



Original Article

Evaluation of the characteristics of rotational activation at high-dominant frequency and complex fractionated atrial electrogram sites during atrial fibrillation

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ABSTRACT

Background: High-dominant frequency (DF) and continuous complex fractionated atrial electrogram (CFAE) sites as surrogates for localized sources maintaining atrial fibrillation (AF) are potential AF ablation targets. This study aimed to evaluate the characteristics of a rotational activation at high-DF and continuous CFAE sites in AF patients.

Methods: Thirty-two consecutive AF patients (5 paroxysmal and 27 non-paroxysmal) underwent ablation using the NavX system. When AF continued after circumferential pulmonary vein isolation (PVI), high-DF sites of ≥ 8 Hz and continuous CFAE sites (fractionated intervals ≤ 50 ms) in the left (LA) and right (RA) atria were recorded using a high-density 20-pole circular mapping catheter for 5 s and ablated. **Results:** The atrial electrogram characteristics during AF were assessed. A total of 2383 AF beats from 89 high-DF and 19 continuous CFAE sites were investigated. A rotational activation of high-DF and continuous CFAE sites was also observed at 4% and 3% of LA, and 4% and 4% of RA sites, respectively. However, rotational activation was identified in 29 (91%) of 32 patients (mean 3.0 ± 2.6 beats per patient, 80% in the LA). Procedural endpoints were achieved in 26 (81%) of 32 patients: AF termination ($n=2$) and AF cycle length slowing of $> 10\%$ ($n=26$).

Conclusions: Rotational activation could be identified in high-DF and continuous CFAE sites during AF, but the documentation was limited. Therefore, only limited effects of rotational activation ablation at high-DF and/or continuous CFAE sites following PVI could be concluded.

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1. Introduction

Pulmonary vein isolation (PVI) has become an accepted treatment for atrial fibrillation (AF) [1]. 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 [2,3]. Complex fractionated atrial electrograms (CFAEs), which are electrograms that demonstrate continuous fractionation and very short cycle lengths during AF, may represent the substrate of AF [2,3]. In addition, atrial sites that represent local electrograms with high-dominant frequencies (DFs) may be associated with AF maintenance [4–6]. We reported that a combined high-DF site and continuous CFAE site (fractionated intervals ≤ 50 ms)

ablation for the atrial substrate following PVI was effective in both paroxysmal and persistent AF [7]. High-DF and continuous CFAE sites as surrogates for localized sources maintaining AF were potential AF ablation targets [7]. On the other hand, localized electrical sources (rotor and focal impulse) have been reported to be prevalent sustaining mechanisms of human AF using a specific computational mapping device [8]. The patients who underwent a focal impulse and rotor modulation (FIRM)-guided ablation maintained a higher freedom from AF. However, AF rotors did not exhibit consistent or characteristic fractionated electrogram features [9,10]. In another report, FIRM-identified rotor sites did not exhibit any quantitative atrial electrogram characteristics and rotor ablation resulted in AF termination or organization in a minority of the patients [11]. Therefore, this study aimed to evaluate the atrial characteristic electrogram features at high-DF and continuous CFAE sites during AF using a high-density 20-pole circular mapping catheter.

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2. Materials and methods

2.1. Study population

A total of 32 consecutive AF patients (57 ± 12 years) between April 2013 and December 2013 were examined in a prospective review. Paroxysmal AF was defined as AF lasting < 7 days, persistent AF as AF lasting ≥ 7 days but < 1 year, and long-standing AF as continuous AF lasting ≥ 1 year [12]. All anti-arrhythmic drugs were discontinued for at least 5 half-lives, and no patients received any oral amiodarone therapy before the electrophysiological study. The protocol was approved by the institution research and ethics committee of Gunma Prefectural Cardiovascular Center on June 15, 2012. All patients provided written informed consent.

2.2. Electrophysiological study

The NavX system (NavX with CFE software, St. Jude Medical Inc., St. Paul, MN, USA) was used for catheter ablation. A 5-F 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 SLO 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 3-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 mapping was performed during AF.

