Burden and Long Firing of Premature Atrial Contraction Early After Catheter Ablation Predict Late Recurrence of Atrial Fibrillation

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Background: Associations between characteristics of premature atrial contraction (PAC) 6 months after catheter ablation (CA) and later recurrence are not known. We investigated the effects of PAC characteristics on long-term outcomes of initially successful atrial fibrillation (AF) ablation.

Methods and Results: In all, 378 patients (mean age 61 years, 21% female, 67% paroxysmal AF) who underwent initial radiofrequency CA for AF without recurrence up to 24-h Holter monitoring 6 months after the procedure were reviewed retrospectively. The calculated number of PAC/24h and the length of the longest PAC run during Holter recording were analyzed. After 4.3±1.2 years (mean±SD) follow-up, 123 (32.5%) patients experienced late recurrence. Patients with recurrence had significantly more PAC/24 h (median [interquartile range] 110 [33–228] vs. 42 [16–210]; P<0.01) and a longer longest PAC run (5 [2–8] vs. 3 [1–5]; P<0.01) than those without. Receiver operating characteristic curve analysis indicated 58 PAC/24 h and a longest PAC run of 5 were optimal cut-off values for predicting recurrence. After adjusting for previously reported predictors of late recurrence, frequent PAC (≥58/24 h) and longest PAC run ≥5 were found to be independent predictors of late recurrence (hazard ratios [95% confidence intervals] 1.93 [1.24–3.02; P<0.01] and 1.81 [1.20–2.76; P<0.01], respectively).

Conclusions: Six months after successful AF ablation, both frequent PAC and long PAC run are independent predictors of late recurrence.

Key Words: Ablation; Atrial fibrillation; Late recurrence; Premature atrial contraction

Since Haïssaguerre et al revealed that the origin of premature atrial contractions (PACs), which initiated atrial fibrillation (AF), was mostly from the pulmonary veins (PVs), catheter ablation (CA) has become a widely accepted intervention for rhythm control of AF. The current standard strategy of CA for AF is PV isolation (PVI).

It is known that a certain number of initially successful cases soon after CA experience late recurrence, even years after the procedure, and it is very common to find recovered PV conduction in such cases. Detecting late recurrence is beneficial to improving patients’ prognosis and quality of life, because this information can help in the selection of antiarrhythmic drugs, determining the necessity for repeat sessions, and managing heart failure. Previous studies reported that persistent AF, age, hypertension, dyslipidemia, wide area circumferential ablation, weight ≥90.72 kg, presence of non-PV triggers, C-reactive protein >0.5 mg/dL, reduction of left atrial (LA) volume, and isolation of fewer PVs were independent factors associated with late recurrence.

With regard to findings during Holter monitoring after CA, two previous reports indicated that the number of

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Factors Predicting Late AF Recurrence After CA

575 patients underwent initial RFCA for AF at our institution

→ 197 patients who experienced recurrence within 6 months or whose Holter recording data were unavailable

→ 378 patients without AF recurrence at 6 months after RFCA

**Figure 1. Flowchart of patient inclusion. AF, atrial fibrillation; RFCA, radiofrequency catheter ablation.**

PACs at 6 months⁸ and 2–8 days¹⁰ after the procedure was a predictor of future recurrence. However, this association has not been established and the underlying mechanism has not yet been determined. Furthermore, PAC characteristics, other than the number of PAC per day, were not examined in those studies. Hence, the aim of the present study was to clarify the effects of PAC characteristics, evaluated on the basis of Holter monitoring findings, on the long-term outcome of initially successful AF ablation.

**Methods**

**Study Design and Population**

This study was a single-center retrospective observational study that enrolled consecutive patients who underwent radiofrequency (RF) CA for AF at Sakurabashi Watanabe Hospital between March 2012 and March 2014. All patients underwent PVI by RF catheter, and some underwent additional ablation if necessary. Patients were excluded if they experienced recurrence before the scheduled 24-h Holter monitoring at 6 months after the procedure with a 3-month blanking period or if they did not undergo Holter monitoring at 6 months after CA. Thus, only patients who did not have AF recurrence before the end of the 24-h Holter monitoring were investigated (Figure 1). Clinical data were collected from patients' medical records.

