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Original Article

Efficacy of atrial substrate modification based on dominant frequency of paroxysmal atrial fibrillation

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ABSTRACT

Background: The endpoint of ablation procedures is suggested to be non-inducibility of paroxysmal atrial fibrillation (PAF). However, the prognosis of induced AF/atrial tachycardia (AT) after pulmonary vein isolation (PVI) in PAF patients remains unclear.

Methods: A total of 122 PAF patients were divided into the following 3 groups: Group 1, 79 without AF/AT induced after PVI; Group 2, 21 with AF/AT induced or sustained after PVI, and followed by a high-dominant frequency (DF) and continuous complex fractionated atrial electrogram (CFAE) site ablation and, if necessary, linear ablation; and Group 3, 22 with external cardioversion of AF/AT induced or sustained after PVI. High-DF (DF $\geq$ 8 Hz) and continuous CFAE (fractionated intervals $\leq$ 50 ms) sites were targeted. The ablation endpoint was non-inducibility of PAF.

Results: In Group 2, AF terminated in 2 patients with a high-DF and continuous CFAE site ablation. In 4 patients, AF induced after cardioversion did not terminate with left atrium linear ablation, and required additional cardioversion. Common atrial flutter in 2 patients terminated with cavotricuspid isthmus ablation. An AT terminated with a roofline ablation. Finally, no AF/AT could be induced in any of the patients in Group 2 after all the procedures. The cumulative freedom from AF/AT recurrence without antiarrhythmic drugs in Groups 1 and 2 was significantly greater than that in Group 3 after 1 procedure during 12 months of follow-up (90% and 91% vs. 64%, Log-rank test $P=0.001$ and $P=0.033$, respectively).

Conclusions: Atrial substrate ablation may improve the clinical outcome after ablation in patients after PVI with residual arrhythmia inducibility.

1. Introduction

Catheter ablation is an effective therapy for atrial fibrillation (AF). Pulmonary vein isolation (PVI) has become an accepted treatment for AF [1]. Atrial substrate modification is considered necessary in patients with non-paroxysmal AF (NPAF) rather than paroxysmal AF (PAF) [2,3]. The endpoint of the ablation procedure has been suggested to be the non-inducibility of PAF. For PAF, an additional ablation of non-PV AF triggers is considered necessary in addition to the PVI. However, prior reports showed AF recurrence rates of 19–33% in the non-induced group and 36–55% in the induced group [4–6]. The diagnostic accuracy of AF induction tests after ablation seems to be low for predicting AF recurrences. Therefore, the need for further ablation of the induced atrial arrhythmias after the PVI in PAF patients remains unclear.

The efficacy of PVI is sometimes insufficient, and atrial substrate modification of target specific AF signals indicating the substrate responsible for AF perpetuation has been proposed [7,8]. Complex fractionated atrial electrograms (CFAEs), which are electrograms that show continuous fractionation and very short cycle lengths during AF, may represent the substrate of AF [7]. In addition, atrial sites that represent local electrograms with high dominant frequencies (DFs) may be associated with AF maintenance [8]. A recent study reported that high-DF sites and continuous CFAE sites as the atrial substrate following PVI were present even in paroxysmal AF [8]. Accordingly, the present study aimed to evaluate the need of such an atrial substrate modification for the induced atrial arrhythmias after circumferential PVI to guide the non-inducibility in PAF patients.

2. Materials and methods

2.1. Study population

A total of 122 consecutive AF patients with PAF (64 $\pm$ 9.3 years) between March 2011 and October 2012 were examined in a

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retrospective review. The protocol was approved by the research and ethics committee of Gunma Prefectural Cardiovascular Center on June 15, 2012. All patients provided written informed consent. The AF duration was 35 ± 47 months (range, 2–240). Paroxysmal AF was defined as AF lasting < 7 days [9]. All antiarrhythmic drugs (AADs) except oral amiodarone administered in 2 patients were discontinued for at least 5 half-lives, and no patients received any oral amiodarone therapy before the electrophysiological study.

