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ORIGINAL ARTICLE

Association of extra-pulmonary vein triggers with low-voltage area and clinical recurrence in patients with atrial fibrillation undergoing catheter ablation

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Abstract

Background and Objectives: Although extra-pulmonary vein (PV) triggers (ExPVTs) play a role in atrial fibrillation (AF) recurrence after catheter ablation (AFCA), the mechanism is unknown. We explored whether the locations of ExPVTs were associated with low-voltage scar areas (LVAs).

Methods: Among 2255 consecutive patients who underwent a de novo AFCA, 1696 (male 72.1%, median 60 years old, paroxysmal 64.7%) were included who underwent isoproterenol provocation and voltage mapping of the left atrium (LA) during their procedures. We investigated the associations between ExPVTs and their mean LA voltage and colocalization of ExPVTs within LVAs (<0.2 mV).

Results: We observed ExPVTs in 181 (10.7%) patients (60 in the LA, 99 in the right atrium [RA], 16 biatrial, and 6 unmappable). A lower mean LA voltage was independently associated with the existence of ExPVTs (OR 0.77 per 1 SD mV increase, 95% CI 0.60–0.99, $p = .039$). Among 76 patients who had $ExPVTs_{[LA]}$, 43 (56.6%) had ExPVTs within LVAs. During a median of a 42-month follow-up, patients with ExPVTs had a higher AF recurrence than those without (HR 1.87, 95% CI 1.48–2.37, Log-rank $p < .001$), but colocalization of ExPVTs and LVAs (Log-rank $p = .544$) and the anatomical location of ExPVTs (Log-rank $p = .084$) did not affect the rhythm outcome.

Conclusions: The presence of ExPVTs was associated with low LA voltage and poor rhythm outcome post-AFCA, but the colocalization of ExPVTs and LVA in LA did not affect rhythm outcome.

KEYWORDS
arrhythmia, atrial fibrillation, catheter ablation, extra-pulmonary vein triggers, low-voltage areas

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia and influences the quality of life by increasing the morbidity and mortality of affected patients.[1] Catheter ablation is an effective treatment for AF.[2] Pulmonary vein (PV) isolation is the mainstay technique of all AF catheter ablation (AFCA) strategies.[3] However, the recurrence rates after an initial ablation procedure are relatively high, ranging from 20% to 80%, and repeat ablation procedures during the long-term follow-up are needed in 30%–70% of patients who receive AFCA for sinus conversion.[4,5] Novel and improved mapping and ablation systems are being developed or are under clinical evaluation to reduce the recurrence rates after AFCA procedures.[6]

Even though many investigators have studied the pathogenesis of arrhythmia recurrence after AFCA, there have been conflicting results. A few studies have demonstrated that arrhythmia recurrence after AFCA is related to PV triggers, which are thought to be caused by PV reconnections in these areas.[7,8] However, in other studies, extra-PV triggers (ExPVTs) have been reported to play important roles in recurrence after AFCA, possibly because of the arrythmogenicity of cardiomyocytes especially in persistent AF (PeAF).[9–11] Thus, obliteration of ExPVTs by focal ablation or isolation of the arrhythmogenic area of clusters of ExPVTs is important to lengthen the arrhythmia-free period.[12]

Our recent study demonstrated that ExPVTs play a role in recurrence after AFCA,[13] but the mechanism has not been clearly elucidated. Thus, we aimed to investigate whether the location of ExPVTs originated within low-voltage scar areas.

2 | MATERIALS AND METHODS

2.1 | Study population

This single-center, retrospective, cohort study protocol adhered to the principles of the Declaration of Helsinki (2013) and was approved by the Institutional Review Board at Yonsei University Health System. Written informed consent for inclusion in the Yonsei AF Ablation Cohort (ClinicalTrials.gov identifier: NCT02138695) was provided by all patients. Among 2255 patients who underwent a de novo AFCA from March 2009 to December 2020, 1696 who underwent postprocedural isoproterenol provocation tests and left atrium (LA) voltage mapping (Vm) during their procedures and protocol-based rhythm follow-up were included. We divided these patients into two groups according to the existence of extra-PV trigger sites, no-ExPVTs, and ExPVTs (Figure 1). The ExPVT patients were subdivided into four subgroups based on the location of the trigger: LA, RA, biatrial, and unmappable groups (Figure 1). LVA was defined as areas with <0.2 mV on LA voltage map, in accordance with previous studies.[6,14–16] Biatrial means that there are multiple foci and the locations of the foci were in both RA and LA. Patients with ExPVTs in the LA were divided further into two subgroups based on the trigger site of the ExPVT and LA voltage mapping: one group whose ExPVT was located in a LVA and one group whose ExPVT was outside of an LVA. Representative 3D mapping images of an ExPVT near an LVA and ExPVT outside of an LVA are shown in Figure 2A,B. We compared the bipolar LA voltage and unipolar LA voltage of the LA subsections based on the presence of an ExPVT. Specifically, the LA extra-PV area was divided into six