This study was approved by the Sakurabashi Watanabe Hospital Ethics Committee (Reference no. 18-48). All patients provided written informed consent for the ablation procedure and the retrospective use of their clinical data.

**Ablation Procedure**

The detailed electrophysiological studies and ablation protocol have been described elsewhere.¹¹ Patient respiration was controlled by bilevel positive airway pressure. A 6-Fr decapolar catheter was placed in the corona sinus via the median antebrachial vein and a 7-Fr decapolar catheter was placed in the superior vena cava and right atrium. A 10-Fr SoundStar ultrasound catheter ( Biosense Webster, Diamond Bar, CA, USA) was inserted into the right atrium via the femoral vein for the anatomic mapping of the LA using the CartoSound module of the CARTO3 system ( Biosense Webster). Two 8-Fr long sheaths (Daig SL0; St Jude Medical, St Paul, MN, USA) were introduced into the LA via the femoral vein after a single Brockenbrough puncture using a RF needle (Japan Lifeline, Tokyo, Japan). An initial intravenous bolus of heparin (150 IU/kg) was followed by continuous infusion (300 IU/kg/h) to maintain an activated clotting time >300 s. RF ablation was conducted using the ThermoCool SmartTouch (Biosense Webster). Electrical isolation of PVs was assessed by a 20-polar ring catheter (LASSO; Biosense Webster). The endpoint of the PVI was the achievement of a bidirectional conduction block between the LA and the PVs. After the completion of PVI, isoproterenol (4–20 µg/min) was infused to examine induced PV reconnections and/or non-PV AF triggers. Ablation of non-PV AF triggers was strongly encouraged. Other additional ablations, such as linear ablation and complex fractionated atrial electrogram ablation, depended on the operator’s judgment. The procedures were performed with patients under conscious sedation with pentazocine, thiamylal sodium, and dexmedetomidine hydroxyzine. All antiarrhythmic drugs, including β-blockers, were discontinued for at least 5 half-lives before the ablation. The ablation protocol for second procedures was the same as for first procedure. We searched for reconnection of PV potentials, identified AF triggers, including those derived from non-PV origins, and attempted to ablate them.

**Patient Follow-up and Study Endpoints**

Patients were followed up at 1, 3, and 6 months after the ablation and were instructed to undergo electrocardiography (ECG) in case of symptoms suggestive of arrhythmia recurrence. Patients were encouraged to check their pulse rate and rhythm three times a day and to visit Sakurabashi Watanabe Hospital if they experienced irregular pulses. In such cases, inspections were conducted using an external loop recorder. Patients routinely underwent 24-h Holter monitoring (RAC-3203 and DSC-5500; Nihon Kohden, Tokyo, Japan) at the 6-month follow-up. After Holter monitoring 6 months after the procedure, scheduled ECG follow-up was performed at least every 6 months. When patients noticed an irregularity of their pulse or symptoms suggestive of recurrence, they were encouraged to visit Sakurabashi Watanabe Hospital. ECG was also performed at every additional visit, and additional Holter ECG monitoring was performed and/or event monitor recordings obtained, if required. Patients who underwent a second
Ablation procedure also underwent 24-h Holter monitoring and were followed-up using the same schedule as that used initially. Holter monitoring data were analyzed by experienced cardiac technicians and reviewed by the attending cardiologists. PAC was defined as a supraventricular complex occurring >30% earlier than the expected R-R interval. Given that there was a variation in the duration of Holter monitoring among patients, PAC/24 h was defined as the calculated number of PAC within a 24-h period. In addition, the longest PAC run was defined as the number of beats in the longest PAC run during Holter monitoring. AF recurrence was defined as documented AF or atrial tachyarrhythmia >30 s. Antiarrhythmic drugs were defined as Vaughan Williams Class I and III drugs and bepridil. Discontinuation of antiarrhythmic drugs was strongly encouraged after the blanking period.