2.3. 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 [4]. A continuous CFAE was defined by an average fractionated interval of ≤ 50 ms, indicating a high degree of temporal stability of the fractionated electrograms maintaining AF [4]. The fast Fourier transform method has been described previously [4]. 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 DF point was determined as the frequency associated with the maximum peak power of the spectrum. Only DF points with a fast Fourier transform ratio of > 0.2 were included [5,6]. The high-DF sites were defined as DFs of ≥ 8 Hz [6].

2.4. Atrial electrogram characteristics analysis

When AF continued after the circumferential PVI, high-DF sites and continuous CFAE sites in the LA and right atrium (RA) were recorded using a high-density 20-pole mapping circular catheter (St. Jude Medical Inc.) for 5 s and ablated. The roving acquisition interval was defined as the mean cycle length of 10 beats using a regular potential from the CS. The creation of a manual propagation map for 5 s during AF was performed and assessed retrospectively. A total of 2383 maps were created. The activation pattern at high-DF and continuous CFAE sites in the LA and RA was classified into the following 6 patterns: rotation, pivot, slow conducting channels, focal, passive, and wave collision (Fig. 1). A rotation was visually defined as a rotational activation of ≥ 1 rotation with a serial electrogram encompassing the time window. A pivot was defined as the core of the rotational activation. All measurements were performed by 2 independent observers

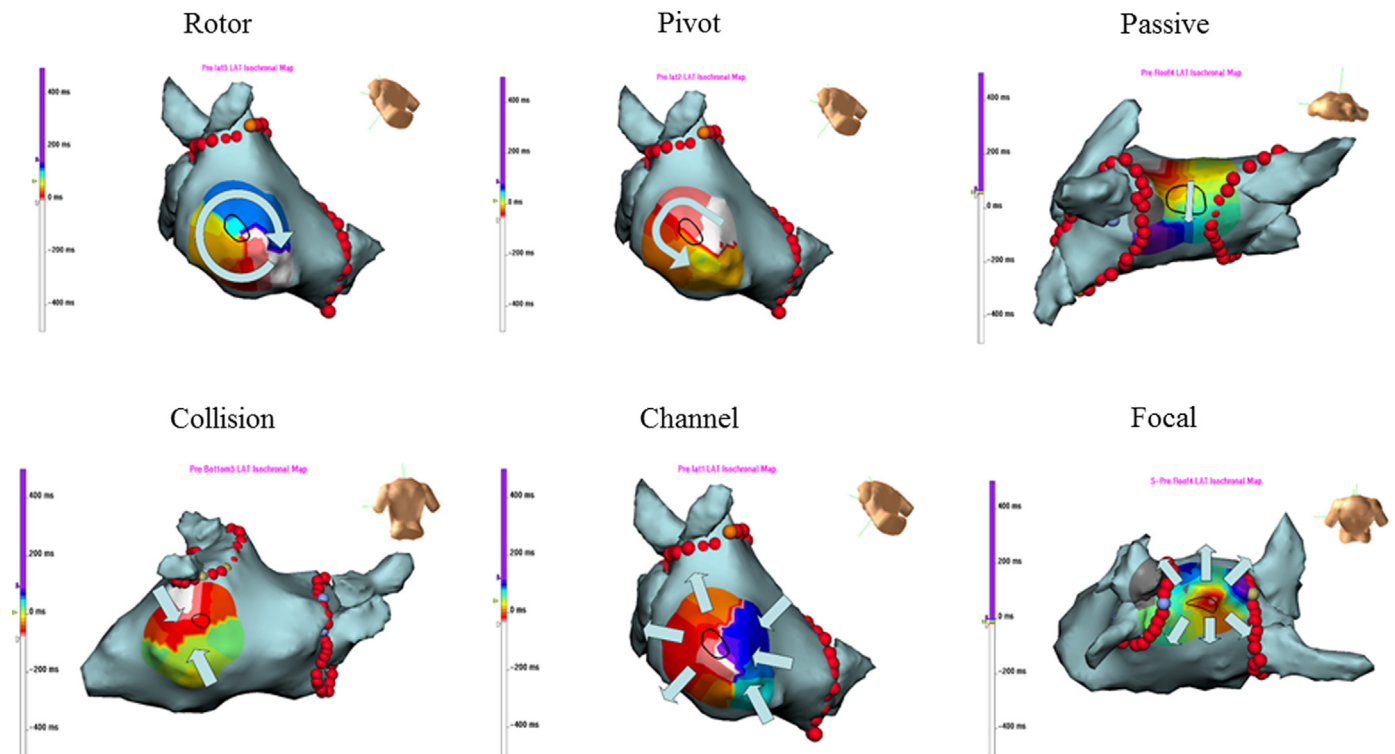


Fig. 1. Representative activation pattern in atrial fibrillation. The activation pattern of 6 typical examples at high-dominant frequency and continuous complex fractionated atrial electrogram sites in atrial fibrillation are shown.

blinded to the ablation sites. If there was an inter-observer difference, the final decision was made by a joint meeting of the observers.

