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CLINICAL RESEARCH

Late recurrence of atrial fibrillation 5 years after catheter ablation: predictors and outcome

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Aims Atrial fibrillation (AF) is a chronic progressive disease that continuously recurs even after successful AF catheter ablation (AFCA). We explored the mechanism of long-term recurrence by comparing patient characteristics and redo-ablation findings.

Methods and results Among the 4248 patients who underwent a *de novo* AFCA and protocol-based rhythm follow-up at a single centre, we enrolled 1417 patients [71.7% male, aged 60.0 (52.0–67.0) years, 57.9% paroxysmal AF] who experienced clinical recurrences (CRs), and divided them according to the period of recurrence: within one year ($n = 645$), 1–2 years ($n = 339$), 2–5 years ($n = 308$), and after 5 years ($CR_{>5\ yr}$, $n = 125$). We also compared the redo-mapping and ablation outcomes of 198 patients. In patients with $CR_{>5\ yr}$, the proportion of paroxysmal AF was higher ($P = 0.031$); however, the left atrial (LA) volume (quantified by computed tomography, $P = 0.003$), LA voltage ($P = 0.003$), frequency of early recurrence ($P < 0.001$), and use of post-procedure anti-arrhythmic drugs ($P < 0.001$) were lower. A $CR_{>5\ yr}$ was independently associated with a low LA volume [odds ratio (OR) 0.99 (0.98–1.00), $P = 0.035$], low LA voltage [OR 0.61 (0.38–0.94), $P = 0.032$], and lower early recurrence [OR 0.40 (0.23–0.67), $P < 0.001$]. Extra-pulmonary vein triggers during repeat procedures were significantly greater in patients with a $CR_{>5\ yr}$, despite no difference in the de novo protocol (P for trend 0.003). The rhythm outcomes of repeat ablation procedures did not differ according to the timing of the CR (log-rank $P = 0.330$).

Conclusions Patients with a later CR exhibited a smaller LA volume, lower LA voltage, and higher extra-pulmonary vein triggers during the repeat procedure, suggesting AF progression.

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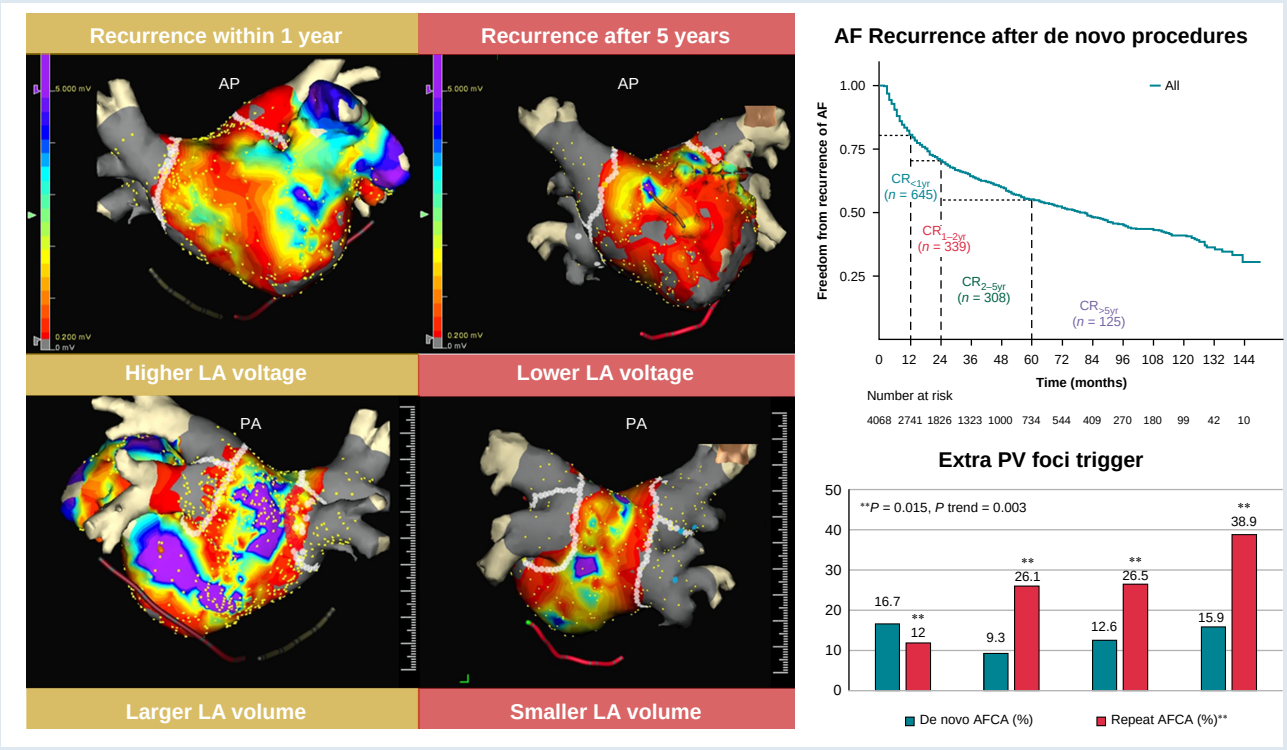
Graphical Abstract



Keywords Late recurrence • Catheter ablation • Left atrial volume • Left atrial voltage • Extra-pulmonary vein trigger

What's new?

- The first atrial fibrillation recurrence 5 years after ablation was independently associated with low left atrial volume, low left atrial voltage, and a lower early recurrence rate than the clinical recurrence within 5 years of ablation.
- Extra-pulmonary vein triggers were significantly more frequent during repeat procedures in patients with very late AF recurrences, suggesting progression of atrial fibrillation.
- Low left atrial voltage and small left atrial volume represent atrial myopathy associated with left atrial remodelling caused by atrial fibrillation progression.

Introduction

Atrial fibrillation (AF) is a chronic progressive disease that is highly prevalent in Korea, occurring in ~1.7% of the Korean population and 0.4–2% of the global population.[1,2] The benefit of early rhythm control in reducing mortality among patients with AF has recently been highlighted; however, AF management that maintains sinus rhythm over long durations has limited efficacy and safety.[3] Compared to antiarrhythmic drugs (AAD), AF catheter ablation (AFCA) has superior efficacy for rhythm control but still has significant AF recurrence rate.[4] The recurrence of AF after AFCA can be attributed to technical failures, such as pulmonary vein (PV) reconnections; however, it may also be influenced by atrial substrate changes, such as atrial myopathy.[5] Moreover, atrial myopathy may be caused by sustained AF or diastolic dysfunction; and may perpetuate AF or increase the risk of stroke.[6]

Long-term follow-up data for AF recurrence after AFCA revealed that some patients remain in sinus rhythm; however, AF often recurs in the long-term.[7] Nevertheless, it is unclear whether the first recurrence 5 years after AFCA is indeed a recurrence or a new AF generation related to AF progression.

