Fibrotic Tissue Properties associated with Atrial Fibrillation Rotors in Patients with Persistent Atrial Fibrillation

Toshihiro Nakamura[1], kunihiko kiuchi[2], Koji Fukuzawa[2], Mitsuru Takami[2], yoshiaki watanabe[2], Yu Izawa[2], hideya suehiro[2], tomomi akita[2], makoto takemoto[2], jun sakai[2], atsusuke yatomi[2], Yusuke Sonoda[2], Hiroyuki Takahara[2], Kazutaka Nakasone[2], Kyoko Yamamoto[2], noriyuki negi[3], Atsushi Kono[2], Takashi Ashihara[4], and Ken-ichi Hirata[2]

[1]Kobe University
[2]Kobe University Graduate School of Medicine
[3]Kobe University Hospital
[4]Shiga University of Medical Science

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Abstract

Background: A computational model demonstrated that atrial fibrillation (AF) rotors could be distributed in patchy fibrotic tissue and play an important role in AF drivers. However, this was not validated in humans. Objective: The purpose of this study was to evaluate the fibrotic tissue properties of AF rotors in patients with persistent AF. Methods: A total of 287 segments in 15 patients with persistent AF (longstanding persistent AF in 9 patients) that underwent AF ablation were assessed. Non-passively activated areas (NPAs), where rotational activation (AF rotor) was frequently observed, were detected by the novel real-time phase mapping (ExTRa Mapping). Atrial fibrosis was detected by late-gadolinium enhancement magnetic resonance imaging (LGE-MRI), and the fibrotic heterogeneity and density were assessed by the entropy (LGE-entropy) and volume ratio of the enhancement voxel (LGE-volume ratio), respectively. Results: NPAs were found in 61 (21%) of 287 segments and were mostly found around the pulmonary vein antrum. A receiver operating characteristic curve analysis yielded an optimal cutoff value of 5.7 and 10% for the LGE-entropy and LGE-volume ratio, respectively. The incidence of NPAs was significantly higher at segments with an LGE-entropy of >5.7 and LGE-volume ratio of >10% than at the other segments (38 [30%] of 126 vs. 23 [14%] of 161 segments, p = 0.001). No NPAs were found at segments with an LGE-volume ratio of >50% regardless of the LGE-entropy. Conclusion: AF rotors are mostly distributed in relatively weak and much more heterogenous fibrotic tissue.

Fibrotic Tissue Properties associated with Atrial Fibrillation Rotors in Patients with Persistent Atrial Fibrillation

Short Title

Relationship between Atrial fibrosis and Atrial Fibrillation Rotors

Toshihiro Nakamura, MD[1], Kunihiko Kiuchi, MD, FHRS[1], Koji Fukuzawa, MD[1], Mitsuru Takami, MD[1], Yoshiaki Watanabe, MD[2], Yu Izawa, MD[1], Hideya Suehiro, MD[1], Tomomi Akita, MD[1], Makoto Takemoto, MD[1],

Jun Sakai, MD[1], Atsusuke Yatomi, MD[1], Yusuke Sonoda, MD[1],

Hiroyuki Takahara, MD[1], Kazutaka Nakasone, MD[1],

Kyoko Yamamoto, MD[1], Noriyuki Negi, RT[3], Atsushi Kono, MD[2],

Takashi Ashihara, MD, PhD[4], Ken-ichi Hirata, MD, PhD[1]

1. Section of arrhythmia, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

2. Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan

3. Division of Radiology, Center for Radiology and Radiation Oncology, Kobe University Hospital, Kobe, Japan

4. Department of Medical Informatics and Biomedical Engineering, Shiga University of Medical Science, Otsu, Japan

Corresponding author: Kunihiko Kiuchi

Section of Arrhythmia, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine

650-0017, Kusunoki-Cho 7-5-2, Chuoh-Ku, Kobe, Japan

Telephone: +81-78-382-5846, Fax: +81-78-382-5859

E-mail: kunihikokiuchi@yahoo.co.jp

Conflict of interest

The Section of Arrhythmia is supported by an endowment from Medtronic JAPAN and Abbott JAPAN. Ken-ichi Hirata chairs the Section, and Koji Fukuzawa and Kunihiko Kiuchi belong to the Section. However, all authors report no conflict of interest for this manuscript's contents.

