-mm tip ablation (NaviStar, Biosense Webster, Diamond Bar, Calif) catheters were used for mapping and radiofrequency ablation. In 1 patient, an 8-mm catheter was used (also NaviStar, Biosense Webster). Before transseptal puncture, heparin was initiated to achieve a goal activated clotting time of $\geq$300 seconds, and this was maintained throughout left atrial access. Three-dimensional electroanatomic mapping was performed with CARTO (Biosense Webster, Inc) or NavX (St Jude Medical, Minneapolis, Minn) systems. Both PV and non-PV triggers were identified using a standard stimulation protocol: (1) graded isoproterenol infusion (starting at 3 $\mu$g/min and increased to a maximum of 20 $\mu$g/min unless limited by nausea or hypotension) and (2) cardioversion of AF induced by burst left atrium or right atrium pacing without and during the administration of 2 to 3 mg/min of isoproterenol. PVs with triggers were defined as veins that were documented to initiate AF and/or reproducible atrial premature complexes based on direct intracardiac recordings and/or activation sequences mimicking PV pace maps.\textsuperscript{19} All bipolar electrograms were filtered at 30 to 150 Hz and displayed on a commercially available electrophysiological recording system (Pnuicka, GE, Houston, Tex). The proximal PV ostium or antrum was determined by (1) electroanatomic mapping and (2) circular mapping catheter location on intracardiac ultrasound.

Isolation of the PVs exhibiting atrial premature beats or triggers of AF was performed. Radiofrequency energy was delivered in the temperature control mode, with a temperature limit of 52°C and power limit of 50 W for the 4-mm tip catheter and 50°C and 50 to 70 W for the 8-mm tip catheter. Power was not decreased for posterior wall sites, as the complication of esophageal injury was not yet described during this time period. However, RF delivery to sites with phrenic nerve capture with pacing was avoided. Lesions were delivered for a maximum of 60 seconds. Successful PV isolation was defined by loss of PV potentials recorded in the circular mapping catheter during sinus rhythm (entrance block) and failure to capture the left atrium during pacing from all bipoles of the Lasso catheter (output, 10 mA; pulse width, 2 ms) exit block.\textsuperscript{20} These maneuvers were repeated after 20 to 60 minutes to exclude acute PV reconnection (entry or exit), for which additional RF lesions were delivered as needed. After isolation of veins was completed, the stimulation protocol was repeated to elicit triggers from other PVs or from non-PV sites, which also were targeted if found to be arrhythmogenic. In the case that no PV triggers were elicited, all PVs were targeted for isolation using the approach described above.

Definitions
The primary outcome of the study was long-term ablation success, defined as freedom from AF off AADs without undergoing another ablation procedure for AF. In secondary analyses, we sought to determine predictors for AF recurrence at 5 years among such patients, including left atrial size, left ventricular ejection fraction, age, sex, hypertension, body mass index, presence of obstructive sleep apnea, number of AF triggers, number of prior ablation attempts, and presence of paroxysmal versus persistent AF. We also analyzed rates of AF freedom after repeat PVI.

Patients were classified as free of AF on AADs if they had no recurrent AF on drug therapy but experienced recurrent AF when AADs were stopped. Those with rare AF recurrence were defined as having fewer than 6 episodes per year that self-terminated within 24 hours or required no more than one cardioversion per year. We defined recurrent AF as any patient requiring a repeat ablation procedure for AF after the first year or any patient with recurrent AF on AADs.

Follow-Up
Patients received an AAD (usually a class IC or III agent) and warfarin after ablation and were typically kept in the hospital on unfractionated heparin infusion until an international normalized ratio $\geq$1.8 was achieved. Long-term follow-up consisted of at least 3 outpatient visits (at 6 weeks, 6 months, and 1 year from the date of ablation procedure). Patients underwent 4-week periods of transtelephonic monitoring immediately after ablation and at 3 to 9 months after ablation when considering cessation of drug therapy. Beyond the 1-year period, patients were encouraged to return for an outpatient evaluation at least annually, but this visit was not mandatory, and our research personnel continued to follow these patients by telephone and by contact with referring care providers for source documentation approximately every 6 to 12 months. At each outpatient visit, patient symptoms were assessed and a 12-lead ECG was recorded. All patients underwent 2D echocardiography during the 6-week and or 6-month visit. In paroxysmal AF patients without AF recurrence, AADs were routinely discontinued at the 6-week clinic visit. For those with persistent AF, AADs were typically continued for 6 months. Patients were instructed to assess their pulse for irregularity at least twice a day and seek additional monitoring if present to help identify asymptomatic AF. For those with AF recurrences beyond the 1-year follow-up, AADs were restarted and repeat ablation was performed according to patient and attending physician preference and driven primarily by the frequency of episodes and severity of symptoms. In patients undergoing repeat ablation, the same stimulation and ablation protocols were repeated; all initially targeted PVs showing recurrent entry or exit were reisolated. At repeat procedure, any PVs that may not have been initially targeted because of failure to demonstrate a reproducible AF trigger were also isolated. No empirical linear left or right atrial lesions were performed unless a reentrant tachycardia was induced or observed clinically.