Therefore, we hypothesized that the characteristics of the first recurrence of AF 5 years after AFCA would differ from AF that recurred earlier. The clinical, electrophysiological, and imaging characteristics of patients who underwent *de novo* AFCA were compared and evaluated by dividing the recurrence period into <1, 1–2, 2–5, and >5 years. This study aimed to explore the mechanism of very late recurrences by comparing patient characteristics and redo-ablation results based on the recurrence period post-AFCA.

Methods

Study population

From March 2009 to June 2021, 4940 patients required AFCA treatment. Among these, 1417 patients who experienced clinical recurrences (CRs) after the first treatment were enrolled in the study (*Figure 1*). The study population was stratified according to the timing of the recurrence. The exclusion criteria were as follows: (i) AF refractory to electrical cardioversion; (ii) AF with rheumatic valvular disease; and (iii) previous AF ablation or cardiac surgery. The study protocol was implemented in compliance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System.

Consent

All participants provided written informed consent for inclusion in the Yonsei AF ablation cohort study.

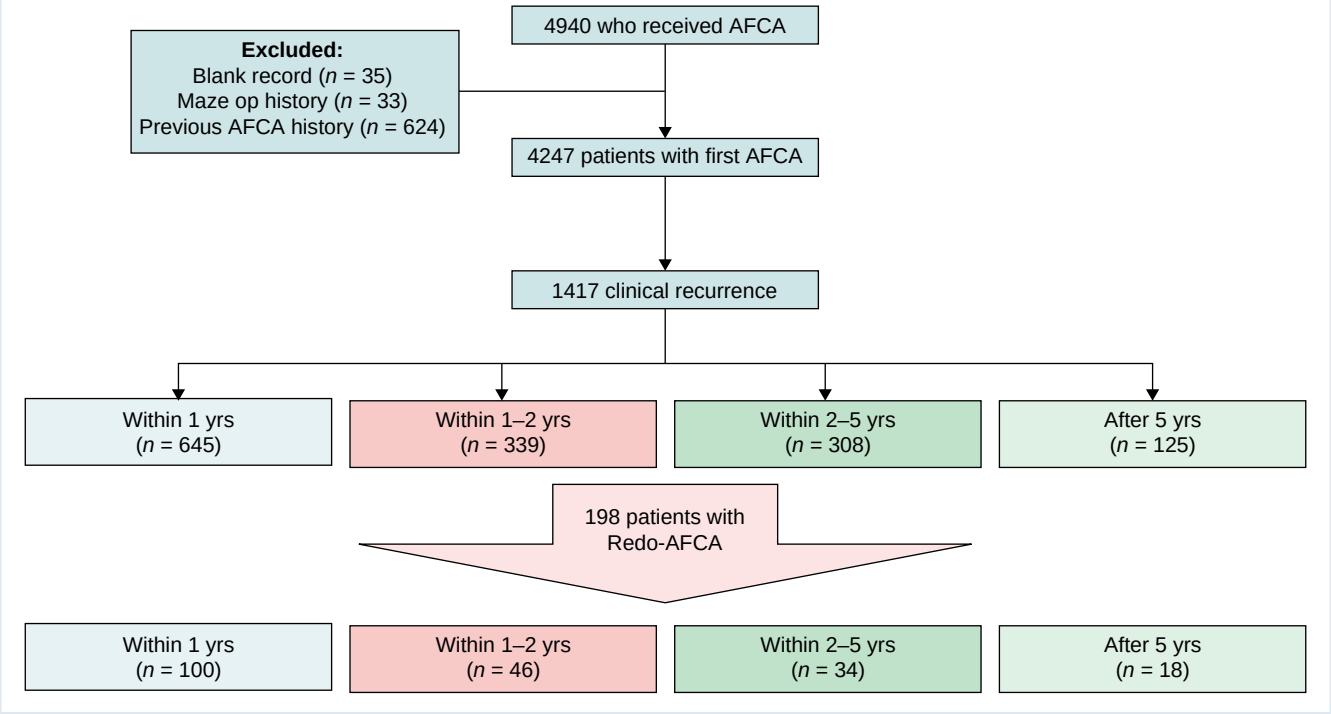


Figure 1 Flow chart of the study. AFCA, atrial fibrillation catheter ablation.

Echocardiography follow-up and cardiac computed tomography evaluation

Transthoracic echocardiography was performed twice: <3 months before the procedure and at the 1-year follow-up. Following the American Society of Echocardiography guidelines, we measured the left atrial (LA) dimensions, left ventricular ejection fraction (LVEF), peak trans-mitral flow velocity (E), and peak septal mitral annular velocity (Em) via tissue Doppler echocardiography.

Computed tomography (CT) was conducted within one month prior to AFCA. Three-dimensional (3D) spiral CT scans (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, Netherlands) were performed on all patients and analysed using an image processing workstation (Aquarius; Tera Recon, Inc., Foster City, CA, USA). Left atrial and pericardial fat volumes were measured as previously described (AMBER, Laonmed Inc., Seoul, Republic of Korea).[8]

Electrophysiological studies and catheter ablation

We used the Prucka CardioLab™ Electrophysiology System (General Electric Medical Systems, Inc., Milwaukee, WI, USA) to record the electrocardiograms and constructed 3D electro-anatomical maps (NavX, Abbott, Inc., Chicago, IL, USA; CARTO system, Biosense Webster, Diamond Bar, CA, USA) using the location information from a circumferential PV-mapping catheter (AFocus, Abbott, Inc., Chicago, IL, USA; Lasso, Biosense-Webster Inc., Diamond Bar, CA, USA) passed through a long sheath. The 3D geometries of the LA and PVs were created using a 3D mapping system and merged with the 3D spiral CT images. We obtained multi-view pulmonary venograms for perfect matching of the 3D-map, CT scans, and fluoroscopy images in all patients, except those with significant renal disease. After transseptal puncture, systemic anticoagulation was initiated with an intravenous bolus of heparin (200 IU/kg), followed by intermittent boluses to maintain an activated clotting time of 350–400 s. We obtained the peak-to-peak amplitude of contact bipolar electrograms from 500 to 1000 points on the LA endocardium during high right atrial pacing at 500 ms, and the mean LA electrogram voltage was calculated. Representative images of the bipolar voltage map and the usual ablation lesion set are shown in Supplementary material online, *Figure S1*.