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Abstract

Background: A computational model demonstrated that atrial fibrillation (AF) rotors could be distributed in patchy fibrotic tissue and play an important role in AF drivers. However, this was not validated in humans. **Objective:** The purpose of this study was to evaluate the fibrotic tissue properties of AF rotors in patients with persistent AF. **Methods:** A total of 287 segments in 15 patients with persistent AF (longstanding persistent AF in 9 patients) that underwent AF ablation were assessed. Non-passively activated areas (NPAs), where rotational activation (AF rotor) was frequently observed, were detected by the novel real-time phase mapping (ExTRa Mapping). Atrial fibrosis was detected by late-gadolinium enhancement magnetic resonance imaging (LGE-MRI), and the fibrotic heterogeneity and density were assessed by the entropy (LGE-entropy) and volume ratio of the enhancement voxel (LGE-volume ratio), respectively. **Results:**NPAs were found in 61 (21%) of 287 segments and were mostly found around the pulmonary vein antrum. A receiver operating characteristic curve analysis yielded an optimal cutoff value of 5.7 and 10% for the LGE-entropy and LGE-volume ratio, respectively. The incidence of NPAs was significantly higher at segments with an LGE-entropy of >5.7 and LGE-volume ratio of >10% than at the other segments (38 [30%] of 126 vs. 23 [14%] of 161 segments, p = 0.001). No NPAs were found at segments with an LGE-volume ratio of >50% regardless of the LGE-entropy. **Conclusion** : AF rotors are mostly distributed in relatively weak and much more heterogenous fibrotic tissue.

Keywords: atrial fibrillation, catheter ablation, rotor, fibrosis, late-gadolinium enhancement magnetic resonance imaging

Introduction

Pulmonary vein isolation (PVI) is an established ablation strategy for patients with paroxysmal AF, but the impact is much less in patients with persistent AF.[1] Late-gadolinium enhancement magnetic resonance imaging (LGE-MRI) has been reported to detect myocardial fibrosis. Furthermore, the progression of atrial

fibrosis could be associated with AF recurrence after catheter ablation.[2] A computer simulation could excellently demonstrate that AF drivers are observed in patchy fibrotic tissue, but not in dense tissue.[3] This indicated the importance of a qualitative and quantitative analysis of fibrotic tissue. However, this has not been validated in humans. Recently, modulation of AF rotors has been proposed as one of the effective ablation strategies for persistent AF.[4] A novel phase mapping system (ExTRa Mapping^{TM}; Nihon Kohden, Japan) has been developed and could provide us with a real-time and fully-automatic creation of each phase map movie, which could identify the location of AF rotors. Our aim of this study was to clarify the relationship between AF rotors detected by the ExTRa Mapping and the tissue properties assessed by LGE-MRI.

Methods

2.1 study population

A total of 15 consecutive patients with persistent AF (n = 6) and long-standing persistent AF (n = 9) that underwent catheter ablation were enrolled in this study. The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of 2019.3.1., Approval No. 190017.

2.2 MRI acquisition

All patients underwent contrast-enhanced MRI using a 1.5-T MR system (Achieva; Philips Medical, Best, The Netherlands) equipped with a 5-channel cardiac coil before the AF ablation. This scan technique has been previously reported.[5] First, contrast-enhancement magnetic resonance angiography (CE-MRA) of the pulmonary vein (PV) - left atrium (LA) anatomy was acquired with a breath-hold three-dimensional (3D) fast field echo (FFE) sequence in the coronal plane during the first pass of a contrast agent (gadobutrol, Gadovist; Bayer Yakuhin, Osaka, Japan) injection at a dose of 0.1 mmol/kg.[6]

The purpose of the scanning in the coronal plane was to reduce the number of acquisition slices and shorten the breath-hold time. Then the LGE-MRI of the LA with the PVs was acquired using a 3D inversion recovery, respiration navigated, electrocardiogram-gated, T1-FFE sequence in the transverse plane 15 minutes after the contrast injection.[7] The typical parameters were as follows: repetition time/ echo time = 4.7/1.5 ms, voxel size = 1.43 × 1.43 × 2.40 mm (reconstructed to 0.63 × 0.63 × 1.20 mm), flip angle = 15°, SENSE factor = 1.8, and 80 reference lines. The inversion time was set at 280 to 320 ms, using a Look-Locker scan. The data acquisition was performed during the mid-diastolic phase of the left ventricle. The typical scan time for the LGE-MRI study was 7 to 12 minutes depending on the patient's heart rate and respiration pattern. The images of the CE-MRA, and LGE-MRI were transferred to customized software (MRI LADE Analysis; PixSpace Inc, Fukuoka, Japan) for a further image post processing and image analysis.

