JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 3, NO. 6, 2017

ISSN 2405-500X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacep.2016.12.008

FOCUS ON PULMONARY VEIN ISOLATION

Development of Nonpulmonary Vein Foci Increases Risk of Atrial Fibrillation Recurrence After Pulmonary Vein Isolation

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ABSTRACT

OBJECTIVES The aim of this paper was to clarify the impact of nonpulmonary vein foci (NPVF) on atrial fibrillation (AF) recurrence after pulmonary vein (PV) isolation.

BACKGROUND NPVF are considered contributing factors for the recurrence of AF after PV isolation, but their exact role remains unclear.

METHODS We retrospectively reviewed 216 patients (paroxysmal AF, n = 172; persistent AF, n = 44) who underwent a second electrophysiological study 6 months after the original PV isolation. Patients with AF recurrence underwent additional ablation procedures for reconnected PV and NPVF. NPVF were detected in the control group and with drug infusion (isoproterenol or isoproterenol with adenosine triphosphate) during the first and second procedure. NPVF detected for the first time in the second session were defined as newly developed, and their effect on AF recurrence after the second procedure was investigated, along with the predictive factors for NPVF development.

RESULTS Patients with AF recurrence after the first session had a significantly higher reconnected PV (91.5% vs. 68.2% in patients without recurrence). NPVF were detected in 20 and 54 patients in the first and second sessions, respectively. Patients with newly developed NPVF had a significantly higher AF recurrence (24.1% vs. 7.4% in patients without newly developed NPVF). Newly developed NPVF and AF recurrence after the first session were independent predictors for AF recurrence after the second procedure, whereas AF history and NPVF in the first session were independent predictors for newly developed NPVF.

CONCLUSIONS NPVF detection and ablation may represent important therapeutic options to prevent AF recurrence, especially in patients who require repeated procedures. (J Am Coll Cardiol EP 2017;3:547–55)

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received June 13, 2016; revised manuscript received November 9, 2016, accepted December 8, 2016.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ATP = adenosine triphosphate

LA = left atrium

new-NPVF = newly developed nonpulmonary vein foci

NPVF = nonpulmonary vein foci

PAF = paroxysmal AF

PeAF = persistent AF

PVI = pulmonary vein isolation

SVC = superior vena cava

Catheter ablation represents standard therapy for patients with atrial fibrillation (AF) (1–3). Several studies have indicated that the major mechanism of AF recurrence after pulmonary vein isolation (PVI) is electrical reconnection between the pulmonary vein (PV) and the left atrium (LA). Multiple PVI sessions can improve the outcomes (4–5).

It has also been reported that the presence of non-PV foci (NPVF) is closely related to AF recurrence after multiple PVI procedures, as well as to very late AF recurrence (6–8). NPVF incidence varies among different reports because of differences in NPVF induction methods, timing of detection, and whether the test was conducted in the first or the second session after AF recurrence (7–11). Moreover, the impact of NPVF on AF recurrence has not been thoroughly evaluated because of the concurrent development of LA-PV reconnection and NPVF. Therefore, the present study used identical NPVF induction methods in the same population to examine NPVF prevalence in the first and second PVI sessions and evaluate the impact of NPVF on AF recurrence after catheter ablation for LA-PV reconnection.

METHODS

STUDY POPULATION. We retrospectively analyzed the records of 284 patients with drug-refractory paroxysmal atrial fibrillation (PAF) (n = 232) or persistent atrial fibrillation (PeAF) (n = 52), who underwent PVI between February 2010 and February 2014 at the Tokyo Metropolitan Hiroo Hospital. All patients provided written informed consent before undergoing the procedures. Data collection was approved by the institutional review board of the hospital.

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Patients with PeAF lasting >1 year (n = 61) were excluded, as they underwent additional linear ablation and ablation for complex fractionated atrial electrogram in the first session. Additional patients were excluded as follows: short interval between the first and second procedures (n = 2); use of amiodarone during the procedure (n = 3); and follow-up <1 year (n = 2).