2.2. Fractionation and frequency analysis

The mapping parameter (CFAE-mean) was defined as an interval-analysis algorithm that measured the average index of the fractionation. Recordings at each site were 5 s in length [8,10,11]. A continuous CFAE was defined by an average fractionated interval (FI) of ≤ 50 ms, indicating a high degree of temporal stability of the fractionated electrograms maintaining AF [11,12]. The fast Fourier transform (FFT) method has been described previously [12]. Signals were truncated to 3.41 s at sampling rates of 1200 Hz, providing 4096 points for analysis (resolution, 0.29 Hz). The signals were rectified and processed by a Hanning window function and filtered from 2 to 100 Hz. The point DF was determined as the frequency associated with the maximum peak power of the spectrum. Only DF points with a fast Fourier transform ratio > 0.2 were included [13,14]. The high-DF sites were defined as DFs of ≥ 8 Hz [14].

2.3. Ablation procedure

A NavX system (NavX with CFE software, St. Jude Medical Inc., St. Paul, MN, USA) was used for catheter ablation. A 5-french deflectable catheter was inserted into the coronary sinus (CS) via the right femoral vein. The trans-septal procedure was performed using fluoroscopic landmarks, and three 8-F SL0 sheaths (St. Jude Medical Inc.) were advanced into the left atrium (LA). After the trans-septal procedure, a single bolus of 5000 U of heparin was administered. A continuous infusion with heparinized saline was administered to maintain an activated clotting time of 300–350 s. The three-dimensional biatrial geometry was created on the NavX system, and sequential contact mapping was performed using a 7-F decapolar circular catheter (Lasso, Biosense-Webster Inc., Diamond Bar, CA, USA). The points in each region were similar in number and nearly equally distributed.

The ablation procedure was performed using an approach consisting of PVI followed by high-DF and continuous CFAE site ablation and, if necessary, linear ablation. When AF organized into AT, activation mapping and ablation were performed. The endpoint of the ablation was non-inducibility. The PVI was performed guided by two 7-F decapolar circular catheters (Lasso, Biosense-Webster Inc.) positioned at the ipsilateral PV ostia. At the anterior aspect of the left PVs, an ablation line was created along the ridge between the left atrial appendage (LAA) and PV ostium. Each radiofrequency (RF) energy application was delivered for 40 s. A 3.5 mm irrigated tip RF catheter (Safire, St. Jude Medical Inc.) was used with the temperature limited to 42 °C and power of 30 W (with a flow rate of 13 mL/min). A maximum power of ≤ 25 W was used while delivering energy to sites near the esophagus. After the elimination or dissociation of the PV potentials, exit block was confirmed by pacing from circular catheters placed within the PVs.

After the PVI, fractionation and frequency analyses were performed for continuous AF or induced AF as mentioned previously [8,15]. All high-DF sites in the LA, right atrium (RA), and inside the CS were targeted for ablation, starting with the highest DF points. Ablation at a DF site was continued for 40–60 s until the local electrograms were eliminated. A maximum power of ≤ 25 W was used while delivering energy inside the CS. After the high-DF site ablation, the continuous CFAE sites were ablated, starting with the shortest fractionated interval points. The continuous CFAE site ablation was performed in the same manner as the high-DF site ablation.

When AF continued despite a high-DF and continuous CFAE site ablation, external cardioversion and induction were performed. For the induced AF, an LA linear ablation consisting of a roof line, inferior mitral annulus line, or mitral isthmus line was performed. When AF continued despite a linear ablation, external cardioversion and induction were performed. The procedure was completed with a cavotricuspid isthmus ablation in all patients who regained sinus rhythm. Finally, we tried to provoke PV reconnections by administering 10-mg intravenous injection of intravenous adenosine triphosphate (ATP) administered during an intravenous isoproterenol infusion (5 μg/min). Additional RF applications were performed to eliminate any ATP-reconnections.