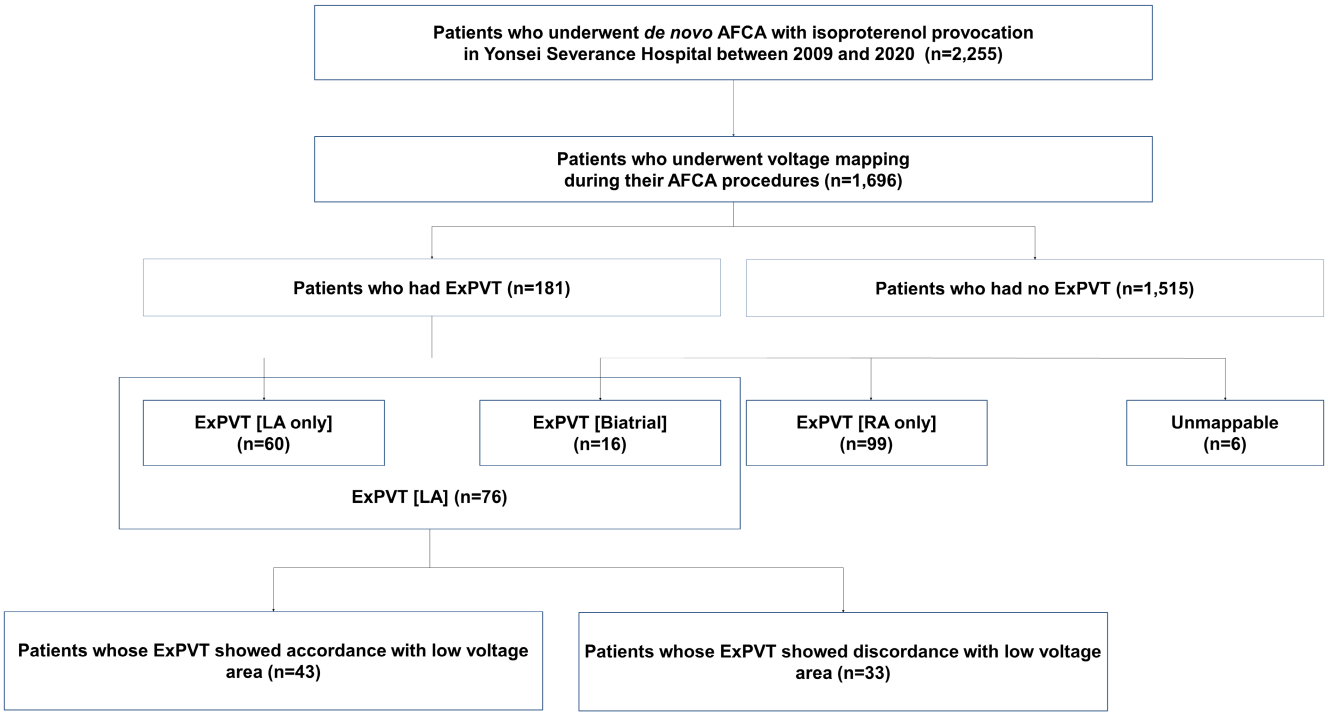

FIGURE 1 Flowchart of the present study. AFCA, atrial fibrillation catheter ablation; ExPVT, extra-pulmonary vein trigger; LA, left atrium; RA, right atrium.

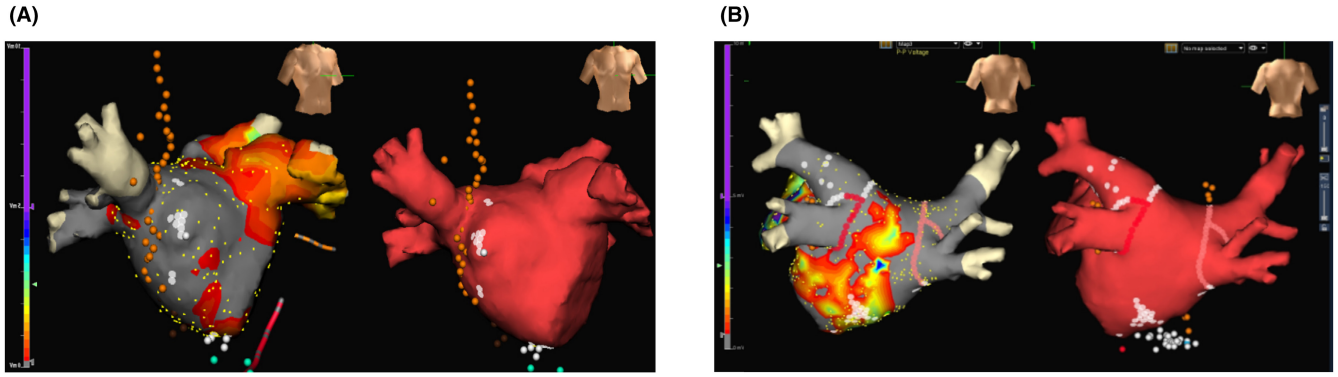

FIGURE 2 Representative 3D images showing an extra-pulmonary vein trigger (ExPVT) near a low-voltage area (A) and outside a low-voltage area (B).

sections (i.e., anterior wall, LA appendage, posterior wall, posterior–inferior wall, left lateral isthmus, and septum).

2.2 | Electrophysiological mapping and catheter ablation

We recorded the intracardiac electrograms using the Prucka CardioLabTM Electrophysiology system (General Electric Medical Systems, Inc., Milwaukee, WI, USA) and generated 3D electroanatomical maps (NavX, Abbott, Inc., Chicago, IL, USA; CARTO system, Biosense Webster, Diamond Bar, CA, USA). The electrophysiological mapping and AFCA were performed as described in our prior study.[13] In brief, AFCA using an open-irrigated tip catheter (Celsius, Johnson & Johnson Inc., Diamond Bar, CA, USA; NaviStar ThermoCool, Biosense Webster Inc., Diamond Bar, CA, USA; ThermoCool SF, Biosense Webster Inc.; Coolflex, Abbott Inc., Minnetonka, MN, USA; 30–35 W; 47°C; FlexAbility, Abbott Inc.; ThermoCool SmartTouch, Biosense Webster Inc., and TactiCath, Abbott Inc.) was carried out as previously described.[12,13] Because we included patients over a relatively long period (12 years), the radiofrequency power for the AFCA varied between 25 and 60 W. The endpoint of ablation at each site was an average impedance decrease of >10% of baseline or an >80% decrease in the local electrogram voltage amplitude. We generated a circumferential pulmonary vein isolation (CPVI) with bidirectional block in all patients. An empirical linear ablation, including a cavotricuspid isthmus, roofline, posterior–inferior line (posterior box lesion), and anterior line, left lateral isthmus ablation, right atrial ablation, or complex fractionated electrogram ablation, was performed at the discretion of the operator.

2.3 | Left atrial voltage mapping

During AFCA, detailed voltage mapping of the LA was performed in sinus rhythm. A decapolar circular mapping catheter (AFocus, Abbott, Inc., Chicago, IL, USA; Lasso, Biosense Webster Inc., Diamond Bar, CA, USA) was used to map the entire LA excluding the PVs. Mapping was guided by intracardiac echocardiography (ICE) and fluoroscopy. Bipolar electrograms (EGMs) were recorded and filtered at 30–400 Hz. RA voltage mapping was not performed.