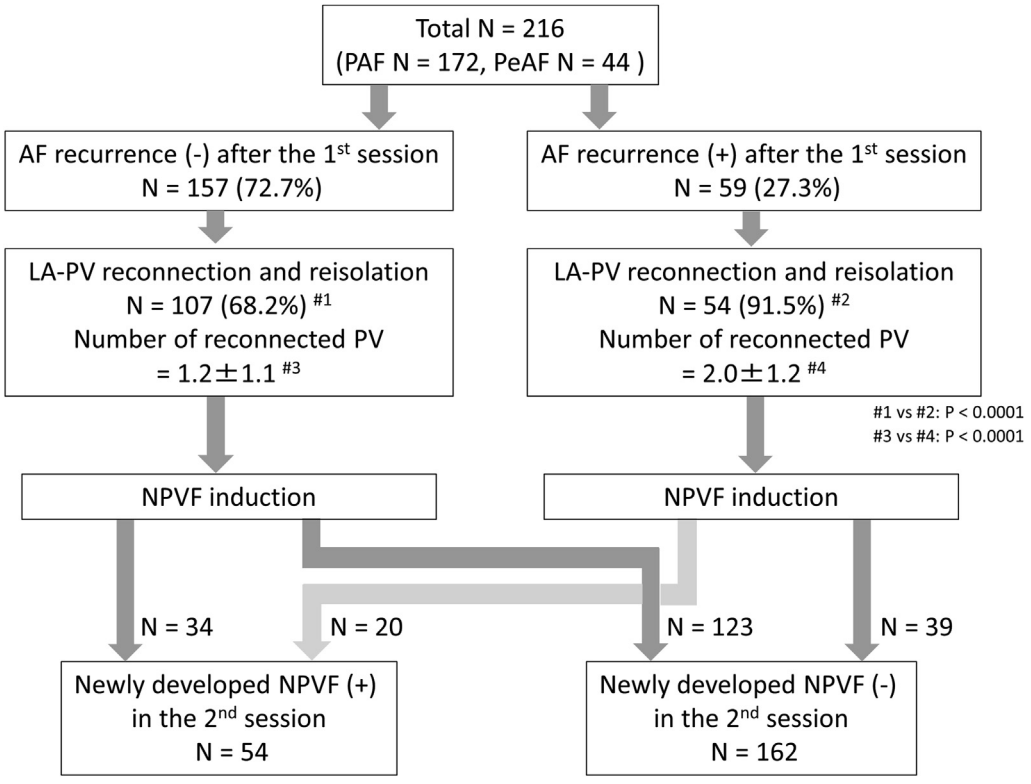
A total of 216 patients (172 with PAF and 44 with PeAF lasting <1 year) were included in this study, representing approximately 76% of the patients treated during the study period. All patients underwent a second electrophysiological study at the 6-month follow-up after the first procedure, regardless of AF recurrence. We performed PVI and catheter ablation for NPVF in the first and second sessions. NPVF detected for the first time in the second session were defined as newly developed NPVF (new-NPVF). Therefore, we assigned each patient to either the new-NPVF(+) or new-NPVF(−) group, depending on whether they developed NPVF between the first and second session (**Figure 1**).

PROTOCOL OF CATHETER ABLATION. Antiarrhythmic drugs were discontinued ≥5 half-lives before ablation. Oral anticoagulants were started at least 1 month before the procedure. Transesophageal echocardiography and multidetector computed tomography were performed to rule out the formation of intra-atrial thrombus. The electrophysiological study was performed under continuous intravenous administration of propofol.

In the first session, all patients underwent circumferential isolation of the ipsilateral PVs at the antrum. Briefly, a Decapolar catheter (Inquiry Luma-Cath; St. Jude Medical, St. Paul, Minnesota) or a 20-polar superior vena cava–right atrium–coronary sinus electrode catheter (BeeAT, Japan Lifeline, Tokyo, Japan) was inserted via the right subclavian vein into the coronary sinus. A transseptal puncture was performed using a Brockenbrough needle or a radiofrequency-powered transseptal needle, under fluoroscopic and/or intracardiac echocardiography guidance. The PVs were mapped using a circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, California; or Inquiry Optima, St. Jude Medical). A 3.5-mm irrigated-tip catheter (ThermoCool Navistar, Biosense Webster; or Cool Path, St. Jude Medical) and a 3-dimensional anatomical mapping system (CARTO, Biosense Webster; or Ensite NavX and Velocity, St. Jude Medical) were used for NPVF mapping and ablation.

