Relationship Between dominant-frequencies/rotors and Low-voltage Areas Using an Advisor HD Grid Mapping Catheter after Pulmonary Vein Isolation of Non-paroxysmal Atrial Fibrillation

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Abstract

Background This study aimed to evaluate the relationship between dominant frequencies (DFs)/rotors and low-voltage areas (LVAs) using the Advisor HD grid (HDG) after pulmonary vein isolation (PVI) in non-paroxysmal atrial fibrillation (AF). Methods A total of 73 non-paroxysmal AF patients were prospectively investigated. After pulmonary vein isolation (PVI), an online real-time phase mapping system was used to detect the location of rotors with critical non-passively activated ratios (%NPs) of[?]50% in each LA segment, and high-DFs of [?]7Hz were simultaneously mapped. After recovering sinus rhythm, LVAs (<0.5mV) were mapped using the HDG. Results Sixty-eight of 73 (93.2%) AF patients had minimum to mild LVAs (<10%) regardless of an enlarged LAD and LA volume (45 ± 6.1 mm and 142 ± 30 ml). There were no significant differences in the max and mean DF values and %NPs between the patients with and without recurrent AF/AT (atrial tachycardia). However, LVAs were significantly greater in the patients with AF/AT than in those without ($6.4\pm8.0\%$ vs. $2.5\pm2.6\%$ P=0.003). Furthermore, the number of high-DF sites overlapping with LVAs was significantly greater in the patients with AF/AT freedom off anti-arrhythmic drugs after the PVI was significantly lower in the patients with high-DFs sites overlapping with LVAs than in those without during 11.6\pm0.8 months of follow-up (35.7% vs. 69.5%, p=0.021). Conclusions High-DF sites overlapping with LVAs detected accurately by the HDG, regardless of whether a minimum to mild extent, might be more selective targets after a PVI in non-paroxysmal AF/AF patients.

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Short title: Atrial low-voltage areas and rotors/dominant frequencies

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Conclusions High-DF sites overlapping with LVAs detected accurately by the HDG, regardless of whether a minimum to mild extent, might be more selective targets after a PVI in non-paroxysmal AF patients.

Key words: atrial fibrillation; catheter ablation; dominant frequencies; low-voltage areas; pulmonary vein isolation; rotors.

Abbreviations

- AF = atrial fibrillation
- AT = atrial tachycardia
- DFs = dominant frequencies
- PVI = pulmonary vein isolation
- %NP = non-passively activated ratio

INTRODUCTION

Pulmonary vein isolation (PVI) has been the cornerstone of atrial fibrillation (AF) ablation. However, the single procedure success rates are limited, particularly in persistent and longstanding persistent AF.¹ However, additional strategies including linear ablation and ablation of complex fractionated atrial electrograms (CFAEs) ^{2,3} have not indicated any efficacy benefit over a PVI alone in non-paroxysmal AF patients. ⁴

A strategy based on low-voltage areas (LVAs) as detected by left atrial (LA) voltage mapping during sinus rhythm (SR) has recently been reported because LVAs are a predictor of AF recurrence after AF ablation.^{5,6,7} Furthermore, the recent utility of the Advisor HD grid HD (HDG) mapping catheter (Abbott Technologies, St Paul, Minnesota, USA) might lead to new and unique mapping techniques. The HDG contributes to the bipolar recording of activation parallel and perpendicular to the splines, which differs from conventional mapping.⁸ Therefore, the HDG can create high density maps to define anatomical substrates regardless of the direction of the activation.

High-DF sites may be potential selective targets for localized sources maintaining AF in non-paroxysmal AF patients.^{9,10,11}However, high-DF areas change spatiotemporally and the DF based ablation is still controversial.¹² Therefore, we previously reported the importance of high-DF sites overlapping with present LVAs using a conventional mapping catheter after the PVI.¹³ Recently, the areas in which rotational activations are frequently observed are automatically detected by a novel phase mapping system among

some ablation strategies targeting AF drivers.¹⁴⁻¹⁶ This study aimed to evaluate the relationship between the DFs/rotors and LVAs detected using the HDG after PVI in non-paroxysmal AF.

