

学位論文

Analysis of the Preferable Site and Stability of Rotational Reentry:
Its Role for the Maintenance of Atrial fibrillation
(心房細動中の Rotational Reentry 興奮の好発部位及び伝導特性の解析と
心房細動維持における役割)

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***Analysis of the Preferable Site and Stability of Rotational Reentry:
Its Role for the Maintenance of Atrial fibrillation***

Short title: *Rotational reentry during Atrial Fibrillation*

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ABSTRACT

Background: It remains unclear whether AF is maintained by rotor.

Methods: We evaluated the significance of rotor during atrial fibrillation (AF). Prevalence, location and stability of rotational reentry (RR) in the left atrium were clarified by endocardial non-contact mapping in 66 AF patients. RR was classified into 3 categories; RR continued at stable site (Stable-RR), RR observed intermittently at the same site (Intermittent-RR) and RR observed at different locations (Different-RR). Catheter ablation was performed in a stepwise fashion (linear roof lesion and complex fractionated atrial electrogram ablation following pulmonary vein isolation) until AF termination and elucidated the consequence of radiofrequency lesion delivered within RR site on AF termination and recurrence.

Results: One-hundred nineteen RRs were observed. There were 54 patients with RR (RR Group) and 22 patients without RR (Non-RR Group). Prevalence of Different-RR (n=81) was significantly higher than Stable-RR (n=16, $p<0.001$) and Intermittent-RR (n=22, $p<0.001$). The intervals involved in RR occupied only 22.4 % of total activation time. There was no significant difference in the prevalence of AF termination nor AF/atrial tachycardia recurrence between RR and Non-RR Groups (46 vs 9 patients, $p=0.317$, and 13 vs 1 patients, $p=0.271$) and between patients in whom radiofrequency lesion was involved in RR and those was not (24 vs 22 patients, $p=0.210$, and 6 vs 7 patients, $p=0.506$).

Conclusions: Most RRs were observed transiently and often shifted its locations. Radiofrequency lesion delivered within RR site did not correlate with AF termination nor recurrence, suggesting that RR is not a driving source during AF.

Key words: atrial fibrillation, mapping, reentry, rotor.

List of abbreviations:

AF = atrial fibrillation

CFAE = complex fractionated atrial electrogram

FIRM = focal impulse and rotor modulation

LA = left atrium

PV = pulmonary vein

RR = rotational reentry

The maintenance mechanism of atrial fibrillation (AF) has not been fully clarified. A stable high frequency reentrant activities, so called rotor, have been proposed as the drivers of AF in the experimental models (1-3). These rotors activate the atria exceedingly high frequencies and result in fraction of the electrograms at periphery of rotor site (3). Narayan et al have reported the presence of stable rotors in humans (4). They observed a discrete number of rotors temporary stable in limited spatial domain and showed that focal impulse and rotor modulation (FIRM) guided ablation of rotor site resulted in AF termination (4). They also reported that patients receiving FIRM-guided ablation maintained high rates of freedom from AF (5). Some recent studies have also shown the usefulness of FIRM-guided ablation (6, 7). Whereas, Benharash et al evaluated the approach of FIRM-guided ablation by analyzing the quantitative characteristics of atrial electrogram used to identify rotors (8). They showed that rotational activation in electroanatomical mapping was not observed at FIRM-identified rotor sites (8). Gianni et al also showed that catheter ablation of FIRM-identified rotor sites lead to AF slowing or organization in a small number of patients and the strategy did not prevent recurrence from atrial tachycardia/AF (9). Recently, we have shown that functionally formed stable rotors were observed in a limited number of AF patients, and these rotors may not be associated with AF maintenance (10). In the present study, we further analyzed the prevalence and stability of the rotational reentrant activation during AF, including not only the stable rotational reentry (RR) but also the short-lived unstable RR. Furthermore, we evaluated whether or not the radiofrequency ablation at the RR site is related to the AF termination and AF recurrence to define the role of RR for AF maintenance.

METHODS

Patients

The study subjects were 66 consecutive patients with AF who were referred for radiofrequency catheter ablation of AF (52 men and 14 women; mean age, 61.2 ± 8.9 years, range, 42-77 years). There were 35 patients with paroxysmal AF and 31 patients with persistent AF. All patients underwent the non-contact mapping of the left atrium (LA). Written informed consent was obtained from each patient. The protocol was approved by Kumamoto University Hospital Human Research Committee.

Electrophysiological Study

All antiarrhythmic medications were discontinued 5 half-life periods before the procedures. In total, 6-Fr 20-pole and 6-Fr quadripolar electrode catheters (St. Jude Medical, MN) were percutaneously inserted from the right jugular and right femoral veins and positioned in the coronary sinus and right ventricular apex, respectively. Two 8-Fr long sheaths (St. Jude Medical) were inserted from the right femoral vein and advanced into the LA. After a trans-septal puncture was achieved, systemic anticoagulation was achieved utilizing intravenous heparin to maintain an activated clotting time of between 300 and 350 seconds. After left atriography, non-contact mapping of the LA was performed during AF. One 8-Fr long sheath in the right femoral vein was exchanged for a 10-Fr sheath. A 9-Fr multi-electrode array catheter (EnSite 3000; St. Jude Medical, MN) was introduced into the LA via a 10-Fr sheath, deployed on a 0.032-inch guide wire with its distal tip fixed in the left superior pulmonary vein (PV). Endocardial mapping of the LA was performed using a non-contact mapping system (EnSite 3000; St. Jude Medical, MN). The details of the EnSite 3000 System have been described previously (10, 11, 12). A 7-Fr large-tip (8 mm in length) deflectable quadripolar electrode catheter (Japan Lifeline, Tokyo) was used for mapping. Bipolar electrograms were filtered

between 50 and 600 Hz and recorded along with the surface electrocardiogram using polygraph (EP-workmate; EP Med. Systems, Inc., Mt Arlington, NJ). Pacing was performed using a cardiac stimulator (SEC-4103; Nihon Kohden, Tokyo).

Catheter Ablation

Radiofrequency catheter ablation was performed in a stepwise fashion using an AF termination as a procedural endpoint (13). First, the ipsilateral PV antrum was isolated during AF. A 7-Fr 20-pole circular mapping catheter (Inquir Optima; St. Jude Medical) was positioned in the left or right superior PV and a 7-Fr large-tip (3.5 mm in length) irrigated ablation catheter (Cool Path Duo; St. Jude Medical) was used for ipsilateral PV isolation. If this failed to terminate AF, the linear roof line lesion joining the right and left superior PVs was created, and then complex fractionated atrial electrogram (CFAE) targeted ablation was performed in a stepwise fashion. AF termination was defined when the AF directly converted to sinus rhythm or regular atrial tachycardia. If AF failed to terminate or converted to regular atrial tachycardia, external electrical cardioversion was used to restore sinus rhythm. Radiofrequency energy (20 to 40 W for 30 to 120 seconds) was delivered with a temperature limit of 40°C, using a cardiac ablation generator (IBI-1500T12; St. Jude Medical) with a flow rate set at 16ml/minute. Along the posterior wall, the maximum power was limited to 25W for 30 seconds.