PV antral isolation was performed using double circular mapping catheters placed within the ipsilateral ostia of the superior and inferior PVs. Radiofrequency energy delivered at 30 W (25 W for posterior wall ablation), with a maximal temperature limit of 43°C, was applied point-by-point for 30 s. The endpoint of PVI was the achievement of a bidirectional conduction block between the LA and PVs. After confirmation of the complete bidirectional block, continuous intravenous administration of isoproterenol (4 μg/min) (2) was initiated, followed by a bolus injection of 40 mg of adenosine triphosphate (ATP) (12) with the isoproterenol infusion to exclude reconduction or ATP-provoked dormant conduction between the PVs and the LA. Catheter ablation was performed to eliminate the presence of reconnection and/or

FIGURE 1 Study Design and Patient Selection Protocol



AF = atrial fibrillation; LA = left atrium; NPVF = non-pulmonary vein foci; PAF = paroxysmal AF; PeAF = persistent AF; PV = pulmonary vein.

dormant conduction. If NPVF were identified with drug infusions, catheter ablation was applied to the foci. To locate the NPVF, the mapping catheters (2 ring catheters and 1 ablation catheter) were originally placed in the right atrium, atrial septum, and LA. Thereafter, upon detection of a reproducible focus (i.e., occurring at least twice in the same area), the catheters were placed around the earliest site to identify the precise focus location. We ablated around the earliest site, and reinitiated NPVF to estimate the effect of ablation. When NPVF were located in the superior vena cava (SVC), the SVC was electrically isolated. The endpoint of catheter ablation for NPVF was to confirm the elimination of all NPVF that initiated AF reproducibly when using ATP and isoproterenol infusion. Untreated NPVF or NPVF with multiple origins were defined as unmappable, and these patients did not receive ablation.

All patients underwent a second electrophysiological study at 6 months after the first session, regardless of AF recurrence. If the patient had recurrence in the form of PeAF, we also performed ablation for the AF substrate. We checked the presence or absence of bidirectional conduction block between the LA and PVs, and ablated any reconnection identified. Afterwards, continuous intravenous administration of isoproterenol (4 μg/min), followed by a bolus injection of ATP (40 mg) with the isoproterenol infusion, was used to reveal LA-PV reconnection and NPVF. Additional ablations were performed for LA-PV reconnection and NPVF, if either or both were present. After the procedures, we applied extra-stimulation (basic cycle length, 400 ms; single and double extra-stimulation, up to effective refractory period) and burst pacing (from 250 ms to 180 ms) to induce uncommon types of atrial flutter; the resulting arrhythmias were treated if they were inducible. If a patient had a recurrence manifested as PeAF, we performed additional ablation for the AF substrate (complex fractionated electrogram, roof, and mitral linear ablation) before checking PV reconduction and NPVF, at the physician's discretion.

FOLLOW-UP. After PVI, patients were discharged from the hospital on oral anticoagulants. Antiarrhythmic drugs could be stopped 3 months after

TABLE 1 Characteristics of Patients Who Underwent Pulmonary Vein Isolation for Paroxysmal or Persistent Atrial Fibrillation

	New-NPVF (−) Group (n = 162)	New-NPVF (+) Group (n = 54)	p Value
Female/male	34/128	15/39	NS
Age (yrs)	61.5 ± 12.0	63.1 ± 14.1	NS
Persistent AF	37 (23.0)	7 (13.0)	NS
AF history (months)	33.2 ± 50.2	63.1 ± 81.2	0.013
CHADS2 score	1.1 ± 1.2	1.2 ± 1.3	NS
Congestive heart failure	20 (12.3)	6 (11.1)	NS
Hypertension	75 (46.3)	21 (38.9)	NS
Diabetes	24 (15.4)	7 (13.0)	NS
Stroke	17 (10.5)	10 (18.5)	NS
Body mass index (kg/m^2)	24.2 ± 3.6	23.8 ± 3.2	NS
Apnea hypopnea index (events/h)	10.0 ± 12.2	8.5 ± 9.7	NS
Organic heart disease	29 (17.9)	12 (22.2)	NS
Ejection fraction (%)	64.1 ± 11.3	63.7 ± 9.7	NS
LA diameter (mm)	39.8 ± 19.1	38.1 ± 6.2	NS
E/e	10.4 ± 5.4	10.0 ± 4.2	NS
LA volume (ml)	120.0 ± 38.4	117.2 ± 36.5	NS
LA-PV reconnection	116 (71.6)	45 (83.3)	NS
Number of reconnected PVs	1.4 ± 1.2	1.6 ± 1.2	NS
Uncommon atrial flutter	12 (7.4)	5 (9.2)	NS
AF substrate ablation	7 (4.3)	2 (3.7)	NS
Cavo-tricuspid isthmus ablation	40 (24.7)	11 (20.4)	NS
Follow-up period after second session (days)	737.5 ± 299.6	848.5 ± 390.8	NS

Values are n, mean ± SD, or n (%). The study population was divided into groups according to whether or not NPVF developed between the first and second sessions of PV isolation: new-NPVF(+) versus new-NPVF(−). LA volume was estimated via computed tomography.

