New Predictor of Very Late Recurrence After Catheter Ablation of Atrial Fibrillation Using Holter Electrocardiogram Parameters

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This study aimed to evaluate the predictors of very late recurrence of atrial fibrillation (VLRAF) after an initial AF catheter ablation (CA) by analyzing the follow-up Holter electrocardiogram. We retrospectively studied patients (n = 253, mean age: 66 years, woman: 30%, paroxysmal AF: 73%) without recurrence of AF within 12 months and the use of antiarrhythmic drugs. In the Holter electrocardiogram analysis, the atrial premature complexes (APCs) burden, the profile of the APCs run and prematurity index of the APCs were evaluated. Fifty-one patients (20%) had VLRAF during the follow-up period (mean follow up: 46 months). Patients with VLRAF had a significantly greater APCs burden (0.318% [0.084 to 1.405] vs 0.132% [0.051 to 0.461], p = 0.022), longer number of APCs run (5 [3 to 11] vs 4 [0 to 7], p = 0.019), and shorter minimum prematurity index of the APCs (47 ± 7 vs 51 ± 6, p = 0.001) than those without VLRAF. The optimal cutoff value for the APCs burden, maximum number of APCs run, and minimum prematurity index of the APCs to predict VLRAF was 0.159%, 10, and 48%, respectively. The minimum prematurity index of the APCs (≤48%) was significantly associated with VLRAF in the multivariate analysis. In conclusion, the minimum prematurity index of the APCs (≤48%) at 12 months after CA was shown to be an independent predictor of VLRAF in patients without antiarrhythmic drugs. Although the index is a very simple parameter automatically calculated by analysis software, it can be an important index for following patients after CA over the long-term. **(Am J Cardiol 2020;133:71−76)**

Pulmonary vein isolation (PVI) has become an established treatment for patients with atrial fibrillation (AF),[1] but cumulative AF recurrences keep increasing over a longer follow up.[2] Atrial premature complexes (APCs) originating from the PVs or triggering AF have been shown to have a short coupling interval.[3] Gang et al[4] reported that many APCs were associated with late AF recurrence after catheter ablation (CA). Therefore, the aim of this study was to elucidate the predictors of very late recurrence of AF (VLRAF) based on a detail analysis of the APCs derived from the follow-up Holter electrocardiogram (ECG).

Methods

We retrospectively studied consecutive symptomatic AF patients who underwent a first CA between January 2011 and Mach 2017 and underwent 24-hour Holter ECGs 12 months after the CA. The exclusion criteria for this study were patients in need of antiarrhythmic drugs more than 3 months after the CA and those with recurrence of AF or atrial tachycardia within 12 months except for during the blanking period (3 months). All patients underwent CA at Osaka Rosai Hospital, according to the current guidelines. The study flow-chart is shown in Figure 1.

The AF type was categorized as paroxysmal AF if self-terminated <1 week; persistent AF if lasting ≥1 week and <1 year or requiring antiarrhythmic drugs or direct current cardioversion to restore sinus rhythm; and long-standing AF if lasting ≥1 year.[5] We defined underlying heart disease as a previous myocardial infarction, previous percutaneous coronary intervention, dilated cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease, or previous cardiac surgery. Valvular heart disease included mitral regurgitation, aortic regurgitation, aortic stenosis, and tricuspid regurgitation with a moderate or severe grade and mild mitral stenosis. All patients underwent transthoracic echocardiography to evaluate the left ventricular function and chamber size before the CA. The study was performed according to the Declaration of Helsinki and Institutional Guidelines. This study protocol was approved by the Institutional Review Board of our hospital.