Study Protocol

The preferable location of RR and its stability were analyzed during AF by the non-contact mapping system. Activation sequence was analyzed for 1000 msec during AF in each patient. Presence of RR was defined when the circular activation around the central line of functional block once completed its whole reentrant activation. The location of RR was identified by 8 divided areas of the LA (roof, left PV, right PV, left atrial appendage, septum, and anterior, lateral

and posterior LA) during AF (Figure 1). To identify the continuity of RR, RR was classified into 3 categories; RR continued more than two times at the same site (Stable-RR), RR which was observed intermittently at the same site (Intermittent-RR) and RR which was observed at different locations (Different-RR). The number of RR, sum of the activation time involved in RR, cycle length of RR and type of RR were compared between paroxysmal and persistent AF. The content of ablation procedure, acute results of ablation procedure and prevalence of AF/atrial tachycardia recurrence after ablation procedure were compared between the patients in whom the RR was observed during AF (RR Group) and those was not (Non-RR Group). Among the patients in the RR Group, these parameters were also compared between patients in whom the ablation lesion was involved in the RR site and those in whom the ablation lesion was not involved in the RR site.

Statistical Analysis

Values are expressed as mean±SD. Differences between clinical variables and electrophysiologic parameters were analyzed using either a paired or an unpaired Student's t test for quantitative data or chi-square analysis for qualitative data. A paired Student t test with Bonferroni correction was used to examine whether the prevalence of Different-RR differ from those of other types of RR. The time to the first AF/atrial tachycardia recurrence was analyzed with the Kaplan–Meier method and compared with the log-rank test. A value of $p<0.05$ was considered statistically significant.

RESULTS

Electrophysiologic Characteristics of RR

The RR was observed in 54 patients (81.8%) (28 paroxysmal AF and 26 persistent AF patients) (RR Group), but was not in the remaining 12 patients

(Non-RR Group). A total number of 119 RRs (range, 1 to 5 per patient) were observed. The sum of the activation time involved in RR was 15236 msec, which occupied 22.4 % of total analyzed intervals. The mean cycle length of RR was 128.0 ± 25.5 msec (range, 77 to 219 msec). Table 1 shows the patient characteristics in patients with RR (RR Group) and without RR (Non-RR Group) (Table 1). There was no significant difference in the age, gender, type of AF and history of AF between RR and Non-RR Groups (Table 1). There was no significant difference in the prevalence of hypertension, diabetes mellitus, cerebrovascular accident, coronary artery disease, body mass index, number of antiarrhythmic drugs used before ablation, administration of amiodarone, left ventricular ejection fraction, left atrial diameter and CHADS2 score between the RR and Non-RR Groups (Table 1).

Location and Stability of RR

The number of RR observed at the roof, anterior LA, septum, left and right PV, left atrial appendage, lateral LA and posterior LA were 39, 28, 28, 16, 1, 1 and 6, respectively (Figure 2A). RR was frequently observed at the roof, anterior LA, septum and PV (right and left PV) (Figure 2A). The number of Stable-RR, Intermittent-RR and Different-RR were 16, 22 and 81, respectively (Figure 2B). The prevalence of Different-RR was significantly higher than that of Stable-RR ($p < 0.001$) and Intermittent-RR ($p < 0.001$) (Figure 2B).

Figure 3 shows the Stable-RR observed during persistent AF. Upper panel shows the isopotential map during RR. The wavefront propagated in a counter-clockwise direction at the anterior LA (panel a to h). The wavefront propagated twice around the anterior LA. The correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to h are shown in the lower panel.

Figure 4 shows the Intermittent-RR observed during paroxysmal AF. Upper panel shows the isopotential map during RR. The wavefront propagated

in a clockwise direction at the anterior LA (panel a to d). The wavefront then propagated to posterior LA (panel e). The wavefront came back to the anterior LA 172 msec later, and propagated around the anterior LA in a clockwise direction again (panel f to i). The correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to d and from f to i are shown in the lower panel.

Figure 5 shows the Different-RR observed during paroxysmal AF. Upper panel shows the isopotential map during RR. The wavefront propagated in a counter-clockwise direction around the right PV once (panel a to d). Then the wavefront propagated to another area. Two-hundred eighteen msec later, the wavefront propagated in a counter-clockwise direction at the roof (panel e to h). The correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to d and those at sites from E to H during wavefront propagation from phase e to h are shown in the lower panel.

Comparison of the Characteristics of RR between the Paroxysmal and Persistent AF

Fifty-seven RRs were observed in the paroxysmal AF patients and 62 RRs were observed in the persistent AF patients, respectively (Table 2). There was no significant difference in the total number of RR (57 vs 62, $p=0.298$), the mean number of RR (2.0 ± 1.0 vs. 2.4 ± 1.2 , $p=0.298$), sum of the interval involved in the RR (7402 msec; 25.8 % vs. 7834 msec; 29.2 %, $p=0.525$), mean cycle length of RR (129.9 ± 27.0 vs. 126.4 ± 24.1 msec, $p=0.525$) between the paroxysmal and persistent AF patients (Table 2). There was no significant difference in the number of Stable-RR (8; 14.0 % vs. 8; 12.9 %, $p=0.699$), Intermittent-RR (8; 14.0% vs. 14; 22.6 %, $p=0.320$) and Different-RR (41; 72.0% vs. 40; 64.5%) between the paroxysmal and persistent AF patients (Table 2). Most of the type of RR was Different-RR both in the paroxysmal and persistent AF patients (Table 2).

Results of Stepwise Catheter Ablation in Patients with and without RR

Table 3 shows the ablation procedure and ablation outcome in the RR Group and Non-RR Groups. There was no significant difference in the ablation procedure between RR and Non-RR Groups (PV isolation; 24 vs 5 patients, $p=0.861$, PV isolation/roof line; 9 vs 2 patient, $p=0.644$ and PV isolation/roof line/CFAE ablation; 21 vs 5 patients, $p=0.553$) (Table 3). Among the total 66 patients, AF termination was observed in 55 patients (46 patients in RR Group; 85.2 % and 9 patients in Non-RR Group; 75.0 %, $p=0.317$) (Table 3). AF converted to sinus rhythm in 30 patients in the RR Group and in 7 patients in the Non-RR Group ($p=0.300$), respectively. AF converted to atrial tachycardia in 16 patients in the RR Group and 2 patients in the Non-RR Group ($p=0.300$), respectively. There was no significant difference in the AF or atrial tachycardia recurrence between the RR and Non-RR Groups during a follow-up periods of 43.7 ± 25.6 months (13 patients; 24.1% vs 1 patient; 8.3 %, $p=0.271$) (Table 3 and Figure 6A).