AF = atrial fibrillation; LA = left atrial; NPVF = nonpulmonary vein foci; NS = not significant; PV = pulmonary vein.

ablation at the physician's discretion. The rhythm and presence of arrhythmias were evaluated based on the patient's symptoms and a resting 12-lead electrocardiogram recorded during regular visits to our outpatient clinic. To detect atrial tachyarrhythmias, 24-h Holter monitoring was also performed at 1, 3, and 6 months after the first procedure, as well as at 1, 3, 6, 12, 18, and 24 months after the final procedure. In this cohort, compliance with the Holter monitoring scheduled after the first and second procedure was 93% and 90%, respectively. The number of patients taking antiarrhythmic drugs at the time of the first session, second session, and at 6 months after the second session was 123 (56.9%), 45 (20.8%), and 20 (9.2%), respectively. Any AF recurrence during the follow-up period after the second PVI session counted as AF recurrence. Recurrent AF and atrial tachyarrhythmias were defined as documented tachycardia lasting longer than 30 s without a blanking period.

STATISTICAL ANALYSIS. Continuous and categorical data are presented as mean ± SD and numbers (percentages), respectively. Categorical variables were analyzed using the chi square test where appropriate; otherwise, Fisher's exact test was used. Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test. The cumulative incidences of arrhythmia recurrences and cardiac events were analyzed using the Kaplan-Meier method and a log-rank test. Multivariate Cox regression analysis was used to determine risk factors for AF recurrence, and logistic regression analysis was used for multivariate analysis of new-NPVF; hazard ratios and 95% confidence intervals were calculated. All analyses were conducted using SPSS version 18.0J (SPSS Inc., Chicago, Illinois). The level of significance was set at $p < 0.05$.