Statistical Analysis
Continuous variables are reported as mean±standard deviation, and categorical variables are reported as proportions. Comparisons of continuous variables were performed using Student $t$ test and categorical variables with Fisher exact test. Significant univariate variables identified in these analyses ($P<0.1$) were incorporated into a Cox proportional hazards stepwise forward regression. Logistic regression was also performed to determine whether there was an association between operator experience (number of cases performed) and ablation outcome. Kaplan–Meier survival estimates were performed to assess long-term outcomes. Analyses were performed using SPSS (Chicago, Ill) version 17.0. A probability value of $<0.05$ was considered significant.

Results
Patient Characteristics and Follow-Up
A total of 239 patients underwent ablation between January 2001 and December 2003. Of these, 140 patients were free of...
AF off AADs at 1 year after the ablation procedure; 17 were excluded because they did not have additional follow-up beyond 1 year; thus, 123 subjects were included in this study. The majority of patients (71%) were undergoing their first AF ablation procedure. Of those who had undergone a prior procedure, 89% (n = 32/36) had a trigger-based, focal PV ablation (2.5 ± 1.1 PVs targeted) in the prior procedure. The mean follow-up duration was 5.9 ± 1.5 years. The mean age was 54 ± 11 years, most (80%) were male, and nearly half had a history of hypertension (see Table). The majority of patients had paroxysmal AF (85%). Among patients included in the cohort who remained AF free after ≥1 year, only 3 (3%) additional patients were lost to follow-up after 5 years. The follow-up in the last year of the study consisted of outpatient clinic visits at the University of Pennsylvania Hospital for 44% of patients, follow-up by phone and review of documentation during a clinic visit with the referring cardiologist in 35%, and phone follow-up only in the remaining 21%.

Primary Outcome
Among patients with freedom from AF 1 year after the procedure, 103 (84%) continued to remain free of AF off AADs 3 years after PVI (see Table and Figure). With each subsequent year, the proportion of patients who maintained sinus rhythm without need for AAD therapy decreased to 77% (n = 93/121) at 4 years and 71% (n = 85/120) at 5 years (see Figure).

Predictors of Long-Term AF Recurrence After Successful PVI
Patients free of AF more than 5 years after initially successful PVI were more likely to have had paroxysmal AF (91% versus 69%, P = 0.005). They also were younger (52 versus 57 years, P = 0.031), had smaller left atrial size (4.2 ± 0.6 cm versus 4.5 ± 0.6 cm, P = 0.006), had fewer AF triggers identified (3.0 ± 1.2 versus 3.7 ± 0.9, P = 0.002), and had fewer PVs isolated (2.9 ± 1.1 versus 3.5 ± 1.0, P = 0.007). There were no significant differences in other characteristics studied between groups, including body mass index, prevalence of hypertension, obstructive sleep apnea, or diabetes and numbers of prior PVI procedures. In multivariate Cox regression analysis, the presence of persistent AF (odds ratio, 2.8; 95% confidence interval, 1.4 to 5.7; P = 0.005) and age (odds ratio, 1.1, 95% confidence interval, 1.0 to 1.1, P = 0.036) independently predicted long-term AF recurrence. There was no association between operator experience and long-term AF recurrence (R² = 0.06, P = 0.66).

Patients With Recurrent AF
In total, 35 patients had recurrent AF an average of 3.3 ± 0.9 years after the index procedure. Ten had only rare AF recurrences, on (n = 3) or off AADs, and 25 continued to have AF despite AAD reinstitution. Fifteen of the latter then chose to undergo repeat ablation an average of 3.0 ± 0.6 years after their initial PVI. In the remaining 10 patients, the burden of AF was deemed acceptable and no additional ablative therapy was performed. The majority of the patients undergoing repeat ablation (73%, n = 11/15) continue to be free of AF after an additional 3.1 ± 1.2 years since redo procedure (6.1 ± 1.2 years since index PVI), with reinstitution of AAD required in only 1. Panel B in the Figure includes the 10 patients who underwent repeat PVI (considered censored at the time of repeat procedure) and who now continue to remain AF free off AAD; including those patients, the 4- and 5-year procedural success is 89% and 81%, respectively. Of note, all of the patients undergoing repeat ablation procedures were found to have reconnections of previously ablated PVs (55/57, or 96%, of PVs).