2.4 | Isoproterenol provocation

Isoproterenol provocation procedures were performed as previously described.[13,17] Isoproterenol (5–20 μg/min depending on β-blocker use with a target heart rate of 120 bpm) was infused for at least 3 min before induction and was maintained for 3 min after the induction of AF or AT. Internal cardioversion was carried out by using biphasic shock (2–20 J) with R wave synchronization (Lifepak12, Physiocontrol Ltd., Redmond, W, USA) if sustained AF or AT was induced. All procedures were conducted under conscious sedation but deep sedation was induced immediately before electrical cardioversion. The procedure was completed when there was no immediate recurrence of AF within 10 min after the isoproterenol infusion with or without cardioversion. An ExPVT was defined as an AF trigger point identified by isoproterenol provocation after bidirectional block of the CPVI. Only single induction was performed before the subsequent ablation process of ExPVTs. If further AF triggers were observed under an isoproterenol effect, the potential location of the ExPVT foci was determined based on contact bipolar electrograms, and a quick but detailed 3D-activation mapping with a multielectrode catheter was conducted. Basically, we performed focal ablation in all cases. However, SVC isolation or posterior wall isolation was performed under the operators' judgments. Based on the 3D mapping, the ExPVT foci were ablated with 35–50 W for 10 s for each lesion until elimination. After the first ablation trial, subsequent isoproterenol provocation procedure was conducted if the ExPVT foci were highly reproducible. However, isoproterenol provocation was not performed second time after the initial try, in general.

2.5 | Postablation management and follow-up

We discharged the patients without AADs except in those who experienced recurrent ExPVTs after the AFCA procedure, symptomatic frequent atrial pre-mature beats, nonsustained atrial tachycardia, or

early recurrence of AF on telemetry during admission. Patients visited the outpatient clinic regularly at 1, 3, 6, and 12 months and then every 6 months or whenever symptoms occurred. All patients underwent an ECG during every visit and 24-h. Holter recordings at 3 and 6 months and every 6 months for 2 years, annually for 2–5 years, and then biannually after 5 years. Holter monitoring or event monitor recordings were obtained when patients reported palpitations suggestive of arrhythmia recurrence. We defined AF recurrence as any episode of AF or AT of at least 30 s in duration.

2.6 | Statistical analysis

Continuous variables are indicated as the mean ± standard deviation (SD) and compared by an independent two-sample *t*-test analysis. Categorical variables are expressed as the number (percentage of the group total) and compared by either a chi-square test or Fisher's exact test. A multivariable logistic regression was applied to identify the predictors associated with the existence of an ExPVT. A Kaplan–Meier analysis with a log-rank test was used to calculate the duration of an AF recurrence-free period and to compare the recurrence rates according to the existence and location of the ExPVT and the presence of an ExPVT inside an LVA. A multivariable Cox regression analysis was performed to identify the predictors associated with a clinical recurrence of AF. The variables with $p < .2$ in the univariable logistic regression were included in the multivariable analysis. A two-sided $p < .05$ was considered statistically significant. The statistical analyses were performed using R version 4.0.2 software (The R Foundation, www.R-project.org, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics

The baseline clinical and echocardiographic characteristics of a total of 1696 AF patients who underwent AFCA with isoproterenol provocation and an LA Vm during their procedures are summarized in Table 1. We observed ExPVTs in 181 patients (10.7%) who were more likely to be female, older, and have higher LA volume indices and a lower mean LA voltage than those with no-ExPVTs. In the multivariable logistic regression analysis, a lower mean LA voltage (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.60–0.99, $p = .039$) was independently associated with the existence of an ExPVT (Table 2).

3.2 | Existence of extra-pulmonary vein triggers and the rhythm outcome

We compared the clinical rhythm outcomes according to the existence of extra-PV foci. During the mean follow-up of 42 (interquartile range [IQR] 21–78) months, patients with ExPVTs had a significantly higher AF recurrence than did those without (HR 1.87, 95% CI 1.48–2.37, Log-rank $p < .001$, Figure 3A). The detailed comparisons of the rhythm outcomes between the no-ExPVT and ExPVT groups are summarized in Table S1. Early recurrence and maintenance of AADs at discharge and 3 months after the procedures were more frequent in the ExPVT groups than no-ExPVT groups (all $p < .001$).

3.3 | Anatomical locations of extra-pulmonary vein triggers

According to the anatomical location of the triggers, we divided the ExPVT group ($n = 181$) into four subgroups: $ExPVT_{[LA]}$ ($n = 60$), $ExPVT_{[RA]}$ ($n = 99$), $ExPVT_{[Biatrial]}$ ($n = 16$), and unmappable ($n = 6$). Table S2 summarizes the baseline clinical and echocardiographic characteristics of the patients with an $ExPVT_{[LA]}$, $ExPVT_{[RA]}$, and $ExPVT_{[Biatrial]}$. The unmappable group was excluded from this comparison because of the very small size of the group. Patients with an $ExPVT_{[LA]}$ were more likely to have diabetes mellitus and higher peak and mean LA pressures during both AF and sinus rhythm as compared to those with an $ExPVT_{[RA]}$ (Table S2). Figure 3B depicts the Kaplan–Meier analysis of the AF recurrence-free survival among the $ExPVT_{[LA]}$, $ExPVT_{[RA]}$, and $ExPVT_{[Biatrial]}$ groups. The location of the trigger sites was not related to clinical recurrence (log-rank $p = .084$) (Figure 3B).

3.4 | Accordance between the locations of extra-pulmonary vein triggers and low-voltage areas

We compared the trigger sites of the 76 patients with ExPVTs located in the LA with their voltage maps and divided the patients into two subgroups: those with an ExPVT inside an LVA (voltage <0.2 mV) ($n = 43$, 56.6%) and those with ExPVTs outside of an LVA ($n = 33$, 43.4%). Patients with ExPVTs inside an LVA showed nonsignificant trends toward a larger LA volume index ($p = .065$) and a larger LA dimension ($p = .072$) than did those with ExPVTs outside of an LVA (Table 3). However, in the logistic regression, larger LA volume index and LA dimension were not independently associated with an ExPVT location in an LVA (Table 4). The association of the ExPVT location and LVA was not significantly related to clinical recurrence (Log-rank $p = .544$; Figure 3C).