METHODS

Study Population

The present study was a prospective observational study that included 81 consecutive patients with nonparoxysmal AF who underwent catheter ablation at our institution between November 2018 and April 2020. Five patients were excluded due to having no multidetector computed tomography (MDCT) images and 3 patients for undergoing additional LA ablation other than the PVI. Finally, a total of 73 persistent and longstanding persistent AF patients were investigated in this study. Persistent AF was defined as AF lasting [?]7 days but <1 year, and longstanding persistent AF as continuous AF lasting [?]1 year.¹⁷ All antiarrhythmic drugs were discontinued for at least 5 half-lives and one patient received oral amiodarone therapy before the catheter ablation. The protocol for this research project was approved by a suitably constituted Ethics Committee of Tohoku Medical and Pharmaceutical University (Date of IRB approval: February 25, 2019; Approval number, 2018-2-104) and it conformed to the provisions of the Declaration of Helsinki. All patients provided written informed consent for the ablation procedure, and the use of their anonymized data in this study.

Catheter Ablation Procedure

The catheter ablation procedure was performed using a NavX system (St. Jude Medical, St. Paul, MN, USA) as described previously.^{10,13,18} A 5-french deflectable catheter was inserted into the coronary sinus (CS) via the right femoral vein. After a single transseptal procedure under intracardiac echocardiography guidance, an 8-F SL0 sheath and Agilis sheath (St. Jude Medical, St. Paul, MN, USA) were advanced into the LA. After the transseptal procedure, a single bolus of 5,000U of heparin was administered. A continuous infusion with heparinized saline was delivered to maintain an activated clotting time of 300 to 350s. The 3D LA geometry was created, and sequential contact mapping was performed using a 7-F decapolar circular catheter (EPstar Libero, Japan-lifeline Co.,Ltd., Tokyo, Japan). The whole LA was divided into eight areas (PVs, roof, left atrial appendage [LAA], septum, lateral, anterior, inferior, and posterior) for a location analysis of the AF substrate. ^{10,13,18} The mapping points in each region were similar in number and nearly equally distributed (LA mean mapping points: 1843+- 501).

The PVI was performed guided by a 7-F decapolar circular catheter positioned at the PV ostia as described previously.^{10,13,18} Each radiofrequency (RF) energy application was delivered for 40s. A 3.5mm irrigated tip RF catheter (FlexAbility TM, St. Jude Medical Inc.) was used with the temperature limited to 42 and power to 30W (25W to sites near the esophagus) with a flow rate of 13 mL/min. After the elimination or dissociation of the PV potentials, exit block was confirmed by pacing from the circular catheter placed within the PVs. After the PVI, DF mapping and rotor mapping were simultaneously performed in the same mapping area as follows. Finally, a LA voltage map was performed during pacing from the distal CS after external cardioversion.

Once in SR, decremental pacing (10 milliseconds steps from 250 to 200 milliseconds, over a period of 10 seconds) at an output of 10mA and 2ms pulse width was performed from the distal CS once, in an attempt to induce an atrial tachyarrhythmia without an isoproterenol injection. An induced AF/atrial tachycardia (AT) was defined as that sustained for at least 2 minutes.¹⁷ When AF/AT continued, external cardioversion was performed. When cavotricuspid isthmus (CTI) dependent AFL was induced, a CTI ablation was performed.

Frequencies Analysis

After the PVI, DF mapping during AF in each area was performed using the fast Fourier transform (FFT) method described previously.^{10,13,18,19} Recordings at each site for 5 seconds were performed using a deflectable 20-pole spiral-shaped catheter with a diameter of 2.5 cm (Reflexion HDTM, St. Jude Medical). Signals were truncated to 5 seconds at a sampling rate of 1,000Hz, providing 4,096 points for analysis (resolution 0.50Hz). The signals were rectified and processed by a Hanning window function and filtered from

2 to 20Hz. The DF analysis was done by an offline FFT analysis using the software implemented in the polygraph (RMC-5000; Nihon Kohden Co., Tokyo, Japan) in real-time and then the DF values were input manually into the NavX system. The DF value was determined as the frequency associated with the maximum peak power of the spectrum. Only DF points with a regularity index [?]0.2 were included.^{10,13,18,19} The high-DF sites were defined as DFs of [?]7Hz. The highest value of the DF in each mapping area in the LA was measured and calculated.