Conclusions
In this single-center experience of proximal PVI isolation with entrance and exit block demonstrated in the treatment of paroxysmal or persistent AF, the majority of patients (84%) with AF freedom 1 year after ablation remained free of AF for up to 3 years. There was an approximate 7% per year late AF recurrence rate, with 77% free of AF at 4 years and 71% remaining free of AF after 5 years. In this typical population of patients presenting for AF ablation, the presence of

Table. Characteristics of Patients With AF Freedom 1 Year After PVI

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 123)</th>
<th>AF Freedom &gt;5 Years (n = 87)</th>
<th>Recurrent AF &lt;5 Years (n = 36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54 ± 11</td>
<td>52 ± 12</td>
<td>57 ± 9</td>
<td>0.031</td>
</tr>
<tr>
<td>Sex, n (% male)</td>
<td>98 (80)</td>
<td>69 (79)</td>
<td>29 (81)</td>
<td>1.000</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.3 ± 6.1</td>
<td>29.5 ± 6.4</td>
<td>28.6 ± 5.4</td>
<td>0.452</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>55 (46)</td>
<td>36 (41)</td>
<td>20 (56)</td>
<td>0.168</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (2)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>0.555</td>
</tr>
<tr>
<td>Obstructive sleep apnea, n (%)</td>
<td>5 (4)</td>
<td>4 (5)</td>
<td>1 (3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Left atrial size, cm</td>
<td>4.3 ± 0.7</td>
<td>4.2 ± 0.6</td>
<td>4.5 ± 0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56 ± 11</td>
<td>57 ± 10</td>
<td>55 ± 14</td>
<td>0.529</td>
</tr>
<tr>
<td>Paroxysmal AF, n (%)</td>
<td>104 (85)</td>
<td>79 (91)</td>
<td>25 (69)</td>
<td>0.005</td>
</tr>
<tr>
<td>No. of PVI procedures, n</td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.5</td>
<td>0.297</td>
</tr>
<tr>
<td>PVs isolated/patient, n</td>
<td>3.0 ± 1.0</td>
<td>2.8 ± 1.0</td>
<td>3.3 ± 0.9</td>
<td>0.014</td>
</tr>
<tr>
<td>AF trigger sites, n</td>
<td>3.2 ± 1.1</td>
<td>3.0 ± 1.2</td>
<td>3.7 ± 0.9</td>
<td>0.002</td>
</tr>
</tbody>
</table>
persistent AF and age were independent risk factors for long-term AF recurrence.

This work represents one of the few available reports of outcomes more than 2 years after PVI. Our study points out that although the majority of patients with AF freedom after a single ablation procedure, AF freedom persists for 84% of patients at 3 years after ablation. However, a late AF recurrence rate of approximately 7% per year persists, with 71% of patients free of AF off drugs at 5 years. B, Including outcome in patients undergoing repeat ablation procedures, 81% remained free of AF at 5 years without the use of AADs. Results from a similar study were recently reported by Shah et al.\textsuperscript{11} in which 264 patients with paroxysmal or persistent AF who were AF-free after \( \geq 1 \) year after segmental PVI were analyzed. At 3 years, AF recurrence rates were 9% and increased to 26% by 5 years. Subject attrition was a significant problem, however, with only 14 patients with continued follow-up after 5 years. In contrast to our population, hypertension and hyperlipidemia both predicted very late AF recurrence.

Several studies have previously reported outcome after 1 year but with a much shorter duration of overall follow-up. A study of 249 patients, with paroxysmal and persistent AF undergoing a first PVI, was recently reported from Ma et al.\textsuperscript{15} Very late AF recurrence, defined as \( > 12 \) months after first PVI, occurred in 32% of patients after an average of 18 months after the procedure. Similar to our findings, presence of persistent AF predicted very late recurrence.