An appropriate oral anticoagulant therapy was given to all patients for at least more than 3 weeks before the CA. All antiarrhythmic drugs were discontinued more than 5 half-lives before the CA. In this study, no patients received

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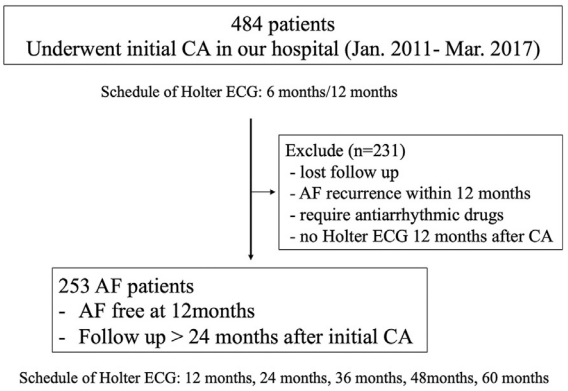

Figure 1. Study flow chart. Details are shown in the methods section. AF = atrial fibrillation; CA = catheter ablation.

any amiodarone. Transesophageal echocardiography was performed to detect thrombi in the left atrium before the CA.

The procedure was performed under moderate sedation with intravenous anesthesia. Heparin was administered at 100 IU/kg immediately after the completion of the vascular access. After a trans-septal puncture, intravenous heparin was infused continuously to maintain an activated clotting time with a target range of 300 to 400 seconds. The ablation procedure for AF was performed by a well-known approach as previously described.[6] In brief, a multipolar electrode catheter was positioned in the coronary sinus through the right subclavian or right internal jugular vein. Single or double multipolar circular catheters were located in the PVs. The PVI was performed with the guidance of a 3-dimensional mapping system (CARTO3, Biosense Webster, Diamond Bar, California), using a noncontact force catheter (THERMOCOOL SF Catheter; Biosense Webster), or contact force catheter (THERMOCOOL SMARTTOUCH Catheter; Biosense Webster). Radiofrequency energy was delivered point-by-point for 25 seconds with a power of 25 to 30 W and limited to 20 to 25 W on the posterior wall of left atrium near the esophagus. The end point of the PVI was the confirmation of bidirectional conduction block between the left atrium and PVs. In the patients with nonparoxysmal AF, if AF lasted after the completion of the PVI, a substrate ablation based on complex fractionated atrial electrogram (CFAE) was performed by the previously reported approach[7] according to the operator's discretion. The end point of the CFAE ablation was the direct termination of AF or conversion to atrial tachycardia. A sustained AT was mapped and ablated with the guidance of 3-demensional electroanatomical mapping. If AF or atrial tachycardia continues even after this approach, an internal electrical cardioversion was performed. Finally, a linear ablation of the cavotricuspid isthmus was performed in almost all patients.

A minimum of a 30-minute waiting period after the completion of the PVI was set to detect PV reconnections. Then, adenosine triphosphate disodium hydrate at 0.4 mg/kg was rapidly administered intravenously to confirm any dormant PV conduction. Additional ablation was applied until the dormant PV conduction was eliminated.

Follow-up visits were scheduled at 1, 3, 6, 12, 24, 36 48, and 60 months. During the follow-up period, 12-lead ECGs were recorded at every visit and 24-hour Holter ECGs were scheduled at 6, 12, 24, 36, 48, and 60 months. If recurrence of AF was suggested from the patient's symptom, additional examinations such as ambulatory 12-lead ECGs, 24-hour Holter ECGs, and event recorders were performed. Recurrence of AF was defined as any AF or atrial tachycardia lasting more than 30 seconds after a 3-month blanking period. Recurrence of AF within the blanking period (3 months) was defined as an early recurrence of AF (ERAF). All antiarrhythmic drugs were discontinued within 3 months after the CA.

The 24-hour Holter ECG was analyzed automatically by an SCM-8000 (Fukuda Denshi Co., Ltd., Tokyo, Japan). APCs were defined as narrow QRS complexes appearing > 30% earlier than expected when compared to the previous RR interval of normal sinus rhythm. In this study, we measured the following parameters:, the APCs burden, profile of the APCs run (≥2 beats), prematurity index of the APCs. The APCs burden was defined as the percentage of the number of APCs out of total heart beats (per 24 hours). The profile of APCs run includes the number of longest APCs run, heart rate of longest APCs run, and heart rate of fastest APCs run. The prematurity index of APCs was calculated as the percentage of the coupling interval of APCs to the mean RR interval of the previous 20 normal beats (Figure 2).