2.3 3D visualization and assessment of the tissue properties

The 3D visualization method for the LGE was as follows. First, the LA in LGE-MRI was segmented semi-manually by contouring the endocardial and epicardial borders of the atrium, including the PVs, while referring to the CE-MRA. Second, the mean value and standard deviation (SD) of the voxel intensity was measured on the "healthy" LA wall where no hyperenhanced areas in LGE-MRA were involved. Third, a voxel intensity histogram analysis of the LA wall identified the LGEs as intensities >1SD on the "healthy" LA wall. Furthermore, the degree of intensity was categorized by a color-coded scaling (green: >1SD: yellow: 2–3SD; red: >3SD). Finally, a 3D reconstruction, color-coded LGE, and volume-rendered LA and PV image generated from the CE-MRA were fused semi-automatically. In this study, atrial fibrosis was defined as an LGE site with a signal intensity of >1SD. To evaluate the fibrotic tissue property, the fibrotic heterogeneity was defined as the value of the entropy (LGE-entropy) according to the Shannon formula:

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atrial-fibrillation

Where Pi was the fraction of elements neighboring the ith element that was a different tissue type than the ith element. The fibrotic density was defined as the volume ratio of an LGE signal intensity >1SD (LGE-volume ratio). To clarify the tissue property associated with AF rotors, a receiver operating characteristic (ROC) curve analysis was performed for the optimal values of the LGE-entropy and LGE-volume ratio.

2.4 Mapping and ablation procedure

Transesophageal echocardiography was performed before the procedure in all patients to exclude any thrombus formation. The patients were studied under moderate to deep sedation while breathing spontaneously. Standard electrode catheters were placed in the right ventricular apex and coronary sinus after which a single transseptal puncture was performed. Unfractionated heparin was administered in a bolus form before the transseptal puncture to maintain an activated clotting time of more than 300 seconds. Mapping and ablation were performed using the NavX system (Abbott, Chicago, IL) as a guide after integration of a 3D model of the anatomy of the LA and PVs obtained from the MRI. A 20-pole circular mapping catheter (Optima^{TM} or Reflexion HD^{TM}, Abbott) and ablation catheter-reconstructed LA posterior anatomy was aligned with the MRI.[8]Subsequently, a phase mapping using the ExTRa Mapping and complex fractionated atrial electrogram (CFAE) mapping using the NavX system were performed simultaneously. As for the CFAE mapping, a definition of the excitation cycle length of below 120 ms was employed.[9]

2.5 Real-Time Phase Mapping

To detect the distribution of the AF rotors, an online real-time phase mapping system (ExTRa Mapping) was used. This mapping system was based on 41 bipolar intra-atrial electrograms (including 9 virtual electrograms) recorded by a deflectable 20-pole spiral-shaped catheter with a diameter of 2.5 cm (Reflexion HD^{TM}, Abbott). The contact was confirmed by the recorded electrograms, fluoroscopy, and 3D geometry. The distance between the mapping points and geometry surface created by the EnSite NavX was set at 5 mm. The data sampling was adopted if there was good contact in the areas where sufficient electrograms could be recorded from the vast majority of the electrodes. When sufficient electrograms were not detected, the sensing threshold was decreased from 0.03 mV to 0.01 mV. Based on the 5-second wave dynamics during AF, each phase map was automatically created. Non-passively activated areas (NPAs), in which rotational activations (AF rotors) were frequently observed, were automatically detected according to the value of the "non-passively activated ratio (%NP)" (the ratio of the non-passively activated period to the recording time).[10] NPAs were determined as areas up to the top 7 highest %NP values, which were above 50% of the %NP value. Thus, the NPAs could be considered as the area where AF rotors could be frequently found. To evaluate the distribution of the NPAs, the region of the whole LA was divided into the following eight segments: PV antrum, roof, anterior, posterior, lateral, bottom, septum, and left atrial appendage (LAA) base segments.

