The Impact of the Atrial Wall Thickness in Less Late-Gadolinium Enhancement Areas on Atrial Fibrillation Drivers in Persistent Atrial Fibrillation Patients

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Abstract

Background: Some of atrial fibrillation (AF) drivers are found in lesser late-gadolinium enhancement (LGE) areas, as well as heterogenous ones. The atrial wall thickness (AWT) has been reported to be important as a possible AF substrate. However, the AWT and degree of LGEs as an AF substrate has not been fully validated in humans. Objective: The purpose of this study was to evaluate the impact of the AWT in lesser LGE areas on AF drivers. Methods: A total of 287 segments in 15 persistent AF patients were assessed. AF drivers were defined as non-passively activated areas (NPAs), where rotational activation was frequently observed, and were detected by the novel real-time phase mapping (ExTRa Mapping). Lesser LGE areas were defined as areas with a volume ratio of the enhancement voxel of <10%. The AWT was defined as the minimum distance from the manually determined endocardium to the epicardial border on the LGE-MRI. Results: NPAs were found in 20 (18.0%) of 131 lesser LGE areas where the AWT was significantly thicker than that in the passively activated areas (PAs) (2.46±0.26 vs. 2.20±0.25 mm, p<0.001). However, NPAs were found in 61 (21.3%) of 287 LGE areas where the AWT was similar to that of the PAs (2.24±0.24 vs. 2.22±0.25 mm, p=0.58). An ROC curve analysis yielded an optimal cutoff value of 2.24 mm for predicting the presence of an NPA in lesser LGE areas. Conclusion: The location of AF drivers in lesser LGE areas might be more accurately identified by evaluating the AWT.

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Running Title

Impact of the Atrial Wall Thickness on Atrial Fibrillation Drivers

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Conflict of interest

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request

Abstract

Background: Some of atrial fibrillation (AF) drivers are found in lesser late-gadolinium enhancement (LGE) areas, as well as heterogenous ones. The atrial wall thickness (AWT) has been reported to be important as a possible AF substrate. However, the AWT and degree of LGEs as an AF substrate has not been fully validated in humans.

Objective: The purpose of this study was to evaluate the impact of the AWT in lesser LGE areas on AF drivers.

Methods: A total of 287 segments in 15 persistent AF patients were assessed. AF drivers were defined as non-passively activated areas (NPAs), where rotational activation was frequently observed, and were detected by the novel real-time phase mapping (ExTRa Mapping). Lesser LGE areas were defined as areas with a volume ratio of the enhancement voxel of <10%. The AWT was defined as the minimum distance from the manually determined endocardium to the epicardial border on the LGE-MRI.

Results: NPAs were found in 20 (18.0%) of 131 lesser LGE areas where the AWT was significantly thicker than that in the passively activated areas (PAs) (2.46±0.26 vs. 2.20±0.25 mm, p<0.001). However, NPAs were found in 61 (21.3%) of 287 LGE areas where the AWT was similar to that of the PAs (2.24±0.24 vs. 2.22±0.25 mm, p=0.58). An ROC curve analysis yielded an optimal cutoff value of 2.24 mm for predicting the presence of an NPA in lesser LGE areas.

Conclusion : The location of AF drivers in lesser LGE areas might be more accurately identified by evaluating the AWT.

Keywords: atrial fibrillation, driver, fibrosis, atrial wall thickness, late-gadolinium enhancement magnetic resonance imaging

Abbreviations:

AF = atrial fibrillation

AWT = atrial wall thickness

CE-MRA = contrast-enhancement magnetic resonance angiography

CT = computed tomography

LA = left atrium

LAA = left atrial appendage

LGE-MRI = late-gadolinium enhanced magnetic resonance imaging

MRs = meandering rotors

MWs = multiple wavelets

NPAs = non-passively activated areas

PAs = passively activated areas

PV = pulmonary vein

PVI = pulmonary vein isolation

RA = right atrium

ROC = receiver operating characteristic

SD = standard deviation

3D = three-dimensional

%NP = non-passively activated ratio

Introduction

Pulmonary vein isolation (PVI) is a well-established ablation strategy for paroxysmal atrial fibrillation (AF), but it is much less effective in persistent AF patients.[1] Late-gadolinium enhanced magnetic resonance imaging (LGE-MRI) has been reported to detect myocardial fibrosis. Furthermore, the progression of atrial fibrosis after catheter ablation may be associated with AF recurrence.[2] It has been previously reported that AF drivers are observed in patchy LGE areas but not in dense LGE areas, in computer simulation models.[3] That shows the importance of a qualitative and quantitative analysis of the LGE areas. Recently, the modulation of the AF drivers has been proposed as one of the effective ablation strategies for persistent AF.[4] To evaluate the location of AF drivers precisely, a novel phase mapping system (ExTRa Mapping^{TM}; Nihon Kohden, Japan) has been developed.[5] ExTRa Mapping is a phase map based on myocardial action potentials, which has been validated by high-resolution optical membrane potential mapping in an animal study.[6] We previously reported that AF drivers detected by the ExTRa Mapping were frequently found in

heterogenous LGE areas assessed by LGE-MRI in persistent AF patients. However, some of them were also found in lesser LGE areas.[7] This has implied that there are other possible structural factors associated with AF drivers. A previous computer simulation study demonstrated the role of the atrial wall thickness (AWT) as a substrate for AF drivers and marker for the identification of AF driver locations in patient-specific atria, and the AWT gradients acted as anchoring points for AF drivers in the absence of fibrosis.[8] However, such an effect of the AWT on AF drivers has not been fully verified in humans. The aim of this study was to evaluate the impact of the AWT in lesser LGE areas on AF drivers in persistent AF patients.

Methods

2.1 Study population

A total of 15 consecutive patients with persistent (n=6) and long-standing persistent (n=9) AF undergoing catheter ablation were enrolled in this study. The protocol of this research project has been approved by the appropriately constituted ethics committee of the institution concerned and complies with the provisions of the Declaration of Helsinki, Committee of 2021.5.25, Approval No.210043.

2.2 MRI acquisition

Before the AF ablation, LGE-MRI was performed in all patients using a 1.5T MR system (Achieva; Philips Medical, Best, The Netherlands) equipped with a 5-channel cardiac coil. This scan technique has been previously reported.[9] First, contrast-enhancement magnetic resonance angiography (CE-MRA) of the pulmonary vein (PV) - left atrial (LA) anatomy was obtained in the coronal plane using a breath-hold three-dimensional (3D) fast field echo sequence after the injection of 0.1 mmol/kg of a contrast agent (Gadobutrol, Gadovist, Bayer Yakuhin, Osaka, Japan).[10] The purpose of the scanning in the coronal plane was to reduce the number of acquisition slices and shorten the breath-hold time. Next, 15 minutes after the contrast injection, LGE-MRI of the LA including the PVs was performed using a lateral 3D inversion recovery, respiratory navigation, ECG gating, and T1-fast field echo sequence.[11] The CE-MRA and LGE-MRI images were transferred to customized software (MRI LADE Analysis; PixSpace Inc, Fukuoka, Japan) for image post-processing and an image analysis.

2.3 3D Visualization and assessment of the tissue properties

To detect lesser LGE areas more sensitively, we used the same protocol as in our previous study.[12] The 3D visualization method for the LGE was as follows. First, the LA in the LGE-MRI was semi-manually segmented by contouring the borders between the endocardium and epicardium of the atrium, including the PVs, with reference 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 hyper-enhanced areas in LGE-MRA were involved. Third, we identified LGEs with an intensity of >1SD on the "healthy" LA wall by a voxel intensity histogram analysis of the LA wall. Furthermore, the degree of the intensity was categorized by a color-coded scaling (green: >1SD: yellow: 2–3SD; red: >3SD). Finally, the 3D reconstruction, color-coded LGE, and volume-rendered LA and PV image generated from the CE-MRA were semi-automatically fused. In this study, atrial fibrosis was defined as an LGE site with a signal intensity of >1SD. To evaluate the fibrotic tissue properties, the fibrotic density was measured as the LGE-volume. The fibrotic density was defined as the volume ratio of an LGE signal intensity > 1SD (LGE-volume ratio). The details of the measurement can be found in the previous publication.[7] In this study, the areas with an LGE-volume ratio of $< 10\%$ were defined as lesser LGE areas, and heterogenous LGE areas were defined as areas with an LGE-volume ratio of $> 10\%$.