3.5 | Bipolar and unipolar voltages of the LA subregions according to the existence of extra-pulmonary vein triggers

As mentioned in Section 2, we classified the LA extra-PV areas of the applicable 76 patients into six sections on the LA voltage map (Figure 4A). Then, we compared the bipolar and unipolar LA voltages of those LA sections by the presence of an ExPVT. LA anterior walls containing ExPVTs had lower bipolar (median 0.4 [IQR 0.2–1.1] vs. 1.0 [IQR 0.6–1.5], $p = .028$) and unipolar voltages (median 0.9 [IQR 0.6–1.9] vs. 1.8 [IQR 1.5–2.6], $p = .018$) compared to anterior walls with no-ExPVT (Figure 4B,C; Tables S3 and S4). We analyzed the proportion of ExPVTs

TABLE 1 Baseline clinical and echocardiographic characteristics of patients stratified according to the existence of extra-pulmonary vein triggers.

	Overall ($n = 1696$)	No-ExPVT ($n = 1515$)	ExPVT ($n = 181$)	p value
Age, years	60 (52–67)	60 (52–67)	62 (55–68)	.016
Male	1222 (72.1)	1111 (73.3)	111 (61.3)	.001
Paroxysmal atrial fibrillation	1091 (64.7)	980 (65.0)	111 (62.0)	.474
Comorbidities				
Heart failure	236 (13.9)	209 (13.8)	27 (14.9)	.765
Hypertension	768 (45.3)	683 (45.1)	85 (47.0)	.688
Diabetes mellitus	267 (15.7)	237 (15.6)	30 (16.6)	.828
Stroke	202 (11.9)	182 (12.0)	20 (11.0)	.797
CHA_2DS_2-VASc score	1 (1–3)	1 (1–3)	2 (1–3)	.189
Echocardiography				
LA dimension, mm	41 (37–46)	41 (37–46)	41 (37–45)	.736
LA volume index, mL/m^2	35.3 (28.3–44.6)	35 (28.2–44.1)	39.2 (29.7–48.3)	.001
LV ejection fraction, %	64 (59–68)	64 (59–68)	64 (59–67)	.742
Eem	9.1 (7.6–12.0)	9.0 (7.4–12.0)	9.4 (8.0–12.0)	.126
RVSP, mmHg	26 (22–30)	26 (22–30)	26 (23–30)	.158
Pericardial fat volume, mL	102.6 (71.5–143.9)	103.5 (72–146.2)	94 (65.6–134.1)	.052
Mean LA voltage, mV	1.4 (1.0–1.9)	1.5 (1.0–2.0)	1.3 (0.8–1.7)	.001
LA pressure, mmHg				
Peak pressure, AF	22 (17–28)	22 (17–28)	22 (16–28)	.902
Mean pressure, AF	12 (9–16)	12 (9–16)	12 (8–16)	.529
Peak pressure, SR	21 (15–28)	21 (15–27)	21 (16–29)	.192
Mean pressure, SR	12 (8–16)	11 (8–16)	12 (8–17)	.295

Note: Values are presented as the median (interquartile range) or number (%).

Abbreviations: AF, atrial fibrillation; Eem, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; ExPVT, extra-pulmonary vein trigger; LA, left atrium; LV, left ventricle; RVSP, right ventricle systolic pressure; SR, sinus rhythm.

originating from LVA of each section on the LA voltage map. LA anterior wall and septum showed higher proportion of ExPVTs originating from LVA (57.1% and 50.0%, respectively) (Figure 4D).

4 | DISCUSSION

4.1 | Main findings

This single-center retrospective cohort study investigated the electro-anatomical location of ExPVTs and the clinical recurrence in AF patients undergoing a de novo catheter ablation. The present study demonstrated ExPVTs in 10.7% (181 of 1696) of the patients, and the existence of ExPVTs was independently associated with a lower mean LA voltage. An ExPVT in the LA was observed in 42.0% (76 of 181) of the patients with an ExPVT. Anterior LA regions containing ExPVTs had a lower voltage compared to those regions without ExPVTs. Patients with an ExPVT had a significantly higher AF recurrence than those without. However, the accordance of the $ExPVT_{[LA]}$ location with an LVA did not affect the rhythm outcome, nor did the anatomical location of the ExPVT.

4.2 | Roles of extra-pulmonary vein triggers in the mechanism of AF

PV reconnections,[7,8] ExPVTs,[9–11] and increased parasympathetic effects contribute to AF recurrence after catheter ablation.[13] Despite the development of efficient catheter ablation methods and improved mapping systems, which have reduced the adverse effects of AFCA, the long-term recurrence rate remains high.[18] It has been reported that a female gender,[19] longer PR interval,[20] being overweight,[21] high LA pressure,[22] and high pericardial fat volume[23] are related to a higher clinical recurrence rate after AFCA.

ExPVTs may be caused by the arrhythmogenic property of cardiomyocytes, which results from a combination of triggered activity, enhanced automaticity, and localized micro-reentry.[9] Our recent study suggested that increased parasympathetic nerve activity and previous ablation lesions may contribute to ExPVTs and recurrence after AFCA.[13] Although many investigators have studied the mechanism of ExPVTs after AFCA, their exact mechanisms are not clear. Here, we demonstrated that the existence of ExPVTs is independently related to a low LA voltage, suggesting that the

TABLE 2 Univariable and multivariable logistic regression analyses for the existence of extra-pulmonary vein triggers.

	Univariable		Multivariable[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, per 1 SD increase	1.23 (1.05–1.44)	.011	1.18 (0.96–1.46)	.125
Male	0.58 (0.42–0.79)	<.001	0.81 (0.52–1.25)	.339
Paroxysmal atrial fibrillation	0.88 (0.64–1.21)	.425		
Comorbidities				
Heart failure	1.10 (0.71–1.69)	.680		
Hypertension	1.08 (0.79–1.47)	.631		
Diabetes mellitus	1.07 (0.71–1.62)	.745		
Stroke	0.91 (0.56–1.48)	.705		
CHA_2DS_2-VASc score, per 1 SD increase	1.06 (0.97–1.28)	.203		
Echocardiography				
LA dimension, per 1 SD mm increase	0.97 (0.83–1.15)	.706		
LA volume index, per 1 SD mL/m^2 increase	1.24 (1.08–1.43)	.003	1.00 (0.80–1.26)	.973
LV ejection fraction, per 1 SD % increase	1.03 (0.88–1.21)	.692		
Eem, per 1 SD unit increase	1.11 (0.96–1.28)	.151	0.94 (0.77–1.16)	.570
RVSP, per 1 SD mmHg increase	1.06 (0.91–1.24)	.461		
Pericardial fat volume, per 1 SD mL increase	0.82 (0.68–1.00)	.044	0.88 (0.71–1.09)	.234
LA voltage, per 1 SD mV increase	0.78 (0.66–0.92)	.003	0.77 (0.60–0.99)	.039
LA pressure, per 1 SD mmHg increase				
Peak pressure, AF	1.02 (0.86–1.21)	.800		
Mean pressure, AF	0.94 (0.79–1.13)	.535		
Peak pressure, SR	1.12 (0.96–1.30)	.158	1.00 (0.98–1.03)	.695
Mean pressure, SR	1.05 (0.90–1.23)	.501		

Abbreviations: AF, atrial fibrillation; Eem, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; ExPVT, extra-pulmonary vein trigger; LA, left atrium; LV, left ventricle; RVSP, right ventricle systolic pressure; SR, sinus rhythm.

