



Efficacy of Complex Fractionated Atrial Electrogram-Guided Extensive Encircling Pulmonary Vein Isolation for Persistent Atrial Fibrillation

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Background: In persistent AF, the effect of adjunctive ablation in addition to PV isolation (PVI) is controversial. We considered a new modified PVI including complex fractionated atrial electrogram (CFAE) area.

Methods and Results: In 57 patients with persistent AF undergoing first ablation, CFAE were mapped before ablation and CFAE-guided extensive encircling PVI (CFAE-guided EEPVI) was performed. The PVI line was designed to include the CFAE area near PV or to cross the minimum cycle length points of the CFAE area near PV (CFAE-guided EEPVI group). The outcome was compared with conventional PVI in 34 patients with persistent AF (conventional PVI group). During a mean follow-up of 365±230 days after the first procedure, AF in 13 and atrial tachycardia (AT) in 9 patients recurred in the CFAE-guided EEPVI group, while only AF in 17 patients recurred in the conventional PVI group. Eight of 9 AT in the CFAE-guided EEPVI group were successfully ablated at second procedure. After first and second procedures, the recurrence of atrial tachyarrhythmia in the CFAE-guided EEPVI group was significantly reduced compared with the conventional PVI group (8 patients, 14% vs. 11 patients, 32%, respectively; $P < 0.01$, log-rank test).

Conclusions: CFAE-guided EEPVI was more effective for persistent AF compared with conventional PVI after first and second procedures, because recurring AT as well as re-conduction of PV was successfully ablated.

Key Words: Atrial tachycardia; Complex fractionated atrial electrogram; Persistent atrial fibrillation; Pulmonary vein isolation; Radiofrequency catheter ablation

Catheter ablation for atrial fibrillation (AF) is effective and is becoming a first-line treatment option. Most cases of paroxysmal AF are triggered by the pulmonary vein (PV), and electrical isolation of the PV (PVI) has been shown to have a high success rate in the treatment of paroxysmal AF.¹ In contrast, PVI for persistent AF does not produce fully satisfactory results. Two different approaches to the ablation for persistent AF have been developed. One is left atrial (LA) linear ablation,² and the other is ablation of complex fractionated atrial electrograms (CFAE).³ The Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF) II was a randomized trial of the adjunctive effectiveness of linear ablation and CFAE ablation, plus PVI.⁴ In that trial neither of the strategies had a superior effect compared with PVI

only. And in a meta-analysis comparing PVI with CFAE ablation plus PVI, CFAE ablation did not improve freedom from AF or from atrial tachycardia (AT).⁵