In this study, we evaluated the AF burden at the time of relapsing AF. The AF burden was defined as the longest AF episode (hours) on the 24-hour Holter ECG, 7-day Holter ECG, and pacemaker device. The AF burden was estimated by the patient's symptoms in the case of AF detected by an 12-lead ECG or event recorder during symptoms involving palpitations or chest discomfort.

The parametric variables are presented as the mean ± standard deviation. The nonparametric variables are presented as the median and interquartile range. The categorical variables are showed as the counts and percentage. Parametric variables were compared using the Student's *t* test and categorical variables using the Chi-square test or Fisher's exact test. Nonparametric variables were compared by the Wilcoxon rank-sum test.

A receiver operating characteristic analysis was performed to determine the optimal cutoff value of the APCs burden, the number of longest APCs run, and the minimum prematurity index of the APCs to predict VLRAF.

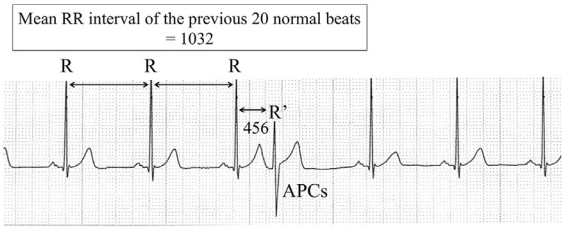

Figure 2. Prematurity index of APCs. APCs = atrial premature complexes.

Univariate and multivariate Cox proportional-hazards models were used to determine the predictors of VLRAF. The following variables were evaluated: the age, woman, body mass index, type of AF (paroxysmal AF vs nonparoxysmal AF), CHA2DS2-VASc score, chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2), underlying heart disease, left atrial diameter, CFAE ablation, ERAF, APCs burden, maximum number of the longest APCs run, minimum prematurity index of APCs. A probability value of p <0.05 was considered statistically significant. The statistical analyses were performed using JMP version 13.0.0 software (SAS Institute Inc., Cary, North Carolina).

Results

Of 484 consecutive patients, 231 patients were excluded from this study due to a lost follow up, relapsed AF and requiring antiarrhythmic drugs. We retrospectively studied 253 consecutive symptomatic AF patients (age 66 ± 9 years, woman: 30%, paroxysmal AF: 73%). During a mean follow up duration of 46 ± 18 months, VLRAF occurred in 51 patients (20%) (VLRAF group). In 51 relapsed AF episodes, 90% had an AF burden >6 minutes, 70% had an AF burden >6 hours, and 40% had an AF burden ≥24 hours. The distribution of the AF burden in our study patients is shown in Figure 3. The baseline characteristics of the study patients are shown in Table 1. Overall, the no-VLRAF group and VLRAF group were well balanced, except for the sex category. The proportion of a CFAE ablation and ERAF exhibited a high tendency in the VLRAF group, but was not significantly. The preprocedural drugs including antiarrhythmic drugs, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, β-blockers, verapamil, digitalis, and statins were similar between the groups. At 12 months of follow-up using Holter ECG recordings, no patients received any antiarrhythmic drugs, and there were no significant differences in β-blocker use between the 2 groups (Table 2).

In the analysis of the 24-hour Holter ECG 12 months after the CA, the VLRAF group had a significantly greater APC burden than the no VLRAF group. In the profile of the APC runs, the VLRAF group had a significantly greater number of the longest APC runs than the no VLRAF group, whereas the other parameters for APC runs were comparable between the 2 groups. The minimum prematurity index of the APCs in the VLRAF group was significantly shorter than that in the no VLRAF group (Table 3).

