

Ablation of persistent atrial fibrillation based on high density voltage mapping and complex fractionated atrial electrograms

A randomized controlled trial

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Abstract

Introduction: Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) catheter ablation. However, a PVI alone has been considered insufficient for persistent AF. This study aimed to evaluate the efficacy of persistent AF ablation targeting complex fractionated atrial electrogram (CFAE) areas within low voltage zones identified by high-resolution mapping in addition to the PVI.

Methods: We randomized 50 patients (mean age 58.4 ± 9.5 years old, 86.0% males) with persistent AF to a PVI + CFAE group and PVI only group in a 1:1 ratio. CFAE and voltage mapping was performed simultaneously using a Pentaray Catheter with the CARTO3 CONFIDENSE module (Biosense Webster, CA, USA). The PVI + CFAE group, in addition to the PVI, underwent ablation targeting low voltage areas (<0.5 mV during AF) containing CFAEs.

Results: The mean persistent AF duration was 24.0 ± 23.1 months and mean left atrial dimension 4.9 ± 0.5 cm. In the PVI + CFAE group, AF converted to atrial tachycardia (AT) or sinus rhythm in 15 patients (60%) during the procedure. The PVI + CFAE group had a higher 1-year AF free survival (84.0% PVI + CFAE vs 44.0% PVI only, $P = .006$) without antiarrhythmic drugs. However, there was no difference in the AF/AT free survival (60.0% PVI + CFAE vs 40.0% PVI only, $P = .329$).

Conclusion: Persistent AF ablation targeting CFAE areas within low voltage zones using high-density voltage mapping had a higher AF free survival than a PVI only. Although recurrence with AT was frequent in the PVI+CFAE group, the sinus rhythm maintenance rate after redo procedures was 76%.

Abbreviations: AF = atrial fibrillation, AT = atrial tachycardia, CFAE = complex fractionated atrial electrogram, CTI = cavo-tricuspid isthmus, ECG = electrocardiogram, ICL = interval confidence level, LA = left atrium, PeAF = persistent AF, PVI = pulmonary vein isolation, RA = right atrium, SCL = shortest complex interval.

Keywords: atrial fibrillation, complex fractionated atrial electrogram, low voltage areas, substrate, voltage mapping

1. Introduction

Pulmonary vein isolation (PVI) is the cornerstone strategy for catheter ablation of atrial fibrillation (AF) in those who do not respond to antiarrhythmic drugs.^[10] However, catheter ablation of persistent AF (PeAF) and long-standing PeAF has had

less favorable outcomes and additional substrate modification methods are often added to the PVI. Although substrate modification is a rational approach when considering the AF mechanism, the procedural success rates and clinical results vary widely.^[6,11,16,19,27] However, recent advances in

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three-dimensional (3D) reconstruction/mapping technologies have provided standardized complex fractionated atrial electrogram (CFAE) maps. In addition, they also have improved the tissue contact and reduced the interelectrode distance, allowing for multipoint recording with a high spatial resolution and improved signal fidelity.

In this study, we evaluated the effects of a substrate modification strategy targeting CFAE areas within low voltage zones identified by the latest 3D mapping technology in persistent and long-standing persistent AF patients.

2. Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1. This clinical trial was designed and reported according to recommendations of the Consolidated Standard of Reporting Trials (CONSORT) statement^[15] (ClinicalTrials.gov Number, NCT 03046043).

2.1. Study population

Fifty drug-refractory, symptomatic persistent and long-standing persistent AF patients scheduled for catheter ablation of AF at our hospital from January to October 2018 were consented for enrollment. Persistent AF was defined as continuous AF lasting

more than 7 days. Long-standing PeAF was defined as continuous AF lasting for ≥ 1 year.^[10] All patients gave their written informed consent for the study and the study protocol was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (March 2017; DSMC 2017-02-034-001). The flow-chart of our study according to the CONSORT guidelines is shown in Figure 1.

Eligible participants were provided unique identification numbers according to study criteria and were assigned to the PVI only group or PVI plus CFAE ablation group (PVI+CFAE). Randomization was done by a clinical research coordinator and a blocked randomization sequence was created with a computerized random number generator and applied with a 1:1 assignment to each group. The study coordinator nurse had informed the investigators of the number.