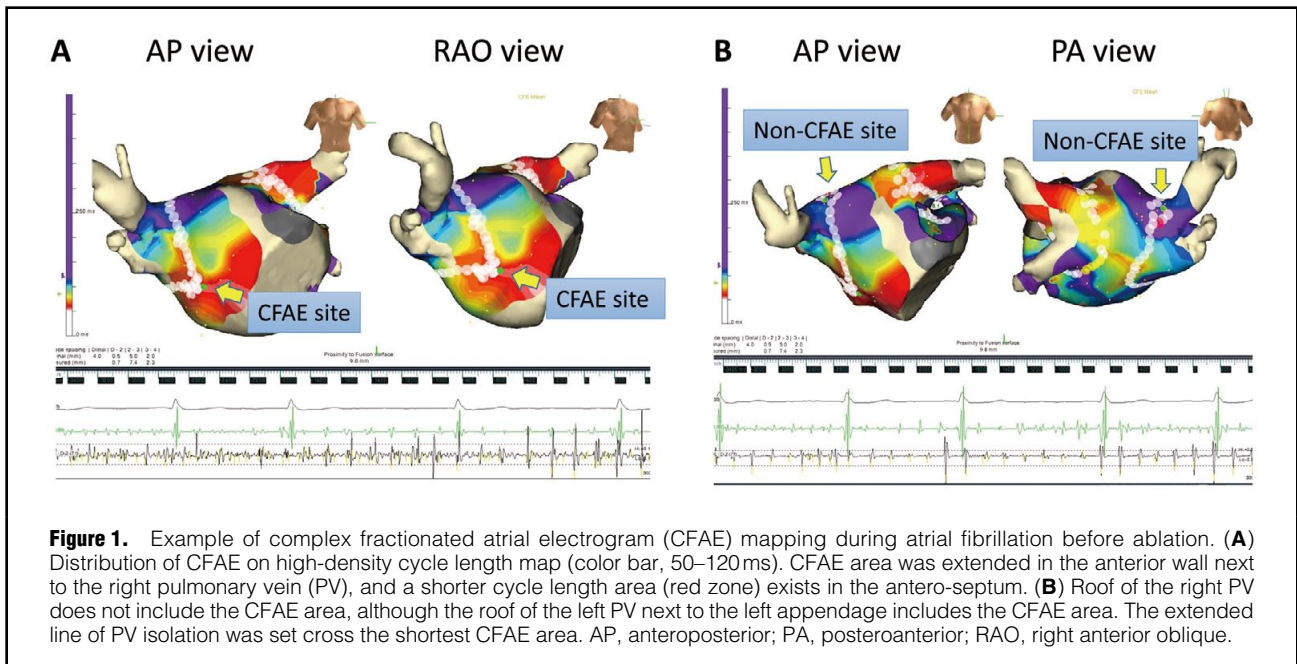
The problem with CFAE ablation is that it can generate a new arrhythmogenic substrate, as well as AT. While original CFAE ablation does not need PVI, a recent strategy involving CFAE ablation after PVI has been developed, which has the possibility to generate a slow conduction zone around the PV. Therefore, modified PVI involving inclusion of the CFAE area has now been developed. This strategy can produce the effect of CFAE ablation without generating an additional arrhythmogenic substrate.

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Methods

Patients

Consecutive patients with persistent AF undergoing first ablation for persistent AF between September 2014 and August 2016 at Kitaharima Medical Center and Kobe University Hospital were enrolled. Persistent AF was defined as continuation of AF >1 week without anti-arrhythmic drugs, and included longstanding AF lasting >1 year. Patients were excluded if LA diameter on transthoracic echocardiogram was >60 mm, left ventricular ejection fraction (LVEF) was <30%, left appendage thrombus was detected on transesophageal echocardiogram immediately before ablation, or if they had prior open surgery.

This study complied with the principles of the Declaration of Helsinki. All patients signed informed written consent to the study protocol, which was approved by the institution Human Research Ethics Committees.

Electrophysiological Studies and Ablation

Electrophysiological studies and catheter ablation were performed with patients under i.v. sedation with propofol, dexmedetomidine, and fentanyl, and non-invasive positive pressure ventilation. A 6-F 20-polar electrode catheter available for intracardiac cardioversion (BeeAT, Japan Lifeline) was inserted into the coronary sinus from the right internal jugular vein. A 6-Fr decapolar electrode and a 4-Fr quadropolar electrode were placed at the right atrium and right ventricle. After trans-septal puncture at the fossa ovalis using an RF needle, two 20-polar circular catheters were placed at both superior PV.

CFAE mapping during spontaneous AF was performed with the EnSite-NavX mapping system (EnSite Velocity, St. Jude Medical) in the CFAE-guided extensive encircling PVI (EEPVI) group. The patients in sinus rhythm before mapping were excluded from the CFAE-guided EEPVI group. The parameters of the automatic algorithm were set

according to a previous report.⁶ Briefly, CFE-mean was the average time interval between consecutive deflections during 5 seconds. The atrial refractory period was set at 50 ms. Mean cycle length <120 ms was defined as CFAE. The 3-D anatomical geometry of the LA and PV antrum was reconstructed. The CFAE data were produced point-by-point using distal bipolar electrodes of the 4-mm flexible tip ablation catheter (CoolFlex, St. Jude Medical) and these data were then correlated with the geometry (**Figure 1**).

The line of the EEPVI was designed to include the CFAE area near the PV or to cross the minimum cycle length points of the CFAE area near the PV. The CFAE areas near the mitral valve or the LA appendage that were separate from the PV antrum were not ablated.