We used an open-irrigation catheter (Celsius, Johnson & Johnson Inc., Diamond Bar, CA, USA; NaviStar ThermoCool, Biosense Webster Inc., Diamond Bar, CA, USA; ThermoCool SF, Biosense Webster Inc.; ThermoCool SmartTouch, 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.) for the AFCA procedure. All patients initially underwent a circumferential PV isolation (CPVI). At the operator's discretion, patients with persistent AF underwent linear or electrogram-guided ablation. After completing the protocol-based ablation, an isoproterenol challenge test was performed to confirm the AF trigger. Isoproterenol (5–20 μg/min depending on the use of beta-blockers with a target heart rate of 120 bpm) was injected for at least 3 min and maintained for another 3 min after AF or atrial tachycardia (AT) induction. If arrhythmia was not induced by itself, AF or AT was induced via high-current burst pacing (10 mA, pulse width 5 ms, Bloom Associate, Denver, CO, USA) for 10 s in the high right atrium (RA) electrodes. This started with a pacing cycle length of 250 ms, which was gradually decreased to 120 ms. If AF or AT was induced, internal cardioversion was performed by using biphasic shock (2–20 J) with R-wave synchronization. The AF trigger immediately following the cardioversion was identified. We ablated the AF triggers and atrial premature beats as much as possible using quick 3D activation mapping. Circumferential PV isolation was performed on all patients during the redo-ablation procedure. In the presence of reconnections of the PV potentials, CPVI ablation was completed, and a bidirectional block was identified. After reinforcing the *de novo* ablation sites, we provoked and ablated extra PV foci with the same protocol as that of *de novo* procedures.

Post-ablation management and follow-up

All patients visited a scheduled outpatient clinic at 1, 3, 6, and 12 months after AFCA and every 6 months thereafter or when symptoms recurred. Each patient underwent electrocardiography (ECG) at each visit. Following the modified 2012 HRS/EHRA/ECAS expert consensus statement guidelines, 24-hour Holter monitoring was conducted at 3 and 6

months, then semi-annually for 2 years, annually for 2 to 5 years, and biennially after 5 years. Whenever patients reported palpitations, Holter or event monitor recordings were obtained to check for arrhythmic recurrence. We defined AF recurrence as any episode of AF or AT that lasted for at least 30 s regardless of the use of AAD. Clinical recurrence was defined as any electrocardiographic documentation of AF recurrence 3 months after the blanking period.

Statistical analysis

Descriptive statistics were reported as mean ± standard deviation or median [interquartile range (IQR)] for continuous variables and frequency and percentage for categorical variables. Categorical variables were compared using the χ^2 test, and continuous variables were compared using either the Wilcoxon rank-sum test or Student's *t*-test, as appropriate. Logistic regression analysis was used to identify the risk factors of CRs and to estimate odds ratios (ORs), 95% confidence intervals, and *P*-values. The variables selected for multivariate analysis were those with *P*-values of <0.2 through, as determined by univariate analysis. Kaplan–Meier analysis with a log-rank test was used to analyse the probability of freedom from AF recurrence after AFCA. Two-sided *P*-values of <0.05 was considered statistically significant. Statistical analyses were conducted using the R software, version 4.1.3 (www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics depending on recurrence timing

Of the 4247 consecutive patients who underwent *de novo* AFCA, we evaluated 1417 patients [aged 60.0 (52.0–67.0) years, 71.7% male, 57.9% paroxysmal AF] who had recurrent AF 3 months after the initial procedure: CR within a year ($CR_{<1\ yr}$) occurred in 645 patients, ~1–2 years ($CR_{1–2\ yr}$) in 339 patients, ~2–5 years ($CR_{2–5\ yr}$) in 308 patients, and after 5 years ($CR_{>5\ yr}$) in 125 patients (*Figure 2A*). *Table 1* presents the baseline characteristics for each group.

For patients with later CRs, the proportion of paroxysmal AF was higher (P = 0.031), and the LA volume (measured by CT, P = 0.003), LA epicardial fat (EAT) volume (CT, P = 0.023), LA voltage (P = 0.003), frequency of early recurrences (P < 0.001), and use of post-procedure AAD (P < 0.001) were significantly lower. Multivariate logistic regression analysis revealed that a $CR_{>5\ yr}$ was independently associated with a smaller LA volume [OR 0.99 (0.98–1.00), P = 0.035], lower LA voltage [OR 0.61 (0.38–0.94), P = 0.032], and lower early recurrence [OR 0.40 (0.23–0.67), P < 0.001; *Table 2*].

Left atrial volume and voltage changes after atrial fibrillation catheter ablation depending on recurrence timing

Figure 3A–D and Supplementary material online, *Table S1* summarize the echocardiographic parameters before and 1 year after AFCA, along with their differences. The LA volume index (LAVI), measured using echocardiography, was significantly lower in the later CR group before (P for trend = 0.006) and 1 year after the procedure (P for trend < 0.001, *Figure 3A*). Among the 1023 patients who underwent both pre- and 1-year post-AFCA echocardiograms, there were significant trends for LA size reduction (P for trend = 0.012; *Figure 3B*). Left ventricular ejection fraction and E/Em ratio did not show significant changes after 1 year (*Figure 3C and D*).

We analysed the LA voltage maps of 888 patients who underwent a de novo AFCA and 134 patients who underwent repeat procedures (see Supplementary material online, *Table S2*). No statistically significant differences were observed between patient who underwent de novo and repeat procedure (P for trend = 0.923). However, LA voltage at the repeat procedure tended to decrease more as the recurrence period was delayed at $CR_{\leq 5\ yr}$, whereas LA voltage tended to increase in the $CR_{>5\ yr}$ group (*Figure 4A*).