[a]Variables with a $p < .2$ in the univariable logistic regression were included in the model.

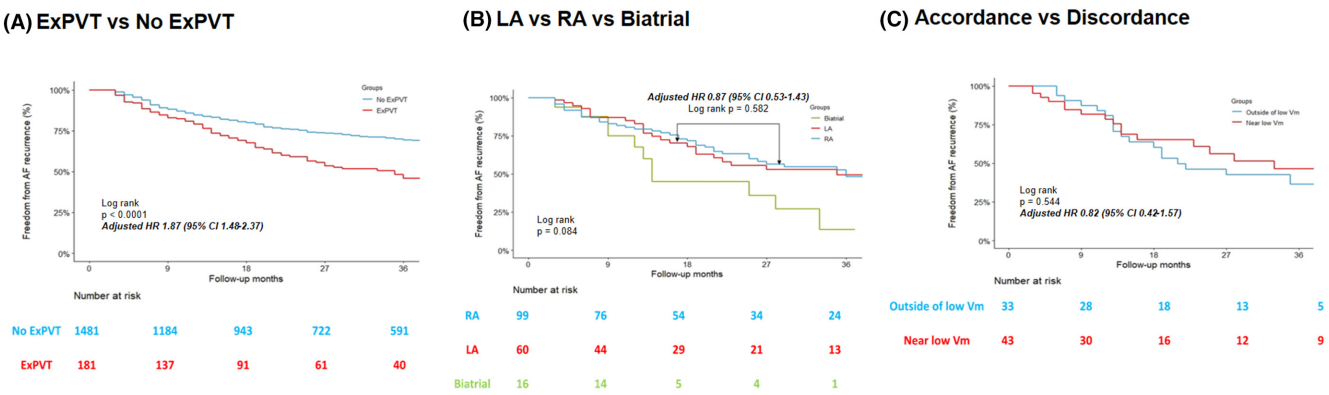

FIGURE 3 Kaplan–Meier analyses of the AF recurrence-free survival according to the presence of an extra-pulmonary vein trigger (ExPVT) (A), location of the ExPVT (B), and concordance between the ExPVT and low-voltage area (C). AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

TABLE 3 Comparison of the baseline clinical and echocardiographic characteristics of patients stratified by the accordance between the extra-pulmonary vein trigger location and low-voltage area.

	ExPVT inside a LVA ($n=43$)	ExPVT outside of a LVA ($n=33$)	p value
Age, years	63.7 ± 9.7	60.1 ± 9.3	.105
Male	29 (67.4)	22 (66.7)	1.000
Paroxysmal atrial fibrillation	23 (53.5)	21 (63.6)	.457
Comorbidities			
Heart failure	7 (16.3)	6 (18.2)	1.000
Hypertension	20 (46.5)	13 (39.4)	.699
Diabetes mellitus	12 (27.9)	9 (27.3)	1.000
Strok	3 (7.0)	3 (9.1)	1.000
CHA_2DS_2-VASc score	2 (1–3)	2 (1–2)	.519
Echocardiography			
LA dimension, mm	43.0 (38.0–47.0)	39.0 (34.0–45.0)	.072
LA volume index, mL/m^2	40.9 (33.6–48.1)	34.2 (27.2–43.1)	.065
LV ejection fraction, %	63.0 (60.0–66.5)	66.0 (58.0–69.0)	.478
Eem	9.4 (8.2–12.3)	9.4 (8.1–12.0)	.598
RVSP, mmHg	26.0 (22.0–33.0)	26.5 (23.0–31.0)	.976
Pericardial fat volume, mL	107.1 (70.7–139.0)	87.6 (61.6–140.0)	.537
Mean LA voltage, mV	1.1 (0.7–1.7)	1.4 (1.0–1.8)	.154
LA pressure, mmHg			
Peak pressure, AF	25.0 (19.5–29.0)	23.5 (20.0–35.0)	.561
Mean pressure, AF	13.3 ± 5.5	15.0 ± 6.0	.252
Peak pressure, SR	27.1 ± 9.8	25.0 ± 8.9	.348
Mean pressure, SR	14.8 ± 6.2	13.5 ± 6.4	.385

Note: Values are presented as the mean ± standard deviation, median (interquartile range), or number (%).

Abbreviations: AF, atrial fibrillation; Eem, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; ExPVT, extra-pulmonary vein trigger; HRV, heart rate variability; LA, left atrium; LV, left ventricle; RVSP, right ventricle systolic pressure; SR, sinus rhythm; Vm, voltage mapping.

scar area may contribute to the arrythmogenicity of the area. Inconsistent with our findings, it has been recently reported that ExPVTs in the LA are clustered in low-voltage/fibrotic areas.[24] The ectopic activity of a fibrotic area might be because of electronic communications between myofibroblasts and surviving atrial cardiomyocytes through gap junctions,[25–27] and pre-existent LA scarring was a strong predictor of recurrence after a CPVI, suggesting that an LVA may have arrhythmogenic activity and contribute to the refractoriness and persistence of AF.[28] In this study, anterior wall sections containing ExPVTs showed a lower voltage than the same anatomical sections without ExPVTs. However, there was no significant difference in the voltage between the other LA sections containing ExPVTs and their controls. There was no significant difference in rhythm outcomes between patients with an ExPVT near an LVA and patients with an ExPVT outside of LVAs. Still, the mechanism by which fibrosis leads to the initiation or perpetuation of AF is not completely understood. In the Efficacy of Delayed Enhancement-MRI-Guided Fibrosis Ablation versus Conventional Catheter Ablation of Atrial Fibrillation (DECAAF II) trial, a fibrosis-targeted ablation with a CPVI, compared with a CPVI alone, did not improve the rhythm outcome,[29] indicating that fibrosis is a marker of LA disease but not necessarily the source of arrhythmogenesis nor of AF perpetuation and electrical and structural derangements cannot be addressed simply by ablation alone. Also, the possibility of a mismatch between the border of epicardial scars and their endocardial exits might explain the discordance between the ExPVT location and LVA. Further studies are needed to clarify the mechanisms of ExPVTs and AF recurrence.