2.4. Induction protocol

The atrial tachyarrhythmia inducibility was evaluated by a stimulation protocol as mentioned previously [15]. Bursts of 10 beats were delivered starting at a cycle length (CL) of 250 ms at a pacing output of 10 mA and 2 ms pulse width. The 10 beat bursts were repeated with 10 ms decrements for each subsequent burst until 2:1 atrial capture or a minimum CL of 190 ms. The stimulation protocol consisting of one induction attempt was performed from the LA using bipolar electrodes in the distal CS without an isoproterenol injection. Induced AF/AT was defined as that sustained for at least 2 min [16].

2.5. Post-procedure care and follow-up

A surface electrocardiogram (ECG) and 24-h Holter monitoring were obtained 1 day after the procedure and repeated 1, 3, 6, 8, 10, and 12 months thereafter by the referring cardiologist in our hospital as mentioned previously [15]. Antiarrhythmic medications were continued for at least 3 months to prevent any early recurrences of AF unless AF continued. When the patients had any clinical symptomatic palpitations after the AF ablation, examinations including an ECG, 24-h Holter monitoring, and assessment of the current condition were also performed on an outpatient basis. AF recurrence was defined as sustained AF lasting more than 30 s and confirmed by ECGs 3 months after the ablation [16]. A repeat ablation procedure was performed if AF recurred or there was an AT lasting more than 30 s. Procedural success was defined as a lack of AF or AT beyond 3 months post-ablation [9].

2.6. Statistical analysis

Continuous data are expressed as means ± SDs. Categorical variables are expressed as numbers and percentages. If the data showed a normal distribution, one-way analysis of variance was performed to identify statistically significant differences between the 3 groups. If the data did not have a normal distribution, the Kruskal–Wallis *H*-test was used. A Bonferroni post hoc test was used to compare the different groups. A Kaplan–Meier event-free survival analysis was conducted to assess the cumulative freedom from AF recurrence. Time-to-event analyses were performed using the Log-rank test. A *P* value of less than 0.05 was considered statistically significant.

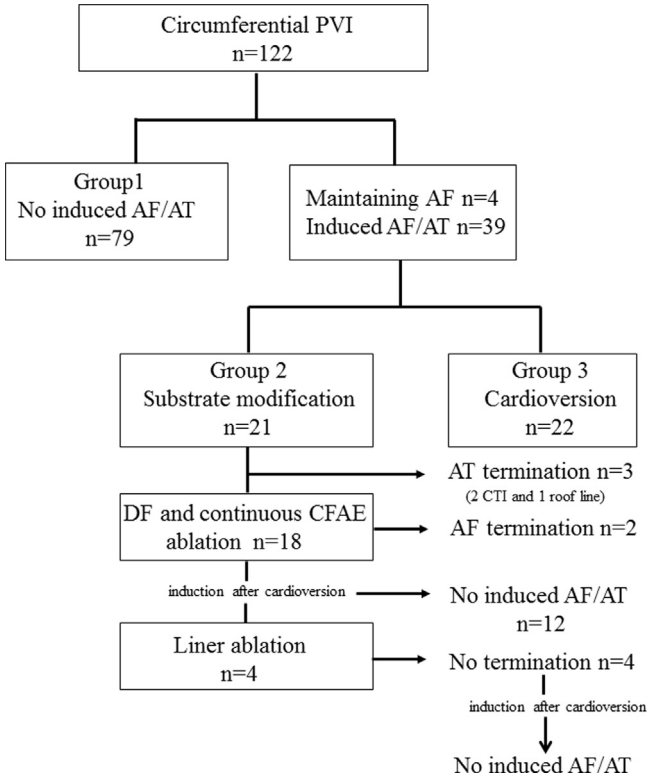

Fig. 1. Flowchart of the patients with the subsequent ablation steps. AF=atrial fibrillation; AT=atrial tachycardia; CFAE=continuous fractionated atrial electrograms; CTI=cavotricuspid isthmus; DF=dominant frequency; PVI=pulmonary vein isolation.