Redo-mapping and the role of extra-pulmonary vein triggers

We performed repeat ablation procedures in 198 patients: 100 $CR_{<1\ yr}$, 46 $CR_{1–2\ yr}$, 34 $CR_{2–5\ yr}$, and 18 $CR_{>5\ yr}$ (*Table 3*). Atrial fibrillation duration differed significantly among the four groups (*P* = 0.001). Although PV reconnection rate remained unaltered, the proportion of extra-PV triggers was significantly higher in patients with later CR (*P* = 0.015; *P* for trend 0.003; *Figure 4B*). The numbers and locations of the extra-PV triggers are summarized in *Table 4*. When comparing the $CR_{\leq 5\ yr}$ and $CR_{>5\ yr}$ groups, the frequency of extra-PV triggers did not differ during *de novo* procedures but was

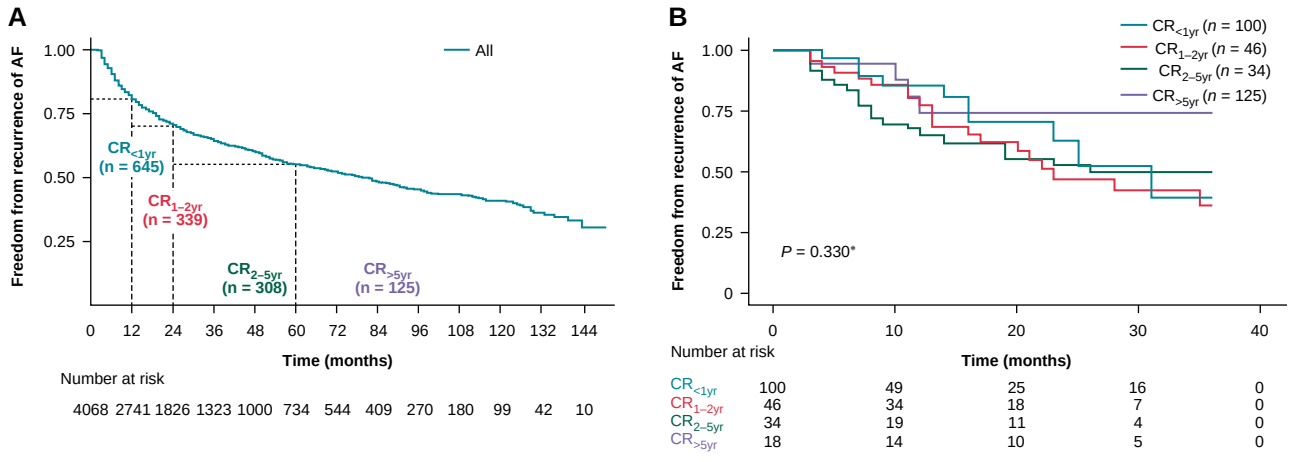


Figure 2 Kaplan–Meier curves of the AF recurrence-free survival (*A*) in *de novo* AFCA and (*B*) in repeat AFCA. *P = 0.12 in $CR_{>5\ yr}$ vs. $CR_{<1\ yr}$, P = 0.11 in $CR_{>5\ yr}$ vs. $CR_{1–2\ yr}$, P = 0.32 in $CR_{>5\ yr}$ vs. $CR_{2–5\ yr}$, P = 0.37 in $CR_{2–5\ yr}$ vs. $CR_{<1\ yr}$, P = 0.47 in $CR_{2–5\ yr}$ vs. $CR_{1–2\ yr}$, and P = 0.97 in $CR_{1–2\ yr}$ vs. $CR_{<1\ yr}$. AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; CR, clinical recurrence; LA, left atrial or left atrium.

Table 1 Clinical and procedural characteristics in the very late recurrence and control groups

	Recurrence within 1 year ($n = 645$)	Recurrence within 1–2 years ($n = 339$)	Recurrence within 2–5 years ($n = 308$)	Recurrence after 5 years ($n = 125$)	*P* value
Age, years	59.0 ± 10.5	58.8 ± 10.4	60.2 ± 10.7	58.0 ± 10.2	0.705
Female, *n* (%)	161 (25.0)	93 (27.4)	106 (34.4)	41 (32.8)	0.014
Paroxysmal AF, *n* (%)	360 (56.1)	185 (54.6)	188 (61.0)	85 (68.0)	0.031
AF duration, months	37.9 ± 40.0	43.0 ± 45.8	41.8 ± 49.7	47.7 ± 63.2	0.272
Body mass index, kg/m^2	25.1 ± 3.4	25.1 ± 3.0	25.2 ± 3.0	24.9 ± 2.8	0.755
CHA_2DS_2VASc	1.7 ± 1.3	1.6 ± 1.5	1.9 ± 1.5	1.7 ± 1.6	0.273
Comorbidity, *n* (%)					
Hypertension	319 (49.5)	148 (43.7)	164 (53.2)	61 (48.8)	0.105
Diabetes	100 (15.5)	49 (14.5)	49 (15.9)	20 (16.0)	0.954
Stroke/TIA	81 (12.6)	37 (10.9)	42 (13.6)	13 (10.4)	0.666
Heart failure	96 (14.9)	43 (12.7)	39 (12.7)	11 (8.8)	0.283
Vascular disease	59 (9.1)	36 (10.6)	39 (12.7)	16 (12.8)	0.326
LA volume (CT)	164.6 ± 50.6	161.7 ± 50.4	160.9 ± 45.8	146.4 ± 41.0	0.003
Pericardial fat volume, cm^3 ($n = 1124$)	115.3 ± 54.1	110.2 ± 50.2	120.3 ± 55.3	111.8 ± 57.3	0.144
EAT volume (CT) ($n = 1384$)	115.7 ± 45.4	109.1 ± 45.2	110.8 ± 45.4	108.3 ± 51.4	0.096
Atrial EAT volume	46.8 ± 20.1	44.2 ± 20.1	43.7 ± 20.0	41.9 ± 22.0	0.023
Ventricular EAT volume	68.7 ± 28.0	65.1 ± 27.2	67.1 ± 27.9	66.4 ± 31.8	0.293
LA wall thickness ($n = 1336$)	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3	0.707
Mean LA pressure ($n = 1113$)	12.7 ± 6.5	12.8 ± 6.0	13.1 ± 6.6	12.6 ± 7.5	0.653
LA wall stress ($n = 1059$)	177.1 ± 108.3	172.8 ± 87.5	177.6 ± 101.0	170.2 ± 111.7	0.728
Mean LA voltage, mV ($n = 888$)	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 0.6	1.1 ± 0.5	0.003
Ablation time, min	65.7 ± 33.5	75.6 ± 32.5	80.4 ± 29.5	85.6 ± 26.2	<0.001
Procedure time, min	156.5 ± 64.5	175.7 ± 62.8	183.4 ± 59.1	195.2 ± 48.9	<0.001
Ablation lesion, *n* (%)					
CPVI	645 (100.0)	339 (100.0)	308 (100.0)	125 (100.0)	
Empirical extra-PV LA ablation	213 (33.1)	143 (42.2)	124 (40.3)	56 (45.2)	0.006
Extra-PV foci trigger ($n = 813$)	57 (16.7)	39 (19.3)	23 (12.6)	14 (15.9)	0.366
Early recurrence	357 (55.3%)	182 (53.7%)	131 (42.5%)	39 (31.2%)	<0.001
As AT	77 (21.6%)	41 (22.5%)	46 (35.1%)	19 (48.7%)	<0.001
Complication, *n* (%)	18 (2.8)	14 (4.1)	19 (6.2)	4 (3.2)	0.095
Major complication, *n* (%)	10 (1.6)	9 (2.7)	8 (2.6)	1 (0.8)	0.442
AAD at discharge, *n* (%)	285 (44.2)	127 (37.5)	110 (35.7)	26 (20.8)	<0.001
AAD at during 3 months, *n* (%)	369 (65.3)	202 (60.3)	183 (59.4)	57 (45.6)	0.001
AAD after 3 months, *n* (%)	385 (60.3)	196 (57.8)	168 (54.5)	50 (40.0)	<0.001
Clinical recurrence as AT	158 (24.5%)	79 (23.3%)	69 (22.4%)	23 (18.4%)	0.506
Clinical recurrence, months	6.1 ± 2.5	16.4 ± 3.4	37.9 ± 10.6	85.4 ± 19.9	<0.001