2.5. Ablation approach

The ablation procedure was performed using an ablation approach consisting of a PVI followed by a high-DF and continuous CFAE site ablation. When AF organized to atrial tachycardia (AT), activation mapping and ablation were performed. The procedural endpoint of the ablation was defined as termination of AF during the procedure or > 10% slowing of the AF cycle length from after the PVI to the end of the high-DF and continuous CFAE site ablation [13]. The AF cycle length was determined for each patient after the PVI and at the end of the high-DF and continuous CFAE site ablation. All cycle lengths recorded for 5 s were measured in the CS and averaged for each cycle length measurement.

The PVI was performed guided by two 7-F decapolar circular catheters (Lasso, Biosense-Webster, Inc.) positioned at the ipsilateral PV ostia [7]. At the anterior aspect of the left PVs, an ablation line was created along the ridge between the left atrial appendage and PV ostium. Each radiofrequency energy application was delivered for 40 s. A 3.5-mm irrigated tip radiofrequency catheter (Safire, St. Jude Medical Inc.) was used with the temperature limited to 42 °C and power to 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 maintained AF and induced AF as mentioned above [7]. All high-DF sites in the LA and RA 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. 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 was maintained after all high-DF and continuous CFAE site ablation procedures, external cardioversion was performed. The procedure was completed with cavotricuspid isthmus ablation in all patients who regained sinus rhythm. Finally, we tried to provoke PV reconnections with a 10-mg intravenous injection of intravenous adenosine triphosphate administered during an intravenous isoproterenol infusion (5 µg/min). Additional radiofrequency applications were performed to eliminate any adenosine triphosphate reconnections [14]. After recovering sinus rhythm, the atrial arrhythmia inducibility was evaluated by the following stimulation protocol. Bursts of 10 beats were delivered starting at a cycle length of 250 ms at a pacing output of 10 mA with a 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 cycle length of 190 ms. The stimulation protocol consisting of 1 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 [15].

2.6. Post-procedure care and follow-up

A clinical interview, 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

Table 1
Patient characteristics.

	All (n=32)	Termination or prolongation (n=26)	No termination or prolongation (n=6)	P-value
Age (years)	57 ± 12	59 ± 7	57 ± 13	0.944
Sex (male/ female)	28/4	23/3	5/1	0.869
Paf/Per/LS	5/16/11	5/11/10	0/5/1	0.832
Duration of AF (months)	36 ± 74	22 ± 36	39 ± 81	0.621
Hypertension	12	8	4	0.189
CHA2DS2-VASc	1.3 ± 1.3	1.2 ± 1.4	1.5 ± 1.4	0.655
Structural heart disease	1	1	0	–
LA diameter (mm)	41 ± 5	40 ± 4	41 ± 5	0.944
LVEF (%)	63 ± 8	62 ± 9	65 ± 7	0.381
BNP (pg/mL)	112 ± 106	111 ± 105	117 ± 122	0.588
Number of failed AAD	0.9 ± 0.8	1.0 ± 0.8	0.7 ± 0.5	0.494

AAD=antiarrhythmic drugs; AF=atrial fibrillation; BNP=brain natriuretic peptide; CHA2DS2-VASc=Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, history of ischemic stroke or TIA, Vascular disease, Age of 65–74 years and Female sex; LA=left atrium; LVEF=left ventricle ejection fraction; Paf/Per/LS=Paroxysmal AF/persistent AF/long-standing AF.

referring cardiologist in our hospital. 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 [12]. 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 [12].