4.3 | Locations of extra-pulmonary vein triggers after pulmonary vein isolation

The most common sources of ExPVTs are the LA posterior wall, interatrial septum (IAS), crista terminalis, LA appendage, superior vena cava (SVC), and coronary sinus.[13] In contrast to a previous study,[24] the proportion of ExPVTs in the LA (33.1%) was lower than that in the RA (54.7%) in the present study. In this study, ExPVTs were most frequently observed at the IAS (22.7%), LA appendage and Ligament of Marshall (22.7%), followed by LA posterior wall

TABLE 4 Univariable and multivariable logistic regression analyses for the accordance between the extra-pulmonary vein trigger location and low-voltage area.

	Univariable		Multivariable[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, per 1 SD increase	1.56 (0.91–2.67)	.108	1.46 (0.84–2.54)	.174
Male	1.04 (0.39–2.72)	.943		
Paroxysmal atrial fibrillation	0.66 (0.26–1.66)	.376		
Comorbidities				
Heart failure	0.88 (0.26–2.90)	.827		
Hypertension	1.34 (0.53–3.36)	.535		
Diabetes mellitus	1.03 (0.37–2.85)	.951		
Stroke	0.75 (0.14–3.98)	.736		
CHA_2DS_2-VASc score, per 1 SD point increase	1.15 (0.74–1.80)	.531		
Echocardiography				
LA dimension, per 1 SD mm increase	1.32 (0.87–2.01)	.197	1.30 (0.84–2.00)	.241
LA volume index, per 1 SD mL/m^2 increase	1.11 (0.75–1.04)	.598		
LV ejection fraction, per 1 SD % increase	1.00 (0.63–1.61)	.988		
Eem, per 1 SD unit increase	1.21 (0.73–2.00)	.452		
RVSP, per 1 SD mmHg increase	1.04 (0.66–1.64)	.855		
Pericardial fat volume, per 1 SD mL increase	1.19 (0.71–2.01)	.513		
Mean LA voltage, per 1 SD mV increase	0.67 (0.42–1.08)	.104	0.74 (0.45–1.20)	.224
LA pressure, per 1 SD mmHg increase				
Peak pressure, AF	0.81 (0.49–1.34)	.404		
Mean pressure, AF	0.70 (039–1.28)	.251		
Peak pressure, SR	1.26 (0.78–2.05)	.344		
Mean pressure, SR	1.25 (0.76–2.04)	.380		

Abbreviations: AF, atrial fibrillation; Eem, ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; ExPVT, extra-pulmonary vein trigger; LA, left atrium; LV, left ventricle; RVSP, right ventricle systolic pressure; SR, sinus rhythm.

[a]Variables with a $p < .2$ in the univariable logistic regression were included in the model.

(12.3%), and coronary sinus (9.2%), which shows some discrepancy with our previous study,[13] where IAS (26.0%), coronary sinus (19.9%), SVC (17.4%), and crista terminalis (8.5%) were the most common sites of ExPVTs when counting the number of extra-PV foci. Patients with an $ExPVT_{[LA]}$ tended to have diabetes more frequently and higher peak and mean LA pressures than those with an $ExPVT_{[RA]}$. However, the location of the ExPVT did not affect the rhythm outcome after AFCA.

4.4 | Clinical implications

Our study showed that ExPVTs in the LA near an LVA did not affect the AF recurrence-free survival, compared with ExPVTs in the LA outside of LVA. Whether ExPVTs were inside the LVA or not did not affect the rhythm outcomes. Nevertheless, the LA Vm may be helpful and important in detecting ExPVTs during AFCA and for planning the therapeutic design because a low mean LA voltage is independently associated with the existence of ExPVTs. We could not establish a conclusion regarding the association of an $ExPVT_{[LA]}$ near an LVA and clinical recurrence after AFCA. Thus, further multi-center prospective studies are needed to confirm our findings.

4.5 | Study limitations

Our study has some limitations. First, this study was performed retrospectively in a single center. Thus, we could not exclude the possibility of selection bias. Second, the ablation strategy for ExPVTs was heterogeneous, and the technical improvement in the AFCA procedure