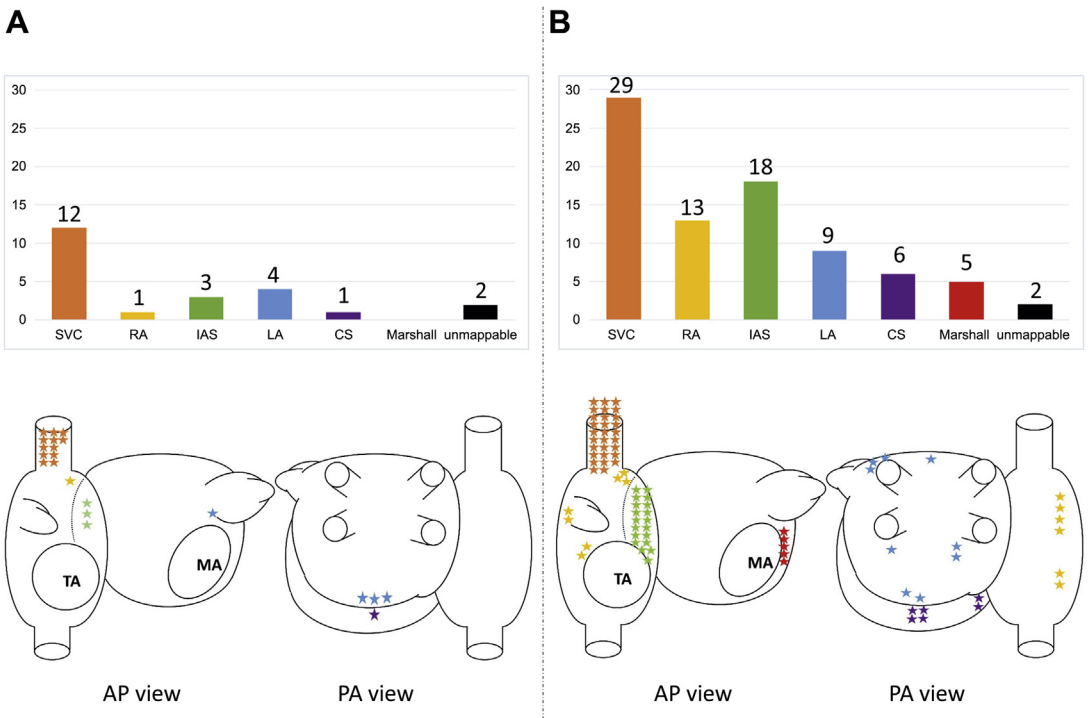
RESULTS

Figure 1 shows the study design and outcomes of catheter ablation in the first and second session. The second session was performed at a mean of 230 days after the first procedure. Of the 216 patients included, 59 (26.9%) had AF recurrence before the second session, with a high rate of LA-PV reconnection (n = 54, 91.5%) and new-NPVF (n = 20, 33.9%). A significant number of patients without AF recurrence also had PV reconnection (n = 107, 68.2%) and new-NPVF (n = 34, 21.7%). The number of reconnected PVs was significantly higher in patients with AF recurrence than in patients without AF recurrence (2.0 ± 1.2 vs. 1.2 ± 1.1, $p < 0.0001$). We performed additional substrate ablation in 9 patients with AF recurrence manifested as PeAF (complex fractionated electrogram ablation in 8 patients; roof and mitral linear ablation in 8 patients).

Depending on the presence of new-NPVF, patients were assigned to either the new-NPVF(+) group (n = 54) or the new-NPVF(−) group (n = 162). The baseline characteristics of the groups are listed in Table 1. AF history, defined as the time from AF diagnosis to the first isolation session, was significantly longer in the new-NPVF(+) group than in the new-NPVF(−) group ($p = 0.0013$), whereas there were no significant differences in other parameters. In addition, AF history did not differ between patients with PAF and those with PeAF (39.2 ± 4.7 months and 46.8 ± 8.9 months, respectively; $p > 0.05$).

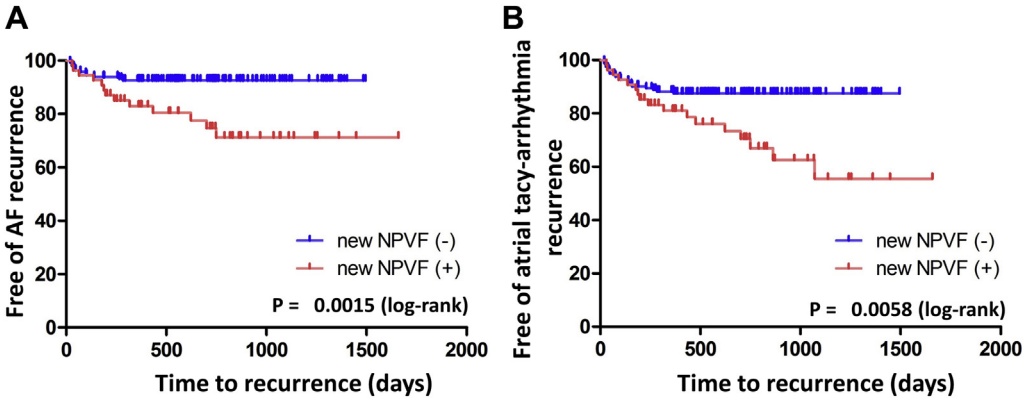
INCIDENCE AND DISTRIBUTION OF NPVF. In the first session, 23 NPVF were documented in 20 patients (9.3%), and SVC firings were dominant (12 of 20, 52.2%) (Figure 2A). Eighty-two new-NPVF in 54 patients (25.0%) were detected in the second session, and 3 cases with recurrences in the SVC area were not included. Regarding mappable NPVF detected in the second session, 46.2% (37 of 80) of foci were induced using isoproterenol infusion alone, and 53.8%

FIGURE 2 **Distribution of Nonpulmonary Vein Foci in the Atria**



(A) In the first PV isolation session, firings in the superior vena cava (SVC) were dominant. **(B)** In the second PV isolation session, the number and prevalence of foci had increased significantly. AP = anteroposterior; CS = coronary sinus; IAS = interatrial septum; LA = left atrium; MA = Marshall vein area; PA = posteroanterior; RA = right atrium; TA = tricuspid annulus area; other abbreviation as in Figure 1.

FIGURE 3 **Kaplan-Meier Event-Free Curve Showing Recurrence of AF and Atrial Tachyarrhythmia After the Second Session of PV Isolation**



(A) Recurrences of AF and **(B)** atrial tachyarrhythmia. Significant differences were noted between the groups of patients with (+) and without (−) newly developed nonpulmonary vein foci (new-NPVF). Abbreviation as in Figure 1.