2.4 Thickness measurement of the LA

As shown in **Figure 1** , the atrial wall thickness (AWT) was defined as the minimum distance from the manually determined endocardium to the epicardial border on the LGE-MRI. Regions of interest were manually drawn in specific atrial regions and the regions of interest -based AWT was estimated in the multiplanar reconstruction images perpendicular to the LA wall. To evaluate the AWT in the lesser LGE areas associated with AF drivers, a receiver operating characteristic (ROC) curve analysis was performed for the optimal values of the AWT predicting AF drivers.

2.5 Real-Time Phase Mapping

After the integration of the anatomical 3D models of the LA and PVs obtained from the MRI, mapping was performed using the NavX system (Abbott, Chicago, IL) as a guide. 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.[13] To detect the distribution of the AF drivers, an online real-time phase mapping system (ExTRa Mapping) was used. The detail of this mapping system was previously described.[7] ExTRa Mapping was applied to persistent AF patients and as a result, each wave dynamics were classified into 3 patterns, meandering rotors (MRs), multiple wavelets (MWs), and planar wave. Planar wave propagation was defined as passive activation, whereas MR and MW were defined as non-passive activations. Furthermore, non-passively activated areas (NPAs), a region where non-passive activations were frequently observed, were automatically detected according to the value of the "non-passively activated ratio (%NP)" (the ratio of the form of MRs and/or MWs assumed to contain AF drivers to the recording time).[5]NPAs were determined as areas up to the top 7 highest %NP values greater than 50%. Thus, the NPAs could be considered as the area where AF drivers could be frequently found. To evaluate the distribution of the NPAs, the region of the whole LA was divided into the following 8 segments: PV antrum, roof, anterior, posterior, lateral, bottom, septum, and left atrial appendage (LAA) base segments. Moreover, we evaluated the proportion of MRs and MWs in the %NP within the NPAs in the lesser and heterogenous LGE areas.

2.6 Relationship between the AWT in the lesser LGE areas and AF drivers

To clarify the relationship between the AWT in the lesser LGE areas and AF drivers, the following were assessed: (1) the distribution of the NPAs, (2) correlation between the AWT and LGE-volume ratio in the NPAs, and (3) optimal AWT in the lesser LGE areas for predicting the NPAs.

2.7 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. The mean AWT was compared among the 8 segments of the whole LA groups using a 1-way ANOVA and post hoc analysis with a Tukey correction for multiple comparisons of data. ROC curves were used to determine the AWT that provided the best sensitivity and specificity for the NPAs. A value of $p < 0.05$ was considered statistically significant. The correlations between two parameters were assessed using Pearson or Spearman rank correlation tests. To assess the proportion of NPAs in each group, a correction for multiple comparisons was performed. All statistical analyses were performed using EZR on R commander, version 1.36 software.

Results

3.1 Patient and procedural characteristics

The patient 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. The mean AWT in 287 areas in the LA in 15 patients was 2.22±0.25 mm.

3.2 Distribution of the NPAs and AWT

NPAs were found in 61 (21%) of 287 segments. Although the NPAs were mostly found around the PV antrum (21 [34.4%] of 61 NPAs), the AWT did not differ at each segment (anterior: 2.27±0.27 mm, bottom:2.25±0.21 mm, LAA base: 2.22±0.20 mm, lateral: 2.20±0.20 mm, posterior: 2.01±0.44 mm, PV antrum: 2.26±0.28 mm, roof: 2.38±0.35 mm, and septum: 2.13±0.23 mm, $p = 0.094$) (**Figure2A**).