Results of Stepwise Catheter Ablation in Patients in whom the Ablation Lesion was Involved in the RR Site and Those was not

In the 54 patients with RR Group, radiofrequency ablation lesion was involved in the RR site in 30 patients but was not in the remaining 24 patients. Table 4 shows the ablation procedure, acute results of ablation procedure and its outcome in patients in whom the ablation lesion was involved in the RR site and those in whom the ablation lesion was not involved. Regarding the procedure, PV isolation alone was more frequent in patients in whom the ablation lesion was not involved in the RR site compared with those in whom the ablation lesion was involved in the RR site (PV isolation; 19 vs 5 patients, $p<0.001$) (Table 4). Whereas, roof line and/or CFAE ablation was more frequent in whom the ablation lesion was involved in the RR site compared with those in whom the ablation lesion was not involved in the RR site (PV isolation/roof line; 8 vs

1 patients, $p=0.029$ and PV isolation/roof line/CFAE; 17 vs 4 patients, $p=0.003$) (Table 4). However, there was no significant difference in the AF termination nor AF/atrial tachycardia recurrence during a follow-up periods of 43.7 ± 25.6 months between these 2 groups (AF termination; 24 patients; 80.0% vs 22 patients; 91.7%, $p=0.210$ and AF/atrial tachycardia recurrence; 6 patients; 20.0% vs 7 patients; 29.2%, $p=0.506$, respectively) (Table 4 and Figure 6B).

DISCUSSION

The major findings of this study are as follows. RR was observed in 54 patients (81.8%). Few RRs were observed at stable site. The RR often shifted to different locations during AF. The interval involved in these RRs occupied only 22.4% of total analyzed intervals. The prevalence, location and the cycle length of RR activation were not different between the paroxysmal and persistent AF. There was no significant difference in the prevalence of AF termination nor AF/atrial tachycardia recurrence between the RR and Non-RR Groups.

Furthermore, there was no significant difference in the prevalence of AF termination nor AF/atrial tachycardia recurrence between the patients in whom the radiofrequency lesion was involved in RR site and those in whom the radiofrequency lesion was not involved in the RR site. These findings suggest that RR did not correlate with AF maintenance.

Prevalence and Location of RR

High frequency sources or rotors have been proposed as drivers of AF in the experimental model (1). AF was suggested to be maintained by the periodic activity of a small number of rotors (2, 3). The rotor activated the atria at exceedingly high frequencies and result in fibrillatory conduction (1). Narayan et al reported that localized stable rotors or focal impulse were detected in 98 (97%) of 101 cases with sustained AF by FIRM analysis using a 64-pole basket catheter (4). They showed that there was 2.1 ± 1.0 sources of which 70% were rotors and 30% focal impulse (4). Similar result was also reported using the same FIRM approach (7). Whereas, Gianni et al examined the localized rotational activation in the LA during AF using a roving 20-pole circular catheter (9). They identified 47 rotational activities in 21 (61%) patients, most of which were identified in the PV antrum (9). However, few rotor sites were sustained for 2.5 seconds, while the majority (91%) were non-sustained. Lin et

al also reported that rotor-like small radius reentrant circuit were identified in a limited number of patients (14). In the present study, few RRs sustained at stable sites and thus most of RR was observed transiently and often shifted to different locations. These findings were seen both in the paroxysmal and persistent AF. Therefore, sustained rotors as demonstrated by the previous studies guided by FIRM (4, 5, 6, 7) were scarcely observed in the present study. Recently, Pathik et al examined whether rotors detected by 2-dimensional phase map, which was used in the FIRM, were present at the corresponding time segments and anatomical locations in 3-dimensional phase map (15, 16). They demonstrated that single wavefront were the most common propagation pattern (50.2%) (16). A total of 34 rotors were seen in 9 of 14 patients, but all rotors were observed transiently (16), being consistent with our results. They also showed that rotors detected in 2-dimensional map were not observed in the corresponding 3-dimensional map (15). Thus, they suggested that multiple assumptions inherent in a regular grid representation of the basket catheter leads to misleading patterns on phase map (16).

Significance of Rotor Activation for the Maintenance of AF

Narayan et al. observed a discrete number of rotors temporary stable in limited spatial domain and showed that ablation of rotor sites, guided by FIRM, resulted in AF termination (4). They also reported that receiving FIRM-guided ablation maintained high rates of freedom from AF (5). Others have also showed the effectiveness of FIRM guided rotor ablation (6, 7, 17). Tilz et al reported that FIRM ablation terminated AF in a significant number of patients (17). Spitzer et al showed that a high degree of success was observed in longstanding persistent AF patients treated for recurrent AF with FIRM-guided rotor ablation (6). Miller et al reported that FIRM-guided ablation produced high single procedure success, mostly in patients with non-paroxysmal AF (7). However, there was no significant difference in the prevalence of AF

termination nor AF/atrial tachycardia recurrence between the RR and Non-RR Groups in the present study. Furthermore, no significant difference was found in the AF termination nor recurrence between patients in whom the radiofrequency lesion was involved and not involved in the RR site. Benharash et al. evaluated the approach of FIRM-guided ablation by analyzing the quantitative characteristics of atrial electrogram used to identify rotors and described acute procedural outcomes of their approach (8). They showed that activation (1>rotation) on electroanatomical mapping was not observable at FIRM-identified rotor sites. They further showed that catheter ablation of rotor sites, even when accompanied by PV isolation, did not result in AF termination in the majority (83%) of patients (8). Gianni et al. reported that FIRM-identified rotor ablation is not effective in obtaining AF termination, organization, or slowing during the procedure (9). After mid-term follow-up, the strategy of ablating FIRM-identified rotors alone did not prevent recurrence from AF (9). Buch et al. also reported that a low rate of acute AF termination and a high rate of recurrence of AF during long-term follow-up in AF patients who underwent FIRM-guided rotor ablation (18). Steinberg et al. reported that long-term clinical results after FIRM ablation showed poor efficacy (19). All these above results of recent studies may indicate that rotor activation observed during AF may not act as the driving source of AF. A recent systematic review which assessed the arrhythmia-free survival from rotor ablation of AF indicated that there was a wide variability in success rate between different centers performing rotor ablation (20). Therefore, it is suggested that rotor targeted ablation needs to be questioned and further information from randomized control studies is required before the efficacy of technique can be confirmed or refused (20). Another recent meta-analysis of FIRM-guided ablation also showed no any therapeutic benefit of PV isolation plus FIRM approach over PV isolation alone (21).

CONCLUSIONS

Rotational reentrant activation was observed during AF, however most of these activations were observed transiently or intermittently and often shifted its location. Activation time involved in the RR occupied limited intervals during AF. Furthermore, presence or absence of radiofrequency energy delivery within the RR site was not associated with AF termination nor recurrence. These suggest that RR does not act as a driving source during AF.