### Table 1. Patient Characteristics

|                      | All patients (n=378) | AF recurrence | P-value |
|----------------------|----------------------|---------------|---------|
|                      |                      | Yes (n=123)   | No (n=255) |         |
| Age (years)          | 60.7±10.2            | 61.5±10.5     | 60.3±10.1 | 0.32    |
| Female sex           |                      | 33 (26.9)     | 47 (18.4) | 0.06    |
| Height (cm)          | 167.4±9.0            | 166.4±9.3     | 167.8±8.8 | 0.15    |
| Weight (kg)          | 68.2±12.7            | 67.1±12.6     | 68.8±12.7 | 0.23    |
| BMI (kg/m²)          | 24.2±3.4             | 24.1±3.5      | 24.3±3.4  | 0.64    |
| Congestive heart failure | 43 (11.3)        | 16 (13.0)     | 27 (10.6) | 0.49    |
| Hypertension         | 177 (46.8)           | 61 (50.0)     | 116 (45.4) | 0.45    |
| Diabetes             | 45 (11.9)            | 9 (7.3)       | 36 (14.1) | 0.06    |
| Ischemic stroke      |                      |               |          |         |
| CHA2DS2-VASc score   |                      |               |          |         |
| 0 or 1               | 204 (54.0)           | 63 (51.2)     | 141 (55.3) | 0.46    |
| 2 or 3               | 141 (37.3)           | 50 (40.7)     | 91 (35.7) | 0.35    |
| ≥4                   | 33 (8.7)             | 10 (8.1)      | 23 (9.0)  | 0.80    |
| Paroxysmal AF        | 252 (66.7)           | 80 (65.0)     | 172 (67.5) | 0.59    |
| Persistent AF        | 86 (22.8)            | 24 (20.0)     | 62 (24.3) | 0.30    |
| Long-standing AF     | 40 (10.6)            | 19 (15.4)     | 21 (8.2)  | 0.03    |
| Hemoglobin (g/dL)    | 14.4±1.3             | 14.2±1.4      | 14.6±1.2  | 0.02    |
| Creatinine (mg/dL)   | 0.83±0.20            | 0.83±0.22     | 0.83±0.19 | 0.80    |
| HbA1c (%)            | 5.8±0.6              | 5.8±0.6       | 5.8±0.5   | 0.86    |
| Uremic acid (mg/dL)  | 5.8±1.4              | 5.9±1.4       | 5.8±1.4   | 0.36    |
| Total cholesterol (mg/dL) | 205.6±37.5         | 207.4±35.9    | 204.8±38.3 | 0.53    |
| LDL-C (mg/dL)        | 120.3±31.2           | 122.3±29.5    | 119.4±32.0 | 0.40    |
| HDL-C (mg/dL)        | 57.6±15.2            | 57.0±14.4     | 57.8±15.6 | 0.61    |
| Triglyceride (mg/dL) | 122.4±70.3           | 123.8±76.4    | 121.8±67.3 | 0.80    |
| CRP (mg/dL)          | 0.05 [0.03–0.1]      | 0.05 [0.03–0.1] | 0.05 [0.03–0.1] | 0.71 |
| IVSd (mm)            | 10.2±1.8             | 10.4±1.8      | 10.2±1.8  | 0.48    |
| PWd (mm)             | 10.0±1.3             | 10.2±1.4      | 9.9±1.3   | 0.04    |
| E/A ratio            | 0.97±0.31            | 0.96±0.37     | 0.97±0.29 | 0.80    |
| Mitral E/e’ ratio    | 9.9±4.7              | 10.2±4.8      | 9.7±4.7   | 0.41    |
| LVEF (%)             | 65.1±8.9             | 65.5±9.0      | 64.9±8.8  | 0.48    |
| LVEDD (mm)           | 46.1±5.0             | 46.3±4.7      | 46.1±5.2  | 0.68    |
| LA diameter (mm)     | 37.3±5.9             | 37.9±5.9      | 37.0±5.9  | 0.17    |
| LA volume (mL)       | 47.3±21.3            | 45.2±16.0     | 48.3±23.5 | 0.24    |
| LA volume index (mL/m²) | 28.1±13.4        | 26.4±9.5      | 29.0±15.0 | 0.11    |

Parametric continuous variables are given as the mean±SD; non-parametric continuous variables are given as the median [interquartile range]. Categorical variables are given as n (%). A, late diastolic mitral valve inflow velocity; AF, atrial fibrillation; BMI, body mass index; CRP, C-reactive protein; E, early diastolic mitral valve inflow velocity; e’, early diastolic mitral annular velocity; HDL-C, high-density lipoprotein cholesterol; IVSd, diastolic interventricular septum wall thickness; LDL-C, low-density lipoprotein cholesterol; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PWd, diastolic posterior wall thickness.