Catheter ablation was performed during sinus rhythm after intracardiac atrial defibrillation. If AF was not terminated by cardioversion, ablation was performed during AF, and cardioversion was performed again after EEPVI.

In the conventional PVI group, 3-D anatomical geometry was determined without CFAE mapping using EnSite-NavX or CARTO (Biosense Webster), and then ipsilateral EEPVI was carried out during sinus rhythm or AF by ablation catheter (CoolFlex, St. Jude Medical or ThermoCool or SmartTouch, Biosense Webster).

After EEPVI was completed, high-dose isoproterenol infusion was carried out. If recurrence of PV conduction or extra PV firing induced AF, additional ablation to the gap of the EEPVI line or the extra PV focus was performed. Then, burst pacing of 10 beats was carried out from 3 different sites: the coronary sinus ostium, high right atrium, and distal coronary sinus. Pacing cycle length was shortened from 300 ms to 2:1 atrial capture. If AT was induced, mapping of the origin or circuit was carried out. Typical atrial flutter was ablated by cavo-tricupid linear ablation. Additional ablation of the roof line or mitral isthmus line for other atrial tachyarrhythmia was not performed at the first procedure.

Table. Patient Characteristics			
	CFAE-guided EEPVI (n=57)	Conventional PVI (n=34)	P-value
Age (years)	65±7.5	63±7.7	NS
Male/Female	48/9	26/8	NS
AF history (months)	29±31	40±32	NS
Persistent AF (months)	13±14	13±13	NS
Left atrial diameter (mm)	42±5.7	43±4.7	NS
LVEF (%)	60±10	58±10	NS
Organic heart disease	TIC 3 DCM 2 CAD 3	TIC 2 DCM 2 Fabry 1	

Data given as mean±SD or n. CAD, coronary artery disease; CFAE, complex fractionated atrial electrogram; DCM, dilated cardiomyopathy; EEPVI, extensive encircling PVI; LVEF, left ventricular ejection fraction; NS, not significant; PVI, pulmonary vein isolation; TIC, tachycardia-induced cardiomyopathy.