A previous report from our laboratory found that weight \( > 200 \) pounds, presence of non-PV triggers, and isolation of fewer PVs, especially the right inferior PV, were independent predictors of late (\( > 12 \) months) AF recurrence.\textsuperscript{8} The present study had significantly longer follow-up and included only patients with \( \geq 1 \) year of AF freedom off of AADs. In this larger group of patients, weight was no longer a predictor of AF recurrence. Technical advances and experience also allowed for easier isolation of the right inferior PV, eliminating lack of right inferior PV isolation as a predictor of recurrent AF.\textsuperscript{11}

A relatively uniform finding among studies that have reported more than 1 year of follow-up is that presence of persistent AF at baseline may adversely affect overall outcomes for PVI.\textsuperscript{3,13–16} Clues to the underlying AF substrate are suggested by the larger left atrial size and higher number of AF triggers in our study, both of which may be surrogates for the extent of left atrial remodeling. Also important to recognize is that the majority of patients in the present study who underwent redo procedures continue to do very well, with a majority of them continuing to remain free of AF off AAD. Repeat ablations are therefore required to maintain AF freedom in an important subset of AF patients. Because fewer than half of the patients with recurrent AF underwent repeat procedures, it should also be noted that many patients have a good clinical outcome after a single procedure, even if they continue to have episodes of AF. The mechanism of AF recurrence late after an initially successful ablation is unknown. Several studies\textsuperscript{21–23} have found that the most common cause of early AF recurrence after ablation is reconnection of the PVs. In our series, 15 of 35 (43%) patients with recurrent AF underwent repeat mapping and ablation. In nearly all cases (96%), reconnection of the arrhythmogenic PVs was noted. Reisolation of the PVs led to freedom from AF in 11 of 15 patients. These findings emphasize the importance of achieving long-term PV isolation in patients with AF referred for ablative therapy. The results are consistent with other reports that have documented PV reconnection and PV triggers in patients with AF recurrence after 1 year.\textsuperscript{3,8,11,12,14,15,22,23}

There are increasing data in the literature that asymptomatic AF is not uncommon after PV isolation.\textsuperscript{24,25} It is possible...
that there were additional patients in our study with asymptomatic AF who were not detected as having AF recurrences. We believe our strategy of using 30-day transtelephonic monitoring twice over a 6-month period and instructions to patients to monitor their pulse daily with continued long-term clinical follow-up over 5 years maximized detection of AF recurrences. Performing periodic continuous monitors for the 5 years after PVI might have detected more asymptomatic AF; however, this would only served to emphasize our results that late AF recurrences continue to occur after AF ablation. In addition, the detection of brief asymptomatic episodes of AF is of unclear significance.

Limitations

It should be emphasized that our results apply to patients who underwent segmental PVI of arrhythmogenic PVs during the 2001 to 2003 period using a standard 4-mm tip ablation catheter. By selecting only patients who had AF freedom after 1 year for the study group, we tried to exclude patients with recurrences of AF due to early PV reconnection. It is also possible that advances in catheter ablation, including use of irrigated tip catheters, more proximal isolation of all PVs, and advanced image integration will improve the long-term success rate of the procedure. However, this will require future long-term follow-up studies. By selecting only patients who had AF freedom after 1 year for the study group, we tried to exclude patients with recurrences of AF caused by early PV reconnection.

Summary

Long-term freedom from AF among patients who underwent segmental PVI before 2001 and 2003 and remained AF-free for at least 1 year is sustained in the majority of patients. However, even after 1 year of AF freedom, recurrent AF may occur in 7% of patients per year. The strongest predictors of recurrent AF in this population are the presence of persistent AF and age. In patients undergoing repeat ablation, the mechanism of late AF recurrence was overwhelmingly associated with PV reconnection. Continued vigilance for recurrent AF after PV isolation is warranted, particularly in older patients with a history of persistent AF.

Disclosures

Drs Gerstenfeld, Callans, and Marchlinski received research funding from Biosense-Webster. No funding was provided for this study.

References


**CLINICAL PERSPECTIVE**

Pulmonary vein isolation is a procedure that is increasingly used for the treatment of atrial fibrillation (AF). However, the long-term success rate of catheter ablation is unknown. We determined 5-year outcomes among patients with freedom from AF for 1 year after catheter ablation. Among 123 patients with freedom from AF after 1 year, the long-term success rate was 85% at 3 years and 71% at 5 years, with an approximate 7% late recurrence rate per year. The long-term success rate improved to 81% among patients undergoing repeat ablation procedures. The only independent predictors of recurrent AF were older age and the presence of persistent AF. These findings suggest that patients and referring physicians must be vigilant about monitoring for late AF recurrences after ablation, particularly in older patients with a history of persistent AF. Caution should be exercised before anticoagulant therapy is withdrawn in patients at risk for cardioembolic stroke.
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