Predictors of Very Late Recurrence of Atrial Fibrillation After Circumferential Pulmonary Vein Ablation

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ABSTRACT

Background: Early recurrence of atrial fibrillation (ERAF) after catheter ablation is common and has been thoroughly studied. However, very late recurrence of atrial fibrillation (VLRAF) is rarely researched, and its characteristics have not been determined.

Hypothesis: The aim of this study was to investigate the clinical characteristics of VLRAF after circumferential pulmonary vein ablation (CPVA), and to identify the risk factors for VLRAF.

Methods: We retrospectively studied 259 consecutive patients with atrial fibrillation (AF) who were referred for CPVA. Clinical variables were investigated and predictors of VLRAF were identified.

Results: A total of 249 patients were enrolled in this study. After a mean follow-up of 18.2 ± 4.4 mo, 14 patients (5.6%) had VLRAF. Patients with VLRAF were more likely than those without recurrence to have ERAF (78.6% versus 17.8%, $p = 0.000$) and persistent AF (50.0% versus 13.0%, $p = 0.000$), but were less likely to achieve pulmonary vein (PV) isolation (78.6% versus 97.6%, $p = 0.000$). Bivariate analysis demonstrated that ERAF (odds ratio [OR] 8.148, 95% confidence interval [CI] 2.197–30.222; $p = 0.002$), persistent AF (OR 8.853, 95% CI 1.773–16.155; $p = 0.003$), and lack of PV isolation (OR 7.530, 95% CI 1.792–33.122; $p = 0.006$) were related to VLRAF. Multivariate logistic regression analysis only identified ERAF as a predictor of VLRAF after CPVA (OR 7.461, 95% CI 1.696–24.836; $p = 0.006$).

Conclusions: Very late recurrence of AF is uncommon after CPVA. That occurs more commonly in patients with ERAF.

Key words: recurrence, ablation, atrial fibrillation

Introduction

Radiofrequency catheter ablation has become an effective treatment for drug-refractory atrial fibrillation (AF).[1–4] Despite constant improvements in clinical outcomes with advances in ablation devices and techniques, the recurrence of atrial tachyarrhythmia (ATa) after catheter ablation is still an ongoing problem.[5,6] Some researchers[5,6] observed that early recurrence of AF (ERAF) did not affect the long-term outcome of catheter ablation for AF. However, very late recurrence of atrial fibrillation (VLRAF) after catheter ablation has rarely been identified or researched.

The main purposes of this study were to observe the clinical characteristics of VLRAF after circumferential pulmonary vein ablation (CPVA), and to identify the risk factors for VLRAF.

Methods

Study Population

We retrospectively studied 259 consecutive patients with AF who were referred to our institute for first-time CPVA. All patients underwent transesophageal and transthoracic echocardiography before catheter ablation for AF. The inclusion criteria were that patients must be ages 20–80 y, have symptomatic AF refractory to at least 2 antiarrhythmic drugs (AADs), and must be considered New York Heart Association (NYHA) class I or II. Exclusion criteria included left ventricular ejection fraction (LVEF) <45%, hemorrhagic diathesis or other contraindication to anticoagulation, left atrial (LA) thrombus, previous AF ablation, and <12 mo of follow-up. Persistent AF was defined as AF that had lasted for more than 7 d prior to ablation, regardless of whether cardioversion had been attempted.

Electrophysiological Study and CPVA

All AADs, except amiodarone, were discontinued for at least 5 half-lives before ablation. Each patient gave written informed consent before undergoing electrophysiological study and ablation.

The technique of CPVA has been described in detail in previous studies.[7,8] Briefly, a quadripolar catheter was advanced via the right femoral vein and positioned in the coronary sinus (CS) for atrial pacing and signal reference. Dual transseptal puncture was performed under fluoroscopic guidance, with delivery of 2 8-F-long sheaths

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(SL1 and SR0, St. Jude Medical, St. Paul, Minn., USA) into the LA. The LA geometry was reconstructed using the Carto system (Biosense Webster, Inc., Diamond Bar, Calif., USA) with a 3.5-mm-tip ablation catheter (ThermoCool Navi-Star, Biosense Webster, Inc., Diamond Bar, Calif., USA). The pulmonary vein (PV) antrum was identified by a combination of venography, electrogram, and the drop-off site of the mapping catheter while dragging it out of the vein. Radiofrequency energy was delivered along the ipsilateral PV antrum at 43°C, with a maximal energy output of 35 W and an external irrigated flow rate of 17 mL/min. Each target site was ablated for 20–30 sec until the local electrogram amplitude was noted to have decreased by ≥80% or to <0.1 mV. After the initial CPVA was completed, all patients without AF termination or AF conversion to atrial tachycardia (AT) would receive cardioversion, and then their PVs were mapped with a decapolar circumferential mapping catheter (Lasso, Biosense Webster, Inc., Diamond Bar, Calif., USA). If any residual PV potentials were documented, additional ablation was performed to eliminate those potentials and to close the gaps in the circumferential lines. The end point of the CPVA procedure was isolation of all PVs as shown by the circumferential mapping catheter.