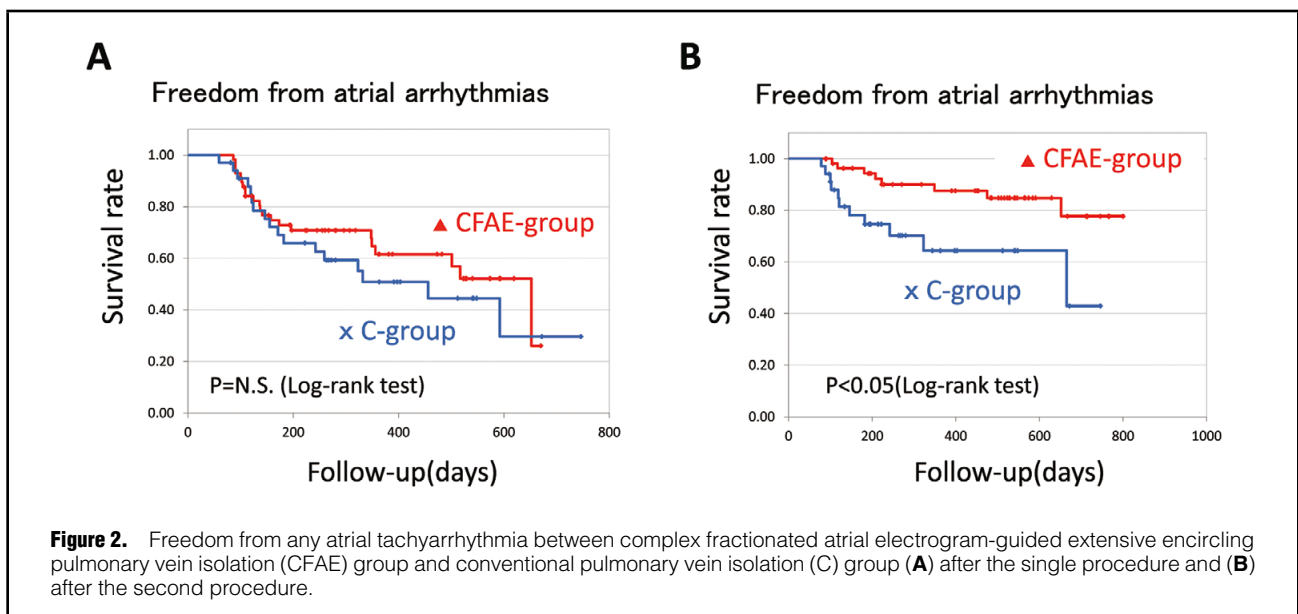


Figure 2. Freedom from any atrial tachyarrhythmia between complex fractionated atrial electrogram-guided extensive encircling pulmonary vein isolation (CFAE) group and conventional pulmonary vein isolation (C) group (**A**) after the single procedure and (**B**) after the second procedure.

Follow-up

Patients were followed up every 4 or 8 weeks at the outpatient clinic. Surface electrocardiograms (ECG) were recorded at each visit, and 24-h Holter recordings were performed at 3 and 6 months after the procedure. When patients had an arrhythmic event, surface ECG were recorded at the outpatient clinic without a pre-booked appointment, and additional 24-h Holter recordings were performed if the surface ECG did not detect any arrhythmias. After a 3-month blanking period following the procedure, occurrence of any sustained atrial tachyarrhythmia including AF and AT >30s without anti-arrhythmic drugs was estimated. If a second procedure was performed in patients with recurrence of atrial arrhythmia, the outcome after the second procedure was also followed.

Statistical Analysis

Continuous data on baseline characteristics are described as mean±SD, and categorical data as n (%). Differences between groups were tested using the unpaired t-test or non-parametric test (Mann-Whitney U-test) for continuous

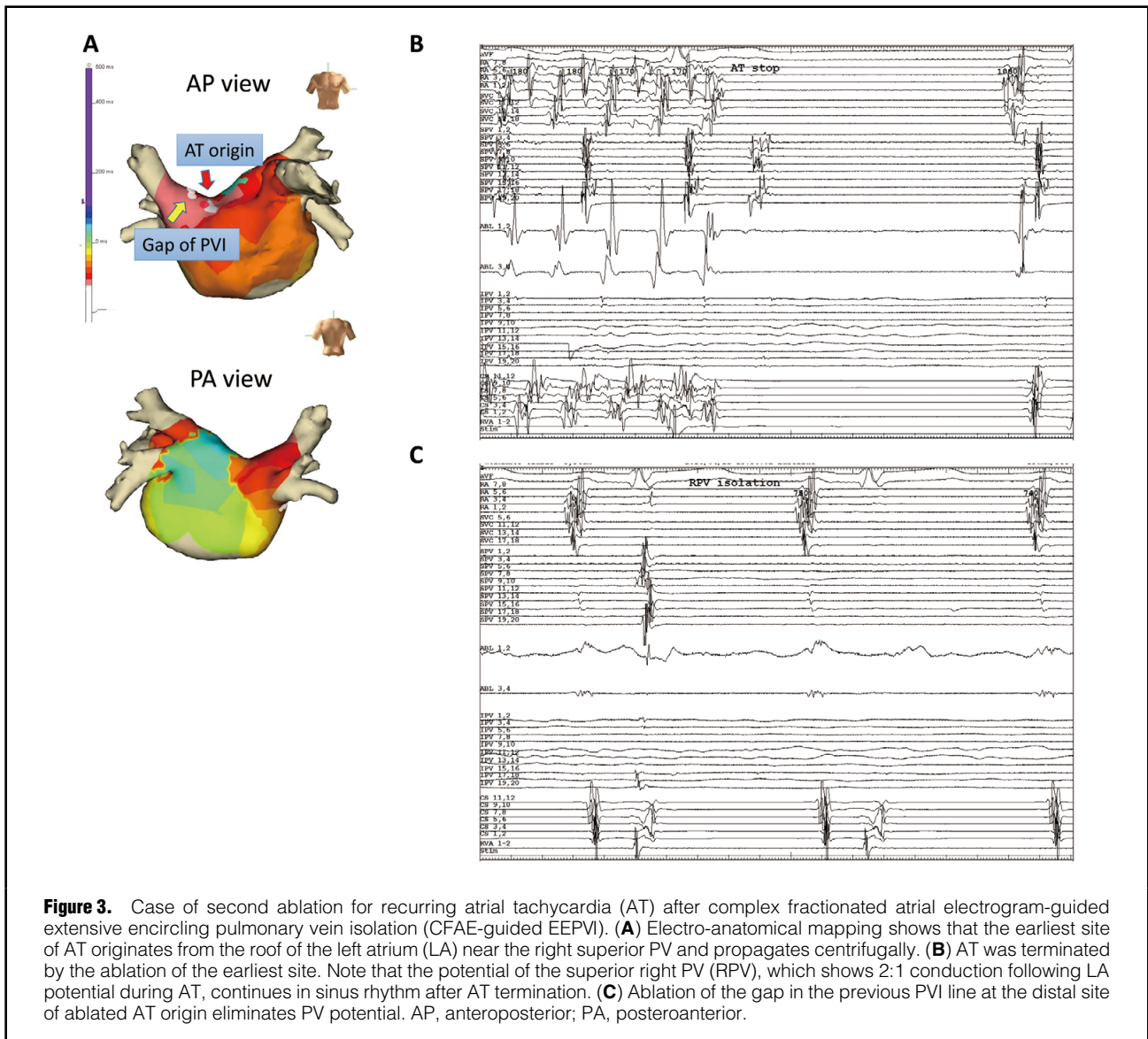
variables, and the chi-squared test or Fisher exact test for categorical variables. Analysis of survival after any atrial tachyarrhythmia was carried out using the Kaplan-Meier method. Comparison of survival curves between groups was assessed using a 2-sided Mantel-Haenszel (log-rank) test.