### Table 2. Details of the Ablation Procedure (n=378)

| Procedure                     | Count (n) |
|-------------------------------|-----------|
| PV isolation                  | 378 (100) |
| CTI block line                | 107 (28.3) |
| Roof line of left atrium      | 4 (1.1)   |
| Mitral valve isthmus block line | 3 (0.8) |
| SVC isolation                 | 6 (1.6)   |
| Non-PV foci ablation          | 5 (1.3)   |
| CFAE ablation                 | 4 (1.1)   |
| GP ablation                   | 0 (0)     |

Data are given as n (%). CFAE, complex fractionated atrial electrogram; CTI, cavotricuspid isthmus; GP, ganglionated plexi; PV, pulmonary vein; SVC, superior vena cava.
Factors Predicting Late AF Recurrence After CA

Statistical Analysis
Parametric and non-parametric variables are given as the mean±SD and the median and interquartile range (IQR), respectively.

patients who experienced AF recurrence before the scheduled 24-h Holter monitoring at 6 months after the procedure with a 3-month blanking period were excluded from the analysis. The primary end point was late recurrence of AF, which was defined as initial AF recurrence after the Holter monitoring at 6 months after the index procedure.

Table 3. Details of Antiarrhythmic Medications at the Time of Holter Monitoring

|                        | AF recurrence | P-value |
|------------------------|---------------|---------|
|                        | Yes (n=123)   | No (n=255) |
| β-blocker              | 25 (20.3)     | 46 (18.0) | 0.59  |
| All antiarrhythmic drugs | 36 (29.3)    | 46 (18.0) | 0.01  |
| Class I                | 20 (16.3)     | 28 (11.0) | 0.15  |
| Class III              | 2 (0.78)      | 0 (0)     | 0.32  |
| Bepridil               | 19 (15.5)     | 14 (5.5)  | <0.01 |

Data are given as n (%). All antiarrhythmic drugs includes Vaughan Williams Class I and III drugs and bepridil. AF, atrial fibrillation.

Table 4. Holter Monitoring Data

|                        | All patients (n=378) | AF recurrence | P-value |
|------------------------|----------------------|---------------|---------|
|                        | Yes (n=123)          | No (n=255)    |         |
| Monitoring duration (h)| 22.6±1.1             | 22.5±1.2      | 0.62    |
| Total no. heart beats/24 h | 106,784.4±13,979.8 | 105,839.5±15,628.0 | 0.39    |
| Heart rate (beats/min) |                      |               |         |
| Maximum                | 116.9±18.0           | 115.2±17.4    | 0.21    |
| Minimum                | 53.9±8.8             | 52.6±10.3     | 0.05    |
| Mean                   | 75.5±9.8             | 74.8±11.0     | 0.33    |
| No. PAC/24 h (beats)   | 57 [19–341]          | 108 [33–996]  | <0.01   |
| PAC burden (%)         | 0.05 [0.017–0.32]    | 0.12 [0.03–0.96] | <0.01 |
| Longest PAC run (beats)| 3 [2–6]              | 5 [2–8]      | <0.01   |

Parametric continuous variables are given as the mean±SD; non-parametric continuous variables are given as the median [interquartile range]. AF, atrial fibrillation; PAC, premature atrial contraction.