According to the receiver operating characteristic analysis, the optimal cutoff value of the APCs burden, the number of longest APCs run, and prematurity index of the

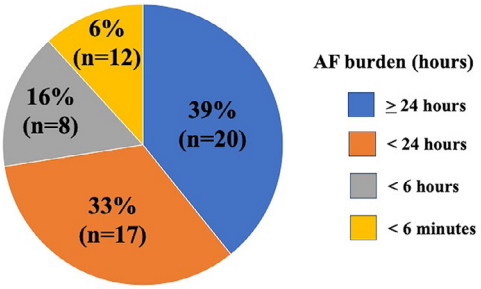

Figure 3. Distribution of AF burden at the timing of VLRAF. VLRAF = very late recurrence of atrial fibrillation.

Table 1
Baseline clinical characteristics

Variable	VLRAF		p-Value
	NO N = 202	YES N = 51	
Age (years)	66 ± 9	65 ± 8	0.598
Woman	54 (27%)	21 (41%)	0.044
Height (cm)	164 ± 9	162 ± 11	0.339
Body weight (kg)	66 ± 12	64 ± 13	0.273
Body mass index (kg/m^2)	24 ± 4	24 ± 4	0.459
Paroxysmal AF	154 (76%)	34 (67%)	0.162
Persistent AF	35 (17%)	10 (20%)	0.704
Long-standing AF	13 (6%)	7 (14%)	0.085
Heart failure	15 (7%)	6 (12%)	0.316
Hypertension	108 (54%)	32 (33%)	0.234
Diabetes mellitus	37 (18%)	8 (16%)	0.944
Cerebral infarction	17 (8%)	2 (4%)	0.277
CHADS2 score	1.0 ± 1.0	1.0 ± 0.8	0.866
CHA2DS2-VASc score	2.1 ± 1.5	2.3 ± 1.3	0.648
Underlying heart disease	40 (20%)	12 (24%)	0.556
Chronic kidney disease	28 (14%)	4 (8%)	0.346
Baseline echocardiography			
LVDd (mm)	49 ± 4	48 ± 5	0.330
LVDs (mm)	30 ± 4	29 ± 4	0.578
LVEF (%)	68 ± 8	67 ± 8	0.471
LAD (mm)	42 ± 6	43 ± 6	0.233
LAA flow (cm/sec)	49 ± 20	48 ± 20	0.754
Ablation procedure			
Cavotricuspid isthmus ablation	178 (88%)	48 (94%)	0.364
Superior vena cava isolation	10 (5%)	3 (6%)	0.345
CFAE ablation	12 (6%)	7 (14%)	0.059
Atrial tachycardia ablation	9 (5%)	2 (4%)	0.867
EARF	43 (21%)	17 (33%)	0.071

AF = atrial fibrillation; CFAE = complex fractionated atrial electrogram; ERAF = early recurrence of atrial fibrillation; LAA = left atrial appendage; LAD = left atrium diameter; LVDd = left ventricular end-diastolic diameter; LVDs = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction; VLRAF = very late recurrence of atrial fibrillation.

Table 2
Medication of pre- and postprocedure

Variable	VLRAF		p-Value
	NO N = 202	YES N = 51	
Preprocedure			
Prior antiarrhythmic drugs	36 (18%)	11 (22%)	0.539
Beta blocker	68 (34%)	22 (43%)	0.207
ACEi/ARB	65 (32%)	18 (35%)	0.672
Verapamil	13 (6%)	5 (10%)	0.373
Digitalis	6 (3%)	3 (6%)	0.391
Statin	35 (17%)	9 (18%)	0.957
12 months after CA			
Beta blocker	29 (14%)	9 (18%)	0.557

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CA = catheter ablation; VLRAF = very late recurrence of atrial fibrillation.

Table 3
Data of Holter ECG on 12 months

Variable	VLRAF		p-Value
	NO N = 202	YES N = 51	
Total recording time (hours)	23.9 ± 0.6	23.9 ± 0.2	0.965
APCs burden (%)	0.132 [0.051-0.461]	0.318 [0.084-1.405]	0.004
Number of longest APCs run (n)	4 [0-7]	5 [3-11]	0.019
Heart rate of longest APCs run (bpm)	134 ± 25	128 ± 25	0.772
Heart rate of fastest APCs run (bpm)	150 ± 28	149 ± 22	0.945
Minimum prematurity index of APCs (%)	51 ± 6	47 ± 7	0.001

APCs = atrial premature complexes; bpm = beats per minute; VLRAF = very late recurrence of atrial fibrillation.