Values are presented as the median ± standard deviation or number (%).
AAD, anti-arrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CPVI, circumferential pulmonary vein isolation; CT, computed tomography; EAT, epicardial fat tissue; E/Em, mitral inflow velocity/mitral annulus tissue velocity; LA, left atrium; LV, left ventricle; PV, pulmonary vein; TIA, transient ischaemic attacks.

significantly higher in the $CR_{>5\ yr}$ group during the repeat procedures (18.3% vs. 38.9%; $P = 0.015$). Although the proportion of superior vena cava (SVC) trigger was tended to be higher in the $CR_{>5\ yr}$ group than in the $CR_{\leq 5\ yr}$ group ($P = 0.051$), the overall location and number of extra-PV triggers did not differ between the two groups. During repeat procedures, 34.0% (16/47) of the extra-PV trigger sites matched the empirical extra-PV LA ablation sites at the *de novo* procedure (32.4% in $CR_{\leq 5\ yr}$ vs. 40.0% in $CR_{>5\ yr}$; $P = 0.654$, see Supplementary material online, *Table S3*). At the median [13.0 (6.00–28.0) months] follow-up after the second procedure, the long-term rhythm outcomes did not differ according to CR timing (log-rank $P = 0.330$; *Figure 2B*).

Table 2 Logistic regression analysis for the predictors of a later clinical recurrence 5 years after AFCA

	Univariate		Multivariate	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age, years	0.99 (0.97–1.01)	0.196	1.00 (0.98–1.02)	0.908
Female, *n* (%)	1.28 (0.86–1.90)	0.216	0.73 (0.44–1.25)	0.246
Paroxysmal AF, *n* (%)	1.65 (1.11–2.45)	0.013	1.27 (0.73–2.26)	0.404
Body mass index, kg/m^2	0.98 (0.92–1.04)	0.474	–	–
CHA_2DS_2VASc	0.95 (0.83–1.09)	0.463	–	–
Hypertension	0.97 (0.67–1.41)	0.891	–	–
Diabetes	1.00 (0.60–1.66)	0.985	–	–
Stroke/TIA	0.75 (0.41–1.40)	0.372	–	–
Heart failure	0.61 (0.32–1.15)	0.125	–	–
Vascular disease	1.27 (0.73–2.22)	0.391	–	–
Early recurrence	0.41 (0.27–0.61)	<0.001	0.40 (0.23–0.67)	<0.001
Clinical recurrence as AF	1.36 (0.85–2.18)	0.196	–	–
LA dimension (Echo)	0.99 (0.96–1.02)	0.349	–	–
LV ejection fraction, %	1.03 (1.00–1.05)	0.027	1.00 (0.98–1.03)	0.815
E/Em	1.01 (0.98–1.05)	0.529	–	–
LA volume (CT)	0.99 (0.98–1.00)	0.001	0.99 (0.98–1.00)	0.035
Pericardial fat volume, cm^3 ($n = 1118$)	1.00 (1.00–1.00)	0.582	–	–
LA wall thickness ($n = 1336$)	0.87 (0.49–1.53)	0.621	–	–
LA wall stress ($n = 1059$)	1.00 (1.00–1.00)	0.610	–	–
Mean LA pressure ($n = 1113$)	1.00 (0.96–1.03)	0.773	–	–
Mean LA voltage, mV ($n = 888$)	0.75 (0.51–1.11)	0.156	0.61 (0.38–0.94)	0.032
Extra-PV foci trigger ($n = 814$)	0.96 (0.52–1.75)	0.882	–	–

AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; CI, confidence interval; CT, computed tomography; LA, left atrium; LV, left ventricle; OR, odds ratio; PV, pulmonary vein; TIA, transient ischaemic attack.

Discussion

Main findings

This single-centre, retrospective cohort study analysed the clinical and electrophysiological characteristics of patients with very late CRs, which occurred 5-year post-treatment. Among the 1417 patients with AF recurrence after AFCA, $CR_{>5\ yr}$ was independently associated with low LA volume, low LA voltage, and low early recurrence rate within 3 months after AFCA. We also found significantly greater extra-PV triggers during repeat procedures in patients with late CR, despite no differences in de novo procedures. However, the rhythm outcomes of the repeat ablation procedures did not differ according to CR timing. These findings indicate that AF progression contributed to a very late $CR_{>5\ yr}$ after AFCA.

Mechanisms of atrial fibrillation recurrence after ablation

Atrial fibrillation catheter ablation has been proved to be the most effective rhythm control method; however, post-procedural long-term results have shown continuous recurrence of atrial tachyarrhythmias.[4] The major mechanisms contributing to AF recurrence after AFCA include technical failure (PV reconnection), extra-PV triggers, autonomic neural activity, and AF progression. Although CPVI is essential in AFCA, PV reconnection remains the major mechanism of recurrence. Park *et al.*[7] reported that, while the number of reconnected PVs was small, extra-PV triggers were more common in long-term recurrences over 3 years. Although the number of reconnected PVs in this study was similar, this difference may have been caused by various factors related to long-term recurrence over 5 years. Erhard *et al.*[9] reported that the PV reconnection rate in patients with recurrence over 5 years was 56%. In this study, PV reconnection was observed more frequently in the $CR_{>5\ yr}$ group than the $CR_{2–5\ yr}$ group, although this difference was not statistically significance. This may be due to the relatively few patients who have undergone repetitive procedures due to recurrence after 5 years. Additionally, further studies have shown that PV reconnection is not necessarily associated with AF recurrence. In a meta-analysis, 58.6% of patients without AF recurrence showed one or more PV reconnections in repeated electrophysiological studies compared to 85.5% of patients with AF recurrence.[10] Therefore, PV reconnection that occurs 5 years after AFCA does not necessarily lead to a CR and might have a different mechanism or meaning compared to the PV reconnection that occurs earlier.