Figure 2. Receiver operating characteristic curves of (A) premature atrial contraction (PAC)/24 h and (B) longest PAC run for late atrial fibrillation recurrence. The C-statistics for PAC/24 h and longest PAC run were 0.63 (95% confidence interval [CI] 0.57–0.69) and 0.62 (95% CI 0.56–0.68), respectively.
respectively. Given that the distribution of C-reactive protein, PAC/24 h, and longest PAC run was non-parametric, these data were analyzed using the Wilcoxon rank-sum test. The significance of differences in patient characteristics between those with and without late recurrence was assessed using Student’s t-test or the Chi-squared test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of PAC/24 h and longest PAC run to predict late recurrence. These cut-off values were then used to stratify the patients. The time to AF recurrence from ablation was illustrated using the Kaplan-Meier method, and the significance of differences among the stratified population was assessed by log-rank test. Patients were censored on the day of the last follow-up. Univariate and multivariate hazard ratios (HRs) were determined by Cox proportional hazard regression models to assess the association of patient characteristics, echo parameter, and Holter parameters with late recurrence. Two-tailed P<0.05 was considered significant. HRs of PAC/24 h ≥58 and longest PAC run ≥5 for late recurrence were evaluated after adjusting for previously known risk factors of late recurrence, namely diabetes, age, sex, hypertension, non-paroxysmal AF, body mass index (BMI), non-PV triggers, and LA diameter. Statistical analyses were performed using JMP Pro 13.1. (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics
Of the 575 consecutive patients, 197 patients who experienced recurrence before the scheduled 24-h Holter monitoring 6 months after the procedure or those who did not undergo Holter monitoring 6 months after CA were excluded. Thus, data from 378 patients were evaluated. The mean patient age was 60.7±10.2 years. Of the patients in the study, 80 (21.2%) were women and 252 (66.7%) had paroxysmal AF. Significantly more patients with late

![Figure 3](image-url). Risk of late atrial fibrillation (AF) recurrence and premature atrial contraction (PAC). Kaplan-Meier plots show the late AF recurrence rate stratified by (A) the calculated number of PAC per 24 h, (B) longest PAC run (during Holter recording), and (C) both.
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Recurrence had long-standing persistent AF. Details of the patients included in the study are given in Table 1. There were 204 (54.0%) patients with a CHA2DS2-VASc score of 0 or 1; the study population was composed of relatively low-risk patients. Results of echo parameter analysis showed that the patients had good left ventricular function and a small LA diameter. All patients underwent PVI, with 28.3% of these patients undergoing cavotricuspid isthmus (CTI) block line. However, few patients underwent additional ablation other than the CTI block line (Table 2). At the time of Holter monitoring, the prevalence of an antiarrhythmic drug prescription was higher among those with late recurrence (29.3% vs. 18.0%; P=0.01), whereas there was no significant difference in β-blocker prescriptions (20.3% vs. 18.0%; P=0.59; Table 3).

Late Recurrence and Holter Monitoring

During a mean follow-up period of 4.3±1.2 years, 123 (32.5%) patients experienced AF recurrence. Holter monitoring detected a median of 53 (IQR 18–322) PACs over a period of 22.6±11.1 h, with PAC/24 h calculated as 57 (IQR 19–341); the median longest PAC run was 3 (IQR 2–8). Patients with recurrence had significantly more PAC/24 h and a longest PAC run than those without recurrence (58 PAC/24 h ≥58 or a longest PAC run ≥5) had an intermediate risk of recurrence (Figure 3C). The late recurrence rate in patients with both, either, or neither PAC/24 h ≥58 and longest PAC run ≥5 was 57.3% (95% CI 46.0–68.0%), 44.2% (31.3–58.0%), and 21.8% (15.4–29.9%), respectively, which can be classified as high, intermediate, and low risks. The HR of late recurrence among the high- and low-risk groups was 3.29 (95% CI 2.13–5.17; P<0.01).

Adjusted Risk for Late Recurrence

The univariate Cox proportional hazard regression model showed that PAC/24 h ≥58 and longest PAC run ≥5 were significantly associated with a high late recurrence rate. There was no significant correlation between PAC/24 h and longest PAC run (r=0.087, P=0.09); thus, we included both in the multivariate Cox proportional hazard regression analysis adjusted for previously reported risk factors of late recurrence. The adjusted HRs of PAC/24 h ≥58 and a longest PAC run ≥5 for late recurrence were 1.93 (95% CI 1.24–3.02; P<0.01) and 1.81 (1.20–2.76; P<0.01), respectively (Table 5).