The tricuspid annulus isthmus (TAI) was ablated to achieve a bidirectional conduction block if a typical atrial flutter (AFL) was documented in the history or occurred spontaneously during the procedure.

Postablation Management

After the procedure, warfarin was administered to all patients for at least 3 mo. The international normalized ratio was maintained at 1.8–2.5. Amiodarone, or propafenone when amiodarone was contraindicated, was administrated after discharge and was discontinued after 3 mo if no recurrence was documented.

Follow-up After CPVA

All patients were followed-up in 2 stages with 12-lead electrocardiograms (ECGs) and 24-h Holter monitoring. The first stage was conducted at 0.5, 1, 3, 6, and 12 mo. The second stage was conducted bimonthly from 12–18 mo. If a patient experienced symptoms suggestive of tachycardia, ECG or 24-h Holter monitoring was performed to determine the cause of the symptoms. A physician also interviewed all patients monthly by telephone to track and update their clinical situations.

Recurrence of AF was defined as any symptomatic episode of ATa, including AF or AT, lasting longer than 30 sec or any episode of asymptomatic ATa lasting more than 5 min on Holter recording. Early recurrence of AF was defined as ATa occurring within 1 mo of ablation. Regardless of whether there was concomitant ERAF, late recurrence of AF (LRAF) was defined as ATa occurring only between 1 mo and 12 mo postablation, and VLRAF was defined as ATa occurring only more than 12 mo after ablation, but no AF observed between 1 mo and 12 mo.

At the end of follow-up, all patients were classified into 3 groups: VLRAF group, LRAF group, and no-recurrence group.

Repeat Catheter Ablation

If ATa occurred continuously, regardless of external cardioversion and AAD therapy, a repeat electrophysiological study and ablation were recommended, but were conducted at least 3 mo after the initial procedure. In the repeat ablation procedure, all reconnected PV conduction was mapped and isolated, and non-PV foci were tracked and ablated. Non-PV foci were identified by the spontaneous onset of ectopic beats initiating AF either at baseline or after provocative maneuver by isoproterenol infusion or burst atrial pacing. The end point of the repeat procedure was reisolation of bilateral PVs and negative induction of ATa under burst atrial pacing and intensive isoproterenol infusion (20μg/min).

Statistics Analysis

Continuous variables are presented as mean±standard deviation. Categorical variables are presented as percentages. Differences between group means were evaluated with *t* tests (continuous variables) or by x^2 analyses (categorical variables) as appropriate. Statistical significance was defined as a 2-tailed p value <0.05.

Variables with p<0.05 in the bivariate analysis were analyzed using multivariate stepwise logistic regression analysis. Statistic analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, Ill., USA). Statistical significance was defined as a p value <0.05.

Results

Clinical Characteristics

Of the 259 consecutive patients, 10 patients were excluded from the study (8 without adequate follow-up and 2 with cardiac deformity). The remaining 249 patients (175 male, aged 56.7±11.2 y) met the inclusion criteria. Of these, 74 had persistent AF (29.7%) (Table 1).

Procedure Results and Findings

The procedure results and findings of CPVA were recorded in Table 2. The TAI was blocked with bidirectional conduction block in 102 patients.

Postoperation Management

Warfarin was administered and monitored in 245 patients (98.4%) for 3 mo, but was replaced by aspirin in 4 patients due to contraindication to the use of warfarin. Amiodarone was administrated to most patients (246 of 249; 98.8%) for 3 mo, but 3 patients received propafenone instead due to thyroid dysfunction.