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REFERENCES

1. Jalife J. Rotors and spiral waves in atrial fibrillation. *J Cardiovasc Electrophysiol.* 2003;14:1665-1680.
2. Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation.* 1998;98:1236-1248.
3. Kalifa J, Tanaka K, Zaitsev AV, Warren M, Vaidyanathan R, Auerbach D, Pandit S, Vikstrom KL, Ploutz-Snyder R, Talkachou A, Atienza F, Guiraudon G, Jalife J, Berenfeld O. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation.* 2006;113:626-633.
4. 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.
5. Narayan SM, Baykaner T, Clopton P, Schricker A, Lalani GG, Krummen DE, Shivkumar K, Miller JM. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *J Am Coll Cardiol.* 2014;63:1761-1768.
6. Spitzer SG, Károlyi L, Rämmler C, Scharfe F, Weinmann T, Zieschank M, Langbein A. Treatment of Recurrent Nonparoxysmal Atrial Fibrillation Using Focal Impulse and Rotor Mapping (FIRM)-Guided Rotor Ablation: Early Recurrence and Long-Term Outcomes. *J Cardiovasc Electrophysiol.* 2017;28:31-38.

7. Miller JM, Kalra V, Das MK, Jain R, Garlie JB, Brewster JA, Dandamudi G. Clinical Benefit of Ablating Localized Sources for Human Atrial Fibrillation: The Indiana University FIRM Registry. *J Am Coll Cardiol.* 2017;69:1247-1256.
8. Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2015;8:554-561.
9. Gianni C, Mohanty S, Di Biase L, Metz T, Trivedi C, Gökoğlan Y, Güneş MF, Bai R, Al-Ahmad A, Burkhardt JD, Gallinghouse GJ, Horton RP, Hranitzky PM, Sanchez JE, Halbfuß P, Müller P, Schade A, Deneke T, Tomassoni GF, Natale A. Acute and early outcomes of focal impulse and rotor modulation (FIRM)-guided rotors-only ablation in patients with nonparoxysmal atrial fibrillation. *Heart Rhythm.* 2016;13:830-835.
10. Yamabe H, Kanazawa H, Ito M, Kaneko S, Ogawa H. Prevalence and mechanism of rotor activation identified during atrial fibrillation by noncontact mapping: Lack of evidence for a role in the maintenance of atrial fibrillation. *Heart Rhythm.* 2016;13:2323-2330.
11. Yamabe H, Morihisa K, Tanaka Y, Uemura T, Enomoto K, Kawano H, Ogawa H. Mechanisms of the maintenance of atrial fibrillation: role of the complex fractionated atrial electrogram assessed by noncontact mapping. *Heart Rhythm.* 2009;6:1120-8.
12. Yamabe H, Morihisa K, Koyama J, Enomoto K, Kanazawa H, Ogawa H. Analysis of the mechanisms initiating random wave propagation at the onset of atrial fibrillation using noncontact mapping: role of complex fractionated electrogram region. *Heart Rhythm.* 2011;8:1228-36.
13. Yamabe H, Kanazawa H, Itoh M, Kaneko S, Ogawa H. Difference in the maintenance mechanism of atrial fibrillation perpetuated after pulmonary

vein isolation between paroxysmal and persistent atrial fibrillation: Effects of subsequent stepwise ablation. *Int J Cardiol.* 2016;210:109-18.

14. Lin YJ, Lo MT, Lin C, Chang SL, Lo LW, Hu YF, Hsieh WH, Chang HY, Lin WY, Chung FP, Liao JN, Chen YY, Hanafy D, Huang NE, Chen SA. Prevalence, characteristics, mapping, and catheter ablation of potential rotors in nonparoxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol.* 2013;6:851-858.

15. Pathik B, Kalman JM, Walters T, Kuklik P, Zhao J, Madry A, Sanders P, Kistler PM, Lee G. Absence of rotational activity detected using 2-dimensional phase mapping in the corresponding 3-dimensional phase maps in human persistent atrial fibrillation. *Heart Rhythm.* 2018;15:182-192.

16. Pathik B, Kalman JM, Walters T, Kuklik P, Zhao J, Madry A, Prabhu S, Nalliah C, Kistler P, Lee G. Transient Rotor Activity During Prolonged 3-Dimensional Phase Mapping in Human Persistent Atrial Fibrillation. *JACC Clin Electrophysiol.* 2018;4:72-83.

17. Tilz RR, Lin T, Rillig A, Heeger CH, Scholz L, Wohlmuth P, Bucur T, Metzner A, Mathew S, Wissner E, Ouyang F, Kuck KH. Focal Impulse and Rotor Modulation for the Treatment of Atrial Fibrillation: Locations and 1 Year Outcomes of Human Rotors Identified Using a 64-Electrode Basket Catheter. *J Cardiovasc Electrophysiol.* 2017;28:367-374.

18. Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: A multicenter experience. *Heart Rhythm.* 2016;13:636-641.

19. Steinberg JS, Shah Y, Bhatt A, Sichrovsky T, Arshad A, Hansinger E, Musat D. Focal impulse and rotor modulation: Acute procedural observations and extended clinical follow-up. *Heart Rhythm.* 2017;14:192-197.

20. Parameswaran R, Voskoboinik A, Gorelik A, Lee G, Kistler PM, Sanders P, Kalman JM. Clinical impact of rotor ablation in atrial fibrillation: a systematic review. *Europace*. 2018 Jan 11. doi: 10.1093/europace/eux370.
21. Mohanty S, Mohanty P, Trivedi C, Gianni C, Della Rocca DG, Di Biase L, Natale A. Long-Term Outcome of Pulmonary Vein Isolation With and Without Focal Impulse and Rotor Modulation Mapping: Insights From a Meta-Analysis. *Circ Arrhythm Electrophysiol*. 2018;11:e005789.

FIGURE LEGENDS

Figure 1. The location of rotational reentry was identified by 8 divided areas of left atrium (LA). LAA, left atrial appendage; LPV, left pulmonary vein; RPV, right pulmonary vein.

Figure 2. Panel A shows the number of rotational reentry (RR) at each location of the left atrium (LA). Panel B shows the prevalence of Stable-RR, Intermittent-RR and Different-RR. Prevalence of Different-RR was significantly higher than that of Stable-RR and Intermittent-RR.

Figure 3. The rotational reentry (RR) which was observed at the stable site of the left atrium (LA) during persistent AF is shown. Upper panel shows the isopotential map during RR. The wavefront propagated in a counter-clockwise direction at the anterior LA (panel a to h). The wavefront propagated twice around the anterior LA. The electrocardiographic leads I and V5, electrograms recorded at coronary sinus (CS) and correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to h are shown in the lower panel. LA, left atrium; LAA, left atrial appendage; LPV, left pulmonary vein; RPV, right pulmonary vein.

Figure 4. The rotational reentry (RR) which was observed intermittently at the anterior left atrium (LA) during paroxysmal AF is shown. Upper panel shows the isopotential map during RR. The wavefront propagated in a clockwise direction at the anterior LA (panel a to d). The wavefront then propagated to posterior LA (panel e). The wavefront came back to the anterior LA 172 msec later, and propagated around the anterior LA in a clockwise direction again

(panel f to i). The electrocardiographic leads I and V5, electrograms recorded at coronary sinus (CS) and correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to d and from f to i are shown in the lower panel. LA, left atrium; LAA, left atrial appendage; LPV, left pulmonary vein; RPV, right pulmonary vein.