Findings After the Second Procedure

In all, 71 patients underwent a second procedure due to AF recurrence. The strategy for the second procedure was to search for reconnected PV potentials, provoked non-PV AF triggers, and attempted to eliminate them; 24-h Holter monitoring was also performed 6 months after the second procedure. According to results of electrophysiological studies after the second procedure, most patients (n=65; 92%) showed reconnection of PVs. Among the 71 patients who underwent a second procedure, 33 received re-PVI alone. In these 33 patients, PAC/24 h decreased significantly after the second procedure (from a median of 239 [IQR 92%] to 101 [IQR 7–1,567]; P<0.01). However, the longest PAC run did not decrease after the second procedure in these patients (from a median of 5 [IQR 3–8] to 4 [IQR 2–7]; P=0.29).

Discussion

Main Findings

The findings of this study indicate that the PAC burden and PAC firing observed at 6 months after CA are predictors of late AF recurrence over the long-term follow-up. The novel findings of this study are that not only is PAC...
burden an independent predictor of late recurrence, but so
too is the length of the longest PAC run; the combination
of these two factors allowed the stratification of patients
into high-, intermediate-, and low-risk groups. Furthermore,
the finding that more PACs were observed in patients with
than without late recurrence was due primarily to the
connected PVs.

Comparison With Previous Studies
Previous studies have reported an association between
PAC burden and AF recurrence,9,10,12 which is consistent
with the findings of the present study. In particular, Gang
et al9 investigated the association between AF recurrence
and PAC burden 6 months after the procedure, a timing
similar to that of the present study. However, the PAC/24h
cut-off value determined in the present study (58) was less
than that reported by Gang et al9 (142). We speculate that
this could be due primarily to the patients in the present
study having less advanced atrial remodeling: the mean LA
diameter of the cohort in this study was 37.3 mm, which is
less that that reported in previous studies (mean LA
diameter ranging between 42.5 and 44.3 mm).13 However,
patient age, sex, and AF subtype were similar between the
present study and that of Gang et al.13 We also speculate
that the differences could also be due, in part, to the present
cohort including more patients who were using antiar-
hythmic drugs at the time of Holter monitoring: the prescrip-
tion rate for antiarrhythmic drugs in the present
study (21.7%) is slightly higher than that reported by Gang
et al9 (between 14% and 18%). Specifically in the present
cohort, patients with late recurrence had more frequent
PACs and a longer PAC run, despite the higher prevalence
of antiarrhythmic medication, than those without recur-
rence. This is probably because the attending cardiologists
hesitated to discontinue antiarrhythmic medication in
cases with frequent PACs early after the procedure.

In addition to PAC/24h, we evaluated the association
between the length of the PAC run and late recurrence and
found that a longer PAC run was significantly associated
with late recurrence. Because the PAC burden and the
length of the PAC run were not significantly correlated, we
used both these factors for risk stratification for late AF
recurrence. Consequently, the combination of PAC/24h
and longest PAC run allowed further risk stratification of
patients into high-, intermediate-, and low-risk groups for
late recurrence (Figure 3C). Previous studies did not
investigate the mechanism of association between the
increased number of PACs and late recurrence. To the best
of our knowledge, the present study is the first to provide
evidence supporting PACs originating from reconnected
PVs as the mechanism contributing to the significant
association between the increased number of PACs and
late recurrence, as discussed below.

Origin of PACs
We evaluated electrophysiological findings for patients
with late recurrence undergoing a second procedure and
their follow-up Holter monitoring data. We focused on
patients who underwent successful re-PVI alone and had
no additional ablation in the second procedure because
ablation of non-PV arrhythmogenicity may affect PACs
from non-PV foci. A significant decrease in the PAC burden
in these patients indicated that the main site of origin of the
PACs was the reconnected PVs. In contrast, the length of
the longest PAC run did not change after the second
procedure in which the PV potential was successfully re-
eliminated. These data indicate that the longest PAC runs
were repetitive firings originating from non-PV foci, or
“short AF” sustained for <30 s and initiated due to a non-
PV arrhythmogenic substrate. Those with a longest PAC
run ≥5 are older and more likely to be female than those
with a longest PAC run <5 (age 64.5±8.9 vs. 58.6±10.3
years, respectively [P<0.01]; females 30.4% vs. 15.8%,
respectively [P<0.01]), although the LA diameter (37.9±6.0
vs. 37.0±5.9 mm; P=0.13) and the prevalence of non-
paroxysmal AF (30.4% vs 34.6%; P=0.40) did not differ
significantly between the 2 group. Given that age and female
sex have been reported as factors for the high prevalence
of a low voltage area in the LA,16 we hypothesize that the
length of the PAC run reflects non-PV arrhythmogenicity.