2.2. Sample size calculation

To date, there are no studies regarding ablation targeting CFAE areas only within low voltage zones. However, Rolf et al reported that the 12-month atrial tachyarrhythmia-free survival was 27% for patients with a PVI only and 70% for patients with additional low voltage area ablation.^[22] Based on this study results, we hypothesized that the difference between the 2 groups in the one-year atrial tachyarrhythmia free survival was 43%. When the power was 80%, and the significance level 0.05, the required

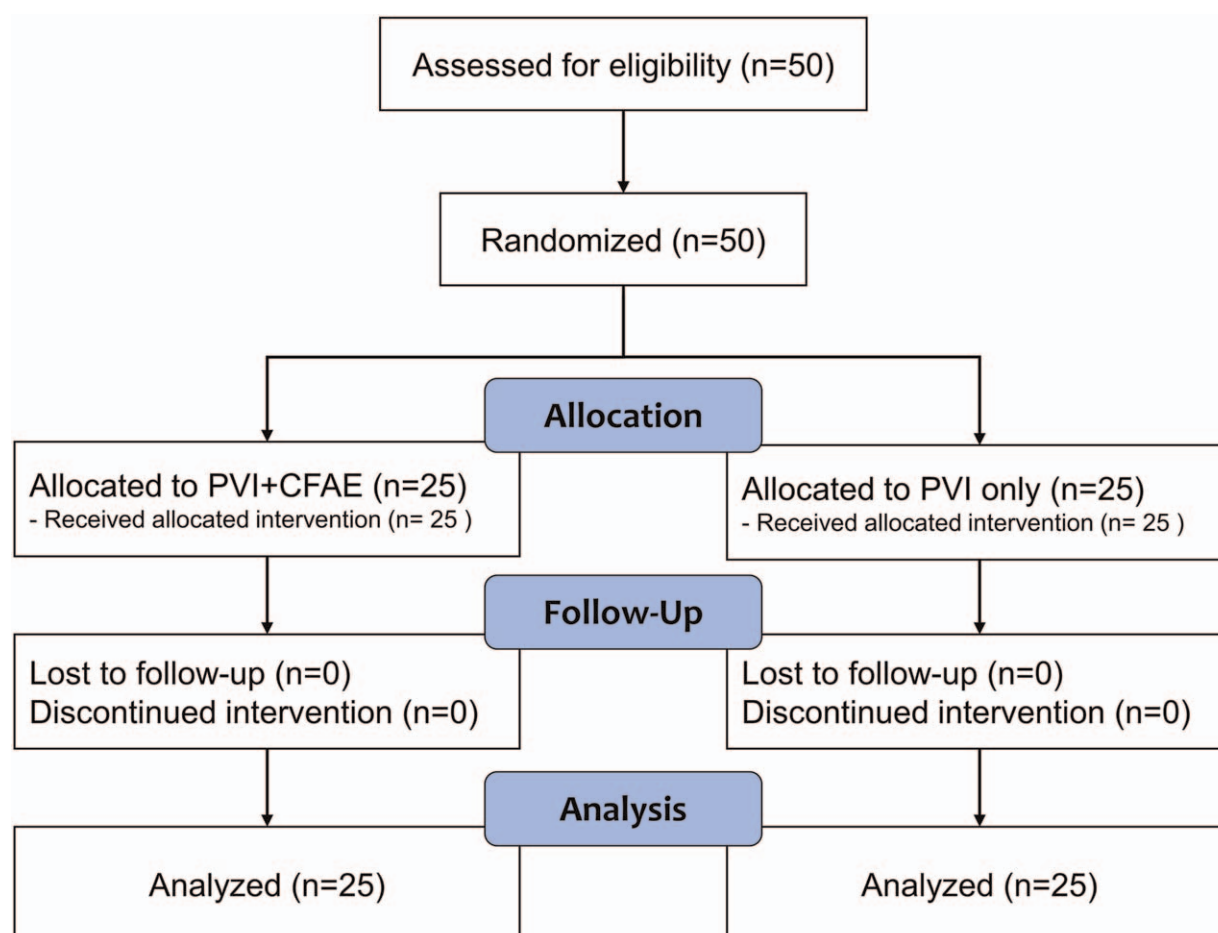


Figure 1. Flow diagram of the study.

number of subjects was 17.3. Considering the dropout rate of 20%, the number of patients required to achieve the purpose of this study was 21.5. Therefore, we assigned 25 patients to each group.

