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Original Article

When Should We Decide to Perform a Repeat Pulmonary Vein Isolation Procedure in Patients with Atrial Fibrillation?

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Background: It is sometimes difficult to differentiate the transient appearance of atrial fibrillation (AF) after pulmonary vein (PV) isolation from a true recurrence of AF. We attempted to differentiate them by analyzing the time course after the procedure.

Methods and Results: 79 patients who underwent PV isolation were divided into two groups (successful: N = 60 and unsuccessful: N = 19) according to the final outcome. Antiarrhythmic drugs were used either temporarily or continuously to treat re-appearance of AF after the procedure. The transient appearance of AF in the successful group gradually faded, while true AF recurrence in the unsuccessful group consistently increased in line with the follow-up (F/U) period. The appearance of AF after 3 months predicted a subsequent failure of the procedure with a positive/negative predictive value of 87/90%, respectively.

Conclusion: Since the transient appearance of AF decreased and the true recurrence of AF increased in line with the F/U period, we should therefore wait at least 3 months before judging the outcome of PV isolation.
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Key words: Atrial fibrillation, Pulmonary vein isolation, Outcome, Recurrence

Introduction

Pulmonary vein (PV) isolation has been shown to be an effective treatment for patients with paroxysmal and persistent atrial fibrillation (AF).[1–4] However, a recurrence of AF following ablation is one of the major limitations of this procedure.[5,6] Although the appearance of AF early after PV isolation is well known to often occur as a transient phenomenon and thereafter it fades out naturally,[7,8] there are sometimes patients who require early repeat procedures due to severe symptoms caused by AF recurrence. Therefore it is useful to know the best timing to judge the outcome of the PV isolation procedure in order to minimize any unnecessary repeat procedures.

Methods

Study subjects

This study consisted of 79 consecutive patients with AF (paroxysmal: 51, persistent: 28, mean age:

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51.5 ± 9.9 years) who underwent PV isolation targeting all four PVs. All patients were subsequently observed for more than 12 months (mean observation period: 27.5 ± 7.6 months).

Electrophysiological study

After each of the patients gave their written informed consent, an electrophysiological study was performed as described previously.[9] A 7F 8-mm-tip quadripolar ablation catheter (7F BlazerII, Boston Scientific) and a decapolar circular mapping catheter (Lasso, Biosense Webster) were placed transseptally at the ostium or antrum of targeted PVs. Selective PV angiography was performed by the hand injection of contrast medium (10–20 ml) in biplane views and then was displayed during the procedure to show the venous anatomy and the location of the left atrium (LA)-PV junction. PV mapping was performed with a steerable circular Lasso catheter with a diameter of either 15, 20, 25 or 30 mm. The PV potentials (PVPs) were defined as described previously and recorded in a bipolar mode of 10 bipoles (1 to 2, 3 to 4, . . ., up to 19 to 20) through band-pass filters of 30 to 500 Hz and an amplification of 1 to 2 cm/mV on polygraphy (EP Med System, Inc).

Ablation procedure

In each case, all four PVs were targeted to be electrically disconnected from the LA. Radiofrequency (RF) current ablation was performed as proximally as possible at its ostium or antrum during either sinus rhythm or AF. The segment of the PV ostial perimeter identical to the earliest activation site with the electrogram polarity reversal[9] was preferentially targeted. RF energy was applied at a target temperature of 50 °C with a power limit of 30 to 35 W for 60 to 90 seconds at each site. The end point was the establishment of the bidirectional block between the LA and PV.[10] After the elimination of all PVPs, an absence of conduction from PV to LA was also confirmed by pacing inside the PV with the Lasso catheter. If the patients had atrial flutter, then cavotricuspid isthmus ablation was also performed. No linear ablation was performed including the posterior left atrium and mitral isthmus. After the complete PV isolation was confirmed, provocative maneuvers (isoproterenol infusion or burst pacing) were performed to reveal other foci and additional RF ablation was performed if necessary.