2.6 CFAE mapping

CFAE mapping and ExTRa Mapping could be simultaneously performed and the correlation between the CFAE area and AF rotors was assessed. To clarify the relationship, we assessed whether the NPAs or passive areas (PAs) could be overlapped with CFAE areas. The overlap of the NPAs or PAs with the CFAE areas was considered positive if the CFAE areas occupied [?]50% of each NPA or PA.

2.7 Relationship between the fibrotic tissue properties and AF rotors

To clarify the relationship between the fibrotic tissue properties and AF rotors, the following were assessed: 1) the distribution of the NPAs, 2) optimal fibrotic heterogeneity and density associated with the NPAs, 3) fibrotic tissue classification according to the fibrotic heterogeneity and density, 4) the incidence of NPAs grouped by the fibrotic tissue properties, and 5) the relationship between the CFAEs and AF rotors.

2.8 Relationship between the fibrotic tissue properties, AF rotors, and AF recurrence

After the ablation, the patients were monitored every 1-3 months. AF recurrence was defined as AF of a duration of [?]30 seconds documented more than several times after the 3-month blanking period. We investigated the tissue properties of the NPAs and relationship between the NPAs and ablation lesions.

2.9 Statistical analysis

Data are expressed as percentages for the nominal variables, medians for the ordinal variables, and means for the continuous variables. Discrete variables were compared using the chi-square or Fisher exact test as appropriate. ROC curves were used to determine the LGE-entropy and LGE-volume ratio that provided the best sensitivity and specificity for the NPAs. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS, Release 24 software (SPSS, Chicago, IL, USA).

Results

3.1 Patients and procedural characteristics

The patients and procedural characteristics are shown in **Table 1** . The mean age was 66+-12 years, mean left atrial dimension 43+-8 mm, and mean left ventricular ejection fraction 60+-8%. Ten (67%) out of 15 patients underwent an initial AF catheter ablation. The time from the MRI acquisition to the AF ablation was 95+-60 days.

3.2 AF rotors and the fibrotic tissue properties

NPAs were found in 61 (21%) of 287 segments and PAs were found in the remaining 226 (79%) segments. The distribution of the NPAs is shown in Figure 1. The NPAs were mostly found around the PV antrum (35%), subsequently anterior (18, and roof (12%) segments.

An ROC curve analysis yielded an optimal cutoff value of 5.7 and 10% for the LGE-entropy and LGE-volume ratio, respectively. As for the optimal LGE-entropy, the sensitivity, specificity, and positive and negative predictive values for the cutoff values were 75.4%, 41.6%, 25.8%, 86.2%, respectively. As for the optimal LGE-volume ratio, the sensitivity, specificity, and positive and negative predictive values for the cutoff values were 67.2%, 49.1%, 26.3%, 84.7%, respectively.

According to an LGE-entropy of 5.7 and LGE-volume ratio of 10%, the fibrotic tissue properties were classified into 4 groups: heterogenous healthy tissue (group 1 [G1]:LGE-entropy of [?]5.7 and LGE-volume ratio of $< 10\%$), heterogenous fibrotic tissue (group 2 [G2]: LGE-entropy of [?]5.7 and LGE-volume ratio of [?]10%), homogenous healthy tissue (group 3 [G3]: LGE-entropy of < 5.7 and LGE-volume ratio of $<10\%$), and homogenous fibrotic tissue (group 4 [G4]: LGE-entropy of < 5.7 and LGE-volume ratio of [?]10%). Figure 2 shows the distribution of both the NPAs and PAs according to the LGE-entropy and LGE-volume ratio. Of interest, no NPAs could be found in regions with an LGE-volume ratio of [?]50%. Figure 3 shows the proportion of NPAs in each group. The proportion of NPAs was significantly higher in G2 than the other groups (38 [30%] of 126 vs. 23 [14%] of 161 segments, $p = 0.001$). Individually, the proportion of the NPAs in G2 was significantly higher than that in G3 and G4. The proportion of NPAs in G2 was higher but was not significant (8 [15.4%] of 52 segments in G1 vs. 38 [30.2%] of 126 segments in G2 vs. 12 [15.2%] of 79 segments in G3 vs. 3 [10.0%] of 30 segments in G4; $p = 0.024$). Although the LGE-entropy and LGE-volume ratio did not differ between the NPAs and PAs, the proportion of the tissue properties (G1 to G4) significantly differed between the NPAs and PAs. As shown in Figure 4, the NPAs could predominantly consist of G2, subsequently G3, but extremely less of G4, while the PAs could equally consist of G1, G2, and G3 (NPAs: 8 [13.1%] in G1, 38 [62.3%] in G2, 12 [20.0%] in G3, 3 [4.9%] in G4; PAs: 44 [19.5%] in G1, 88 [38.9%] in G2, 67 [29.6%] in G3, 27 [11.9%] in G4). Figure 5 shows a representative case. Five NPAs were continuously distributed on the anterior roof of the LA where both the LGE-entropy and LGE-volume ratio were higher than 5.7 and 10%, respectively. The fibrotic tissue properties could be considered heterogenous fibrotic properties (G2).