2.3. Ablation procedure

All antiarrhythmic agents were stopped at least 5 half-lives before the procedure except for amiodarone, which was stopped at least 8 weeks pre-ablation. Multi-slice computed tomography scans and transesophageal echocardiography were performed in all patients prior to the procedure. The ablation procedure was performed under conscious sedation with remifentanyl and midazolam. Three multipolar catheters were inserted through the left femoral region and placed in the right atrium, coronary sinus, and His bundle. Two 8.5 Fr non-steerable long sheaths (Swartz™ Braided Transseptal Guiding Introducer SL1, St. Jude Medical, St. Paul, MN) were placed in the right atrium through the right femoral region and inserted into the left atrium (LA) using one or 2 transseptal punctures. After the transseptal puncture, an activated clotting time of over 350 seconds was maintained with intermittent boluses of intravenous heparin. The anatomical structure was identified through the LA and PV angiography. Thereafter, a 3.5 mm irrigated ablation catheter with contact force monitoring (ThermoCool SmartTouch SF) and a Pentaray Catheter (Biosense Webster, Inc., Diamond Bar, CA, USA) were introduced through the sheaths.

Ablation was performed with a SmartTouch SF ablation catheter in a power-controlled mode using a power of 30 to 35 W for a duration of 25 to 30 seconds. Ablation of the posterior wall was performed with a power of 20 to 25 W for 15 to 20 seconds. The circumferential PVI was performed with a point-by-point ablation at the junction between the LA and PVs and an automated annotation program (VisiTag™ module) was used. The endpoint of the PVI was bidirectional conduction block of the PVs identified by a multipolar catheter. Entrance block was defined as the absence of any electrical activity within the PV antrum. If remnant potentials were present, the dissociation was demonstrated by local PV capture without conduction to the LA to prove exit block.^[2]

In the PVI only group, electrical cardioversion to sinus rhythm was performed if the patient was still in AF after the PVI. If AF organized into atrial tachycardia (AT) during the PVI, the AT was mapped and ablated. If the patient had a history of typical atrial flutter, linear ablation targeting the cavo-tricuspid isthmus (CTI) was conducted. Non-inducibility tests were not performed in this group of patients.

In the PVI+CFAE ablation group, ablation targeting the CFAE areas within low voltage zones was performed in addition to the PVI. High-density voltage and CFAE mapping were performed during an AF state using a Pentaray catheter with the CARTO3 CONFIDENSE module (Biosense Webster, Inc., Diamond Bar, CA, USA) before the ablation start. Automatic characterization of the CFAE signals was performed with a CARTO CFAE software module (Biosense Webster, Inc., Diamond Bar, CA, USA). Further, visually detected CFAE areas by the operator were manually annotated. A low voltage zone was defined as an area with bipolar peak-to-peak voltage amplitudes of <0.5 mV. The CFAEs were defined by the system based on the peak-to-peak (P-P) interval in milliseconds. The minimal amplitude threshold and maximal amplitude threshold were set to ± 0.05 millivolt (mV) and ± 0.15 mV, respectively, and the minimal interval and

maximal interval between 2 consecutive peaks was set to 50 to 120 m/sec. The CFAE areas were identified and displayed in a color-coded manner according to the parameters using an algorithm with the interval confidence level (ICL) and shortest complex interval (SCI) parameters. Areas with the shortest SCI and a high ICL within low voltage areas were targeted first, followed by longer SCI regions (up to 120 ms). Radiofrequency energy was delivered at target sites for 30 to 60 seconds until the local electrograms were completely eliminated (Fig. 2A and B). If AF persisted after the LA ablation, the CFAE areas within the low voltage zones in the right atrium (RA) were mapped and ablated. If AF organized into atrial tachycardia (AT) during the CFAE area ablation, the AT was mapped and ablated (Fig. 2C and D). If AF persisted even after ablation targeting the CFAE areas with low voltage zones, electrical cardioversion was performed.

2.4. Outcomes

The primary outcome of our study was the freedom from any atrial tachyarrhythmia recurrence at the 1-year follow-up without antiarrhythmic drug treatment after a single ablation procedure. The secondary endpoints were the procedure time, fluoroscopy time, and complications.

2.5. Follow-up

Anti-arrhythmic agents were discontinued after a 3-month blanking period. An electrocardiogram (ECG) and 24-hour Holter monitoring were obtained right after the procedure and at 3, 6, and 12 months after the ablation. ECG and Holter monitoring were also performed whenever the patient had symptoms suggesting an arrhythmia recurrence. Recurrence of an atrial tachyarrhythmia was defined as the detection of AF or AT lasting more than 30 seconds on the 12-lead ECG or 24-hour Holter monitoring after the 3-month blanking period.