Moreover, the PV reconnection rate was 15% in the second-look mapping study and 62–95% in the redo-mapping study after AF recurrence.[7,11,12] The number of reconnected PVs was greater for earlier AF recurrence timing, but the paradoxically lower recurrence rate after the second ablation procedure alludes to a contribution of extra-PV triggers.[7,11] Kim *et al.*[13] reported that the presence of an extra-PV trigger was observed in 11.7% of *de novo* AFCA cases and 28.6% of redo-procedures, and that 30% of extra-PV triggers were associated with

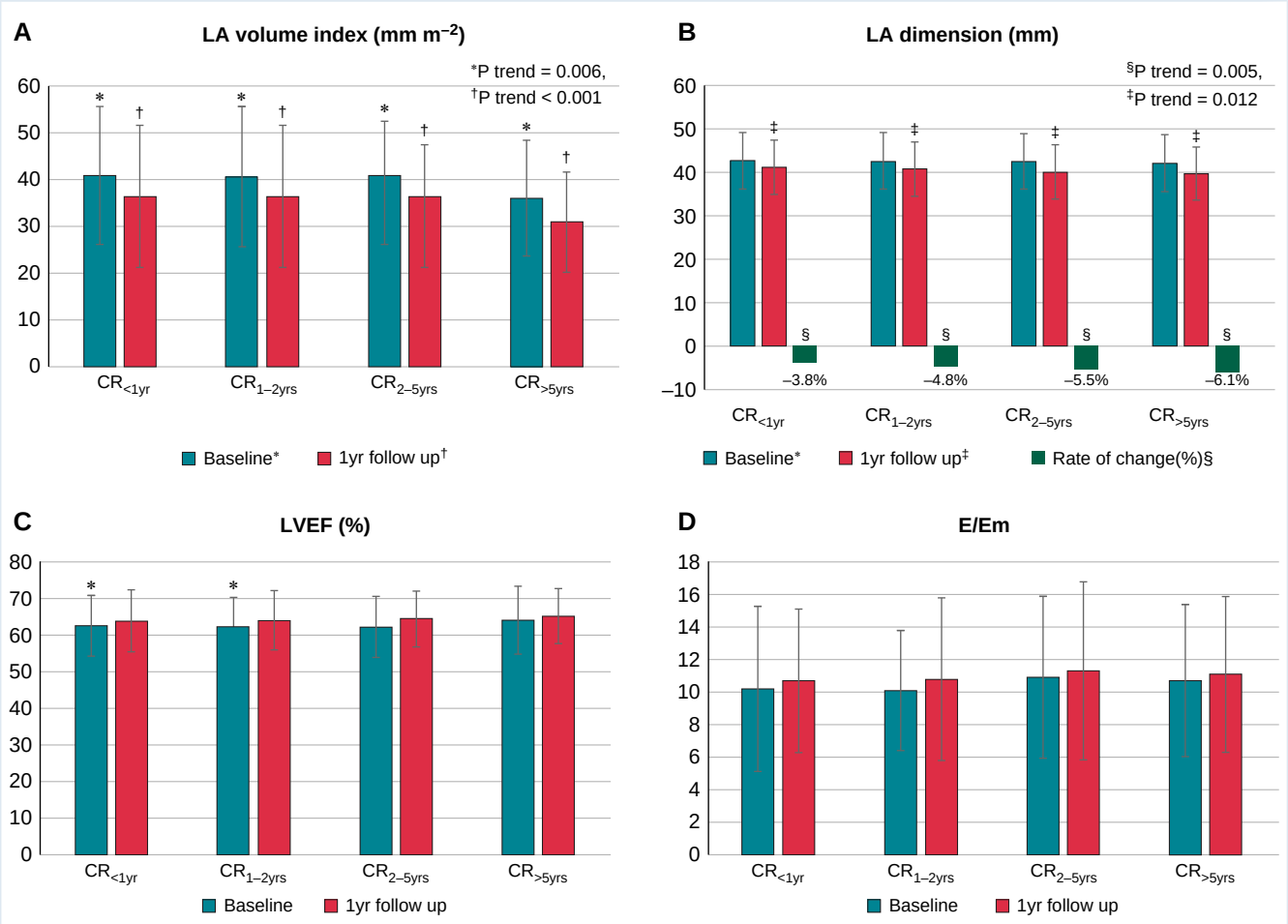


Figure 3 Change in echocardiography parameters of baseline and 1-year follow-up. (*A*) LA dimension, (*B*) LA volume index, (*C*) LVEF, (*D*) E/Em. Overall, there were significant trends for a lower LAVI and greater LA size reduction in patients with later CR. AFCA, atrial fibrillation catheter ablation; CR, clinical recurrence; LA, left atrial or left atrium; LVEF, left ventricular ejection fraction.

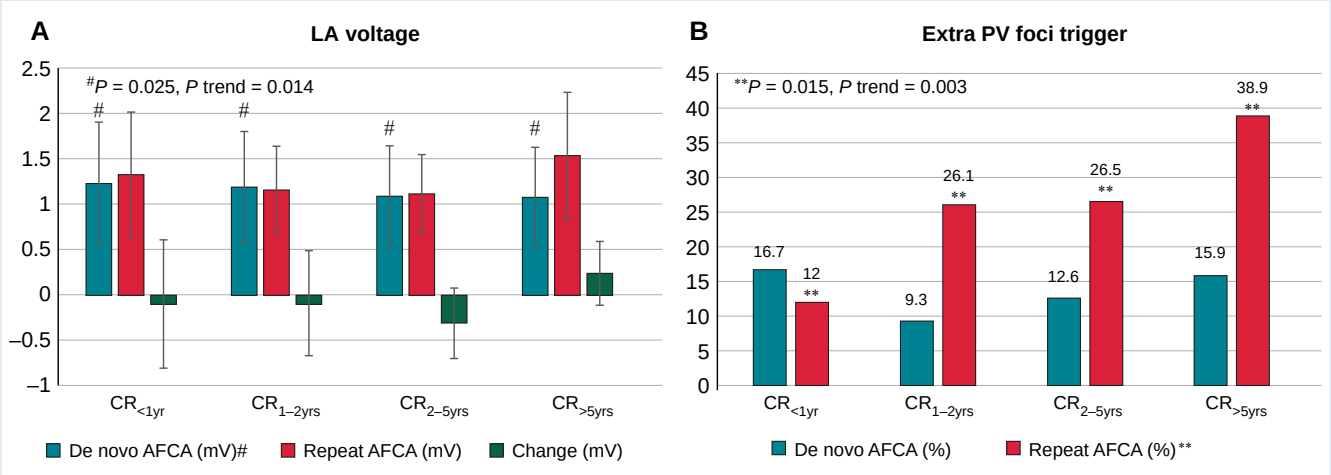


Figure 4 Comparison of the LA voltage (*A*) and extra PV foci trigger (*B*) in *de novo* and redo-procedure. AFCA, atrial fibrillation catheter ablation; CR, clinical recurrence; LA, left atrial or left atrium; PV, pulmonary vein.