3. Results

3.1. Patient characteristics

A total of 122 consecutive PAF patents were enrolled. At the beginning of the procedure, 19 (16%) of the patients were in AF. While AF/AT could not be induced in 79 (65%) of the patients after the PVI (Group1), AT/AT could be induced in 39 (32%), and AF continued in 4 (3%). The patients, except for those in Group 1, were retrospectively divided into 2 groups as follows: Group 2, 21 with AF/AT induced or sustained after the PVI, and followed by a high-DF and continuous CFAE site ablation and, if necessary, linear ablation; and Group 3, 22 with external cardioversion for the AF/AT induced or sustained after the PVI (Fig. 1). The patient characteristics are summarized in Table 1. There were no significant differences in the patient characteristics except for the left ventricular ejection fraction. However, the left ventricular ejection fraction in all patients was within the normal range. None except for 4 patients (2 with hypertrophic cardiomyopathy and 2 with a previous myocardial infarction) had structural heart disease.

3.2. AF substrate mapping analysis after the PVI

High-DF sites were mainly observed on the posterior wall (10.6 Hz) and septum (10.7 Hz) of the LA in Group 2 after the PVI. High-DF sites after the PVI were observed at an average of 5.0 ± 3.3 sites (3.3 ± 2.3 in the LA and 1.8 ± 1.6 in the RA) per patient. Continuous CFAE sites after the PVI were observed at an average of 1.2 ± 2.4 sites (0.9 ± 2.3 in the LA and 0.2 ± 0.4 in the RA) per patient.

Table 1
Baseline characteristics.

	All ($N=122$)	Group 1 ($n=79$)	Group 2 ($n=21$)	Group 3 ($n=22$)	P value
Age (years)	64 ± 9.3	64 ± 10	65 ± 8.4	66 ± 8.4	0.485
Men	86 (71%)	55 (70%)	17 (81%)	14 (64%)	0.449
History of AF (months)	35 ± 47	33 ± 45	50 ± 67	29 ± 27	0.302
CHA2DS2-VASc score	1.7 ± 1.3	1.7 ± 1.3	1.7 ± 1.3	1.6 ± 1.1	0.969
0 or 1	57	37	10	10	0.990
2 or more	65	42	11	12	0.990
Hypertension	67 (55%)	46 (58%)	11(52%)	10 (45%)	0.555
LA diameter (mm)	39 ± 6.8	39 ± 7.4	39 ± 6.2	38 ± 4.6	0.854
LVEF (%)	67 ± 8.5	68 ± 9.0	63 ± 7.1*	67 ± 6.6	0.047
BNP (pg/mL)	74 ± 78	77 ± 75	91 ± 110	44 ± 34	0.108
Number of failed AADs	1.1 ± 0.5	1.1 ± 0.4	1.1 ± 0.4	1.2 ± 0.9	0.365

Data given as n, n (%), or mean $\pm$ SD. AADs=antiarrhythmic drugs; AF=atrial fibrillation; BNP=B-type natriuretic peptide; LA=left atrium; LVEF=left ventricular ejection fraction.

* $P < 0.05$ vs. Group 1.

3.3. Short-term outcome of all procedures

The procedural parameters and follow-up data are summarized in Table 2. Fig. 1 shows a flowchart of the patients with the subsequent ablation steps. In Group 2, the AF terminated in 2 patients (a DF at an anterior site and CFAE at a posterior site, respectively) by ablation at high-DF and continuous CFAE sites (Fig. 2). In 2 patients, common atrial flutter was terminated by cavotricuspid isthmus ablation. A case of AT was terminated by roofline ablation. Cardioversion was performed for continuous AF in 16 of 21 patients. In 4 patients, AF induced after cardioversion for continuous AF did not terminate after an LA linear ablation consisting of a roof line, inferior mitral annulus line, or mitral isthmus line, and required cardioversion once more. Finally, no AF or other atrial arrhythmias could be induced in any of the patients in Group 2 after all the procedures. In Group 3, AF in 20 patients and AT in 1 patient could be induced, and AF continued in 1 patient after the PVI. Cardioversion was performed for all ATs induced or sustained after the PVI.