APCs to predict VLRAF was ≥0.159% (area under curve 0.639, 95% confidential interval: 0.555 to 0.723), ≥10 (area under curve 0.626, 95% confidential interval: 0.539 to 0.712), and ≤48% (area under curve 0.658, 95% confidential interval: 0.575 to 0.742), respectively. The sensitivity and specificity of each cutoff value were 0.706 and 0.564, 0.333 and 0.861, 0.628 and 0.643, respectively.

The univariate Cox proportional-hazards model demonstrated that the ERAF, APCs burden (≥0.159%) and the minimum prematurity index of APCs (≤48%) were significantly associated with a VLRAF, but only the minimum prematurity index of the APCs (≤48%) was significantly associated with a VLRAF in the multivariate Cox proportional-hazards model adjusted for the risk factors of VLRAF (Table 4).

Discussion

This study has elucidated the predictors of VLRAF in patients without antiarrhythmic drugs after the initial CA, using the parameters automatically calculated by the analysis software of the 24-hour Holter ECG. The main findings of this study were as follows: (1) ERAF, APCs burden of ≥0.159%, and minimum prematurity index of the APCs of ≤48% were associated with VLRAF; (2) in particular, a prematurity index of the APCs of ≤48% was an independent risk factor for VLRAF.

Yamane et al[8] investigated the APCs burden before and after the CA. This study have showed that a successful CA significantly reduced the APCs burden over the long term, whereas APCs burden in patients with recurrent AF returned to the level of the APCs burden before the CA within 6 months. Gang et al[4] have demonstrated that APCs of ≥142 beats per day were associated with a recurrence of AF based on the analysis of the Holter ECG 6 months after the CA. Inoue et al[9] also emphasized the clinical significance of the APCs burden (≥58 beats per day). However, since the APCs burden is affected by antiarrhythmic drugs and beta blockers, the cutoff value of APCs burden should be interpreted carefully. Several studies have shown that APCs preceding AF were more frequent as compared to APCs occurring remote from AF episodes.[10–12] Since the APCs burden on the Holter ECG without AF episodes is not necessarily high, it is presumed that the APCs burden of ≥0.159% was not an independent predictor of VLRAF in our study.

Little has been reported about the impact of APCs run on VLRAF. In the present study, the length of APCs run of ≥10 beats was not significantly associated with VLRAF. However, Inoue et al[9] reported that longer APCs run of

Table 4
Cox regression analysis of factors affecting VLRAF after AF ablation procedure

	Univariate		Multivariate	
	Hazard ratio (95% confidential interval)	p	Hazard ratio (95% confidential interval)	p
Age (years)	1.00 (0.964-1.030)	0.779	1.03 (0.927-1.027)	0.342
Woman	1.54 (0.870-2.686)	0.129	1.15 (0.530-2.492)	0.721
Body mass index (kg/m^2)	1.04 (0.884-1.047)	0.392	1.08 (0.829-1.036)	0.181
Non paroxysmal AF	1.63 (0.885-2.890)	0.114	1.14 (0.526-2.361)	0.724
CHA2DS2-VASc score	1.03 (0.851-1.251)	0.729	1.03 (0.693-1.345)	0.878
Chronic kidney disease	0.60 (0.181-0.482)	0.296	0.57 (0.112-1.365)	0.184
Underlying heart disease	1.12 (0.558-2.077)	0.741	1.06 (0.474-2.243)	0.878
Left atrial diameter	1.03 (0.980-1.081)	0.244	1.04 (0.970-1.121)	0.251
CFAE ablation	1.64 (0.672-3.436)	0.255	1.06 (0.374-2.748)	0.906
ERAF	1.89 (1.029-3.349)	0.041	1.98 (0.985-3.826)	0.055
APCs burden (≥ 0.159%)	2.31 (1.288-4.343)	0.005	1.84 (0.883-3.992)	0.105
Number of longest APCs run (≥ 10)	1.70 (0.958-2.976)	0.069	1.17 (0.609-2.230)	0.638
Minimum prematurity index of APCs (≤ 48%)	3.07 (1.746-5.587)	< 0.001	2.48 (1.294-4.912)	0.006