3.3 Relationship between the AWT and LGE volume-ratio

The distribution of the NPAs and passively activated areas (PAs) according to the AWT and LGE-volume ratio are shown in Figure 3. Lesser LGE areas were found in 131 (45.6%) of 287 areas and heterogenous

LGE areas in 156 (54.4%) of 287 areas. The AWT correlated negatively with the LGE-volume ratio among the total areas (r = -0.190, p = 0.001) (**Figure 3A**). Of note, this correlation was significant for the NPAs but not the PAs (NPA: r = -0.542, p < 0.001; PA: r = 0.056, p = 0.400) (**Figure 3B,C**).

3.4 NPAs and the AWT in lesser LGE areas

NPAs were found in 20 (15.3%) of 131 lesser LGE areas where the AWT was significantly thicker in the NPAs than PAs (NPAs: 2.46±0.26 mm vs. PAs: 2.20±0.25 mm, p < 0.001). However, NPAs were found in 61 (21.3%) of 287 LGE areas where the AWT was similar to that of the PAs (NPAs: 2.24±0.24 mm vs. PAs: 2.22±0.25 mm, p = 0.58) (**Figure 2B**).

3.5 Optimal AWT of lesser LGE areas predicting AF drivers

An ROC curve analysis yielded an optimal cutoff value of 2.24 mm for predicting the presence of an NPA in lesser LGE areas. As for the optimal AWT, the sensitivity, specificity, and positive and negative predictive values for the cutoff values were 85.0%, 59.5%, 27.4%, 95.7%, respectively. When the sensitivity rather than specificity was prioritized, the optimal cutoff value was 2.08 mm. When the specificity rather than sensitivity was prioritized, the optimal cutoff value was 2.40 mm. The sensitivity, specificity, and positive and negative predictive values for each cutoff value are shown in **Table 2** . A representative case is shown in **Figure 4** . Five NPAs were found in lesser LGE areas where the AWT was thicker than 2.24 mm.

3.6 Comparison of the proportion of MRs/MWs in the %NP between lesser and heterogenous LGE areas

The proportion of MRs in the %NP was significantly higher in lesser LGE areas than in heterogenous LGE areas (Less LGE: 65.7±0.08% vs. Heterogenous LGE: 59.0±0.10%, p = 0.01). On the other hand, the proportion of MWs in the %NP was significantly lower in lesser LGE areas than heterogenous LGE areas (Less LGE: 34.3±0.08% vs. Heterogenous LGE: 41.0±0.10% p = 0.01) (**Figure 5**).

Discussion

4.1 Main findings

This study demonstrated that (1) the AWT correlated with the LGE-volume ratio negatively in the NPAs, (2) the AWT in the NPAs was significantly thicker than that in the PAs in lesser LGE areas, and (3) the proportion of MRs in the %NP was significantly higher in lesser LGE areas than heterogenous LGE areas, whereas the proportion of MWs was higher in heterogenous LGE areas.

4.2 AWT on MRI images

Recently, computed tomography (CT) images have been used to estimate the AWT.[14] Despite its high spatial resolution, CT is inherently low in soft-tissue contrast, making the detection of atrial borders very difficult. The use of iodine-based contrast agents can increase the contrast of the endocardial borders, however, identifying the epicardial borders remains challenging. Even if the fact that MRI is noninvasive and provides superior soft-tissue contrast compared to CT, few MRI-based studies have been reported to measure the AWT of the LA in AF patients. A previous study regarding the LA wall thickness measured by CT images demonstrated that the mean LA wall thickness in chronic AF and paroxysmal AF was 2.1± 0.2 mm and 2.4 ± 0.2 mm, respectively.[14] In this study, the AWT measured by MRI was 2.22±0.25 mm in 15 persistent AF patients, in good agreement with the previous study.