Figure 5. The rotational reentry (RR) which was observed at different location of the left atrium (LA) during paroxysmal AF is shown. Upper panel shows the isopotential map during RR. The wavefront propagated in a counter-clockwise direction around the right pulmonary vein once (panel a to d). Then the wavefront propagated to another area. Two-hundred eighteen msec later, the wavefront propagated in a counter-clockwise direction at the roof (panel e to h). The electrocardiographic lead I, electrograms recorded at coronary sinus (CS) and correspondent unipolar electrograms at sites from A to D during wavefront propagation from phase a to d and those at sites from E to H during wavefront propagation from phase e to h are shown in the lower panel. LA, left atrium; LAA, left atrial appendage; LPV, left pulmonary vein; RPV, right pulmonary vein.

Figure 6. Panel A shows the Kaplan-Meier estimates of the atrial fibrillation (AF) or atrial tachycardia (AT) free survival ratio in the RR Group (blue line) and Non-RR Group (red line). Panel B shows the Kaplan-Meier estimates of the AF/AT free survival ratio in patients in whom the radiofrequency (RF) ablation lesion was involved in the RR site (red line) and those in whom the RF lesion was not involved in the RR site (blue line). Time to first electrocardiogram-documented recurrence of AF/AT after the ablation procedure. Months of follow-up (months), timed after the ablation procedure.

Table 1. Patient Characteristics

Patient Characteristics	RR Group (n = 54)	Non-RR Group (n = 12)	P-value
Age (y)	62.1 ± 9.1	57.3 ± 7.2	.061
Sex : male	42 (77.8%)	10 (83.3%)	.506
Paroxysmal AF	28 (51.9%)	7 (58.3%)	.684
Persistent AF	26 (48.1%)	5 (41.7%)	.684
History of AF (mo)	54.4 ± 45.8	35.6 ± 33.5	.185
Hypertension	42 (77.8%)	7 (58.3%)	.152
Diabetes mellitus	3 (5.6%)	2 (16.7%)	.221
CVA	5 (9.3%)	2 (16.7%)	.375
CAD	2 (3.7%)	0	.667
BMI (kg/m ²)	24.2 ± 3.4	24.4 ± 4.2	.938
No. of AAD before ablation	37 (68.5%)	6 (50.0%)	.188
Amiodaron	0	0	
LV ejection fraction (%)	62.7 ± 6.2	60.9 ± 7.8	.457
LAd (mm)	38.5 ± 4.4	40.1 ± 5.0	.223
CHADS2 score	1.0 ± 0.8	1.2 ± 1.3	.826

Values are presented as mean ± SD or as n (%)

AAD=Antiarrhythmic drug; AF=atrial fibrillation; BMI=body mass index; CAD=coronary artery disease; CVA=cerebrovascular accident; LAd=left atrial dimension; LV=Left ventricular; No=number; RR=rotational reentry.

Table 2. Comparison of Characteristics of Rotational Reentry between Paroxysmal and Persistent Atrial Fibrillation

	Paroxysmal AF (n=28)	Persistent AF (n=26)	P-value
Total No. of RR	57	62	.298
Mean No. of RR (per patient)	2.0 ± 1.0 (range; 1-5)	2.4 ± 1.2 (range; 1-5)	.298
Sum of the interval involved in RR (msec)	7402 (25.8%)	7834 (29.2%)	.525
Mean CL of RR (msec)	129.9 ± 27.0 (range; 77-219msec)	126.4 ± 24.1 (range; 79-178)	.525
Type of RR			
Stable-RR	8 (14.0%)	8 (12.9%)	.699
Intermittent-RR	8 (14.0%)	14 (22.6%)	.320
Different-RR	41 (72.0%)	40 (64.5%)	.810

Values are presented as mean ± SD or as n (%)

AF=atrial fibrillation; CL=cycle length; No=number; RR=rotational reentry.

Table 3. Comparison of Ablation Procedure and Outcome between the Rotational Reentry Group and Non-Rotational Reentry Group

	RR Group (n=54)	Non-RR-Group (n=12)	P-value
PVI	24 (44.4%)	5 (41.7%)	.861
PVI + roof	9 (16.7%)	2 (16.6%)	.644
PVI + roof + CFAE	21 (38.9%)	5 (41.7%)	.553
Acute result of ablation procedure			
AF termination (+)	46 (85.2%)	9 (75.0%)	.317
Sinus	30 (65.2%)	7 (77.8%)	.300
AT	16 (34.8%)	2 (22.2%)	.300
AF termination (-)	8 (14.8%)	3 (25.0%)	.317

Values are presented as n (%)

AF=atrial fibrillation; AT=atrial tachycardia; CFAE=complex fractionated atrial electrogram; PVI=pulmonary vein isolation; RR=rotational reentry.

Table 4. Comparison of Ablation Procedure and Outcome between Patients in whom Radiofrequency Lesion was involved in the Rotational Reentry Site and those was not

	RF lesion in RR (+) n=30	RF lesion in RR (-) n=24	P-value
PVI	5 (16.7%)	19 (79.2%)	<0.001
PVI + roof	8 (26.7%)	1 (4.2%)	.029
PVI + roof + CFAE	17 (56.6%)	4 (16.6%)	.003
Acute result of ablation procedure			
AF termination (+)	24 (80.0%)	22 (91.7%)	.210
Sinus	11 (45.8%)	18 (81.8%)	.012
AT	13 (54.2%)	4 (18.2%)	.012
AF termination (-)	6 (20.0%)	2 (8.3%)	.210

Values are presented as n (%)