2.7. Statistical analysis

Continuous data are expressed as the mean ± SD. Comparisons of normally distributed data were performed through the use of an unpaired Student *t*-test. Comparisons of data not normally distributed were performed using a Wilcoxon signed-rank or rank-sum test for unpaired data, respectively. Categorical variables are expressed as numbers and percentages. A value of *P* < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The patients' characteristics are summarized in Table 1. A total of 32 consecutive AF patients (5 paroxysmal and 27 non-paroxysmal) were enrolled. The patients included 16 (50%) with persistent AF (duration 7.1 ± 3.6 months, range 2–12) and 11 (34%) with long-standing persistent AF (duration of 86 ± 112 months, range 17–408). None except for 1 with dilated cardiomyopathy had structural heart disease.

3.2. AF wavelet activation analysis after the PVI

A total of 2383 AF beats from 89 high-DF and 19 continuous CFAE sites were investigated (Table 2). The high-DF sites were

frequently located on the bottom, anterior, and septal regions of the LA, and the septal and lateral regions of the RA (Fig. 2). The continuous CFAE sites were frequently located on the posterior and septal regions of the LA and lateral region of the RA (Fig. 2). High-DF and continuous CFAE sites in the cavotricuspid isthmus were observed in 17% and 20% of patients, respectively. The mean high-DF value was 9.7 ± 1.0 Hz in the LA and 9.6 ± 0.7 Hz in the RA.

A rotational activation at high-DF sites (Fig. 3) was also observed at 4% of LA and 4% of RA sites (Table 2). A rotational activation at continuous CFAE sites was also observed at 3% of LA and 4% of RA sites. The AF maintenance-related activation (rotation, pivot, slow conducting channels, and focal) was detected in 23% in the LA and 20% in the RA of all high-DF sites and 23% in the LA and 28% in the RA of all continuous CFAE sites. However, rotors were identified in 29 (91%) of 32 patients (mean 3.0 ± 2.6 per patient, 80% in the LA) (Table 3). A mean of 1.3 ± 0.7 rotations per rotor was observed. There were no significant differences between

the patients with and without achievement of procedural endpoints for the number with rotors, but the mean high-DF site in the RA was significantly lower in the patients without achievement of procedural endpoints.

3.3. Acute and chronic outcome of all procedures

Procedural endpoints were achieved in 26 (81%) of 32 patients: AF termination ($n=2$) and slowing of the AF cycle length of $>10\%$ (mean 31 ± 41 ms, $n=26$). The procedural parameters and follow-up data are summarized in Table 4. At the beginning of the procedure, 28 patients were in AF, and 4 in AF induced during mapping. The AF was terminated in 2 of 32 patients by ablation, 1 with longstanding AF at a continuous CFAE site within the CS, and 1 with paroxysmal AF at a high-DF site in the anterior LA. After the PVI and high-DF and continuous CFAE site ablation following cardioversion, AF could not be induced in 24 of 32 patients, while AF and atrial flutter could be induced in 7 and 1 patient(s), respectively. One atrial flutter was terminated by a roof-line ablation. Freedom from AF recurrence off and on anti-arrhythmic drugs was achieved in 24 of 32 (75%) and 26 of 32 (81%) patients after 1 procedure, respectively, during a 12 month follow-up. However, there were no differences in the AF freedom between the patients with and without achievement of procedural endpoints. There were no cases of cerebral infarctions, cardiac perforations, tamponades, PV stenosis, or atrial-esophageal fistulae.

4. Discussion

The major findings of this study were, (1) rotational activation could be detected in about 4% of all AF beats recorded in high-DF and continuous CFAE sites using a high-density 20-pole circular

Table 2
Distribution of AF propagation patterns.

Sites, n	LA		RA	
	DF (66)	CFAE (14)	DF (23)	CFAE (5)
Rotation	74 (4%)	2 (3%)	18 (4%)	1 (4%)
Pivot	204 (11%)	6 (9%)	48 (10%)	3 (12%)
Channel	102 (6%)	5 (7%)	18 (4%)	3 (12%)
Focal	32 (2%)	3 (4%)	10 (2%)	0
Passive	653 (36%)	30 (43%)	174 (38%)	13 (52%)
Collision	436 (24%)	23 (33%)	102 (22%)	5 (20%)
N/A	369 (20%)	1 (1%)	94 (20%)	0
All AF beats, n	1824 (100%)	70 (100%)	464 (100%)	25 (100%)

AF=atrial fibrillation; CFAE=complex fractionated atrial electrogram; DF=dominant frequency; LA=left atrium; RA=right atrium.