Clinical outcome and patient follow-up

In this study, we waited at least 6 months before the outcome of the procedure was judged. An "unsuccessful" procedure was defined as the reappearance of AF which was sustained more than 1 minute, while a "successful" procedure was defined as the disappearance of AF during the 6 months of observation period. When frequent AF episodes appeared within 6 months after the procedure, antiarrhythmic drugs (AADs) were administered either temporarily or continuously. Generally, AADs were gradually tapered and discontinued during the course of observation period, however, they were maintained in some cases on the basis of patients' wishes even if stable sinus rhythm was kept during F/U period. All patients were given a periodical follow-up (once a month) in an outpatient clinic and a recurrence of AF was evaluated based on the symptoms, ECG recordings and 24-hour ambulatory monitorings (1, 3, 6, 9, and 12 months after the procedure). Repeat PV isolation procedures were recommended for patients who were judged to be "unsuccessful" after being treated with this procedure.

Statistical analysis

All values are expressed as mean ± SD. A statistical analysis was performed using Student's *t*-test (unpaired) or chi-square analysis. Differences with $p < 0.05$ were considered to be statistically significant.

Results

Patient characteristics and procedure outcome

In total, 98% (311/316) of the targeted PVs were electrically isolated from LA during the session.

Table 1 Comparison of characteristics of successful and unsuccessful group.

	Successful Group (n = 60)	Unsuccessful Group (n = 19)	P value
Age (yrs)	51.9 ± 9.9	51.3 ± 10.0	NS
Men/women	51/9	18/1	<0.0001
Paroxysmal AF/ persistent AF	43/17	8/11	0.028
Duration of AF (yrs)	4.2 ± 4.1	5.6 ± 5.3	NS
EF (%)	65.7 ± 5.3	64.4 ± 11.6	NS
Left atrial diameter (mm)	36.9 ± 5.2	37.6 ± 4.6	NS
Organic heart disease (+/−)	17/43	7/12	NS
Antiarrhythmic drugs	3.5 ± 1.4	3.3 ± 1.3	NS

AF indicates atrial fibrillaiton; EF, ejection fraction.

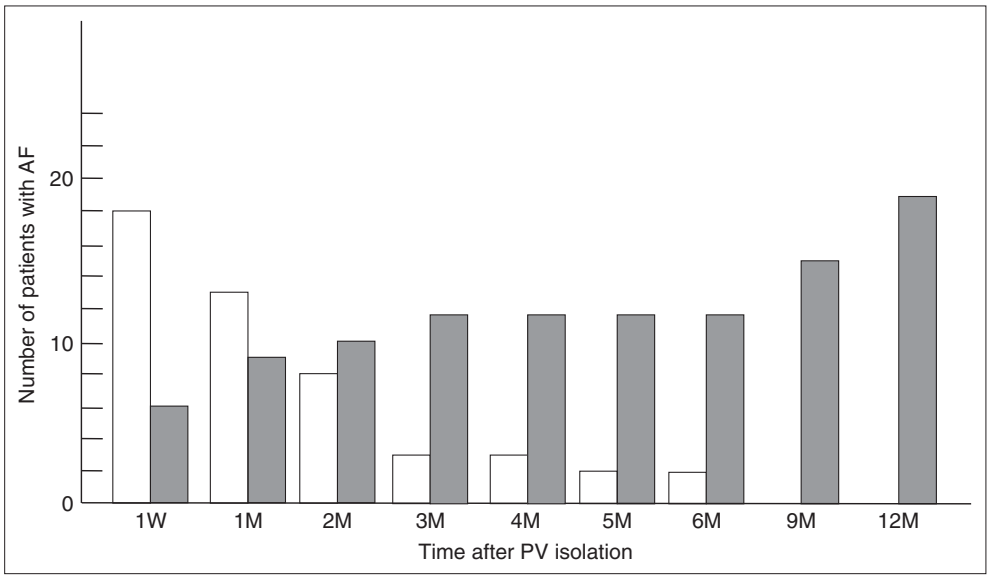

Figure 1 The relationship between the time course and AF appearance.
The white and gray bars represent AF recurrence at each month in the successful and unsuccessful group, respectively. 1 W and 1–6 M indicate 1 week and 1–6 months after ablation, respectively.