3.3 AF rotors and the tissue properties in patients with AF recurrence

AF recurrence was observed in 5 (33%) of 15 patients. In the patients with AF recurrence, NPAs were found in 20 (33%) of 61 segments. The highest %NP value, LGE-entropy, and LGE-volume ratio at the NPAs did not differ between the patients with and without AF recurrence (highest %NP value: 68.0+-13.3 vs. 69.0+-9.2, p = 0.167; LGE-entropy: 6.0+-0.36 vs. 6.0+-0.47, p = 0.287; LGE-volume ratio: 12.2+-9.6 vs. 19.0+-12.1, p = 0.171).

Of the 5 patients with AF recurrences, 2 had a relatively low highest %NP value (51% and 57%). As for the tissue properties of the 2 NPAs, they had a relatively low LGE-entropy and LGE-volume ratio (LGE-entropy: 5.8 and 5.5; LGE-volume ratio:8.1 and 3.2; respectively).

The remaining 3 patients had the high highest %NP value (81%, 71% and 67%), however, a direct RF application was not performed at the NPA, because they were included within the PVI or Box lesion line.

3.3 Relationship between the CFAE areas and AF rotors

Figure 6 shows the proportion of CFAE areas between the NPAs and PAs. Fifteen (25%) of 60 NPAs overlapped with CFAE areas, while 49 (21%) of 227 PAs also overlapped with CFAE areas. The proportion of CFAE areas did not differ between teh NPAs and PAs (p = 0.441). A representative case showed that a CFAE area could be found on the LA septum where no NPAs could found (Figure 5).

Discussion

4.1 Main findings

This study demonstrated that (1) NPAs were mostly found around the PV antrum, (2) the fibrotic tissue properties of the NPAs predominantly consisted of heterogenous fibrotic tissue with an LGE-entropy of [?] 5.7 and LGE-volume ratio of [?] 10%, (3) no NPAs could be found in the dense fibrotic tissue areas with an LGE-volume ratio of [?] 50%, and (4) there was no significant correlation between the NPAs and CFAE areas.

4.2 AF rotors and the PV antrum

Guillem et al. reported that rotors could be initiated by a focal ectopic discharge and wavefront break.[11] The other previous studies demonstrated that the sleeve of the PV was thickest at the venoatrial junction and often consisted of 2 or more layers.[12,13] Those anatomical findings indicated the presence of thick and anisotropic myocardial structures in the PV antrum. Thicker parts of the PVs with anisotropic properties may provide the substrate for a functional line of block during rotor activation. In this study, the NPAs were mostly found around the PV antrum, which was completely consistent with the previous study.[10]Furthermore, the tissue properties of the NPAs around the PV antrum also predominantly consisted of G2 and subsequently G1. The tissue properties of G1 indicated heterogenous and healthy tissue and this heterogeneity might have been caused by the wall thickness and anisotropic myocardial structures but not myocardial fibrosis.