Real-Time Phase Mapping

In the same areas where the DF mapping was performed, mapping during AF was simultaneously performed using an online real-time phase mapping system (ExTRa MappingTM, Nihon Kohden Co., Tokyo, Japan) as described previously.¹⁶ This mapping system was based on 41 bipolar intraatrial electrograms (including 9 virtual electrograms) recorded by a deflectable 20-pole spiral-shaped catheter with a diameter of 2.5 cm. The contact was confirmed by the recorded electrograms, fluoroscopy, and 3D geometry. The distance between a mapping point and the geometry surface created by the EnSite NavX was set at 5 mm. The data sampling was adopted as good contact in areas where sufficient electrograms could be recorded from the vast majority of the electrodes. Based on the 5-s wave dynamics during AF, each phase map was automatically created by ExTRa Mapping. Non-passively activated areas, in which rotational activations were frequently observed, were automatically detected by ExTRa Mapping. The value of the "non-passively activated ratio" (%NP), which is the ratio of the form of rotors and multiple wavelets assumed to contain AF drivers to the recording time, was automatically calculated from the 5-s real-time phase map created by ExTRa Mapping.¹⁶ Of the 5-s map, the activation sequences during 720 ms (60 msx12 consecutive time windows) of representative episodes were depicted as images.

LVA mapping and analysis

After external cardioversion, a detailed bipolar LA voltage map was constructed during pacing from the distal CS in all patients. The LVA mapping method has been described previously.^{5,6,7} The mapping points were systematically acquired with the HDG, which has 16 electrodes and 3 mm equidistant electrode spacing to create a high density contact voltage map via the Ensite Velocity 3D mapping system. The algorithm displays the signals amalgamated from orthogonal recordings of each bipole and displays the highest amplitude signal (HD wave solution). An interpolation threshold of 10 mm on the NavX system was used for the surface color projection. Adequate endocardial contact was evaluated by stable electrograms and consideration of the distance to the geometry surface. Only true sinus beats were selected. Bipolar electrograms were filtered by a bandpass of frequencies between 30 and 500Hz. In accordance with the previous studies 5,6,7 , an LVA was defined as an area with a bipolar peak-to-peak electrogram amplitude of <0.5mV and electrical scar areas as <0.1mV. The LA surface area was defined as the LA body area without the PV antrum regions inside the PVI line. The registration for evaluating the MDCT image with the NavX map consisted of an AF image imported (pre-ablation) with a post cardioversion SR map in all patients in order to obtain the anatomical information, and the overlap between the LVAs and high-DF sites was evaluated manually by 2 independent blinded observers.

Post-procedure Care and Follow-up

Antiarrhythmic medications were continued for at least 3 months to prevent any early recurrences. A clinical interview, surface ECG, and 24-h Holter monitoring were performed 1 day after the procedure and repeated 1, 3, 6 and 12 months after the catheter ablation. AF/AT recurrence was defined as sustained AF/AT lasting more than 30s, which occurred more than 3 months after the catheter ablation.¹⁷

Statistical Analysis

The continuous variables are presented as the mean +- standard deviation together with the 95% confidence intervals. Categorical variables were expressed as numbers and percentages. The significance of any differences between the two groups was analyzed with an unpaired t -test and Mann-Whitney U test for continuous variables, and with a Fisher's exact probability test for categorical variables. A predictive analysis of AF recurrence during the follow-up period was assessed using multivariate Cox proportional hazard regression models. A multivariate analysis with multivariate Cox proportional hazard regression models was performed to isolate the independent criteria of AF recurrence after ablation. Only the variables with significant P-values in the univariate analysis were included in the multivariate Cox proportional hazard regression. A Kaplan-Meier event-free survival analysis was conducted to assess the cumulative freedom from AF recurrence. A value of P<0.05 was considered statistically significant.

Results

Patient Characteristics

The AF patients were divided into two groups: patients without AF/AT recurrence (n=46) and those with AF/AT recurrence (n=27). The patient characteristics are shown in **Table 1**. The patients included 19 with persistent AF and 54 with longstanding persistent AF (mean duration 25+-18 months). The mean LA diameter (LAD) and LA volume were 45+-6.1 mm and 142+-30 ml, respectively. The patient characteristics and laboratory data except for the LV ejection fraction did not significantly differ between the two groups. None except for 6 (2 with hypertrophic cardiomyopathy, 3 with mitral regurgitation, and 1 with old myocardial infarctions) had structural heart disease.