TABLE 2 Univariate and Multivariate Analysis of Predictors for Atrial Fibrillation Recurrence After the Second Session of Pulmonary Vein Isolation

	Univariate Analysis		Multivariate Analysis	
	HR	p Value	HR	p Value
Age (yrs)	1.018 (0.982–1.054)	0.331		
Hypertension	0.588 (0.254–1.362)	0.215		
Body mass index (kg/m^2)	1.018 (0.920–1.127)	0.725		
AF history (months)	1.005 (1.000–1.009)	0.034	1.002 (0.998–1.007)	0.290
PV reconnection	4.027 (0.948–17.095)	0.059		
NPVF in the first session	1.362 (0.407–4.550)	0.616		
New-NPVF	3.325 (1.517–7.289)	0.003	2.533 (1.114–5.758)	0.027
LA volume (ml)	1.008 (0.998–1.017)	0.128		
AF recurrence after the first session	3.577 (1.620–7.900)	0.002	2.920 (1.301–6.553)	0.009
Persistent AF	0.989 (0.371–2.636)	0.983		

Newly developed NPVF (new-NPVF) were defined as NPVF that were not present in the first session of PV isolation.

HR = hazard ratio; other abbreviations as in Table 1.

(43 of 80) of foci were induced using ATP and isoproterenol infusion. The mean number of electrical cardioversion required to precisely locate a focus was 4.56 (4.98 for NPVF induced by ATP) and the mean number of ATP infusion was 2.95 in the second session (3.98 for NPVF induced by ATP). Although the doses of drugs for NPVF induction were identical in both sessions, the incidence of NPVF was higher in the second session than in the first. As to the sites of NPVF, the SVC area was dominant in the first session, but they were widely distributed in the second session and found in the SVC area (n = 29), right atrium (n = 13), interatrial septum (n = 18), LA (n = 9), coronary sinus (n = 6), and Marshall vein area (n = 5) (Figure 2B). Two patients had unmappable NPVF in the first session (2 of 20, 10%) and 2 in the second session (2 of 54, 3.7%).

CLINICAL OUTCOMES AFTER THE SECOND SESSION. The mean follow-up period after the second session was a mean 757.6 days. During the follow-up period, 25 patients (11.6%) had AF recurrence. AF recurrence rates were significantly higher in the new-NPVF(+) group than those in the new-NPVF(−) group (24.1%, 13 of 54 vs. 7.4%, 12 of 162, p = 0.001). Atrial tachyarrhythmia recurrence rates were significantly higher in the new-NPVF(+) group than those in the new-NPVF(−) group (31.5%, 17 of 54 vs. 12.3% 20 of 162, p = 0.001).

Kaplan-Meier event-free analysis showed that the AF recurrence rate (Figure 3A) and atrial tachyarrhythmia (Figure 3B) after the second session was higher in the new-NPVF(+) group than in the new-NPVF(−) group. Multivariate analysis revealed that new-NPVF and AF recurrence after the first session were independent predictors for AF recurrence after the second session (Table 2), whereas new-NPVF, AF recurrence after the first session, and LA volume were independent predictors for atrial tachyarrhythmia recurrence after the second session (Table 3). The AF history and NPVF in the first session were independent predictors for new-NPVF (Table 4).

DISCUSSION

The major findings of this study are as follows: 1) the prevalence of NPVF was significantly higher in the second session than in the first; 2) new-NPVF in the second session were strongly correlated to AF recurrence after repeated catheter ablation; and 3) AF history and AF recurrence after the first session were predictors for identifying patients who were likely to develop new-NPVF. This is the first report to focus on the prevalence of NPVF in the first and second sessions within the same study population and using a uniform induction method for NPVF, and to evaluate impact of NPVF prevalence on AF recurrence after PVI with possible exclusion by LA-PV reconnection.

THE INCIDENCE AND MECHANISM OF NEW-NPVF. In previous reports, the proportion of NPVF in patients with AF recurrence after PVI was 45.8% (8), which was higher than the rate in the first session (19.4% to 28%) (10,13,14). The present study found the proportion of patients with NPVF was 9.6% in the first session, lower than in previous reports, because we estimated NPVF after PVI. The proportion of patients with NPVF in the second session was also lower than in previous reports, which might be due to inclusion of patients without AF recurrence after the first session and a relatively short interval between the 2 sessions. Among the patients with AF recurrence after the first session, 19 (33.9%) had new-NPVF, indicating increased prevalence of NPVF as a trigger for recurrent AF after PVI. Since the study took place in the same population with the same induction method for NPVF in both sessions, PVI reduced the dominance of the PV as AF foci and shifted their role to the NPVF.