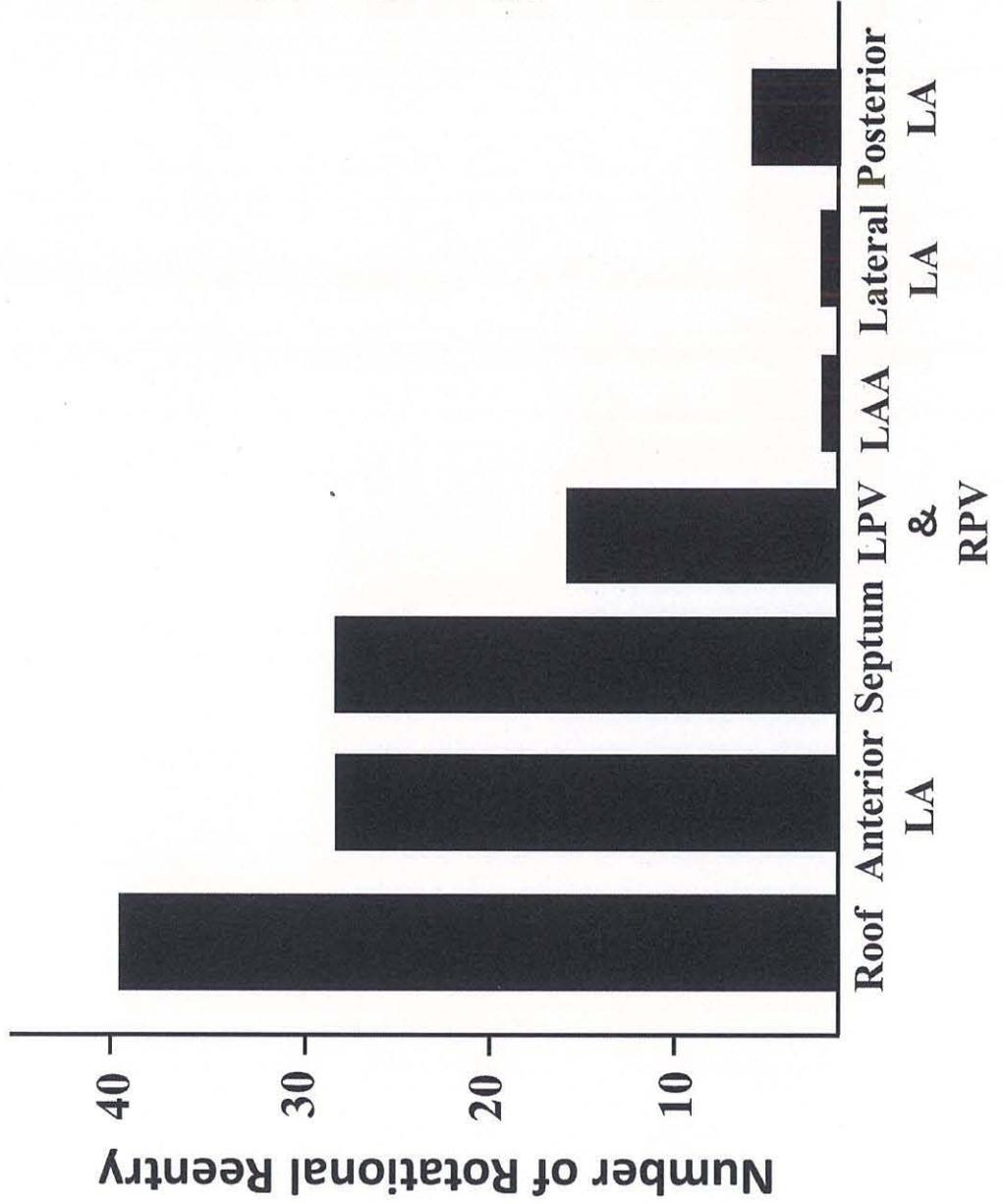
AF=atrial fibrillation; AT=atrial tachycardia; CFAE=complex fractionated atrial electrogram; PVI=pulmonary vein isolation; RF=radiofrequency; RR = rotational reentry.

Figure 1



Figure 2

(A)



(B)