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TABLE 1: Patient baseline characteristics

Age (y)	56.7±11.2
Male sex (%)	175 (70.3%)
History (y)	6.8±6.7
Persistent AF (%)	74 (29.7%)
Hypertension (%)	100 (40.2%)
Diabetes mellitus (%)	28 (11.2%)
Coronary artery disease (%)	12 (4.8%)
Prior ischemic stroke (%)	16 (6.4%)
AADs usage prior to initial ablation	
β-Blocker (%)	230 (92.4%)
Propafenone (%)	153 (61.4%)
Amiodarone (%)	219 (88.0%)
Diameter of left atrium (mm)	38.5±6.1
LVEDV	66.4±23.2
LVESV	46.3±22.0
E peak	64.1±23.8
LVEF	63.0±8.4

Abbreviations: AADs = antiarrhythmic drugs; AF = atrial fibrillation; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

TABLE 2: Patient clinical characteristics

PV isolation (%)	238 (95.6%)
External cardioversion (%)	56 (22.5%)
X-ray exposure time (mm)	31±12
Procedure time (mm)	213±41
ERAF (%)	74 (29.7%)
LRAF (%)	66 (26.5%)
VLRAF (%)	14 (5.6%)
Free of AF (mo)	14.4±7.0
Fellow-up (mo)	18.2±4.4

Abbreviations: AF = atrial fibrillation; ERAF = early recurrence of AF; LRAF = late recurrence of AF; PV = pulmonary vein; VLRAF = very late recurrence of AF.

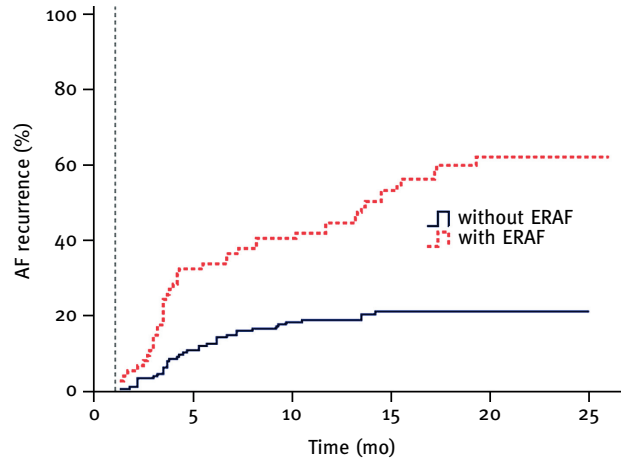

Figure 1: Time to recurrence of AF in patients with or without ERAF (vertical dashed line on left = 1 mo of follow-up).

Follow-up of Recurrence

After a mean follow-up of 18.2±4.4 mo, 74 patients (29.7%) had ERAF, and 80 patients (32.1%) experienced ATa recurrence more than 1 mo postoperation; of whom 66 (26.5%) had LRAF and 14 (5.6%) had VLRAF. The clinical characteristics and noninvasive management of patients with ATa recurrence are summarized in Table 3. The remaining 169 patients (67.9%) had no documented ATa recurrence after 1 mo postoperation (no-recurrence group).

Most of the baseline and clinical characteristics in the VLRAF and no-recurrence groups were comparable (Table 4). However, patients in the VLRAF group were more likely to have ERAF, persistent AF, and external cardioversion during catheter ablation than patients in the non-recurrence group. Patients with VLRAF were also less likely to have PV isolation. The trend of ERAF being associated with an increased risk of VLRAF was manifested in the Kaplan-Meier curve (Figure 1).

Among the patients with recurrence, those with VLRAF had a high incidence of persistent AF and ERAF, and a low rate of PV isolation (Table 5).

Predictors of VLRAF

Bivariate analysis identified ERAF (OR 8.148, 95% CI 2.197–30.222; p = 0.002), persistent AF (OR 8.853, 95% CI 1.773–16.155; p = 0.003), and lack of PV isolation (OR 7.530, 95% CI 1.792–33.122; p = 0.006) as being related to VLRAF. Multivariate logistic regression analysis only identified ERAF as a predictor of VLRAF after CPVA (OR 7.461, 95% CI 1.696–24.836; p = 0.006).

Repeat Ablation for AF

In the 52 patients who underwent repeat catheter ablation, 6 with VLRAF and 46 with LRAF, PV conduction recovery was observed in 45 patients (86.5%; 4 with VLRAF and 41 with LRAF), and non-PV foci were identified and ablated in 14 patients (26.9%; 4 with VLRAF and 10 with LRAF). Non-PV

TABLE 3: Clinical characteristics and management of patients with recurrent ATa

	Time to first ATa	Type of recurrent ATa			Management of recurrent ATa		
	Episode	AF	AF plus AF	AT	Reversion to SR by EC	Reversion to SR by AADs	Spontaneous reversion
ERAF group (n = 74)	5.9±5.1 d	36 (48.7%)	16 (21.6%)	22 (29.7%)	10	16	15
LRAF group (n = 66)	4.7±2.6 mo	42 (63.6%)	13 (19.7%)	11 (16.7%)	4	5	1
VLRAF group (n = 14)	14.9±1.9 mo	12 (85.7%)	2 (14.3%)	0	0	2	1