4.3 AF rotors and the fibrotic tissue properties

The development and progression of atrial fibrosis are considered as the substrate for AF perpetuation. LGE-MRI has been developed to visualize and quantify the extent of atrial fibrosis. The DECAAF multicenter prospective study demonstrated that atrial fibrosis estimated by LGE-MRI independently predicted AF recurrence after catheter ablation.[14] Furthermore, computer simulations demonstrated AF rotors located in boundary zones between fibrotic and non-fibrotic tissue.[4] To quantitatively characterize the fibrosis spatial patterns in each computer simulation model, the fibrosis density and fibrosis entropy were calculated. The local fibrosis density value was calculated as the proportion of fibrotic elements among all elements within the surrounding sub-volume. The local fibrosis entropy in each element was calculated as the level of disorganization within the surrounding sub-volume, quantified based on the modified Shannon entropy. However, this has not been verified in clinical use. In this study, the incidence of NPAs was higher in fibrotic tissue areas with an LGE-entropy of [?]5.7 (G1 and G2) as compared to that with an LGE-entropy of <5.7 (G3 and G4). No NPAs could be found in dense fibrotic tissue areas with an LGE-volume ratio of >50% regardless of the LGE-entropy. This indicated that the NPAs could be associated with tissue properties

with fibrotic heterogeneity (entropy) rather than the fibrotic volume. The dense fibrotic tissue areas with an LGE-volume ratio of >50% appeared to be scar without electrical activity. This result was consistent with the computer simulation model. We found that the atrial myocardium consisted of different fibrotic tissue properties. Although it was not statistically proven, we speculated that the myocardial fibrosis gradually progressed and the fibrotic heterogeneity increased, which could have provided heterogenous fibrotic tissue where the AF rotors were frequently found. Those fibrosis patterns might correspond to the patchy LGE sites on the LGE-MRI. Further, the fibrosis progression decreased the fibrotic heterogeneity and increased the fibrosis volume, which could have provided the homogenous fibrosis tissue, namely dense scar. This tissue property might play an important role as an obstacle for macro-reentrant atrial tachycardia but not AF. Of importance, we might have to pay attention to the early stage fibrotic tissue properties (G1) that could progress to patchy fibrotic tissue associated with AF rotors in the future.

AF recurrence was observed in the patients with the slow highest %NP values where direct RF applications were performed or with the high highest %NP values where direct RF applications were not performed. The tissue properties of NPAs with a low highest %NP were characterized as having a low LGE entropy and LGE-volume ratio, which was categorized as G3. We speculated that those NPAs were an unmatured AF substrate and the effect of an NPA-targeted ablation would be less at the NPAs with G3 tissue properties as compared to that with G1 or G2 tissue properties. As for the catheter intervention for NPAs, direct RF applications were recommended in the previous study. That was because the real AF drivers were considered to be contained in the NPAs where rotational activations were frequently observed.[10] When considering the reconduction of the ablation line, a direct RF application at the NPA would be necessary even though that area was locked in the PVI or Box lesion line.

4.4 Other AF substrates and AF rotors

Recent clinical and experimental studies have demonstrated that persistent AF might be maintained by AF rotors but the mechanisms linking rotor formation and persistent perpetuation are still unknown. Narayan et al. reported biatrial basket- and specific software-based mapping to delineate the stable AF rotor sources.[15]Haissaguerre et al. developed specific algorithms to identify localized sources and atrial propagation occurring simultaneously during ongoing AF using body surface mapping.[16] However, a poor electrode contact would lead to an insufficient verification of the imaging algorithms.[17] The previous studies reported that low voltage areas (LVAs) or CFAE areas could be associated with an AF substrate, but the relationship between that substrate and AF rotors is still in debate.[18] CFAEs are also considered ablation targets, but a multicenter trial showed that there was no additional benefit of a CFAE-targeted ablation in patients with persistent AF.[19] In this study, no significant correlation between the NPAs and CFAE areas could be found, which was completely consistent with the previous report.[10]Several limitations could be found to accurately assess the unstable and meandering rotors by the conventional mapping methods based on the bipolar electrogram. First, the bipolar electrograms depended on the orientation of the electrode catheters to the propagating wavefront and cardiac rhythm. Of note, the distribution of the LVAs could change according to the pacing site. Second, the true myocardial activation and near far-field myocardial activation were mixed and those could not be distinguished by the bipolar electrograms during AF.