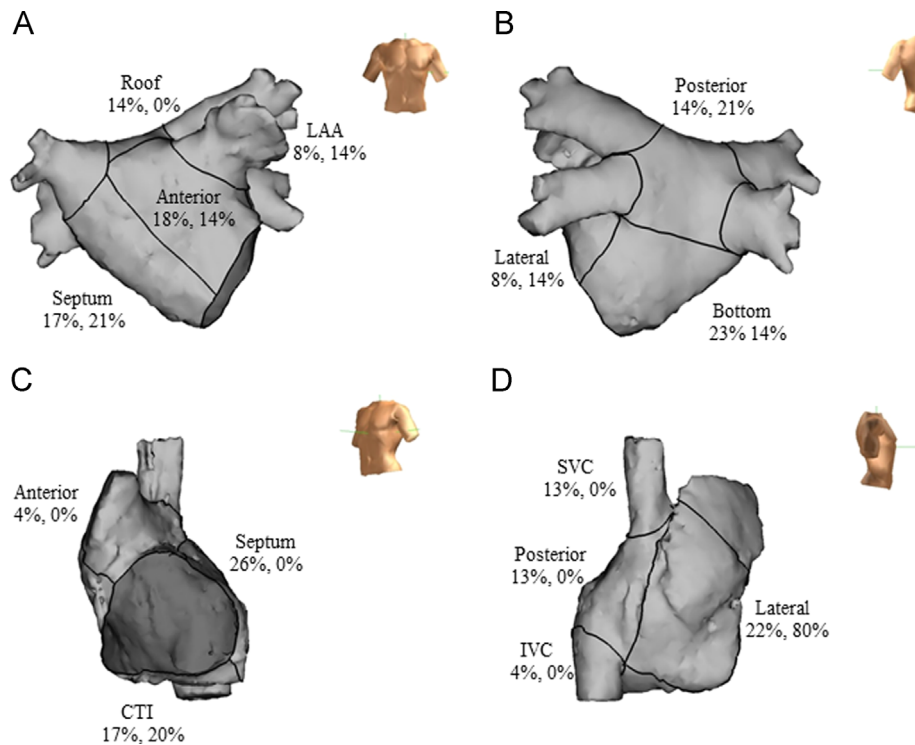


Fig. 2. Segmentation of the atrium. The left atrium was segmented into 9 areas (A, B), and the right atrium into 7 areas (C, D). The coronary sinus is not shown. The distribution of the high-dominant frequency sites (former) and continuous complex fractionated atrial electrogram sites (latter) are shown. CTI=cavotricuspid isthmus; IVC=inferior vena cava; LAA=left atrial appendage; SVC=superior vena cava.

mapping catheter. However, a rotational propagation of at least ≥ 1 was identified in 29 (91%) of 32 patients; (2) procedural endpoints were achieved in 26 (81%) of 32 patients: AF cycle length slowing of $> 10\%$ including AF termination; and (3) AF freedom without antiarrhythmic drugs was achieved in 24 of 32 patients (75%) during 12 months of follow-up. In this study, we demonstrated that rotational activation could be identified in

high-DF and continuous CFAE sites during AF although the documentation was limited, and ablation at high-DF and continuous CFAE sites resulted in a good long-term outcome.

4.1. AF electrogram characteristics at high-DF and continuous CFAE sites

A combined high-DF site and continuous CFAE site ablation for the atrial substrate following PVI terminated AF in only 24% of patients, but obtained good long-term results in both paroxysmal and persistent AF [7]. However, whether the high-DF and continuous CFAE sites have such atrial electrogram characteristics as rotational activation has not been fully investigated. Although Narayan et al. described that a FIRM-guided ablation could terminate AF in 56% of patients [8], FIRM-identified rotor sites did not exhibit quantitative atrial electrogram characteristics, and rotor ablation resulted in AF termination or organization in a minority of patients in another report [11]. Further, histograms of the dominant frequency at all rotor and non-rotor sites show a similar frequency distribution [11]. In this study, there was no difference in the recurrence rate of AF between the patients with and without achievement of a procedural endpoint. Accordingly, the clinical value of a rotational activation ablation in the high-DF and continuous CFAE sites may be limited. Actually, the correlation between the rotational atrial activation and maintenance of AF has not been fully resolved. A comparison of ablation strategies with and without a rotational activation ablation may be important for evaluating the effectiveness of a rotational activation ablation. However, the ineffectiveness of the rotational activation ablation at the high-DF and/or continuous CFAE sites following PV isolation may be concluded.