3.4. Long-term outcome of all procedures

The freedom from AF/AT recurrence without antiarrhythmic drugs was 85% in the PAF patients after 1 procedure over a mean follow-up of 12 months (Group 1: 90% and Group 2 and 3: 77%). The recurrence in 1 patient after 3 months was in the form of AT. The cumulative freedom from AF/AT recurrence without antiarrhythmic drugs in Group 1 and Group 2 was significantly greater than that in Group 3 after 1 procedure during 12-months of follow-up (90% and 91% vs. 64%, Log-rank test $P=0.001$ and $P=0.033$, respectively) (Fig. 3). There were no cases of cerebral infarction, cardiac perforation, tamponade, PV stenosis, or atrial-esophageal fistula.

4. Discussion

The major findings of this study were as follows: (1) the atrial substrate modification for the patients with induced ATs after the PVI was effective for AF/AT freedom during 12 months of follow-up and (2) a high-DF and continuous CFAE ablation and linear ablation following the PVI could lower the AF inducibility. This guide of the non-inducibility after the PVI may be useful for

Table 2
Procedural parameters and follow-up data.

	All ($N=122$)	Group 1 ($n=79$)	Group 2 ($n=21$)	Group 3 ($n=22$)	P value
Procedural data					
Total procedure duration (min)	182 ± 50	184 ± 48	217 ± 51*	139 ± 17**,†	0.001
Ablation time for PVI (min)	42 ± 11	44 ± 11	38 ± 7*	34 ± 8**	0.001
Ablation time for DF ablation (min)	–	–	7.6 ± 4.2	–	–
Ablation time for CFAE ablation (min)	–	–	4.9 ± 2.8	–	–
AF at the beginning of the procedure	19 (16%)	10 (13%)	6 (29%)	3 (14%)	0.198
AF maintenance after PVI	5 (4%)	0	4 (19%)**	1 (5%)†	0.001
AF inducibility	34 (28%)	0	14 (67%)**	20 (95%)**	0.001
ATs inducibility	4 (3%)	0	3 (14%)**	1 (5%)	0.004
Clinical outcome					
AF/AT recurrence after 3 months	18 (15%)	8 (10%)	2 (10%)	8 (36%)**,†	0.006
2 procedures	3 (3%)	2 (3%)	1 (5%)	0 (0%)	0.604
AADs usage	16 (13%)	7 (6%)	1 (5%)	8 (36%)*,**	0.001
AT recurrence	1 (1%)	0	0	1 (5%)	–

Data given as n, n (%), or mean ± SD. AADs=antiarrhythmic drugs; AF=atrial fibrillation;
AT=atrial tachycardia; CFAE=continuous fractionated atrial electrogram; DF=dominant frequency; PVI=pulmonary vein isolation.

* $P<0.05$ vs. Group 1.
** $P<0.01$ vs. Group 1.
† $P<0.01$ vs. Group 2.