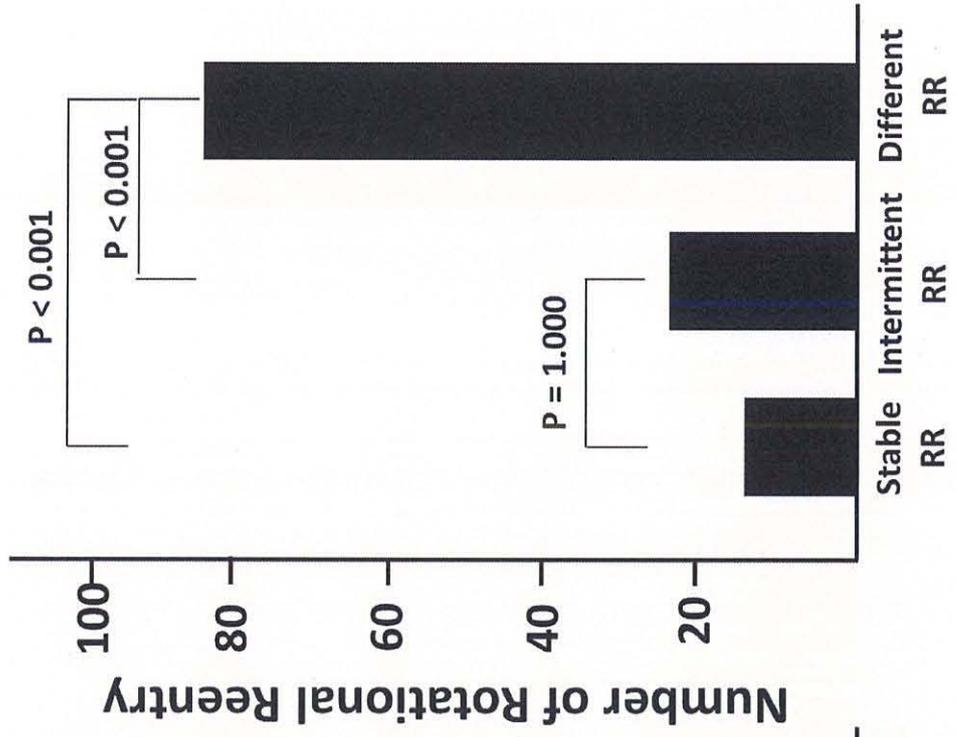


Figure 3

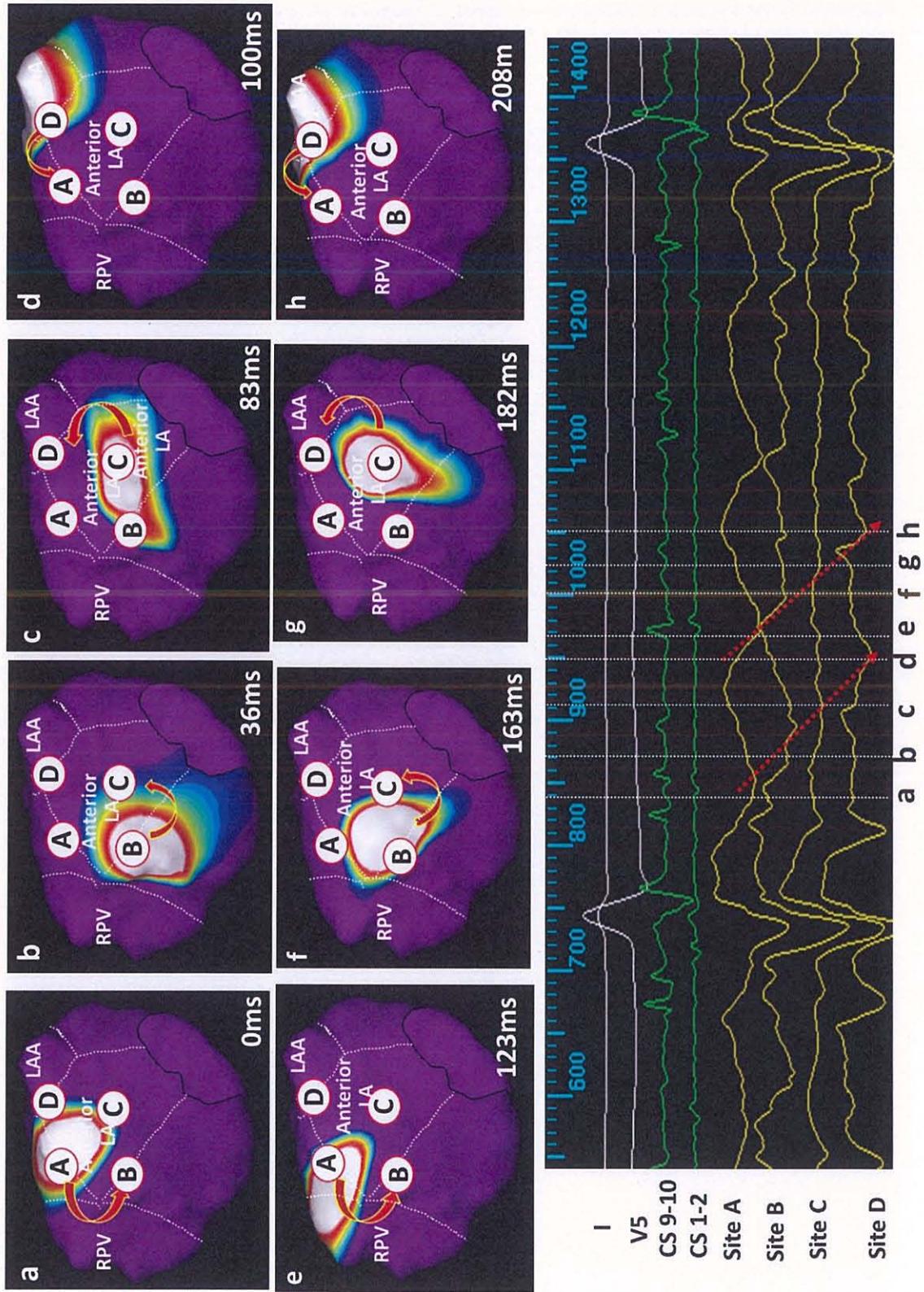


Figure 4

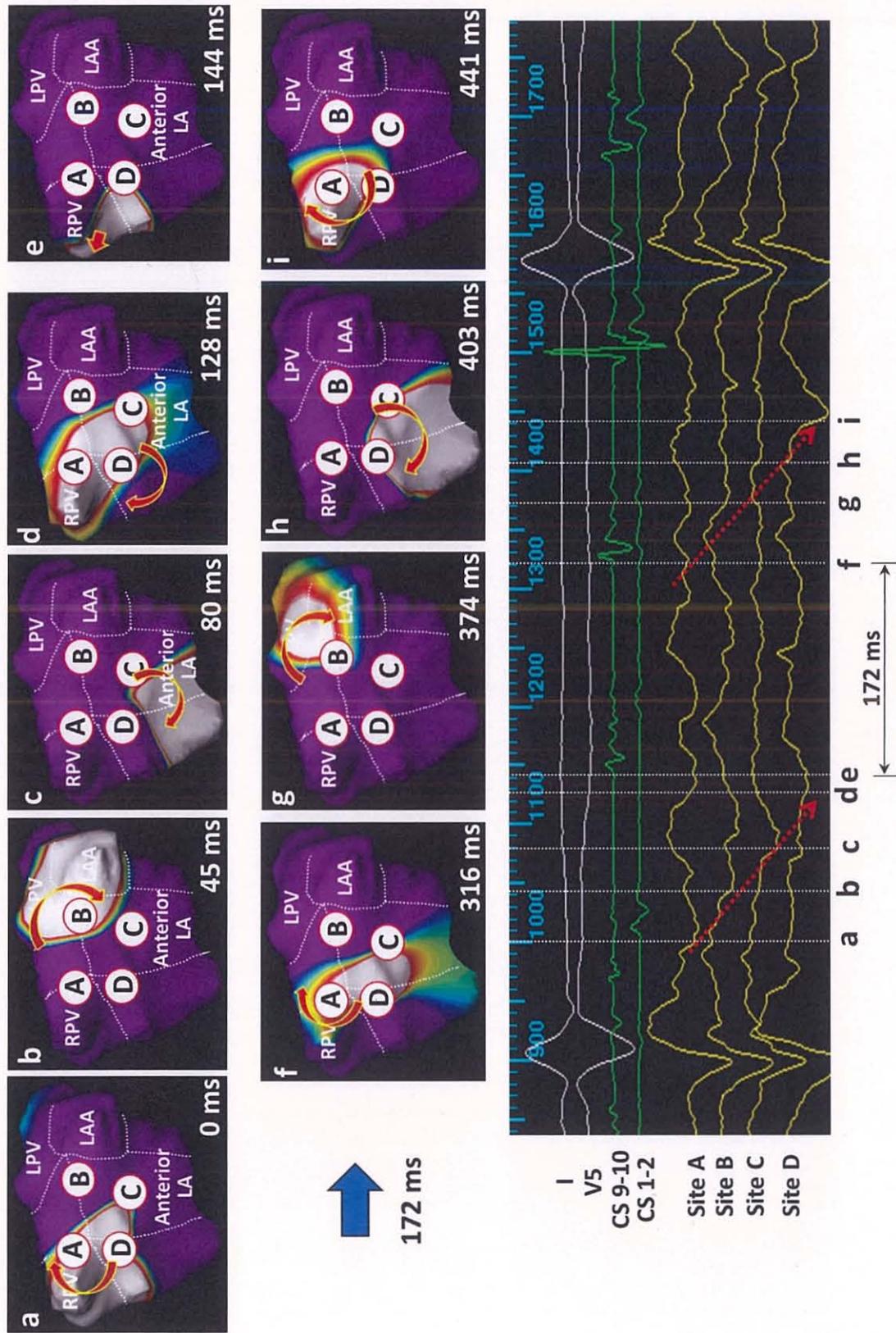