Table 3 Characteristics of the patients who underwent a repeat ablation procedure according to the recurrence period ($n = 198$)

	Recurrence within 1 year ($n = 100$)	Recurrence within 1–2 years ($n = 46$)	Recurrence within 2–5 years ($n = 34$)	Recurrence after 5 years ($n = 18$)	*P* value
Age, years	59.34 ± 9.95	62.30 ± 9.16	62.06 ± 10.75	64.39 ± 8.93	0.106
Female, *n* (%)	21 (21.00)	14 (30.43)	8 (23.53)	4 (22.22)	0.671
Paroxysmal AF, *n* (%)	54 (54.00)	24 (52.17)	20 (58.82)	13 (72.22)	0.481
AF duration, months	68.24 ± 43.88	73.33 ± 47.26	94.29 ± 46.10	116.47 ± 60.55	0.001
Body mass index, kg/m^2	24.91 ± 3.12	25.29 ± 2.88	25.11 ± 2.96	24.13 ± 3.39	0.583
CHA_2DS_2VASc	1.72 ± 1.36	2.17 ± 1.68	2.24 ± 1.72	1.78 ± 1.44	0.200
Comorbidity, *n* (%)					
Hypertension	38 (38.00)	28 (60.87)	17 (50.00)	8 (44.44)	0.075
Diabetes	16 (16.00)	7 (15.22)	8 (23.53)	2 (11.11)	0.686
Stroke/TIA	16 (16.00)	7 (15.22)	8 (23.53)	1 (5.56)	0.432
Heart failure	21 (21.00)	9 (19.57)	7 (20.59)	5 (27.78)	0.887
Vascular disease	3 (3.00)	2 (4.35)	1 (2.94)	0 (0.0)	0.921
LA dimension (Echo), mm	41.82 ± 6.48	42.85 ± 7.03	40.97 ± 4.86	40.17 ± 5.82	0.316
LV ejection fraction, %	62.76 ± 8.16	61.72 ± 7.84	64.24 ± 6.43	59.11 ± 12.11	0.171
E/Em	10.10 ± 4.30	10.64 ± 4.90	10.98 ± 3.29	12.24 ± 3.79	0.275
Pericardial fat volume, cm^3	121.28 ± 66.64	104.90 ± 51.15	106.12 ± 58.62	90.77 ± 43.54	0.474
LA wall thickness, mm	1.97 ± 0.37	2.03 ± 0.30	1.91 ± 0.31	2.04 ± 0.29	0.604
Mean LA pressure, mmHg ($n = 115$)	13.49 ± 6.70	13.24 ± 5.45	14.82 ± 7.38	11.94 ± 6.51	0.552
LA wall stress ($n = 110$)	190.49 ± 85.40	237.55 ± 111.41	205.25 ± 99.91	159.31 ± 74.50	0.095
Mean LA voltage, mV ($n = 134$)	1.33 ± 0.69	1.29 ± 0.66	1.12 ± 0.43	1.54 ± 0.70	0.990
ΔLA voltage (vs. *de novo*) ($n = 96$)	−0.10 ± 0.71	−0.09 ± 0.58	−0.31 ± 0.39	0.24 ± 0.35	0.200
Presence of a PV reconnection	89 (89.0)	36 (78.3)	26 (76.5)	15 (83.3)	0.187
Number of PV reconnections	2.2 (1–3)	1.7 (1–3)	1.8 (1–2)	1.7 (1–2.75)	0.101
Extra-PV foci triggers	12 (12.00)	12 (26.09)	9 (26.47)	7 (38.89)	0.015
Ablation time, min	28.13 ± 16.21	25.18 ± 16.03	24.22 ± 17.95	20.94 ± 8.11	0.251
Procedure time, min	120.91 ± 42.39	133.39 ± 114.03	116.65 ± 44.14	98.00 ± 29.23	0.268
Complication, *n* (%)	4 (4.00)	0 (0.0)	2 (5.88)	2 (11.11)[a]	0.207
Major complication, *n* (%)	2 (2.00)	0 (0.0)	1 (2.94)	0 (0.0)	0.658
AAD at discharge, *n* (%)	37 (37.00)	17 (36.96)	7 (20.59)	6 (33.33)	0.346
AAD after 3 months, *n* (%)	39 (39.00)	20 (43.48)	13 (38.24)	7 (38.89)	0.955
Early recurrence	34 (34.00)	12 (26.09)	10 (29.41)	3 (16.67)	0.452
Clinical recurrence, Months	9.49 ± 7.79	15.52 ± 10.23	15.20 ± 8.87	16.40 ± 16.92	0.064
Clinical recurrence as AT	7 (18.92)	6 (28.57)	4 (40.00)	2 (40.00)	0.403

Values are presented as the median ± standard deviation or number (%).
AAD, anti-arrhythmic drugs; AF, atrial fibrillation; CT, computed tomography; LA, left atrium; LV, left ventricle; OR, odds ratio; PV, pulmonary vein; TIA, transient ischaemic attack.
[a]There was one case of transient sinus node dysfunction and arteriovenous fistula in the $CR_{\leq 5\ yr}$ group.

previous ablation sites. Consistent with the current study, the presence of an extra-PV trigger was a significant predictor of poorer rhythm outcomes after *de novo* or redo ablations.[7,14] Furthermore, post-AFCA parasympathetic nerve activity is another key factor significantly associated with AF recurrence, which is influenced by both the ablation lesion set and sex of the patient.[14,15]

Atrial myopathy and extra-pulmonary vein triggers

Atrial fibrillation is a chronic and progressive disease, characterized by atrial remodelling.[16] The extent of atrial electro-anatomical remodelling is indicated by atrial size or volume, reduced atrial endocardial voltage, and late gadolinium enhancement on cardiac magnetic resonance imaging.[17] Long-term AF may cause atrial fibrosis, which in turn contributes to atrial myopathy and the long-term persistence of AF.[18] Atrial myopathy affects AFCA outcomes and long-term AF recurrence rates.[17,19] A meta-analysis of observational studies showed weak evidence that LA volume predicted AF recurrence; however, in a 10-year follow-up study after AFCA, a larger LA diameter was the only predictor of AF recurrence, reflecting the underlying atrial remodelling process.[20,21] A low mean LA voltage was independently associated with stiff LA physiology, which had a lower compliance and increased LA pressure.[22] In the current study, the LA volumes