2.6. Statistical analysis

For the statistical analysis, a Student *t* test or Mann–Whitney *U* test was used for the comparison of the continuous variables between the 2 groups and a Chi-Squared or Fisher exact test was used for the categorical data. Kaplan–Meier survival estimates were used to compare the degree of recurrence of AF or the incidence of atrial arrhythmias. The data analyses were performed with IBM SPSS Statistics version 23 software (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

The mean age of total patients was 58.4 ± 9.5 years and 43 (86%) patients were male. The mean AF duration was 24.0 ± 23.1 months and mean LA dimension 4.9 ± 0.5 cm. The baseline characteristics between the PVI only group and PVI + CFAE group did not differ. The results are summarized in Table 1.

3.2. Procedural results

In the PVI only group, in one patient the AF terminated into sinus rhythm by a PVI only. Additional CTI linear ablation for CTI dependent macroreentrant atrial flutter was performed in 4

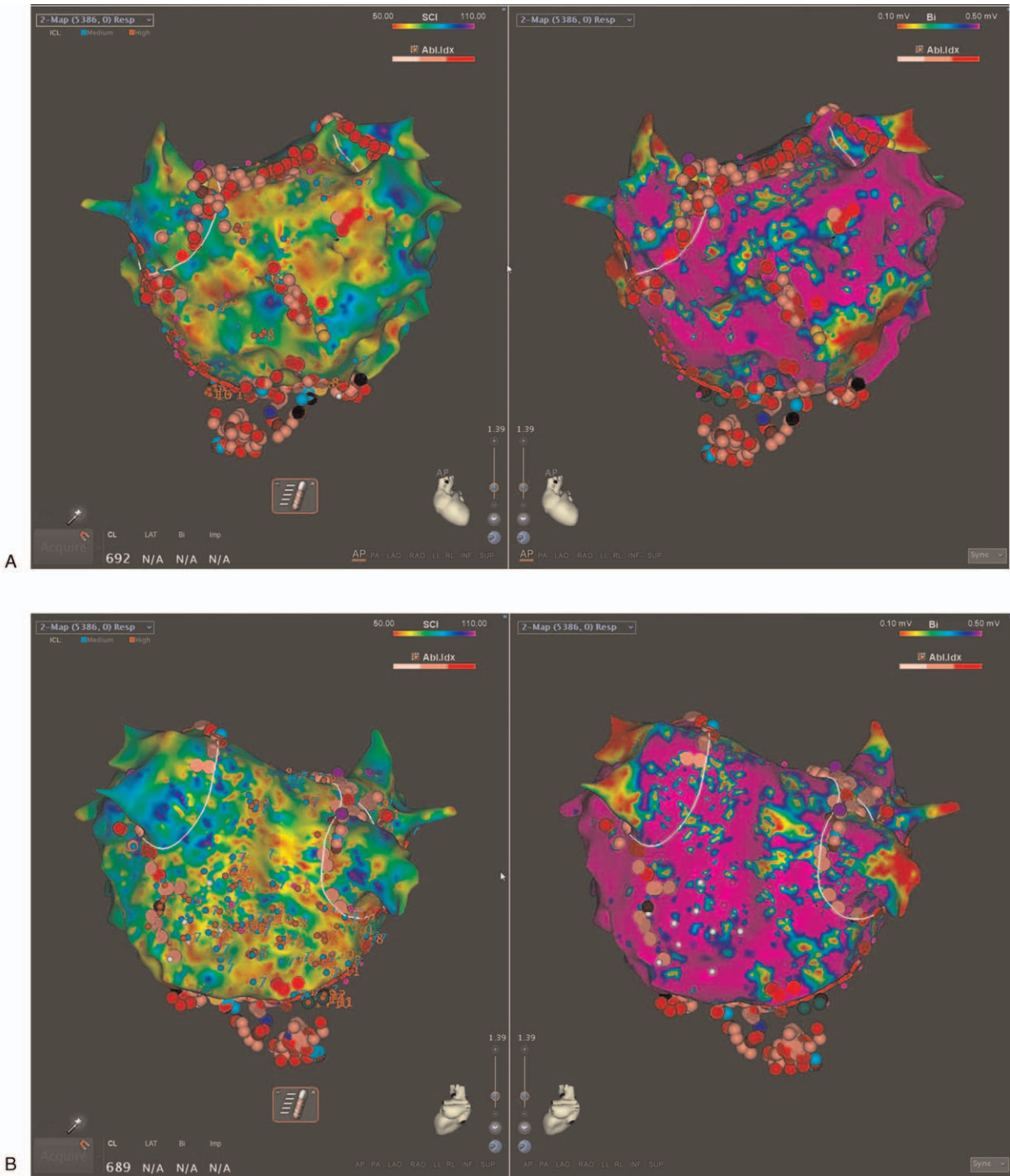


Figure 2. Examples of electroanatomic maps of a low voltage complex fractionated atrial electrogram (CFAE) ablation. (A) Antero-posterior view and (B) Postero-anterior view of the left atrium (LA) after ablation. The left side of Figure A/B is a CFAE map and the right side a voltage map. (C) During an LA roof area CFAE ablation, atrial fibrillation converted into atrial tachycardia (AT). (D) During a CS os ablation, the AT terminated, and sinus rhythm was restored in the patient. The CFAE area was tagged with an azure dot. The ablation points are the pink and red dots. The blue dot is the AT termination site.

patients. In the PVI+CFAE group, additional RA ablation was performed in 64% (16 of 25) of the patients. Termination of AF during ablation was observed in 60% (15 of 25) of the patients (directly to sinus rhythm: 1 patient, conversion to AT: 14 patient). The most common site for AF termination was the LA septum (7 of 15). In 5 patients, the AF organized into AT during the ablation in the RA. Overall, 32% (8 of 25) of the patients

were converted to sinus rhythm by ablation. Non-inducibility was achieved in 56% of the patient. No major procedure related complications occurred. One patient in the PVI+CFAE group developed a groin hematoma after the procedure. The procedure time, fluoroscopy time, and ablation time were significantly longer in the PVI+CFAE group. The major procedural results are summarized in Table 2.