In this study, we could detect a rotational activation in only 4% of all AF beats recorded in all high-DF and continuous CFAE sites. The characteristics of rotor drift and temporal instability may make it difficult to map rotors completely using a high-density 20-pole circular mapping catheter [8]. However, ablation at these sites could achieve procedural endpoints of an AF cycle length of $> 10\%$ in the majority of patients and good long-term results. Therefore, the high-DF and continuous CFAE sites may be related to anchoring to sites harboring high-frequency sites of rotor meandering [16].

4.2. Targets of ablation

There is controversy concerning how to ablate rotors [8]. Ablation at the center of a rotor could terminate AF in a minority of patients as described in a previous report [11]. In this study, a

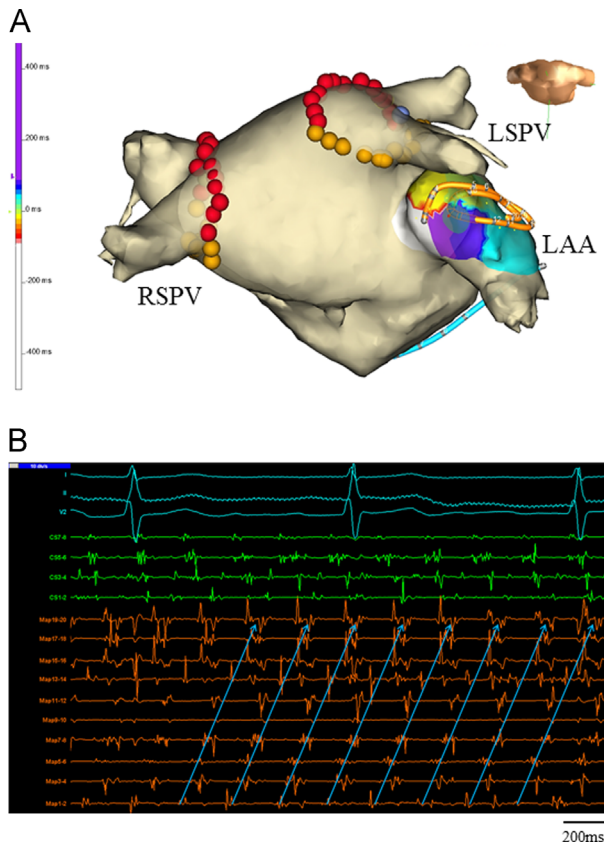


Fig. 3. Regional activation sequence of electrograms on the circumferential mapping catheter positioned in the left atrial appendage. Repetitive rotational activity at high-dominant frequency sites (10 Hz) in atrial fibrillation was detected at the LAA after the pulmonary vein isolation (red and yellow tags) using a high-density 20-pole mapping catheter (map) (A). Repetitive rotational activation sequences of electrograms on the circumferential mapping catheter in the LAA are shown (B). LAA=left atrial appendage; LSPV=left superior pulmonary vein; RSPV=right superior pulmonary vein.

Table 3
Mapping results.