To make it possible to achieve a rapid prediction of the atrial excitation during AF, both a computer simulation (in silico) part and specialized artificial intelligence part were incorporated into the ExTRa Mapping system.[10] Combined with the timing of the action potential onset determined by the intra-atrial signals, the in silico part calculated the virtual atrial action potentials based on the in silico model of human persistent AF.[20]Recently, an experimental study has excellently demonstrated that the phase map sequence of the ExTRa Mapping is consistent with that of high-resolution optical mapping.[21] Therefore, we considered that the ExTRa Mapping provided us more specific ablation targets associating with AF drivers.

Furthermore, LGE-MRI could provide us with the fixed tissue properties regardless of the cardiac rhythm and pacing site. Considering both the electrical and structural substrate obtained by ExTRa Mapping and LGE-MRI, we might overcome those conventional mapping limitations.

4.5 Clinical implications

We previously reported successful ExTRa Mapping and LGE-MRI guided ablation as a case report.[22] In that case, RF applications at NPAs on the bottom of the posterior LA outside the box lesion could convert AF to common atrial flutter. The tissue properties of the NPAs were G2. That indicated that an NPA with a heterogenous fibrotic tissue property (G2) was considered as the most important ablation target. The question is whether we should consider the PAs with G2 properties as ablation targets. In this study, the PAs with G2 properties were also found. Although such tissue properties were not "currently" associated with AF rotors, we speculated that they could potentially harbor AF rotors in the near future due to the progression of myocardial fibrosis. To improve the long-term outcome after catheter ablation, we should consider that these PAs with G2 properties could be acceptable as ablation targets. Finally, we strongly recommended that the dense fibrotic tissue should be excluded from the ablation targets.

4.6 Study limitations

Our study had several limitations. First, the sample size was relatively small. Second, some patients underwent a prior ablation. In such cases, we could not completely discriminate between the ablation lesions and pre-existing atrial fibrosis around the PVs. Furthermore, the LGE site might have been overestimated on the posterior wall adjacent to the vertebrae and anterior wall adjacent to the aortic cusp due to wall compression by those organs. Third, the novel phase mapping system employed in this study might have include some unknown limitations, because this system is widely available in Japan, but not in other countries. We hope this system will spread to the rest of the world in the future. Fourth, we directly observed the AF wave dynamics in real-time by applying our novel phase mapping system, but it was still very difficult to extract the real AF drivers from the various NPAs detected by this system. Although not all NPAs coincided with true AF drivers, we strongly believe that most NPAs with high %NP values contained, more or less, true AF drivers.

Conclusions

The AF rotors were mainly located in the heterogenous fibrotic tissue which could be detected by the LGE-MRI. A combination of ExTRa Mapping and LGE-MRI made it possible to specifically identify the electrical and structural substrates associating with the AF rotors.

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References

1. Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. Lancet. 2016;388:829-840.

2. Khurram IM, Habibi M, Gucuk Ipek E, et al. Left atrial LGE and arrhythmia recurrence following pulmonary vein isolation for paroxysmal and persistent AF. JACC Cardiovasc Imaging. 2016;9:142-148.

3. Zahid S, Cochet H, Boyle PM, et al. Patient- derived models link re-entrant driver localization in atrial fibrillation to fibrosis spatial pattern. Cardiovasc Res 2016;110:443-454.

4. Dzeshka MS, Lip GY, Snezhitskiy V, Shantsila E. Cardiac fibrosis in

patients with atrial fibrillation: mechanisms and clinical implications.

J Am Coll Cardiol. 2015;66:943-959.

5. Kiuchi K, Okajima K, Shimane A, et al. Visualization of the radiofrequency lesion after pulmonary vein isolation using delayed enhancement magnetic resonance imaging fused with magnetic resonance angiography. J Arrhythm. 2015;31:152-158.

6. Kiuchi K, Okajima K, Shimane A, Shigenaga Y. Visualization of pulmonary vein-left atrium reconduction site on delayed-enhancement magnetic resonance imaging in the second atrial fibrillation catheter ablation. Circ J. 2014;78:2993-2995.

7. McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol. 2014;7:23-30.

8. Kiuchi K, Kircher S, Watanabe N, et al. Quantitative analysis of isolation area and rhythm outcome in patients with paroxysmal atrial fibrillation after circumferential pulmonary vein antrum isolation using the pace-and-ablate technique. Circ Arrhythm Electrophysiol. 2012;5:667-675.

9. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044-2053.

10. Sakata K, Okuyama Y, Ozawa T, et al. Not all rotors, effective ablation targets for nonparoxysmal atrial fibrillation, are included in areas suggested by conventional in-direct indicators of atrial fibrillation drivers: ExTRa Mapping project. J Arrhythm. 2018;34:176-184.

11. Guillem MS, Climent AM, Rodrigo M, Fernandez-Aviles F, Atienza F, Berenfeld O. Presence and stability of rotors in atrial fibrillation: evidence and therapeutic implications. Cardiovasc Res. 2016;109:480-492.

12. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1999;10:1525-1533.

13. Tagawa M, Higuchi K, Chinushi M, et al. Myocardium extending from the left atrium onto the pulmonary veins: a comparison between subjects with and without atrial fibrillation. Pacing Clin Electrophysiol 2001;24:1459-1463.

14. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014;311:498-506.

15. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628-636.

16. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014;130:530-538.

17. Benharash P, Buch E, Frank P, et al. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. Circ Arrhythm Electrophysiol. 2015;8:554-61.

18. Yamaguchi T, Tsuchiya T, Nakahara S, et al. Efficacy of Left Atrial Voltage-Based Catheter Ablation of Persistent Atrial Fibrillation. J Cardiovasc Electrophysiol. 2016;27:1055-1063.

19. Verma A, Jiang CY, Betts TR, et al. STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372:1812-1822.

20. Ashihara T, Haraguchi R, Nakazawa K, et al. The role of fibroblasts in complex fractionated electrograms during persistent/permanent atrial fibrillation: implications for electrogram-based catheter ablation. Circ Res. 2012;110:275-284.

21. Tomii N, Asano K, Seno H, Ashihara T, Sakuma I, Yamazaki M. Validation of Intraoperative Catheter Phase Mapping Using a Simultaneous Optical Measurement System in Rabbit Ventricular Myocardium. Circ J 2020;84:609-615

22. Nakamura T, Kiuchi K, Fukuzawa K, et al. Successful modulation of atrial fibrillation drivers anchoring to fibrotic tissue after Box isolation using online real-time phase mapping system: ExTRa Mapping. J Arrhythm. 2019;00:1-4.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Figure legends

Figure 1 The distribution of the NPAs detected by ExTRa Mapping. LAA = left atrial appendage; NPA = non-passively activated area; PV = pulmonary vein.

Figure 2 The distribution of the NPAs and PAs according to the LGE-entropy and LGE-volume ratio. The NPAs (red) and PAs (blue). The NPAs and PAs were classified into 4 groups (group1 to 4) according to an LGE-entropy of 5.7 and LGE-volume ratio of 10%. LGE = late gadolinium enhancement; NPA = non-passively activated area; PA = passively activated area.

Figure 3 The proportion of NPAs grouped by the tissue properties.

NPA = non-passively activated area.

Figure 4 The proportion of fibrotic tissue properties between the NPAs and PAs. NPA = non-passively activated area; PA = passively activated area.

Figure 5 Representative case in our study. ExTRa Mapping with the NavX system in the AP (A) and PA (B) views. The 3D ablation tags were colored as red, pink, light pink, and gray according to the LSI values (red: >5; pink: >4; light pink: >3; and gray: <3.0). The red, orange, yellow, green, and light blue circles indicate the NPAs with a high %NP of 84, 67, 60, 54, and 52%, respectively. The 3D LGE-MRI of the LA in the AP (C) and PA (D) views. The red, orange, yellow, light blue and green circles correspond to those in panel A. Five NPAs continuously distributed on the anterior roof of the LA where both the LGE-entropy and LGE-volume ratio were higher than 5.7 and 10%, respectively. AP = anterior-posterior; CFAE = complex fractionated atrial electrograms; LA = left atrium;

LGE-MRI = late-gadolinium enhancement magnetic resonance imaging; LSI = lesion size index; NPA = non-passively activated area; PA = posterior-anterior; %NP = non-passively activated ratio.

Figure 6 Relationship between the CFAE areas and NPAs. The no relationship between the CFAE areas and NPAs was found. CFAE = complex fractionated atrial electrograms; NPA = non-passively activated area.

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