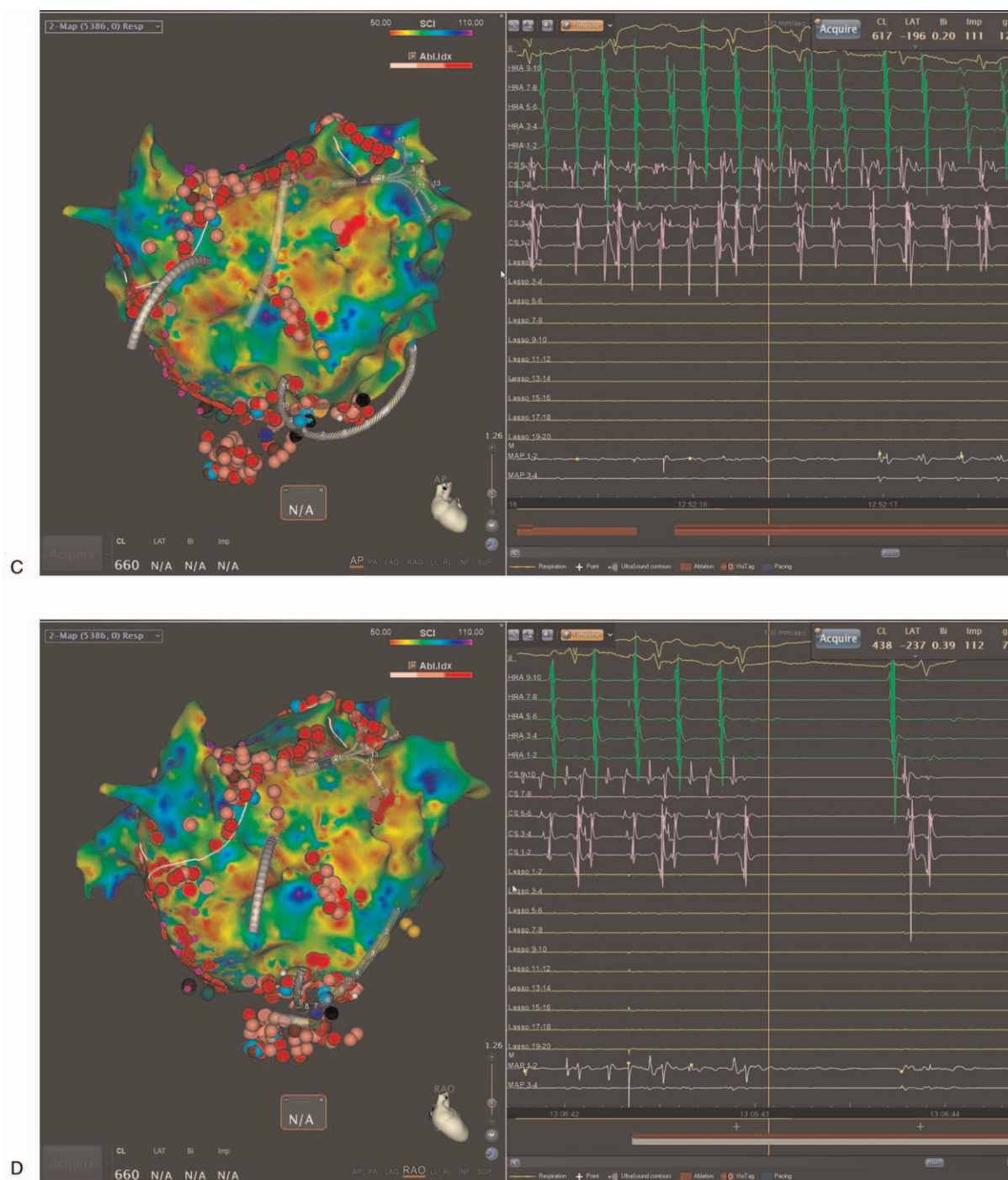


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3.3. Clinical follow-up results

The PVI+CFAE group had a significantly higher 1-year AF-free survival without antiarrhythmic drugs than the PVI only group (84.0% in the PVI+CFAE group vs 44.0% in the PVI only group, $P=.006$, Fig. 3A). However, the AT/AF-free survival after a single procedure demonstrated no difference between the 2 groups (60.0% in the PVI+CFAE group vs 40.0% in the PVI only

group, $P=.329$, Fig. 3B). Three patients in the PVI +CFAE group and 4 in the PVI only group received redo procedures during the follow-up period (re-isolation of PVs and CFAE ablation for the purpose of the achievement of non-inducibility, and the strategy used during the index procedure was not preserved). The sinus rhythm maintenance with a redo procedure at 1 year was 76.0% (19/25) and 64.0% (16/25) in the patients in the PVI+CFAE and

Table 1**Baseline characteristics of the patients.**

	Total (n = 50)	PVI + CFAE (n = 25)	PVI (n = 25)	P value
Age	58.4 ± 9.5	58.8 ± 9.3	57.9 ± 9.8	.600
Female	7 (14.0)	5 (20.0)	2 (8.0)	.417