Procedural Characteristics

The procedural characteristics are shown in **Table 2**. Though the total procedure time significantly differed between the two groups, the RF time for the PVI did not differ between the two groups. There were no patients with AF termination. Therefore, all patients finally needed external cardioversion after the PVI.

Frequencies and Phase mapping Analysis

According to the frequencies and phase mapping analysis, all mapping sites (n=835, 11.4 sites per patient) were divided into 4 types (**Table 3**). However, there were no significant differences among the 4 types between the patients with and without recurrent AF (**Table 2**). The max-DF value and max-%NP per patient were 6.7+-0.9 Hz and 65+-11 % after the PVI, respectively. There were no significant differences between the patients with and without recurrent AF in the max-DF value, max-%NP, mean DF value, and mean %NP (**Table 2**). The number of high-DF sites[?]7Hz in the LA was 2.4+-3.7 per patient after the PVI, and the number of %NPs[?]50% was 9.1+-4.7 per patient after the PVI (**Table 2**). A %NP[?]50% and high-DF sites[?]7Hz were frequently identified in the inferior and anterior regions of the LA, respectively (**Figure 1A**).

LVA mapping and analysis

Two different voltage maps were created using the 2 HDG bipolar configurations (along the spline and HD wave solution). There was a significant difference in the LVAs/LA surface between that using the HD wave solution and that along the spline (3.9+-11% vs. 7.3+-14%, P<0.001) (Figure 2). The extent of the LVZ was calculated as the percentage of the LA surface area and was categorized into stages 1 (minimum LVA, <5%), 2 (mild, [?]5% to <20%), 3 (moderate, [?]20% to <30%), and 4 (extensive, [?]30%). Sixty-eight of 73 (93.2%) patients with AF had minimum to mild LVAs (<10%) using the HDG with the HD wave solution regardless of an enlarged LAD and LA volume.

As shown in **Figure 1B**, LVAs were found in 194 (23.2%) sites out of 835. LVAs were frequently identified in the septal, anterior, and posterior regions of the LA. There was a significant difference in the LVA (<0.5mV)/LA surface area between the patients with and without recurrent AF/AT (6.4+-8.0% vs. 2.5+-2.6% P=0.003) as shown in Table 3. In addition, though there was no significant difference in the number of %NPs[?]50% that overlapped with LVAs between the two groups (0.9+-1.1 vs. 0.6+-1.0, P=0.178), there were a significant difference in the number of high-DF sites [?]7Hz that overlapped with LVAs between the two groups (0.5+-0.8 vs. 0.2+-0.7, P=0.026). Further, high-DF sites [?]7Hz overlapping with LVAs were frequently identified in the septal, roof, and inferior regions of the LA and the %NPs[?]50% overlapping with LVAs in the anterior and septal regions (**Figure 1C**). Furthermore, the number of sites that overlapped with all regions (LVAs, high-DF sites [?]7Hz and %NPs[?]50%) included only 6 (0.7%) out of 835 sites (1 anterior, 2 posterior, 1 septal, 1 roof, and 1 LAA). A representative case is shown in **Figure 3**.

Outcome of the Catheter Ablation

A Kaplan-Meier event-free survival analysis was conducted to assess the cumulative freedom from AF/AT recurrence. One patient had AT recurrences after one procedure. The atrial arrythmia freedom off antiarrhythmic drugs after the PVI was significantly lower in the patients with high-DFs sites [?]7Hz overlapping with LVAs than in those without high-DFs sites overlapping with LVAs during 11.6+-0.8 months of follow-up (35.7% vs. 69.5%, p=0.008). (**Figure 4A**). However, there was no significant difference in the %NPs[?]50% overlapping with LVAs between the two groups (**Figure 4B**). The number of patients receiving post ablation anti-arrhythmic drugs (AADs) during the follow-up was 16 (22%) among those with recurrent AF. There were no cases of cerebral infarctions, cardiac tamponade, PV stenosis, or atrial-esophageal fistulae.