Mechanism of Late Recurrence Development
Our data indicated that the number of PACs and the
length of the PAC run were independently associated with
the risk of late recurrence. The increased number of PACs
in patients with late recurrence was due primarily to the
reconnected PVs. PV reconnection is presumed to occur
early on after the PVI procedure. In this study we electively
included patients without recurrence at 6 months after the
index procedure, and even those with PV reconnection did
not experience recurrence for 6 months despite the PV
reconnection, which suggests that these patients did not
have a suitable substrate to initiate AF at that time point.
With regard to the length of the PAC run, the long PAC
firings may include “short AF”, which is not sustained for
more than 30 s. Non-sustained AF may develop due to the
absence of sufficient substrate required to perpetuate AF.
Because arrhythmogenic substrates can progress with
time,14 frequent PACs and long PAC runs may be suitable
triggers to initiate and perpetuate AF during the follow-up
period owing to the newly developed substrate, which would
result in late recurrence. Therefore, the management of risk
factors associated with the progression of AF substrate,
such as hypertension, sleep apnea, heart failure, and obesity,
would be especially important in these patients.

Clinical Implications
Considering that both the number of PACs and the length
of PAC firing are relatively easy to assess through 24-h
Holter monitoring, these parameters are useful in clinical
practice to identify patients who are at high risk of AF
recurrence and need careful observation. It has been
reported that AF ablation possibly reduces the risk of
stroke and mortality16–19 and AF recurrence was associated
with an increased stroke rate.17 Thus, early recognition of
AF recurrence is expected to be useful in reducing the risk
of stroke and heart failure.

Study Limitations
The study findings should be interpreted with consideration
of the study limitations. First, given that this study was
observational in nature and conducted at a single center,
the results are affected by the patients’ background and the
ablation strategy used at the center. Hence, the cut-off
values for PAC/24h and longest PAC run cannot be
applied universally. In particular, the present study cohort
had a small LA diameter, indicating that these patients are
in the less advanced stage of substrate progression than the
general population undergoing CA for AF. Second, we do
not know whether performing Holter monitoring at 6
months after CA is the best time to predict late recurrence, because we have no other Holter monitoring data. Third, we cannot ignore the possibility of underestimating the AF recurrence rate owing to asymptomatic recurrence. Fourth, the prevalence of the sleep apnea syndrome, which causes the progression of LA remodeling, is unknown because of the data were not available. Finally, we could only demonstrate the major origin of the PAC burden after CA in patients with late recurrence in some patients. The coupling interval of PACs can be an indication because PACs derived from the PVs have a short coupling interval, as reported previously. However, no data were available regarding the coupling interval of PACs in the present study. Moreover, the resolution of the Holter recording was not suitable to investigate PAC origins based on P-wave morphology. Therefore, further studies are needed to elucidate the underlying mechanism.

**Conclusions**

The data indicate that PAC burden and PAC run in initially successful AF ablation cases are highly associated with late recurrence. An increase in PACs from reconnected PVs was suggested as the mechanism contributing to the significant association between the number of PACs and AF recurrence. It is clinically important to carefully monitor patients with high PAC burden or long PAC firing after an initially successful AF ablation.

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**Conflict of Interest**

K. Inoue has received honoraria from Johnson and Johnson KK, Medtronic Japan, Bayer Yakuhin, Nihon Boehringer Ingelheim, Bristol Myers Squibb, and Daiichi-Sankyo. The other authors declare no conflicts of interest.

**Data Availability**

Deidentified participant data will not be shared.

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