Male	43 (86.0)	20 (80.0)	23 (92.0)	
Height	167.6 ± 9.1	167.4 ± 9.0	167.9 ± 9.3	.698
Weight	75.5 ± 13.4	72.8 ± 11.7	78.2 ± 14.8	.139
BSA	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	.258
BMI	26.8 ± 3.5	25.9 ± 3.0	27.6 ± 3.7	.320
Risk factor				
HF	8 (16.0)	4 (16.0)	4 (16.0)	1.000
HTN	25 (50.0)	14 (56.0)	11 (44.0)	.396
DM	9 (18.0)	5 (20.0)	4 (16.0)	1.000
History of a CVA	10 (20.0)	6 (24.0)	4 (16.0)	.480
Peripheral Vascular Disease	1 (2.0)	1 (4.0)	0 (0.0)	1.000
CHA ₂ DS ₂ -Vasc Score	1.6 ± 1.4	1.8 ± 1.4	1.4 ± 1.4	.220
AF Duration (Month)	24.3 ± 22.9	21.4 ± 26.2	27.1 ± 19.2	.250
Echocardiography				
EF	58.7 ± 10.6	59.4 ± 11.4	57.9 ± 10.0	.547
LAD	4.9 ± 0.5	4.9 ± 0.4	5.0 ± 0.6	.083
LAV	120.5 ± 36.0	118.6 ± 33.3	122.4 ± 39.2	.839

Values are presented as the mean ± standard deviation or n (%). BMI = body mass index, BSA = body surface area, CFAE = complex fractionate atrial electrogram, CVA = cerebrovascular disease, DM = diabetes mellitus, EF = ejection fraction, HF = heart failure, HTN = hypertension, LAD = left atrial dimension, LAV = left atrial volume, PVI = pulmonary vein isolation, SR = sinus rhythm.