Abbreviations: AADs = antiarrhythmia drugs; AF = atrial fibrillation; AT = atrial tachycardia; ATa = atrial tachyarrhythmia; EC = external cardioversion; ERAF = early recurrence of AF; LRAF = late recurrence of AF; SR = sinus rhythm; VLRAF = very late recurrence of AF.

triggers were documented in the posterior wall of the LA (5 of 14), crista terminalis (3 of 14), superior vena cava (3 of 14), and mitral valve annulus (3 of 14). Patients with VLRAF were more likely to have non-PV foci (66.7% versus 21.7%; p = 0.020) and an increased LA diameter (40.3±3.7 mm versus 36.6±3.9 mm; p = 0.032).

Complications

Procedure-related complications were documented in 7 patients (2.8%). Mild pericardiac effusion was detected in 1 patient and was resolved without pericardiocentesis within 5 d. Two patients had a transient stroke, but both recovered before discharge. Four patients experienced a severe hematoma; requiring blood transfusion in 1 case.

Discussion

Main Findings

The main purposes of this study were to observe the characteristics of VLRAF following CPVA and to identify predictors of VLRAF. The results show that the incidence of VLRAF is low (5.6%) and that it is associated with the presence of ERAF. Furthermore, ERAF was identified to play an important role in the occurrence of LRAF.

VLRAF After Catheter Ablation

Until now, the mechanism of VLRAF was rarely studied, and there has not been a consensus on conclusions in the reports published to date. Heish et al. observed that the incidence of VLRAF was 6%[9] and demonstrated that non-PV foci were the essential trigger for VLRAF.[10] Recently, Mainigi et al.[11] reported a similar incidence of VLRAF (7.9%) and demonstrated that obese weight was a predictor for VLRAF. In our study, the low incidence of VLRAF (5.6%) was consistent with these studies, and the clinical characteristic most likely to predict VLRAF was the presence of ERAF. Although we did not evaluate the association between body weight and VLRAF, we also determined the relationship between non-PV foci and VLRAF. The incidence of non-PV foci in our VLRAF group (66.7%) was significantly higher than the incidence reported in other studies.[10,11] This discrepancy may be explained by the different ablation algorithm of CPVA in our study. Different than those studies, we only performed CPVA and PV isolation and did not perform extra operations in the initial procedure (e.g., non-PV foci mapping and inductive maneuver of ATa after PV isolation).

For patients with VLRAF, why did their ATa recurrence occur so late? Some studies[10,11] showed VLRAF associated with the existence of non-PV foci. Furthermore, the anatomic character of non-PV foci is prone to delay the recurrence.[10–13] Thus, it is speculated that non-PV foci, although their incidence is rare, may be omitted in the initial ablation under a PV-target ablation strategy, and the chances of delayed recurrence (i.e., VLRAF) aroused by non-PV foci will increase.

Predictive Value of ERAF After Catheter Ablation

Some previous studies have shown that ERAF does not affect the final outcome of catheter ablation for AF.[5,6] However, the predictive value of ERAF for long-term outcome (more than 1 y) has seldom been studied. Lee et al.[14] observed that ERAF affected the long-term outcomes of catheter ablation for paroxysmal AF and predicted the onset of LRAF. Our study enrolled an extensive scope of patients with AF, including 74 cases of persistent AF (29.7%), and our results were comparable. Based on these findings, the predictive value of ERAF for long-term outcomes after ablation can be applied to all types of AF.

Traditionally, ERAF has been considered to be a result of the resumption of early electrical activity in ablation lines.[15–17] However, ERAF can also affect the remodeling of atrial anatomy after catheter ablation. In our study, most patients (83.5%) with VLRAF who had ERAF had an increased LA diameter at the time of their repeat ablation procedure. In a recent study by Chang et al.,[18] patients with VLRAF had increased atrial dimensions at their repeat ablation procedure. It can be presumed that ERAF may interrupt the process of postablation remodeling and result in incomplete remodeling of atrial anatomy, and can increase the risk for VLRAF.