Results

Patient Characteristics

A total of 57 patients in the CFAE-guided EEPVI group and 34 patients in the conventional PVI group were enrolled in this study. There was no difference between the 2 groups in age (65±7.5 vs. 63±7.7 years, respectively), sex, duration of AF history (29±31 vs. 40±32 months, respectively), or duration of persistent AF until procedure (13±14 vs. 13±13 months, respectively). LA dimension and LVEF on ultrasound cardiography were similar between the 2 groups (42±5.3 vs. 43±4.7 mm, 59±11 vs. 58±10%, respectively; **Table**).

There was no death, stroke, or cardiac infarction as a result of the procedure. Cardiac tamponade occurred in 1



patient in the CFAE-guided EEPVI group, who recovered promptly after percutaneous pericardial drainage.

CFAE Mapping

In all patients in the CFAE-guided EEPVI group, CFAE mapping was able to be performed. Many CFAE near the PV antrum were recorded at the roof of the left superior PV near the LA appendage, and on the anterior side of the right PV near the atrial septum. The site of the shortest cycle length in this CFAE area was designated as the line of PVI. CFAE at the left posterior wall were crossed by the closed isolation line of the PV, but in some cases CFAE in the space between the PV could not be ablated because the lines of the right and left PVI were separated >1.5cm to avoid the isthmus-related macro-reentrant AT.

Outcome

During a mean follow-up period of 365 ± 230 days after the first procedure, AF or AT recurred in 22 patients (39%) in the CFAE-guided EEPVI group and in 17 patients (50%)

in the conventional PVI group. There was no significant difference between the 2 groups (**Figure 2A**). AT recurred in 9 and AF in 13 patients in the CFAE-guided EEPVI group, while AF recurred in all of the 17 patients in the conventional PVI group. The second procedure was performed in 20 patients, including the 9 patients with AT recurrence in the CFAE-guided EEPVI group. PV conduction recurred in 27 PV (68%; 14 right PV and 13 left PV) and all PV were isolated again. Seven of 9 recurring AT could be mapped. The majority of the mechanisms of AT were related to recurrent gaps in the ablated line, and none was due to peri-mitral or roof-dependent macro-reentrant AT. In 2 patients, intra-PV tachycardia showed AT originating from a gap in the PVI. In 1 patient, AT was related to double gaps in the PVI line, each of which showed an exit and entrance of the macro-reentrant tachycardia between the LA and PV. In 2 patients, AT originated from a focal source near the PVI line (**Figure 3**). In 1 patient, AT was caused by incessant firing of the site in the right atrium. In 2 patients, the origin of AT was not detected