Table 2**Procedural and clinical outcomes.**

	Total (n = 50)	PVI + CFAE (n = 25)	PVI only (n = 25)	P value
Procedure time (min)	155.3 ± 45.0	190.4 ± 33.9	118.7 ± 17.1	<.001
Fluoroscopy time (min)	17.3 ± 8.5	21.3 ± 7.7	13.3 ± 7.4	<.001
Ablation time (min)	54.5 ± 24.9	70.7 ± 21.4	38.3 ± 16.0	<.001
1-year AF-free, n (%)	32 (64.0)	21 (84.0)	11 (44.0)	.006
1-year AT/AF free, n (%)	25 (50.0)	15 (60.0)	10 (40.0)	.329
Recurrent patients with AT	7 (14.0)	6 (24.0)	1 (4.0)	.044
Redo procedure, n (%)	7 (14.0)	3 (12.0)	4 (16.0)	.687
Patients with sinus rhythm after the initial procedure	25 (50.0)	15 (60.0)	10 (40.0)	.329
Patients with sinus rhythm at 1-year, n (%)	33 (66.0)	19 (76.0)	16 (64.0)	.359

AF = atrial fibrillation, AT = atrial tachycardia, CFAE = complex fractionate atrial electrogram, PVI = pulmonary vein isolation.

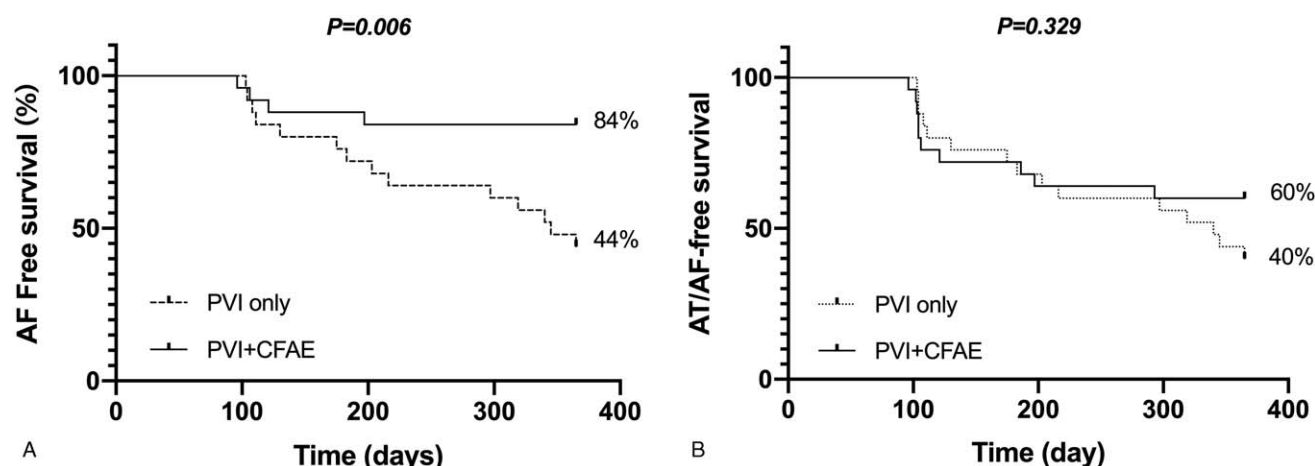


Figure 3. Comparison of the Kaplan–Meier survival curves for the one-year freedom from atrial tachyarrhythmias after ablation between the 2 groups. (A) The pulmonary vein isolation (PVI) + complex fractionated atrial electrogram (CFAE) ablation group had a higher one-year atrial fibrillation free survival than the PVI only group. (B) However, there was no significant difference in the one-year atrial fibrillation / atrial tachycardia free survival between the 2 groups.

PVI only groups, respectively ($P=.359$). AF termination during the procedure was not related to a low recurrence rate of atrial tachyarrhythmias (recurred in 6/15 in termination group vs 4/10 in the no-termination group). During one-year of the follow-up period, no patients experienced any late complications. One patient in the PVI+CFAE group received a permanent pacemaker implantation due to sick sinus syndrome after sinus rhythm restoration during the follow-up period.

4. Discussion

Our study showed that ablation targeting the CFAE areas within low voltage zones guided by high-density mapping in addition to the PVI in patients with persistent and long-standing persistent AF had a significantly better one-year outcome in terms of the AF-free survival. However, the overall atrial tachyarrhythmia-free survival did not differ. Especially, recurrence with AT was more frequent in the additional CFAE ablation arm.