After 27.5 ± 7.6 months of follow-up, 19 (24%) patients were classified as belonging to the "unsuccessful" group while the remaining 60 (76%) patients were classified as belonging to the "successful" group for this procedure. The clinical characteristics of both groups are given in **Table 1**. The greater number of patients with persistent AF and a male gender were included in the "unsuccessful" group in comparison to the "successful" group ($p < 0.05$ and $p < 0.001$, respectively).

In the "unsuccessful" group ($N = 19$), AF appeared in 32% (6/19), 53% (10/19), 53% (10/19), 63% (12/19), 63% (12/19), and 63% (12/19) of patients at 1 week, 1, 2, 3, 4, and 5 month after PV isolation procedure, respectively. As shown in **Figure 1**, the frequency of AF increased in the "unsuccessful" group in line with the time after the procedure. On the other hand, in the "successful" group ($N = 60$), the frequency of AF decreased in line with the duration of the F/U period (30% (18/60), 22% (13/60), 13% (8/60), 5% (3/60), 5% (3/60), and 3% (2/60) at 1 week, 1, 2, 3, 4, and 5 months after the PV isolation procedure respectively). In total, the appearance of AF at 1 week, 1, 2, 3, 4 and 5 months predicted the final success or failure of this procedure with a positive/negative predictive value of 25/76%, 41/82%, 56/85%, 80/89%, 80/89% and 86/89%, respectively (**Table 2**). The appearance of AF later than 3 months, but not within 3 months after the PV isolation, correlated well with a poor long-term outcome ($p < 0.01$). In the "successful" group, 13% (8/60) of patients temporarily and 10% (6/60) of patients continuously needed to take previously ineffective AADs to prevent AF recurrence (6: bepridil, 4: pilsicanide, 2: cibenzoline, 1: disopyramide, 1: flecainide). On the other hand, in the "unsuccessful" group, all 19 patients experienced AF recurrence even under AADs (8: bepridil, 6: pilsicanide, 2: cibenzoline, 1: disopyramide, 1: flecainide, 1: pirmenol).

Among the 19 patients classified as "unsuccessful", 17 patients underwent repeat PV isolation procedures (2 patients refused). Re-conduction of previously isolated PVs were seen in 3.3 ± 0.5 PVs in all 17 patients. 16/17 (94%) patients were free from AF after repeat ablation. In addition, 2 patients underwent an ablation of non-PV foci in addition to PV isolation.

Complications

Cardiac tamponade occurred in one patient during the procedure, which was relieved by percutaneous drainage. In addition, an asymptomatic left inferior PV stenosis (50–75%) was observed a long time after the procedure in one patient.

Discussion

This study shows that there are two types of AF recurrence after the PV isolation procedure. One is a transient re-appearance of AF while the other type is a true recurrence of AF requiring repeat PV isolation

Table 2 Predictive accuracies of AF recurrence for the final outcome.

	1 W	1 M	2 M	3 M	4 M	5 M	6 M
Sensitivity	32%	47%	53%	63%	63%	63%	63%
Specificity	70%	78%	87%	95%	97%	97%	97%
PPV	25%	41%	56%	80%	80%	86%	86%
NPV	76%	82%	85%	89%	89%	89%	89%

PPV indicates positive predictive value; NPV, negative predictive value; 1 W, 1 week after ablation; 1–6 M, 1–6 months after ablation.

procedures. Although it is quite difficult to discriminate these two types of AF recurrence from the ECG findings, the time course of their appearance or disappearance may be useful for their differentiation. We found that the former type of AF recurrence appears at a relatively early phase during the observation period and then subsides naturally, whereas the latter increases in line with the observation period. Since the positive and negative predictive value of the AF appearance for the failure of the procedure reached up to 80% and 89% at 3 month F/U, respectively, we determined that we should wait at least 3 months before making a final judgment to perform repeat procedures in order to avoid unnecessary ablation procedures.