Table 4 Locations of the extra-PV trigger in patient who experienced clinical recurrences

Patients with isoproterenol provocation	*De novo* procedures[a]		Redo-procedures[b]	
	$CR_{\leq 5\ yr}$ ($n = 725$)	$CR_{>5\ yr}$ ($n = 88$)	$CR_{\leq 5\ yr}$ ($n = 180$)	$CR_{>5\ yr}$ ($n = 18$)
Extra PV trigger, *n* (%)	118 (16.3)	14 (15.9)	33 (18.3)*	7 (38.9)*
Extra-PV foci site				
Coronary sinus and LOM	40 (5.5)	5 (5.7)	8 (4.4)	3 (16.7)
High septum including Bachmann's bundle area	39 (5.4)	3 (3.4)	14 (7.8)	3 (16.7)
SVC	20 (2.8)**	6 (6.8)**	2 (1.1)	1 (5.6)
Crista terminalis	18 (2.5)	0 (0.0)	3 (1.7)	2 (11.1)
LA posterior wall	18 (2.5)	0 (0.0)	5 (2.8)	0 (0.0)
LAA	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
RA sinus venosa	6 (0.8)	1 (1.1)	4 (2.2)	1 (5.6)
Multifocal triggers or unmappable	6 (0.8)	1 (1.1)	6 (3.3)	1 (5.6)
Patients with proved extra PV foci	($n = 118$)	($n = 14$)	($n = 33$)	($n = 7$)
Number of extra-PV foci per patient, *n* (%)***				
Single focus	85 (72.0)	11 (78.6)	19 (57.6)	4 (57.1)
Double foci	25 (21.2)	2 (14.3)	8 (24.2)	1 (14.3)
Multifocal triggers	8 (6.7)	1 (7.1)	6 (18.2)	2 (28.6)

Values are presented as number (%).
AFCA, atrial fibrillation catheter ablation; LA, left atrium; LAA, left atrial appendage; LOM, ligament of Marshall; PV, pulmonary vein; RA, right atrium; SVC, superior vena cava.
[a]Patients [$n = 132$, 16.2% (132/813)] with extra-PV trigger found during the isoproterenol provocation test ($n = 813$) among patients who experienced recurrence after *de novo* AFCA.
[b]Patients [$n = 40$, 20.2% (40/198)] with extra-PV-trigger found in isoproterenol test when repeated procedures were performed among recurrent patients ($n = 198$).
*$P = 0.015$, $CR_{\leq 5\ yr}$ vs. $CR_{\leq 5\ yr}$ in redo-mapping.
**$P = 0.051$, $CR_{\leq 5\ yr}$ vs. $CR_{\leq 5\ yr}$ in *de novo* mapping.
***There were no statistically significant differences between the groups.

measured by CT were smaller and LA voltages lower in patients with recurrences beyond 5 years. These features may represent the slow progression of atrial myopathy, which may be a major risk factor for very late CRs. Additionally, heart failure can induce AF through structural and haemodynamic changes in the LA, such as dilatation, elevated pressure, and fibrosis due to LV dysfunction.[23] A previous study revealed that patients with LV dysfunction had significantly higher risk of worse outcomes, including all-cause death, hospitalization for heart failure, stroke, or systemic embolism than those with preserved LV function.[24] Nevertheless, the effect of LVEF on rhythm outcomes after catheter ablation in these studies was not significant. Similarly, LVEF was not a statistically significant predictor of AF recurrence in the present study. Sugumar *et al.*[25] reported that atrial electrical recovery was observed following the restoration of sinus rhythm, and LV function improved after AFCA. Therefore, although there was no statistical significance in this study, LA voltage measured during repeated procedures slightly increased in patients with $CR_{>5\ yr}$ who maintained sinus rhythm for a relatively long period.

Moreover, LA remodelling is associated with the presence of extra-PV triggers.[13] The need for ablation beyond the PV remains controversial; however, non-PV areas can be the source of AF initiation and maintenance. The most common areas were the SVC, ligament of Marshall, coronary sinus, crista terminalis, and posterior LA wall. The LA appendage (LAA) is also an underrecognized AF trigger. Prospective elimination of the distal coronary sinus to LA connections added to standard PV isolation and non-PV trigger ablation reduced AF recurrence.[26] LAA electrical isolation reduces atrial arrhythmia recurrence in patients with long-standing persistent AF; however, there are concerns regarding acute procedural complications or cerebral thrombo-embolism.[27] Extra-PV triggers the initiation of AF, and the substrate created by atrial remodelling plays an important role in inducing AF persistence. To break this link, extra-PV trigger ablation may be an important strategy in patients with very late recurrence.

Clinical implications

Although AFCA procedures have been performed over the last 24 years with improving results, AF remains an incurable disease.[5] Atrial fibrillation is an age-dependent, progressive, chronic disease that requires long-term care. This study observed that 8.8% of patients who underwent AFCA had an AF recurrence after 5 years, which we associated with AF progression. However, >40% of AF cases recur as subclinical or minimally symptomatic AF.[28] Taking this into account, rhythm monitoring and guideline-based antithrombotic therapy should not be neglected, even in patients without long-term AF recurrences after AFCA.[29] In addition, AADs should be considered in the treatment of AF recurrence caused by extra-PV triggers, to lower the AF burden.

Limitations

This study has some limitations. First, this observational cohort study was conducted at a single centre. Secondly, we did not include patients who underwent cryoballoon ablation due to the absence of a voltage map. Thirdly, an inherent selection bias may be possible since we did not perform voltage mapping in all patients, and isoproterenol provocation tests were performed in 57.4% of the patients who underwent the *de novo* procedure. However, we performed the isoproterenol provocation test on all 198 patients who underwent repeat procedures. Fourthly, the long duration of enrollment and follow-up resulted

in changes to the in-catheter technology and ablation strategies, which may have affected the ablation results. Fifthly, the number of patients who underwent repeat procedures after AF recurrence was limited. Lastly, Holter or ECG monitoring might be insufficient in detecting subclinical AF recurrence, and the rate of progression to permanent AF could have been underestimated.

We found that a post-AFCA $CR_{>5\ yr}$ was independently associated with low LA volume, low LA voltage, and low early recurrence rate after AFCA. Extra-PV triggers during repeat procedures were significantly greater in patients with late CRs, whereas no difference was observed in patients who underwent the de novo procedure. Thus, our findings suggest that AF progression contributes to late $CR_{>5\ yr}$ after AFCA.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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