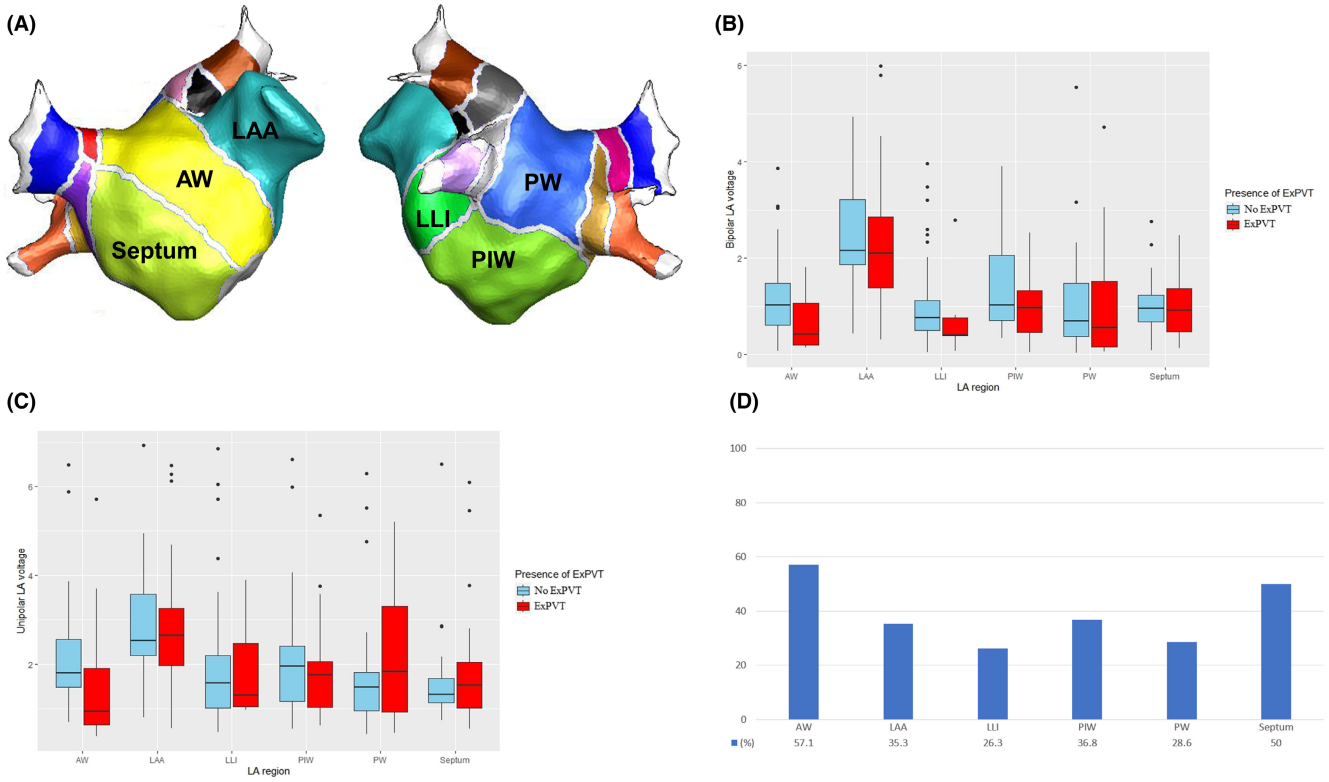

FIGURE 4 Six sections of the left atrial (LA) extra-pulmonary vein area (A), comparison of the bipolar (B) and unipolar voltages (C) of the LA sections according to the presence of an extra-pulmonary vein trigger (ExPVT). The proportion of ExPVTs originating from LVA of each section of LA (D). AW, anterior wall; LAA, left atrial appendage; LLI, left lateral isthmus; PIW, posterior–inferior wall; PW, posterior wall.

during the duration of this retrospective cohort period may have affected the long-term clinical recurrence. Third, the number of patients with ExPVTs in the LA was relatively small and limited a conclusion based on the mechanism. Fourth, a voltage mapping in right atrium was not performed in this study. Therefore, we were not able to assess the ExPVTs in right atrium or interatrial septum electroanatomically. Fourth, our study was conducted based on a longitudinal prospective cohort data from 2009 to 2020, which was before the introduction of high-density mapping catheters such as PENTARAY or GRID catheters. Thus, for consistency, we used decapolar circular mapping catheters for all patients throughout the study. Lack of using high-density mapping catheters is one limitation of this study. Fifth, we performed subsequent isoproterenol provocation test if the ExPVT foci were highly reproducible, but we did not generally perform isoproterenol provocation test second time. Thus, in cases which second time isoproterenol provocation test was not performed, it is difficult to know whether the AFCA was successful or not. Finally, we excluded those patients who did not undergo an isoproterenol provocation test, which may have resulted in selection bias.

5 | CONCLUSIONS

The presence of an ExPVT was associated with a low LA voltage and poor rhythm outcome after AFCA, but the colocalization of the ExPVTs and LVA in LA did not affect rhythm outcome.

AUTHOR CONTRIBUTIONS

Conceptualization: Park IJ, Kim D, and Pak HN. *Data curation*: Kim D and Pak HN. *Formal analysis*: Park IJ and Kim D. *Investigation*: Park IJ, Kim D, and Pak HN. *Methodology*: Kim D and Pak HN. *Resources*: Kim D, Yu HT, Kim T-H, Uhm J-S, Joung B, Lee M-H, Hwang C, and Pak HN. *Validation*: Park IJ, Kim D, Yu HT, Kim T-H, Uhm J-S, Joung B, Lee M-H, Hwang C, and Pak HN. *Writing—original draft*: Park IJ, Kim D, and Pak HN. *Writing—review and editing*: Kim D, Yu HT, Kim T-H, Uhm J-S, Joung B, Lee M-H, Hwang C, and Pak HN.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

ETHICS STATEMENT

This study adhered to the principles of the Declaration of Helsinki (2013) and was approved by the Institutional Review Board at Yonsei University Health System.

PATIENT CONSENT STATEMENT

Written informed consent for inclusion in the Yonsei AF Ablation Cohort (ClinicalTrials.gov identifier: NCT02138695) was provided by all patients.