	All (n=32)	Termination or prolongation (n=26)	No termination or prolongation (n=6)	P-value
High-DF sites in LA (n)	2.1 ± 1.0	2.1 ± 1.1	1.8 ± 0.8	0.464
High-DF sites in RA (n)	0.7 ± 0.9	0.6 ± 0.8	1.0 ± 1.6	0.832
Mean high-DF sites in LA (Hz)	9.7 ± 1.0	9.8 ± 1.0	9.5 ± 0.7	0.320
Mean high-DF sites in RA (Hz)	9.6 ± 0.7	9.7 ± 0.7	8.6 ± 0.5	0.018
Continuous CFAE sites in LA (n)	0.4 ± 0.9	0.5 ± 1.0	0.2 ± 0.4	0.655
Continuous CFAE sites in RA (n)	0.2 ± 0.4	0.2 ± 0.4	0	0.494
LA rotational activation of high-DF sites (beat)	2.3 ± 1.8	2.4 ± 1.8	2.0 ± 2.3	0.524
RA rotational activation of high-DF sites (n)	0.6 ± 1.6	0.7 ± 1.8	0	0.408
LA rotational activation of continuous CFAE sites (beat)	0.1 ± 0.4	0.1 ± 0.4	0	0.906
RA rotational activation of continuous CFAE sites (beat)	0.0 ± 0.2	0.0 ± 0.2	0	0.906
Number of patients with rotational activation (n)	29 (90%)	25 (96%)	4 (67%)	0.356
LA Focal of high-DF sites (beat)	1.0 ± 1.6	1.2 ± 1.7	0.3 ± 0.5	0.408
RA Focal of high-DF sites (beat)	0.3 ± 0.8	0.4 ± 0.9	0.2 ± 0.4	0.981

AAD=antiarrhythmic drugs; CFAE=complex fractionated atrial electrogram; DF=dominant frequency; LA=left atrium; RA=right atrium.

Table 4
Ablation results.

	All (n=32)	Termination or prolongation (n=26)	No termination or prolongation (n=6)	P-value
Total procedure duration, min	204 ± 30	207 ± 29	192 ± 36	0.207
Total ablation time, min	56 ± 10	57 ± 10	51 ± 10	0.285
Ablation time for PVI, min	38 ± 7	39 ± 8	37 ± 6	0.944
Ablation time for additional substrate ablation, min	6 ± 5	7 ± 5	4 ± 3	0.173
2 procedures	3	3	0	–
AADs after procedure	8	7	1	0.724
AF freedom without AADs	24 (75%)	19 (73%)	5 (83%)	0.724

AAD=antiarrhythmic drug; AF=atrial fibrillation; PVI=pulmonary vein isolation.

high-DF and continuous CFAE site ablation also resulted in AF termination in 2 patients. However, in a case with AF termination, sequential high-DF sites were occasionally identified at anterior sites, and the sequential ablation resulted in transecting the rotor. Therefore, a line of conduction block from the rotor core to an anatomical barrier or PVI line may effectively treat rotor-driven fibrillation. However, AF termination may not necessarily be required for a good long-term outcome as described in the STAR AF II trial [17]. Modification of anchor sites harboring meandering rotors may be needed. In this study, a transitional rotational activation could be identified in high-DF and continuous CFAE sites during AF. There may be a limitation of the detection due to rotor drift and temporal instability using a high-density 20-pole circular catheter. However, an AF maintenance-related activation (rotation, pivot, slow conducting channels, and focal) was detected in 20–28% of patients in the LA and RA in high-DF and continuous CFAE sites during AF. Therefore, these sites may be adequate targets for modifying an anchor harboring meandering AF, which is different from a strategy of involving the trail of a rotor. Furthermore, the formation of the AF substrate is influenced by epicardial adipose tissue [18].

4.3. Study limitations

There were several limitations to this study. First, this was a non-randomized, observational study with a relatively small population. Therefore, a potential selection bias of the clinical variables and different atrial substrates might have existed. Second, AF recurrence was evaluated using surface ECGs and 24-h Holter monitoring. Accordingly, asymptomatic AF recurrences may have been overlooked in the present study. Third, mapping at high-DF and continuous CFAE sites using a high-density 20-pole circular catheter may have been underestimated due to rotor drift and temporal instability. Finally, a comparison of the pulmonary vein antrum isolation alone and rotational activation ablation alone or rotational activation ablation followed by pulmonary vein antrum isolation may be needed for the evaluation of the effectiveness of the rotational activation ablation. Further, rotational activation mapping and ablation at sites without high-DF or continuous CFAE recording during AF may be needed.

5. Conclusions

Ablation at high-DF and continuous CFAE sites resulted in prolongation of the AF cycle length in the majority of patients with a good long-term outcome. A rotational atrial electrogram could be found in high-DF and continuous CFAE sites during AF. However, the documentation was limited using a high-density 20-pole circular mapping catheter. The limited effect of the rotational

activation ablation at the high-DF and/or continuous CFAE sites following PV isolation was concluded.

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Conflict of interest

None.

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