Previous studies reported a high recurrence rate after catheter ablation in patients with persistent and long-standing persistent AF.^[25] To overcome this limitation, various ablation strategies have been attempted. Atrial fibrosis is the hallmark of structural remodeling and atrial fibrosis with its border zones has been identified as an important substrate for focal and reentrant activity maintaining AF.^[8,18] The late gadolinium enhancement in the MRI has been reported to be associated with atrial fibrosis,^[14] and there are several studies that have reported that the late gadolinium enhancement correlates with low voltage areas in electroanatomic mapping.^[13,24] In lieu of this, one of the additional ablation strategies for AF is targeting areas of atrial fibrosis based on low voltage zones identified on voltage mapping.^[7] Current approaches to low-voltage areas include a low voltage area isolation, linear ablation across a low-voltage area, and homogenization of a low voltage area.^[23] Another approach is targeting specific electrogram characteristics within low voltage areas in addition to a PVI.^[5,9] One recent study demonstrated that electrogram-guided ablation targeting only low-voltage areas of less than 0.4mV in the LA and RA in addition to the PVI resulted in a 71.4% sinus rhythm maintenance rate after a single procedure during a mean follow-up of 21.1 ± 0.8 months.^[5]

The multicenter randomized trial, Substrate and Trigger Ablation for Reduction of Atrial Fibrillation 2 (STAR-AF 2) study, failed to reveal the clinical significance of CFAE-targeted ablation in the patients with persistent AF.^[26] However, the detection algorithm of the CFAEs in the STAR-AF2 study was based on the NaVX mapping system has a different algorithm than the CARTO system using the SCI and ICL software (CARTO CFAE software module, Biosense Webster, Inc., Diamond Bar, CA, USA).^[16] In addition, a multielectrode mapping catheter with 1-mm electrodes (Pentaray catheter, Biosense Webster, Inc., Diamond Bar, CA, USA) used with the CARTO3 CONFIDENSE module can conduct high resolution mapping with an accurate electrogram and time annotation. Further, during the CFAE ablation, extensive ablation often occurs, and unnecessary ablation can affect both the atrial contraction and atrial compliance.^[21]

Under this background, we hypothesized that ablation targeting CFAE areas only within low voltage zones using this latest high-density mapping technology with a multielectrode catheter and standardized CARTO CFAE mapping system could improve the results of the AF ablation in persistent and long-

standing persistent AF patients. In our study, the one-year AF/AT-free survival rates of the PVI only group was 40% and that result demonstrated the need for an additional or alternative strategy to achieve better results. In the PVI+CFAE group, the 1-year AF-free survival rate was 84% and with a redo-procedure, 76% of patients were maintained in sinus rhythm without any anti-arrhythmic drugs. This result was better than some other studies, especially considering that the patients in this study had more long-standing persistent AF and a larger LA size than in those other studies.^[5,12] In addition, entrainment mapping maneuvers with the current activation mapping technology allows precise activation mapping of ATs, hence, provides a clearer target for the procedure compared than for AF. Indeed, previous reports on RFCA of recurrent AT have shown favorable acute termination rates and a long-term arrhythmia freedom, which are in line with our study results.^[1,3,4] Therefore, recurrence with ATs may be a step toward long-term sinus rhythm maintenance.^[1]

One of the issues was the rhythm during the voltage/CFAE mapping. The voltages in the atrium are usually lower during AF than during sinus rhythm. Most of the previous studies performed voltage mapping during sinus rhythm. However, there has been no consensus for which rhythm is the most appropriate for substrate mapping. Selective ablation based on voltage mapping during AF had a relatively good procedural success rate^[9] and another recent study reported that voltage mapping during AF is superior to mapping during sinus rhythm for localizing areas of delayed enhancement on the MRI.^[20] Our study performed voltage/CFAE maps during AF. If the CFAE arm, the patients were in sinus rhythm at the beginning of the procedure, and the patients were induced into AF.

4.1. Limitations

Although randomization was performed, the small number of enrolled patients in a single center was the major limitation of our study. In addition, most patients were male, and there were several clinically important differences between groups, such as the body mass index and AF duration (even if they were not statistically significant). Ibutilide, which can improve the results of the CFAE ablation, was not available in our country.^[17] As is well known, conventional CFAE ablation has many clinical limitations such as a long procedure/fluoroscopy time, frequent recurrences of AT, and requires multiple procedures for sinus rhythm maintenance.^[28] Although we used the state of the art technology and equipment, these disadvantages of the CFAE ablation were still identified in our study.

5. Conclusion

Persistent AF ablation targeting CFAE areas only within the low voltage zones in addition to the PVI using a high-density mapping technology with a multielectrode catheter and the CARTO standardized CFAE mapping system had a higher AF free survival as compared to a PVI only. Although the recurrence of AF or AT did not differ in the PVI+CFAE group, the sinus rhythm maintenance rate after a redo procedure was 76%, which was higher than that in many studies including a similar patient group.

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