AF = atrial fibrillation; APCs=atrial premature complexes; CFAE = complex fractionated atrial electrogram; ERAF = early recurrence of atrial fibrillation; VLRAF = very late recurrence of atrial fibrillation.

≥5 beats was associated with a late recurrence of AF. They reported that the patients with a longest APCs run of ≥5 beats are elderly and consist of more females than those with a longest APCs run of <5 beats (age 65 ± 9 vs 59 ± 10 years, $p < 0.01$; females 30% vs 16%, $p < 0.01$). Patients in our study were older (mean age: 66 vs 61 years) and more women (30% vs 21%) than those in their study. The different patient backgrounds may have affected the cutoff value. Since the number of APCs run may be affected by aging and gender, it was considered that further study is required to determine the optimal cutoff value predicting recurrence of AF.

Kanda et al[13] reported that APCs triggering AF had a shorter coupling interval than non-AF-triggers based on the analysis of the intracardiac recordings during CA. Short-coupled APCs can also be closely involved in the initiation of AF. Capucci et al[14] demonstrated that the coupling interval of APCs eliciting AF was significantly shorter than that of isolated APCs although the basal heart rate preceding AF was almost similar to that remote from AF. Autonomic nerve activity was not considered to be significantly involved in the coupling interval of the APCs eliciting AF. Vinsenti et al[15] reported the features of APCs at the onset of AF by a detailed analysis of Holter ECGs. This study demonstrated that AF following a bradycardia, which meant an increased vagal tone, was elicited by APCs with long coupling interval, but the prematurity index of such APCs is significantly smaller than that of APCs triggering AF without bradycardia. The prematurity index of the APCs may play an important role in the initiation of AF independent of autonomic activity. These results were consistent with our findings that a minimum prematurity index of the APCs of ≤48% was an independent risk factor for VLRAF.

Waktare et al[10] demonstrated that the distribution of the coupling intervals of APCs eliciting AF was similar to that of those not eliciting AF. They noted that the initiation of AF was associated with a specific coupling interval of APCs, not a shorter coupling interval. These findings may be related to the fact that a minimum prematurity index of APCs of ≤48% did not have a very high sensitivity to predict VLRAF.

Recently, AF episodes of over 6 minutes, 5.5 hours, or 24 hours have been shown to be associated with an increased risk of an ischemic stroke.[16–18] In our study, of 51 relapsed AF episodes, 90% had an AF burden >6 minutes and 70% had an AF burden >6 hours. Therefore, the AF recurrence episodes detected in this study had clinical significance, and predictive indicators of such AF recurrence are of great importance in following patients after CA over the long term.

In conclusion, the minimum prematurity index of the APCs (≤48%) derived from the 24-hour Holter ECG 12 months after the CA was an independent and significant risk factor for VLRAF.

Author Contributions

All authors substantially contributed to the work and met the authorship criteria as follows:

Conception and design or analysis and interpretation of the data: **Yasuyuki Egami, Kohei Ukita, Akito Kawamura, Hitoshi Nakamura, Yutaka Matsuhiro and Koji Yasumoto.** Drafting of the manuscript or revising it critically for its important intellectual content: **Masaki Tsuda, Naotaka Okamoto, Akihiro Tanaka, Yasuharu Matsunaga-Lee, Masamichi Yano and Ryu Shutta.** Final approval of the manuscript submitted: **Yasushi, Sakata, Masami Nishino and Jun Tanouchi.**

Disclosures

The authors have no conflicts of interest to disclose.

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