Although there may be multiple causes for transient appearance of AF after PV isolation, it has been shown to be mainly related to the acute inflammatory change in the tissue resulting from the application of RF energy.[7,8] Previous reports demonstrated that RF application induces the local proliferation of inflammatory cells (subclinical pericarditis), and it takes several weeks for the disappearance of these inflammatory changes.[11,12] The gradual disappearance of transient AF recurrence over several weeks in this patient population was closely compatible with the histopathogenic changes documented above.

There have been several reports regarding the causes of true AF recurrence after the PV isolation procedure. The main cause of AF recurrence has been shown to be the recovery of PV-LA conduction.[13–16] Callans et al.[15] reported that a recovery of PV-LA conduction was observed in 97% of patients, and 86% of them were free of AF after repeat PV isolation procedures. Ouyang et al.[16] also reported recovered PV-LA conduction to be observed in 81% of patients at the repeat procedure, and 95.5% of them were free from AF after repeat PV isolation procedure. In this study, a recovered PV-LA conduction was observed in 3.3 ± 0.5 PVs in all 17 patients who underwent repeat procedures for the recurrence of AF. In addition, 94% of them subsequently became free from AF after the repeat sessions. These results suggest a recovery of PV-LA conduction to be the main and exclusive cause of true AF recurrence after the PV isolation procedure and vigorous attempts of repeat PV isolation is recommended for the complete cure of AF.

In this study, re-conduction of previously isolated PVs were observed in all patients (mean 3.3 PVs) who underwent repeat PV isolation. Since repeat procedure was not performed in the successful group, presence/absence of PV re-conduction in cases without AF-recurrence was not known. As shown above, 10% of patients in the successful group continuously took AADs during the whole observation period. Those findings might suggest that patients in the successful group were more sensitive to AADs compared to those in the unsuccessful group, and re-conducted PVs were pharmacologically re-isolated, as shown by Kumagai et al.[17]

There have been a few studies describing relatively poor long-term outcome in cases with early AF appearance after PV isolation. Oral et al.[7] reported that about 30% of patients with early AF appearance (within 2 weeks after the procedure) were free from AF without AADs during a mean F/U period of 7 months. O'Donnell et al.[18] also reported that 39% of patients with early AF appearance (within 3 months) were free from AF under AADs during a mean observation period of 9 months. In this study we showed a much higher long-term successful rate (67%) with or without AADs. Although the reason of these discrepancies among studies is not known, they might be caused by different PV isolation protocols. Isolation of all four PVs was achieved in only 28% of patients in the study of Oral et al. and also only 2.5 PVs (mean) per patient were isolated in the O'Donnell study. In our study, all four PVs were successfully electrically isolated in 98% of cases, which would be related to the better long-term outcome of our patients with early AF re-appearance after PV isolation.

Limitations

There are several limitations in this study. First,

because the clinical outcome of the PV isolation procedure was judged based on the patients' symptoms, serial ECGs, and 24-hour ambulatory monitoring, patients with asymptomatic AF recurrences could thus have been underestimated. Second, a relatively small number of patients were evaluated in this study. Studies with a larger number of patients should therefore be performed for a more detailed analysis.

Conclusion

A transient AF appearance after the PV isolation procedure generally fades out during a 3 month observation period, while the true AF recurrence increases in line with the time after the procedure. We should wait at least 3 months before judging the outcome of PV isolation to avoid any unnecessary repeat ablation procedures.

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