4.3 Correlation between the AWT and fibrosis

A recent study showed that a thicker LA wall was associated with a stronger atrial maintenance substrate in patients with LA enlargement assessed by echocardiography.[15] An enlarged LA and a thickened LA wall might seem to be contradicted. A thickened LA wall may implicate the stage of inflammation, edema. With the progression of AF to end-stage disease, remodeling may advance to atrial fibrosis, leading to a thinner AWT. Moreover, the observation of fractionated electrical activity with a low voltage on the electroanatomic map may be predictive of a high risk of AF initiation and persistence. The loss of an adaptive atrial thickening

may be the tipping point at which fibrosis and scar become irreversible.[16] In our study, the LA wall thickness was negatively correlated with the LGE-volume ratio and the correlation was significant at only the NPAs but not the PAs, which was consistent with these previous results.

4.4 Impact of the AWT on AF drivers in lesser LGE areas

Recent computational studies of patient-specific atrial models, based on the reconstruction of fibrosis from LGE-MRI, have provided mechanistic insights into the role of fibrosis in the dynamics of electrical re-entrant drivers sustaining AF. Zahid et al. have demonstrated that AF was sustained by re-entrant drivers persisting in fibrosis border zones.[3] We previously reported that the LGE properties in anchoring AF drivers predominantly consist of heterogenous LGE areas in persistent AF patients. However, AF drivers are also observed in lesser LGE areas.[7] Roy et al. reported that the AWT gradients played an important role in anchoring AF drivers in the absence of fibrosis.[8] In an optical mapping ex vivo study of perfused right atria from explanted diseased human hearts, activation delays between the endocardium and epicardium during atrial pacing were more prominent in areas with an increased wall thickness, transmural fiber orientation angle gradient, and interstitial fibrosis.[17] Therefore, thicker parts of the LA could be the 3D rotational substrate perpetuating AF due to long activation delays between the endocardium and epicardium. However, those have not been validated in humans.

In our study, there was a significant difference in the proportion of MRs/MWs in the %NP between the lesser and heterogenous LGE areas. Handa et al. recently reported that the fibrosis pattern alters the mechanism of the fibrillatory organization and its persistence in Langendorff-perfused rat hearts. They demonstrated that meandering rotational activation was mainly found with less fibrosis and less gap junction uncoupling and it disorganized into multiple wavelets in the progression of atrial fibrosis and gap junction uncoupling.[18] Therefore, we speculated that the NPAs in lesser LGE areas might have been mainly caused by a complex fiber orientation in the three-dimensionally large space between the endocardium and epicardium. This might facilitate long activation delays between the endocardium and epicardium, which result in a 3D rotational substrate perpetuating AF. To the best of our knowledge, this is the first human study focusing on the impact of the AWT in lesser LGE areas on AF drivers using LGE-MRI.

4.5 NPAs with a greater AWT

A previous study provided simultaneous endo-epicardial high-density mapping data of breakthroughs during AF and demonstrated that the large majority of breakthroughs are explainable by transmural conduction.[19] Recently, Parameswaran et al. analyzed simultaneously acquired endo-epicardial right atrial recordings from 14 persistent AF patients undergoing cardiac surgery, collected with a high-density grid electrode array (interelectrode distance of 3 mm).[20] They demonstrated that endo-epicardial dissociation is highly dynamic and wavefront propagation heterogeneous, suggesting that targeting a single focus of the endo-epicardial dissociation or breakthrough is unlikely to prevent recurrence of AF. This is consistent with the concept of ExTRa Mapping, in which persistent AF encountered in clinical practice is mostly driven by spatially and temporally unstable rotors rather than stationary stable rotors.[5] To rapidly predict the atrial excitation during AF, both a computer simulation (in silico) part and special artificial intelligence part were incorporated into the ExTRa Mapping system. The in silico part computed virtual atrial action potentials based on an in silico model of the human persistent AF in combination with the timing of the action potential generation determined by the intra-atrial signals.[21] Recent experiments have successfully shown that the phase map sequence of ExTRa Mapping is consistent with high-resolution optical mapping.[6]Ashihara et al. demonstrated a great catheter ablation outcome using ExTRa Mapping in persistent AF patients for maintaining sinus rhythm.[5] This indicated that NPAs detected by ExTRa Mapping should contain the true AF drivers. Therefore, we believed that ExTRa Mapping would provide a more specific ablation target relevant to the cause of AF.