Several mechanisms might be considered for the NPVF increase in the second session. In the first session, we might have modified not only the NPVF with PVI but also the autonomic tone, which may have indirectly suppressed NPVF. Because autonomic tone changes after PVI are reported to be reversible (15,16), NPVF might be easily provoked in the chronic phase. In this study, NPVF originating from the interatrial septum accounted for 22% (18 of 82) of cases. A previous study also showed that 18.1% of NPVF originated in the interatrial septum in the second session for AF recurrence (8). Conversely, the prevalence of NPVF originating from the interatrial septum in the first session is reported to be 4% to 10% (10,17,18).

The possibility that interatrial septum puncture affected NPVF must be considered.

OUTCOME AFTER THE SECOND SESSION. Takigawa et al. (8) reported that NPVF is an important risk factor for AF recurrence after the second session in patients with PAF; this finding was confirmed by the present study. In addition, patients without AF recurrence 6 months after the first session had new-NPVF and AF recurrences after the second procedure in this study. The latter findings may indicate that these patients are prone to develop late recurrence after PVI. Takigawa et al. (8) also found that unmappable NPVF were detected in 16.9% of patients with AF recurrence after the first session and had close correlation to further AF recurrences after the second session. The proportion of patients with unmappable NPVF was higher than in our study because the dose of isoproterenol was different (5 to 15 μg/min vs. 4 μg/min). Administration of high-dose isoproterenol was reported to be useful to detect AF trigger and improve clinical outcome (11,19,20). It is unknown whether NPVF provocation with high dose isoproterenol detects patients with clinical NPVF or causes nonclinical NPVF, making it difficult to treat clinical NPVF. Smaller doses of isoproterenol might be sufficient because patients with new-NPVF in our study had almost the same recurrence rate as patients with successfully treated NPVF in the previous study (8).

Additional ablation for new-NPVF may be highly recommended to avoid future recurrences because complete elimination of NPVF brought good outcomes after the procedures (8,10,11,17,18). In this study, after additional ablation for LA-PV reconnection and new-NPVF, patients with new-NPVF had a higher AF recurrence rate than those without. The results might be partly explained by findings that patients with NPVF in the LA area had a higher recurrence rate than those with NPVF in the SVC or crista terminalis (19); moreover, using general anesthesia could have led to underestimation of the NPVF. In patients who show new-NPVF, long follow-up with additional medication with β-blockers and/or antiarrhythmic drugs may be needed.

PREDICTORS FOR NEW-NPVF. AF history and NPVF in the first session were shown to be predictors for new-NPVF. Kurotobi et al. (13) reported that a longer AF duration was associated with NPVF in patients with PAF. Their results were compatible with those noted in our study. They also reported that NPVF were detected more frequently in patients with PeAF than in those with PAF. In our study, AF type was not related to new-NPVF, likely because we did not include patients with PeAF lasting more than 1 year, and thus the AF duration did not differ between patients with PAF and those with PeAF (PAF: 39.4 ± 4.8 months vs. PeAF: 46.6 ± 8.7 months, $p > 0.05$).

Lee et al. (14) reported that sex and LA enlargement were associated with NPVF, but sex and LA volume were not predictors for new-NPVF; this might be due to a different approach followed in their study, whereby NPVF were estimated only before PVI in the first session. The distribution of NPVF in the study of Lee et al. was quite different from that noted in our investigation.

AF TRIGGERS AND ORIGIN. Jiang et al. (21) reported that a high incidence of PV reconnection was observed in patients with and without AF recurrence. In our study, patients without AF recurrence after the first session had high PV reconnection rate (68.2%, 107

TABLE 3 Univariate and Multivariate Analysis of Predictors for Atrial Tachyarrhythmia Recurrence After the Second Session of Pulmonary Vein Isolation