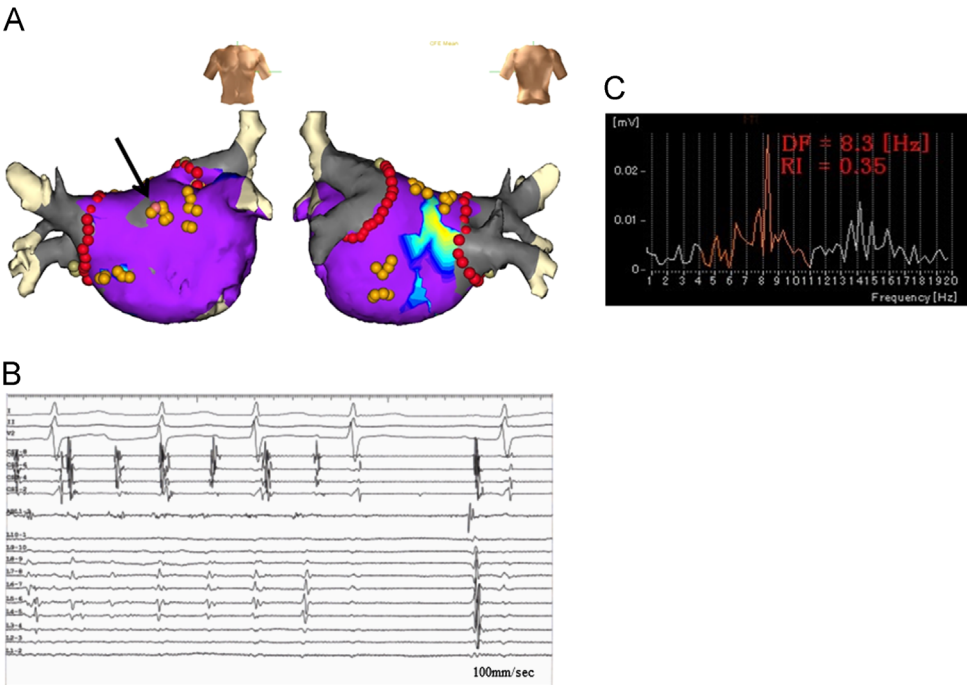

Fig. 2. Ablation of high-DF sites for induced AF after circumferential PVI in a PAF patient. (A) For induced AF after the circumferential PVI (red tag), all high-DF sites (orange tag) in the LA were targeted for ablation starting with the highest DF points. (B) By ablation at a high-DF site (8.3 Hz) at an anterior site (pink tag), the AF terminated. (C) The high-DF site was determined as the frequency associated with the maximum peak power of the spectrum. Non-CFAEs in the CFAE mean maps were defined as those with a fractionated interval of >120 ms (purple). ABL=ablation catheter; AF=atrial fibrillation; CFAE=complex fractionated atrial electrograms; CS=coronary sinus; DF=dominant frequency; L=left superior pulmonary vein; LA=left atrium; RI=regularity index; PVI=pulmonary vein isolation.

decision-making regarding the need for additional ablation in patients with PAF.

4.1. Previous studies

The inducibility did not necessarily predict the prognosis [4–6]. These conflicting results may depend on the differences in the modest or aggressive pacing protocols of inducibility: the location of the pacing sites (RA and/or CS), minimum burst CL from 150 to 200 ms, with or without isoproterenol use, and the definition of the induced atrial arrhythmias (10 s up to 10 min) [4–6]. Furthermore, AF could be induced with an aggressive stimulation protocol in all patients [17]. The induction of short-term AF may be regarded as a rather non-specific phenomenon [6]. Therefore, there was a limitation concerning a more aggressive stimulation protocol after the AF ablation for the prognosis and guiding further additional lesion sets in induced atrial arrhythmias because of the increase in the number of non-specific AF inductions [4–6].

Our data showed AF/AT freedom rates of 90% in Group 1 and 91% in Group 2 with a possible minimal ablation after the PVI by

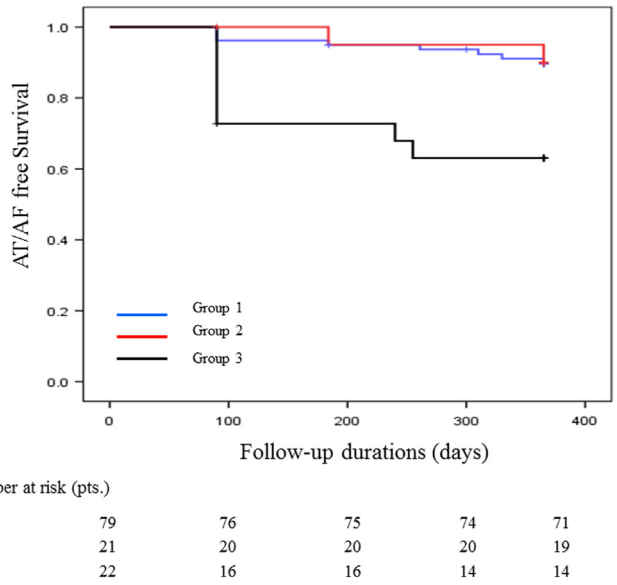

Fig. 3. Comparison of the freedom from AF/AT recurrence. The cumulative freedom from AF/AT recurrence without antiarrhythmic drugs in Group 1 and Group 2 was significantly greater than that in that in Group 3 after 1 procedure during 12-months of follow-up (90% and 91% vs. 64%, Log-rank test $P=0.001$ and $P=0.033$, respectively). AF=atrial fibrillation; AT=atrial tachycardia.

using a comparable non-aggressive stimulation protocol. Furthermore, both the inducibility and recurrence might be in the form of AF in almost all cases.