because the AT was not induced in the second ablation. All AT except for 2 of unknown origin were successfully ablated. Additional SVC isolation and extra PV focus ablation in 8 patients, linear ablation in 6 patients, and CFAE ablation in 4 patients were performed. In contrast, the second ablation was performed in 10 patients in the conventional PVI group. PV potential recurred in 16 PV (80%; 10 right PV and 6 left PV). All PV were isolated again and additional SVC isolation in 3 patients, linear ablation in 2 patients, and CFAE ablation in 1 patient were performed. After the first and second procedures, the recurrence rate of any atrial tachyarrhythmia in the CFAE-guided EEPVI group was significantly reduced compared with the conventional PVI group (8 patients, 14% vs. 11 patients, 32%, $P < 0.01$, respectively; **Figure 2B**).

Discussion

In this study, we performed CFAE-guided EEPVI in 57 patients with persistent AF, compared with conventional EEPVI in 34 patients with persistent AF. The main finding was that CFAE-guided EEPVI significantly reduced recurrence of atrial tachyarrhythmia without anti-arrhythmic drugs after the second procedure compared with conventional EEPVI.

PVI for Persistent AF

PV are the main trigger source of persistent AF as well as paroxysmal AF, but the success rate of PVI is limited. The rate of freedom from AF/AT after PVI for persistent AF varies from 36% to 86%.⁷⁻¹¹ Persistent AF includes a varying degree of substrate lesions, which may expand depending on the duration of AF, age, or underlying heart disease. Seitz et al reported that PV activity during AF decreases with AF chronicity, LA dilatation, and LVEF and is related to ablation outcome.⁶ In many previous reports, the line of PVI was not mentioned. It is important to identify the line of PVI covering the substrate surrounding the PV. Larger isolation of the PV antrum is thought to produce a better outcome, but it is not clear how the isolation line should be extended to the posterior or roof or anterior of the left atrium. CFAE may be able to identify the ideal line of PVI. Recent technology has enabled visualization of driving wavelets during AF, and many rotor sites exist around the PV.¹ CFAE sites may be related to rotor sites and CFAE-guided EEPVI is reasonable to eliminate the AF substrate near PV.

In this study, there was no difference in recurrence rate of atrial tachyarrhythmias after a single procedure between the CFAE-guided EEPVI group and conventional PVI group, although this outcome was similar to previous reports. One reason is thought to be the similar rate of PV re-connection between the 2 groups. In CFAE-guided EEPVI, the isolated area was wider and the length of the ablation line was longer compared with conventional EEPVI. This may cause more gaps. Second, a contact force-sensing catheter was not used in most cases because it was not available until the latter part of the study period in Japan. This may affect the primary success rate of first PVI.

AT After PVI

Wasmer et al reported that approximately 4% of the patients developed AT after circumferential antral PVI.¹² The mechanism of AT after PVI was reported to be both

focal and macro-reentrant tachycardias. Most macro-reentry tachycardias had peri-mitral or roof-dependent transmission.^{12,13} Gerstenfeld et al reported that many focal AT after PVI are caused by a focal reentrant circuit located at the PV ostium.¹³ The present results were similar to that report. In contrast, Oral et al reported that 26% of the patients after CFAE ablation had recurrent atrial flutter, most of which were due to macro-reentry.⁷