	Univariate Analysis		Multivariate Analysis	
	HR	p Value	HR	p Value
Age (yrs)	1.023 (0.993–1.053)	0.140		
Hypertension	0.770 (0.396–1.498)	0.442		
Body mass index (kg/m^2)	1.031 (0.948–1.122)	0.470		
AF history (months)	1.003 (1.000–1.007)	0.086		
PV reconnection	4.003 (1.227–13.059)	0.022	2.712 (0.813–9.048)	0.105
NPVF in the first session	1.176 (0.417–3.322)	0.759		
New-NPVF	2.537 (1.328–4.846)	0.005	2.241 (1.154–4.352)	0.017
LA volume (ml)	1.009 (1.001–1.017)	0.023	1.009 (1.001–1.016)	0.022
AF recurrence after the first session	3.370 (1.757–6.463)	0.001	2.472 (1.273–4.803)	0.008
Persistent AF	1.306 (0.616–2.768)	0.486		

New-NPVF were defined as NPVF that were not present in the first session of PV isolation.
Abbreviations as in Tables 1 and 2.

TABLE 4 Univariate and Multivariate Analysis for Predictors of Newly Developed Nonpulmonary Vein Foci in Patients Undergoing Multiple Sessions of Pulmonary Vein Isolation

	Univariate Analysis		Multivariate Analysis	
	HR	p Value	HR	p Value
Age (yrs)	1.011 (0.985–1.037)	0.412		
Male	0.578 (0.291–1.150)	0.351		
Hypertension	0.738 (0.394–1.384)	0.344		
Body mass index (kg/m^2)	0.988 (0.913–1.070)	0.769		
AF history (months)	1.007 (1.002–1.012)	0.004	1.008 (1.003–1.013)	0.002
PV reconnection	1.983 (0.897–4.382)	0.091		
LA volume (ml)	0.999 (0.990–1.007)	0.728		
AF recurrence after the first session	1.855 (0.959–3.587)	0.066		
Persistent AF	0.503 (0.210–1.207)	0.124		
NPVF in the first session	3.455 (1.351–8.831)	0.010	3.925 (1.515–10.171)	0.005

New-NPVF were defined as NPVF that were not present in the first session of PV isolation.
Abbreviations as in Tables 1 to 3.

of 157), and new-NPVF was an independent predictor for AF recurrence after the second session, even when these foci were ablated. These data indicate the limits of PVI therapy for AF triggers. Substrate ablation is reported as a complement or alternative to PVI (22–24), and recent reports have shown the efficacy of ablation of AF source (25,26). This new ablation strategy might be suitable for patients who have new-NPVF after repeated PVI procedures.

STUDY LIMITATIONS. This was a single-center retrospective study. The recurrence rate after the first session might have been underestimated because the follow-up period was short (230 days). Because we induced NPVF after PVI, the proportion of patients with NPVF might be underestimated; indeed, NPVF occurrence was lower than that reported in previous studies. However, it is time-consuming to detect NPVF before PVI due to multiple firing from the PVs and NPVF, which were likely eliminated by PVI. It might be clinically important to know the distribution of NPVF after PVI. Although repeat PVI was performed after 6 months, LA-PV reconnection could not be eliminated completely, and some patients might have had AF recurrence due to LA-PV reconnection even after the second session. We did not target NPVF that did not induce AF, which might have influenced our results. Finally, electrocardiography and 24-h Holter electrocardiographic monitoring every 3 to 6 months after the procedure is insufficient to detect AF episodes in patients with asymptomatic AF recurrence.

CONCLUSIONS

Despite its limitations, our study has clearly shown that a higher number of NPVF were detected in the second session of PVI, and the distribution of NPVF location and number were also different than those noted during the first session. Moreover, the occurrence of NPVF developed after the first PVI session was correlated with AF recurrence after catheter ablation of LA-PV reconnection. Patients with a long AF history and AF recurrence after the first session may need additional ablation for NPVF or AF triggers, with long-term follow-up.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: New-NPVF, defined as NPVF detected during the electrophysiological study or catheter ablation after an initial procedure of PVI for the treatment of AF, are associated with an increased risk of AF recurrence. History of AF and the presence of NPVF at the first isolation session represent independent predictors for new-NPVF. These findings suggest that the detection and ablation of NPVF are highly recommended therapeutic options for decreasing the rate of AF recurrence after repeated isolation procedures, as well as the limits of therapy for AF triggers.

TRANSLATIONAL OUTLOOK: A large-scale prospective study is warranted for further elucidation of the role of NPVF in late recurrence of AF.

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KEY WORDS **adenosine triphosphate, atrial fibrillation, isoproterenol, nonpulmonary vein foci, pulmonary vein isolation**