Predictors of AF recurrence

A univariate Cox proportional hazard regression analysis, including of the AF duration, LA diameter, EF, LA volume, CHA2DS2-VASc score, LVA/LA surface area after the PVI, max-DF value, max-%NP value, high-DF sites overlapping with LVAs, and %NP>50% sites overlapping with LVAs, indicated that the LVA/LA surface area after the PVI (hazard ratio [HR] 1.066; confidence interval [CI], 1.017-1.117, P=0.007) and high-DF sites overlapping with LVAs (HR 1.031; CI, 1.083-5.381, P= 0.031) were significantly associated with AF/AT recurrence. In a multivariate analysis, the LVA/LA surface area after the PVI (HR 1.079; CI, 1.026-1.134, P=0.003) and high-DF sites overlapping with LVAs (HR 2.842; CI, 1.238-6.527, P= 0.014) were independent predictors of AF recurrence.

Discussion

Major findings

The major findings of the present study were: (1) Most AF patients had minimum to mild LVAs using the HDG (HD wave solution) regardless of an enlarged LAD and LA volume. (2) There were no significant differences in the max and mean DF values and %NP after the PVI between the patients with and without recurrent AF/AT. (3) The LVAs, regardless of a minimum to mild extent, were significantly indicated to be greater in the patients with recurrent AF/AT than in those without. (4) The number of high-DFs sites overlapping with LVAs was significantly greater in patients with recurrent AF/AT than in those without. (5) The atrial arrythmia freedom off AADs after the PVI was significantly lower in the patients with high-DF sites overlapping with LVAs than in those without during 11.6+0.8 months of follow-up.

LVAs detected using the HDG

An increased amount of fibrosis as detected by LA voltage mapping has been shown to be a predictor of AF/AT recurrence after AF ablation.^{5,6,7} The extent of the LVAs was categorized on the basis of the LA fibrosis grade evaluated by delayed-enhancement magnetic resonance imaging (MRI).^{20,21} However, the definition of the LVAs and their correlation with histological fibrosis remains controversial, because the bipolar voltage amplitudes depend on the electrode orientation relative to the direction of the wavefront, electrode length, interelectrode spacing, and tissue contact.²² Furthermore, the HDG when used for bipolar recording can record not only the parallel but also the perpendicular activation to the splines, which differs from conventional mapping.²³ Therefore, the HD grid could create high density maps to define anatomical substrates regardless of the direction of the activation. In this study, the HDG drastically decreased the extent of the LVA. The HDG may improve the directional sensitivity and exclude any false low-voltages, and can detect the AF substrate more accurately, which would lead to a more effective ablation strategy.²³

Frequencies and rotor mapping after a PVI

Atrial sites that represent local electrograms with high-DFs may be associated with AF maintenance.^{10,13,18} In addition, Sakata et al.¹⁶ demonstrated that real AF drivers are contained in the non-passively activated areas where rotors and/or multiple wavelets are most frequently observed during a short recording time (5-s)

with high reproducibility of the %NP. The distribution of the high-DF sites in the LA was similar to that of the %NP[?]50% after the PVI in this study. In the previous report, the highest DF and rotor positions were robust markers of the driver location during AF using a computational study.²⁴ However, in this study there were no significant differences in the DF, %NP value, and combination of the DF and %NP between the patients with and without recurrent AF/AT. An index such as the DF or %NP may not always reflect the critical AF drivers. Furthermore, a combination of the DF and LVA may be needed for the detection of the critical targets for an atrial substrate modification.

The sites overlapping with LVAs

In the previous study, 77% of the high-DF sites overlapped with LVAs in the LA¹³ using conventional mapping catheters, while only 2.6% (22 sites out of 835) overlapped using the HDG in this study. However, there was a significant difference in the number of high-DF sites overlapping with LVAs between the patients with and without recurrent AF/AT. The HDG might drastically exclude false LVAs, which would help detect the AF substrate more accurately.

Furthermore, though the number of %NP[?]50% sites overlapping with LVAs in the LA was greater, there was no significant difference in that number between the patients with and without recurrent AF/AT. The %NP indicated the frequency of the presence of rotors within a relatively large mapping area (diameter of 2.5 cm), and the area overlapping with LVAs may not always reflect the exact overlapping sites between the rotors and LVAs.