It was previously reported that AF recurrence correlated with the emergence of new AF drivers after catheter ablation, where they occurred in locations distinctly different from those of the original ones.[22] To eliminate all of them, electrophysiological mapping, such as ExTRa mapping, should be performed repeatedly, however,

it would result in a prolongation of the procedure time. Considering this issue, LGE-MRI is useful for planning the ablation strategy, as it can narrow down the target to be ablated preoperatively.

4.6 Clinical implications

As we previously reported, the AF drivers were mainly be located in heterogenous LGE areas, which could be detected by LGE-MRI.[7] Preprocedural LGE-MRI could evaluate the LA wall thickness as well as LGE areas precisely and would be useful to predict the AF drivers in the lesser LGE area. This would help in planning where to ablate in addition to the PVI at a point before the ablation procedure and might reduce frequent electrophysiological mapping. We believed that this would make a significant contribution to the realization of an AF ablation with a higher specificity. Finally, we strongly recommended that thinner AWT areas in lesser LGE areas should be excluded from the ablation targets.

4.7 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 sites 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. Moreover, it might have been difficult to measure the thickness of the posterior LA wall with consistency in all patients. Thirdly, the new phase-mapping system adopted in this study may have had unknown limitations because it is widely used in Japan but not in other countries. We expect that this system will be widely used worldwide in the future. Fourth, mapping was not performed in the right atrium (RA) because of the stability of the mapping catheter and the reproducibility of the LGE-MRI assessment in the RA. Finally, no histological validation was performed in the LGE areas. LGE-MRI has a potential risk of over- and under- estimating fibrosis.

Conclusions

The AF drivers were likely to be located in thick AWT areas in lesser LGE areas, which were possible ablation targets. Preprocedural LGE-MRI was considered to be useful for identifying such specific areas associated with AF drivers.

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Figure 1 The measurement of the atrial wall thickness in our representative case. A, B) Axial, C, D) coronal and E, F) sagittal views of the atria from one representative subject overlaid, in the bottom row, with the performed manual segmentations. Ao, aorta; LA, left atrium; LAA, left atrial appendage; PA, pulmonary artery; LV, left ventricle; RA, right atrium.

Figure 2 The mean AWT in each segment of the whole left atrium (A) and mean AWT in the NPAs and PAs in lesser LGE and all LGE areas (B). AWT, atrial wall thickness; LAA, left atrial appendage; LGE, late gadolinium enhancement; NPA, non-passively activated area; PA, passively activated area. PV, pulmonary vein.

Figure 3 The distribution of the NPAs and PAs according to the AWT and LGE-volume ratio. The NPAs (red) and PAs (blue). The AWT correlated negatively with the LGE-volume ratio in the total areas (A). This correlation was stronger in the NPAs (B) than PAs (C). AWT, atrial wall thickness; LGE, late gadolinium enhancement; NPA, non-passively activated area; PA, passively activated area.

Figure 4 Representative case in our study. ExTRa Mapping with the NavX system in the AP (A) and PA (B) views. The red, yellow, green, and light blue circles indicate the NPAs with a high %NP of 73, 59, 57, and 55%, respectively. The 3D LGE-MRI of the LA in the AP (C) and PA (D) views. The red, yellow, green, and light blue circles correspond to those in panel A. Despite the low value of the LGE-volume ratio, these 5 areas were determined to be NPAs and their AWT was thick.

AP, anterior-posterior; AWT, atrial wall thickness; 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 5 The proportion of MRs and MWs in the %NP of NPAs in lesser LGE and heterogenous LGE areas. LGE, late gadolinium enhancement; MR, meandering rotors; MW, multiple wavelets; NPA, non-passively activated area; %NP, non-passively activated ratio.

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