4.2. Substrate modification in PAF patients

The endpoint of ablation procedures has been suggested to be the non-inducibility of PAF. In PAF, an additional ablation of non-PV AF triggers initiating AF is considered necessary in addition to PVI [9]. However, the success rates free of antiarrhythmic drugs and overall success rates were 74.9% and 83.2%, respectively, in the patients with paroxysmal AF in the updated worldwide survey [1]. This may indicate the presence of other atrial substrates that help maintain AF. A high-DF and continuous CFAE ablation following PVI could also lower the AF inducibility. Furthermore, the use of PVI with CFAE ablation for PAF patients did not increase the rate of freedom of ATs, compared to the use of PVI alone in a previous report by Hayward et al (79% vs. 74%) [18]. Substrate ablation using CFAE and linear ablation were verified in the STAR AF II trial as well [19]. However, in the present study, the number of continuous CFAEs and high-DF sites as an atrial substrate was lower than that previously described [8], which may be associated with the AF maintenance. Further, a linear ablation involving a roof line or mitral isthmus line was needed in only 4 of 21 (19%) patients in Group 2 because of the achievement of a lower inducibility by a high-DF and continuous CFAE ablation. Therefore, by limiting the extent of the RF applications to the atria, this strategy may help limit occurrences of post-ablation ATs that follow a more aggressive ablation, which differs from the results of the STAR AF II trial [19–21].

High-DF and continuous CFAE sites were used as a clinical surrogate for localized AF sources. We previously reported that a $\geq$ 10% CS CL prolongation [15] without any acute AF termination was observed during the PVI followed by a combined high-DF and continuous CFAE site ablation and that this strategy could also render AF non-inducible. This suggested that the atrial substrate was modified irrespective of AF termination. The high-DF sites are reported to be related to the center of a focal-firing rotor or local reentry circuit and to harbor high-frequency sites, producing a favorable condition for maintenance of AF [22]. Therefore, the elimination of the harbor sites may render AF non-inducible.

4.3. Clinical implications

A prognosis of induced AF/AT after the PVI in PAF patients remains unclear. However, the AF/AT freedom without antiarrhythmic drugs was lower in the induced Group without a substrate modification. Therefore, a modification of atrial substrates with high-DF sites and continuous CFAE sites among the many CFAEs as a surrogate for sources of AF maintenance may be needed. Furthermore, relatively fewer potential targets for AF ablation may be adequate to modify atrial substrates. AF/AT could be induced in 35% of cases after the PVI, which means that a circumferential PVI is a very effective approach for substrate modification, and that atrial structural and functional impairment emerged owing to atrial fibrosis resulting from atrial progressive structural remodeling among the patients with PAF [23]. However, a more aggressive stimulation protocol after AF ablation may produce an increase in the number of non-specific AF inductions [4–6].

4.4. Study limitations

The present study has some limitations. First, it was a single-center retrospective study with a relatively small population. Therefore, selection bias of the clinical variables and different atrial substrates among groups might have existed. Second, the difference in total procedure time and ablation time for PVI might have resulted in better durability of PVI and clinical outcome. However, we performed a final verification and elimination of dormant PV conduction at the end of procedure in all patients. Third, we used a non-aggressive stimulation protocol without an isoproterenol infusion to decrease the non-specific atrial arrhythmias and additional lesion sets. Finally, AF recurrence was evaluated using surface ECGs and 24-hour Holter monitoring. Accordingly, asymptomatic AF recurrences may have been overlooked in the present study. An implantable loop-recorder may reveal a more accurate AF recurrence rate.

5. Conclusions

Non-inducibility of AF/AT after the PVI indicated a greater AF/AT freedom. A guide of the non-inducibility after the PVI may be useful for deciding whether additional ablation is needed in patients with PAF. Atrial substrate ablation may improve the clinical outcome after ablation in patients after PVI with residual arrhythmia inducibility.

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Conflict of interest

All authors declare no conflict of interest related to this study.

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