High-DF areas change spatiotemporally and the DF based ablation is still controversial.¹² However, drivers are harbored within/in the vicinity of LVAs, and fractionated activity, rotational activity, and discrete rapid local activity during AF in LVAs may contribute to the formation of high-DFs.^{7,15} The selection of high-DF sites overlapping with LVAs as targets may correct the shortcoming of an ablation based on the DF.¹³ In this study, a combination of frequency mapping and LVA mapping using the HDG could detect the critical selective atrial substrate necessary to maintain AF. Therefore, this strategy using the HDG could avoid any excessive RF applications as compared to that using conventional mapping.

Study limitations

The present study was limited in several ways. First, this was a single-center, nonrandomized observational study. Second, missed brief or silent AF episodes may have been underestimated in the present study because of noncontinuous monitoring during the follow-up. Third, LVA mapping in the RA could not be performed due to the long procedure. Fourth, there may have been the possibility that the voltage mapping and phase mapping may not have been adequately performed with sufficient catheter contact with the atrial tissue because we did not use a contact force sensing catheter for the mapping. Finally, we could not evaluate the efficacy of the ablation of the high-DF sites that overlapped with LVAs.

Conclusions

Most AF patients had only minimum to mild LVAs using the HDG regardless of an enlarged LAD and LA volume. However, the minimum to mild LVAs were significantly greater in the patients with recurrent AF/AT than in those without. The HDG might drastically exclude false LVAs, which would help detect the AF substrate more accurately. Furthermore, high-DFs sites overlapping with LVAs detected by the HDG might be more selective targets after the PVI in non-paroxysmal AF patients.

Conflicts of Interest

All authors declare no conflict of interest related to this study

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Figure Legends

Figure 1.

Voltage maps created using the 2 HDG bipolar configurations. A. along the spline B. HD wave solution.

The low voltage areas (LVAs)/left atrial (LA) surface was 20.5% (A) and 14.3% (B), respectively. The red tags show the PVI ablation points. The color-coding was defined as follows: <0.1mV=scar (gray), 0.1 to 0.5mV=diseased atrial tissue, and >0.5mV=healthy atrial myocardium (purple).

Figure 2.

The distribution of the DFs, rotors and LVAs in the LA after the PVI

A. The %NPs[?]50% and high-DF sites[?]7Hz were frequently identified in the inferior and anterior regions of the LA, respectively. B. LVAs were frequently identified in the septal, anterior, and posterior regions of the LA. C. High-DF sites [?]7Hz overlapping with LVAs were frequently identified in the septal, roof, and inferior regions of the LA and %NPs[?]50% overlapping with LVAs in the anterior and septal regions.

Figure 3.

(A) A voltage map in the left atrium (LA) after the PVI. Minimum low voltage areas (LVAs) (LVAs/LA: 2.3%) were found in the posterior LA. The red tags show the PVI ablation points. (B) The spectrum of high-DF sites overlapping with LVAs in the posterior LA (7.2Hz with RI 0.72) (pink tag). (C) Electrograms in the posterior LA after the PVI. Intra-atrial bipolar electrograms recorded by a 20-pole spiral-shaped catheter during atrial fibrillation (AF) are shown. The mean AF cycle length is 148 ms. (D) ExTRa Mapping of the posterior LA after the PVI. The activation sequences during 720ms of data (60-msx12 consecutive time windows) are shown. The white lines indicate the head of the wavefronts and white arrows the direction of the wavefronts. In this case, a wavefront traveling in the posterior LA forms a rotor lasting for 3 rotations. The nonpassively activated ratio (%NP) is 53%.

Figure 4.

Kaplan-Meier event-free survival analysis for the cumulative freedom from AF /AT recurrence.

A. The atrial arrythmia freedom off anti-arrhythmic drugs after the PVI was significantly lower in the patients with high-DFs sites [?]7Hz overlapping with LVAs than in those without during 11.6+0.8 months of follow-up (35.7% vs. 69.5%, p=0.008). B. There was no significant difference in the %NP sites [?]50% overlapping with LVAs between the two groups.

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