Figure 5

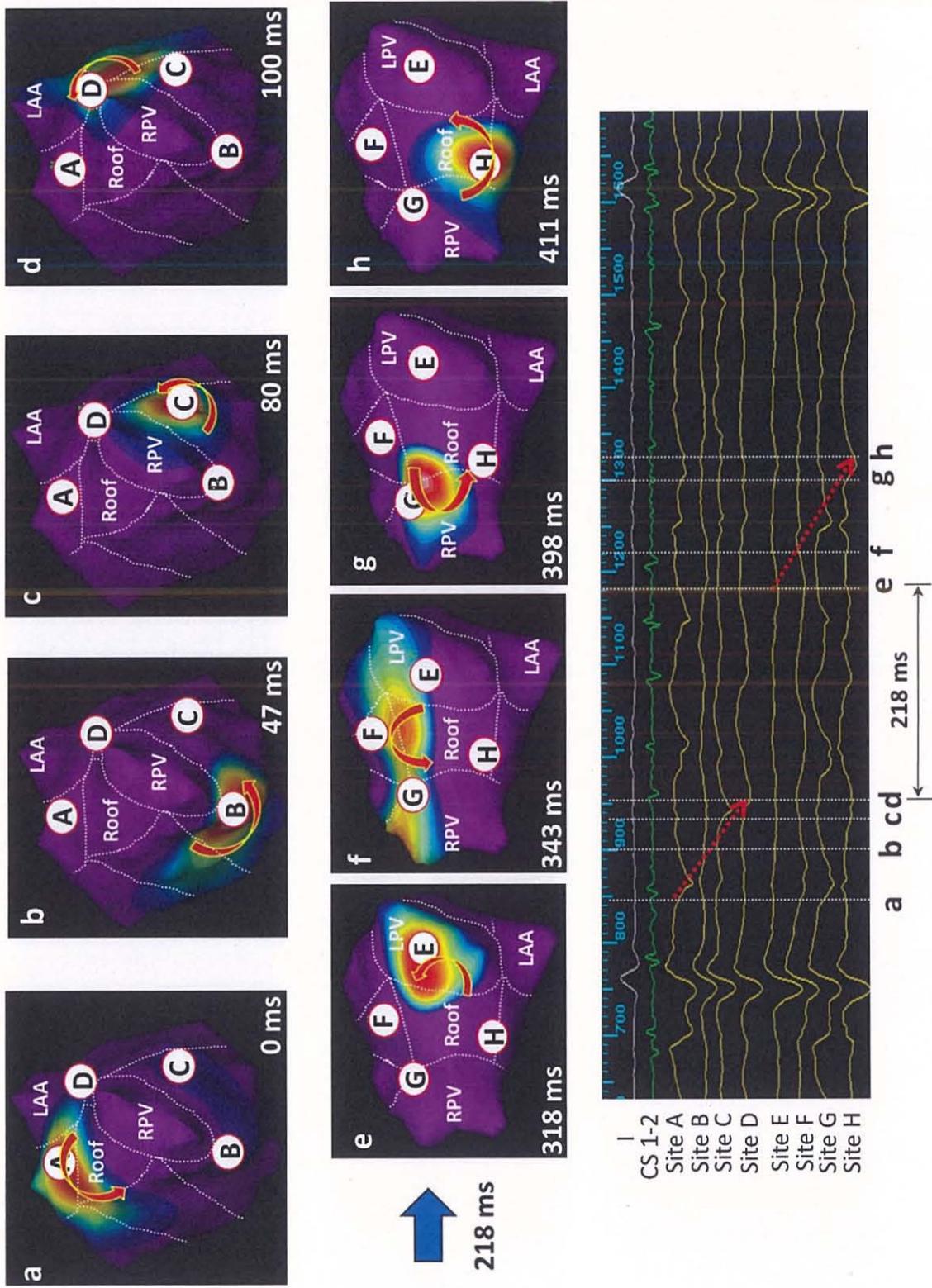
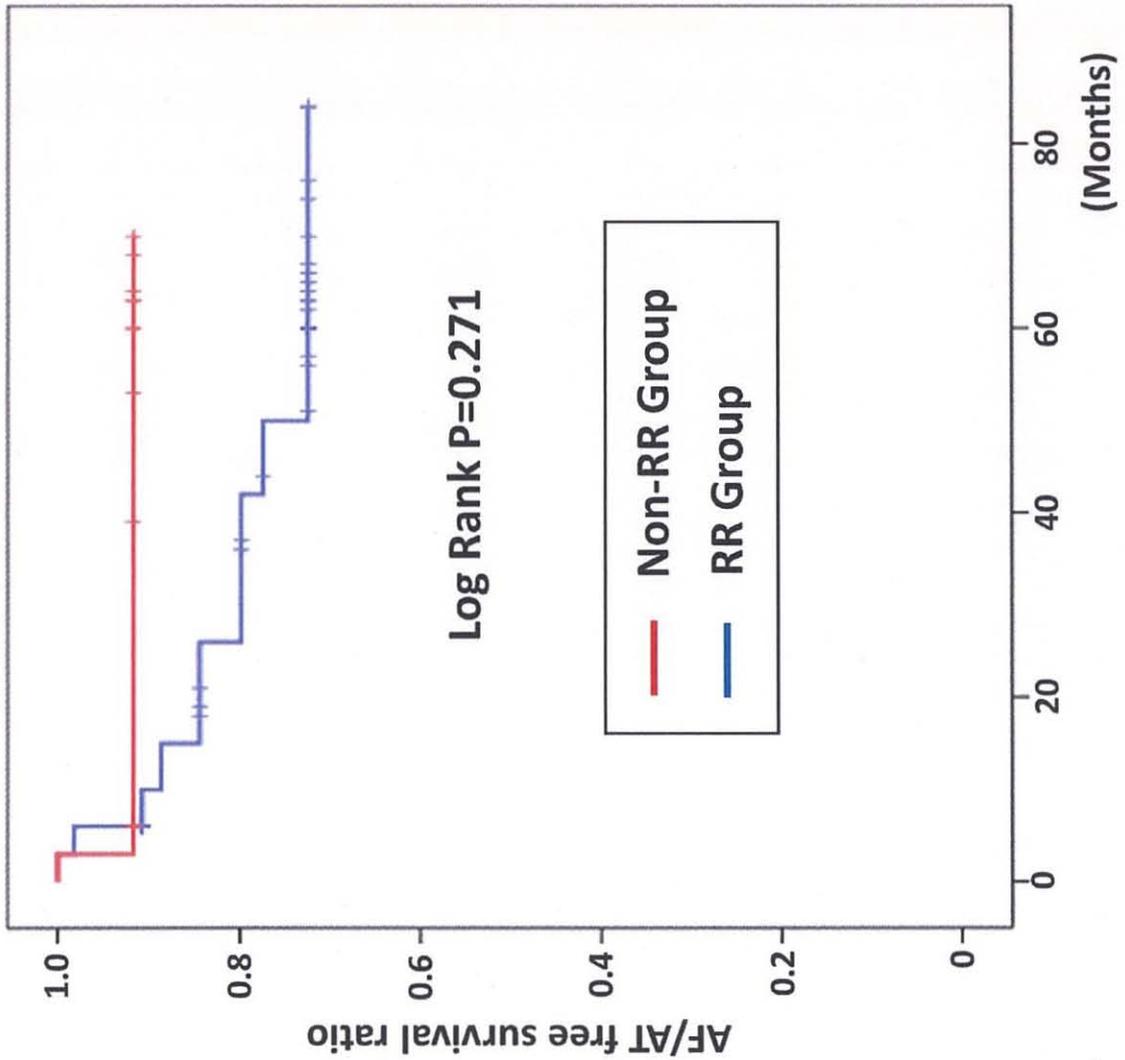


Figure 6

(A)



(B)