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REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995;155:469–73.
2. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al. Effect of catheter ablation vs. medical therapy on quality of life among patients with atrial fibrillation: the CANANA randomized clinical trial. JAMA. 2019;321:1275–85. https://doi.org/10.1001/jama.2019.0692
3. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. J Am Coll Cardiol. 2006;48:2340–7. https://doi.org/10.1016/j.jacc.2006.08.037
4. Tzou WS, Marchlinski FE, Zado ES, Lin D, Dixit S, Callans DJ, et al. Long-term outcome after successful catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3:237–42. https://doi.org/10.1161/CIRCEP.109.923771
5. O'Neill MD, Wright M, Knecht S, Jaïs P, Hocini M, Takahashi Y, et al. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. Eur Heart J. 2009;30:1105–12. https://doi.org/10.1093/eurheartj/ehp063
6. Rolf S, Kircher S, Arya A, Eitel C, Sommer P, Richter S, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014;7:825–33. https://doi.org/10.1161/CIRCEP.113.001251
7. Nilsson B, Chen X, Pehrson S, Køber L, Hilden J, Svendsen JH. Recurrence of pulmonary vein conduction and atrial fibrillation after pulmonary vein isolation for atrial fibrillation: a randomized trial of the ostial versus the extra-ostial ablation strategy. Am Heart J. 2006;152(537):e1–e8. https://doi.org/10.1016/j.ahj.2006.05.029
8. Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, et al. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. Circulation. 2005;111:127–35. https://doi.org/10.1161/01.CIR.0000151289.73085.36
9. Della Rocca DG, Tarantino N, Trivedi C, Mohanty S, Anannab A, Salwan AS, et al. Non-pulmonary vein triggers in nonparoxysmal atrial fibrillation: implications of pathophysiology for catheter ablation. J Cardiovasc Electrophysiol. 2020;31:2154–67. https://doi.org/10.1111/jce.14638
10. Briceño DF, Patel K, Romero J, Alviz I, Tarantino N, Della Rocca DG, et al. Beyond pulmonary vein isolation in nonparoxysmal atrial fibrillation: posterior wall, vein of Marshall, coronary sinus, superior vena cava, and left atrial appendage. Card Electrophysiol Clin. 2020;12:219–31. https://doi.org/10.1016/j.ccep.2020.01.002
11. Della Rocca DG, Mohanty S, Trivedi C, Di Biase L, Natale A. Percutaneous treatment of non-paroxysmal atrial fibrillation: a paradigm shift from pulmonary vein to non-pulmonary vein trigger ablation? Arrhythm Electrophysiol Rev. 2018;7:256–60. https://doi.org/10.15420/aer.2018.56.2
12. Della Rocca DG, Di Biase L, Mohanty S, Trivedi C, Gianni C, Romero J, et al. Targeting non-pulmonary vein triggers in persistent atrial fibrillation: results from a prospective, multicentre, observational registry. Europace. 2021;23:1939–49. https://doi.org/10.1093/europace/euab161
13. Kim D, Hwang T, Kim M, Yu HT, Kim TH, Uhm JS, et al. Extra-pulmonary vein triggers at *de novo* and the repeat atrial fibrillation catheter ablation. Front Cardiovasc Med. 2021;8:759967. https://doi.org/10.3389/fcvm.2021.759967
14. Mannion J, Hong K, Lennon SJ, Kenny A, Galvin J, O'Brien J, et al. Comparing left atrial low voltage areas in sinus rhythm and atrial fibrillation using novel automated voltage analysis: a pilot study. Cardiol Res. 2023;14:268–78. https://doi.org/10.14740/cr1503
15. Park JH, Pak H-N, Choi EJ, Jang JK, Kim SK, Choi DH, et al. The relationship between endocardial voltage and regional volume in electroanatomical remodeled left atria in patients with atrial fibrillation: comparison of three-dimensional computed tomographic images and voltage mapping. J Cardiovasc Electrophysiol. 2009;20:1349–56. https://doi.org/10.1111/j.1540-8167.2009.01557.x
16. Park JH, Joung B, Son N-H, Shim JM, Lee MH, Hwang C, et al. The electroanatomical remodelling of the left atrium is related to $CHADS_2$/CHA_2DS_2VASc score and events of stroke in patients with atrial fibrillation. Europace. 2011;13:1541–9. https://doi.org/10.1093/europace/eur135
17. Kim IS, Yang PS, Kim TH, Park J, Park JK, Uhm JS, et al. Clinical significance of additional ablation of atrial premature beats after catheter ablation for atrial fibrillation. Yonsei Med J. 2016;57:72–80. https://doi.org/10.3349/ymj/2016.57.1.72
18. Park JW, Yu HT, Kim TH, Uhm JS, Kim JY, Joung B, et al. Trends and outcome of catheter ablation of atrial fibrillation over 9 years-focus on empirical extra-pulmonary vein ablation. Circ J. 2019;83:304–12. https://doi.org/10.1253/circj.CJ-18-0928
19. Yu HT, Yang PS, Kim TH, Uhm JS, Kim JY, Joung B, et al. Poor rhythm outcome of catheter ablation for early-onset atrial fibrillation in women: mechanistic insight. Circ J. 2018;82:2259–68. https://doi.org/10.1253/cirj.CJ-17-1358
20. Park J, Kim TH, Lee JS, Park JK, Uhm JS, Joung B, et al. Prolonged PR interval predicts clinical recurrence of atrial fibrillation after catheter ablation. J Am Heart Assoc. 2014;3:e001277. https://doi.org/10.1161/JAHA.114.001277
21. Baek YS, Yang PS, Kim TH, Uhm JS, Kim JY, Joung B, et al. Delayed recurrence of atrial fibrillation 2 years after catheter ablation is associated with metabolic syndrome. Int J Cardiol. 2016;223:276–81. https://doi.org/10.1016/j.ijcard.2016.08.222
22. Park J, Joung B, Uhm JS, Shim CY, Hwang C, Lee MH, et al. High left atrial pressures are associated with advanced electroanatomical remodeling of left atrium and independent predictors for clinical recurrence of atrial fibrillation after catheter ablation. Heart Rhythm. 2014;11:953–60. https://doi.org/10.1016/j.hrthm.2014.03.009
23. Kim TH, Park J, Park JK, Uhm JS, Joung B, Lee MH, et al. Pericardial fat volume is associated with clinical recurrence after catheter ablation for persistent atrial fibrillation, but not paroxysmal

atrial fibrillation: an analysis of over 600-patients. Int J Cardiol. 2014;176:841–6. https://doi.org/10.1016/j.ijcard.2014.08.008
24. Kawai S, Mukai Y, Inoue S, Yakabe D, Nagaoka K, Sakamoto K, et al. Non-pulmonary vein triggers of atrial fibrillation are likely to arise from low-voltage areas in the left atrium. Sci Rep. 2019;9:12271. https://doi.org/10.1038/s41598-019-48669-1
25. Miragoli M, Gaudesius G, Rohr S. Electronic modulation of cardiac impulse conduction by myofibroblasts. Circ Res. 2006;98:801–10. https://doi.org/10.1161/01.RES.0000214537.44195.a3
26. Yue L, Xie J, Nattel S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. Cardiovasc Res. 2011;89:744–53. https://doi.org/10.1093/cvr/cvq329
27. Miragoli M, Salvarani N, Rohr S. Myofibroblasts induce ectopic activity in cardiac tissue. Circ Res. 2007;101:755–8. https://doi.org/10.1161/CIRCRESAHA.107.160549
28. Verma A, Wazni OM, Marrouche NF, Matin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45:285–92. https://doi.org/10.1016/j.jacc.2004.10.035
29. Marrouche NF, Wazni O, McGann C, Greene T, Dean JM, Dagher L, et al. Effect of MRI-guided fibrosis ablation vs conventional catheter ablation on atrial arrhythmia recurrence in patients with persistent atrial fibrillation: the DECAAF II randomized clinical trial. JAMA. 2022;327:2296–305. https://doi.org/10.1001/jama.2022.8831

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