In CFAE-guided EEPVI, AT recurred after the first procedure more often than in the conventional PVI group. The majority of the mechanisms of AT were related to a recurring gap in the ablation line and were successfully ablated, while none of the peri-mitral or roof-dependent macro-reentrant AT recurred. It is of considerable interest that some recurring AT originated from the LA close to the PVI line. This suggests that AF rotor outside the PVI may change to focal AT due to elimination of the surrounding substrate of fibrillatory conduction, and that AF rotor within the PVI may recur as gap-related AT. Narayan et al reported on the efficacy of rotor ablation for persistent AF, and that many rotors exist near the PV.¹⁴ Lin et al reported that in dominant frequency analysis of AF, CFAE ablation in the vicinity of the dominant frequencies sites correlated with a higher procedural AF termination.¹⁵ Yamabe et al reported that a focal discharge initiating AF derived from the CFAE area as well as from the PV.¹⁶ These reports indicate that CFAE-guided EEPVI is reasonable in order to obtain adjunctive effect.

Previous CFAE Ablation Reports

Nademanee et al first reported a high success rate of CFAE ablation for AF,³ but the following reports and meta-analysis were controversial.⁹ The STAR AF II trial reported that CFAE ablation plus PVI did not improve the success rate compared with PVI alone.⁴ In many reports on CFAE ablation, the ablation sites were chosen in a non-consistent manner, and this may have contributed to the production of new arrhythmogenic substrates and AT. In the present CFAE-guided EEPVI group, after the single procedure, 41% of the recurrence consisted of AT. But the mapping of AT in the second procedure showed a focal source from a gap in the PVI line during PV tachycardia; macro-reentry between LA and PV through double gaps; and localized reentry at the LA near the line and right atrium. All AT except for 2 of unknown origin were successfully ablated and the outcome after second ablation was favorable. This suggests that CFAE-guided EEPVI did not produce another arrhythmogenic source.

Another Adjunctive Therapy With PVI

Our approach is similar to stepwise ablation, but additional CFAE ablation after PVI has a possibility to leave the arrhythmogenic source near the PV line or make a new substrate. In fact, many recurring AT after first ablation originated from para-PV sites. Rotor ablation is thought to be reasonable to eliminate spiral waves or localized reentry. The CONFIRM trial showed that ablation guided by focal impulse and rotor modulation (FIRM) using a computational mapping system was more durable than conventional trigger-based ablation in preventing 3-year AF recurrence,¹⁴ but Buch et al reported that long-term clinical results after FIRM ablation showed poor efficacy.¹⁷ Non-invasive body surface mapping to detect distribution of reentrant drivers was tried,¹⁸ and ablation targeting these drivers in a multi-center trial resulted in favorable

AF-free survival at 1 year.¹⁹ These new approaches to identify rotors of AF can improve the success rate of AF ablation.

Study Limitations

Several limitations to this study warrant mention. First, CFAE mapping may depend on the contact of the catheter. If the contact force of a catheter on the endocardium is not sufficient, the atrial activation shows low voltage and the atrial cycle length is underestimated. The Navx system can automatically exclude mapping data far from the geometry of the surface. Furthermore we used only distal electrodes of the ablation catheter for CFAE mapping, and confirmed the contact of the catheter and atrial electrograms at each point. Second, CFAE from the right atrium were not analyzed in this study. CFAE in the right atrium as well as LA have been described, and Chen et al reported that half of the patients with persistent AF refractory to LA ablation successfully converted to AT or SR during CFAE-guided ablation at the right atrium.²⁰ In cases of AF recurrence but not of AT after CFAE-guided EEPVI, CFAE in the right atrium might be targeted in the second procedure. Third, this study was not designed as a randomized controlled trial and the statistical analysis might have been influenced by the relatively small size of the subject group. In the future a large-scale randomized trial will be necessary.

Conclusions

The CFAE area of the roof of the left superior PV near the LA appendage and anterior side of the right PV near the atrial septum were widely isolated compared with conventional PVI. CFAE-guided EEPVI was more effective in patients with persistent AF compared with conventional PVI after first and second procedure. Half of recurring atrial tachyarrhythmias were AT, and all AT except for 2 of unknown origin were successfully ablated in the second procedure. This suggests that CFAE-guided EEPVI eliminates the substrate of fibrillatory conduction surrounding the PV and changes AF to AT.

Disclosures

The authors declare no conflicts of interest.

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