TABLE 4: Clinical characteristics of patients with VLRAF or without recurrence

	VLPxAF group (n = 14)	Nonrecurrence group (n = 169)	p-value
Age (y)	55.2±10.5	56.5±11.3	0.69
Male sex (%)	10 (71.4%)	117 (69.2%)	0.86
History (y)	6.1±5.3	6.3±6.3	0.91
Persistent AF (%)	7 (50.0%)	22 (13.0%)	0.000[a]
Hypertension (%)	7 (50.0%)	71 (42.0%)	0.56
Diabetes mellitus (%)	0	21 (12.4%)	0.16
Coronary artery disease (%)	0	12 (7.1%)	0.30
Prior ischemic stroke (%)	1 (7.1%)	10 (5.9%)	0.83
AADs usage prior to initial ablation			
β-blocker (%)	13 (92.9%)	158 (93.5%)	0.93
Propafenone (%)	10 (71.4%)	103 (60.9%)	0.44
Amiodarone (%)	12 (85.7%)	149 (88.2%)	0.79
Diameter of left atrium (mm)	39.1±5.3	38.2±6.2	0.57
LVEDV	69.0±27.0	66.4±23.0	0.70
LVESV	52.5±25.9	47.1±23.2	0.48
E peak	70.1±30.7	62.6±21.7	0.40
EF	60.9±5.8	63.6±8.0	0.24
PV isolation (%)	11 (78.6%)	165 (97.6%)	0.000[a]
External cardioversion (%)	7 (50.0%)	31 (18.3%)	0.005[a]
X-rays expose time (min)	30±11	31±13	0.95
Procedure time (min)	212±45	214±40	0.94
Early recurrence (%)	11 (78.6%)	30 (17.8%)	0.000[a]

[a]p<0.05. *Abbreviations*: AADs = antiarrhythmia drugs; AF = atrial fibrillation; EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; PV = pulmonary vein.

TABLE 5: Clinical characteristics of patients with VLRAF or LRAF

	VLRAF group (n = 14)	LRAF group (n = 66)	p-value
Age (y)	55.2±10.5	57.6±11.0	0.46
Male sex (%)	10 (71.4%)	48 (72.7%)	0.92
History (y)	6.1±5.3	8.0±7.7	0.41
Persistent AF (%)	7 (50%)	15 (22.7%)	0.038[a]
Hypertension (%)	7 (50%)	22 (33.3%)	0.24
Diabetes mellitus (%)	0	7 (10.6%)	0.20
Coronary artery disease (%)	0	0	
Prior ischemic stroke (%)	1 (7.1%)	5 (7.6%)	0.96
AADs usage prior to initial ablation			
β-blocker (%)	13 (92.9%)	60 (90.9%)	0.56
Propatone (%)	10 (71.4%)	53 (80.3%)	0.46
Amiodarone (%)	12 (85.7%)	62 (93.9%)	0.29
Diameter of left atrium (mm)	39.1±5.3	39.1±6.1	0.99
LVEDV	69.0±27.0	65.8±23.2	0.66
LVBSV	52.5±25.9	43.1±11.1	0.16
E peak	70.1±30.7	68.3±27.0	0.85
EF	60.9±5.8	61.9±9.5	0.72
PV isolation (%)	11 (78.6%)	62 (93.9%)	0.016[a]
External cardioversion (%)	7 (50.0%)	18 (27.3%)	0.096
X-ray exposure time (min)	30±11	32±8	0.92
Procedure time (min)	212±45	215±33	0.91
Early recurrence (%)	11 (78.6%)	33 (50.0%)	0.051[b]

[a]p<0.05; [b]p = 0.051. *Abbreviations*: AADs = antiarrhythmic drugs; AF = atrial fibrillation; EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LRAF = late recurrence of AF; VLRAF = very late recurrence of AF; PV = pulmonary vein.

Clinical Implications

The association between ERAF and long-term outcomes has been identified in the present study. It is suggested that intensive monitoring of an ATa episode during the early postoperational period is necessary. If ERAF was documented, the risk for subsequent recurrence may be increased, and further, longer follow-up is somewhat needed. In addition, because of the close relationship between non-PV foci with VLRAF, mapping and intervention for non-PV foci may be the optimal strategy for future ablation.

Limitations

Some asymptomatic recurrence is difficult to detect using the present follow-up designs. Some underlying risk factors may therefore be neglected or less studied. It is also difficult to explore and interpret the mechanism of VLRAF with only

6 patients with VLRAF who underwent repeat RF catheter ablation. A prospective study with a more sensitive follow-up design and a larger number of cases is needed to further study this issue.

Conclusions

Very late recurrence of AF is uncommon after CPVA, which occurs more commonly in patients with ERAF.

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