ATRIAL FIBRILLATION

RESEARCH ARTICLE

Characterization of Drivers in Patients with Persistent Atrial Fibrillation to Identify Substrate Based Rotor Ablation Targets

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ABSTRACT. Recent clinical trials have shown that targeting rotors and focal impulses (FIs) during atrial fibrillation (AF) ablation improves outcomes. This study evaluated whether a novel computational mapping algorithm (CMA) could identify FIs and rotors, and characterize rotors when incidentally ablated resulting in rhythm changes. Three-dimensional (3D) left atrial electro-anatomic maps were created from signals recorded from multipolar circular mapping catheters in 61 patients undergoing persistent AF ablation. Forty of 61 were of adequate quality for analysis. CMA employing an AF pattern recognition algorithm created 3D panoramic AF maps identifying drivers of AF (FIs and rotors) post procedure. Rotors were further classified as substrate based (SBR) or non-substrate based (NSBR) on the basis of rotor stability, proximity to voltage transition zones and complex fractionated atrial electrograms (CFAEs). Incidentally ablated identified AF drivers, including SBRs and NSBRs, were evaluated for rhythm changes. A total of 172 drivers were identified in 40 patients (4.3 ± 2.2 drivers/patient). Seventy percent were rotors (120/172) and 30% were FIs (52/172). Sixty-seven percent of rotors were classified as SBR versus 33% as NSBR. Incidental ablation of SBRs resulted in rhythm change 91% of the time versus only 24% of the time for NSBR (p < 0.00001).

Conclusions: Incidental ablation of SBRs resulted in rhythm change significantly more frequently than ablation of NSBRs. Identification of drivers and classification of rotors based on substrate properties may allow a more tailored ablation approach in patients with persistent AF.

KEYWORDS. ablation, atrial fibrillation, computational mapping algorithm, mapping, rotor characterization algorithm rotors.

Introduction

Atrial fibrillation (AF) currently afflicts 2–3 million people in the United States and is estimated to affect 6–12 million US adults by 2050.¹ The cornerstone of catheter-based treatment of symptomatic AF is based on the observation by Haissaguerre et al.² of ectopic beats originating from the pulmonary veins (PVs) triggering AF. While isolation of the PVs improves
outcomes in patients with paroxysmal AF, additional ablation is often required in patients with persistent and longstanding persistent AF, with poor results. Recent imaging modalities using intracardiac basket catheters and high-density body surface electrodes have enabled panoramic imaging of AF, providing insights into the mechanisms that drive and maintain persistent and longstanding persistent AF. Targeted ablation of AF drivers such as rotors and focal impulses (FIs) has improved freedom from AF. What constitutes a rotor and whether all rotors identified by various imaging modalities should be ablated is currently debated. This study evaluated a spatiotemporal computational mapping algorithm (CMA) applying a novel AF pattern recognition or “CS phase-synchronization algorithm” with data from stationary and roving multipolar catheters creating panoramic three-dimensional (3D) AF maps enabling direct visualization of rotors and FIs. Identified rotors were then subjected to a rotor characterization algorithm (RCA), which classified them as substrate-based rotors (SBRs) or non-substrate-based rotors (NSBRs) based on electrophysiological properties, including reproducibility over different phases of AF, proximity to voltage transition zones, and presence of complex fractionated atrial electrograms (CFAEs). Incidental ablations of identified and characterized AF drivers were evaluated for rhythm changes.

Methods

Study population

This study was approved by the human institutional review board at Mercy Hospital, St. Louis, MO, USA. Sixty-one patients undergoing radiofrequency ablation for symptomatic AF were enrolled from April, 2013, until August, 2014. Of the 61 patients, 40 cases were of adequate sampling quality to allow for appropriate analysis. Before the procedure, anti-arrhythmic medications were discontinued for a minimum of five half-lives and for at least 1 month for amiodarone, when possible. All patients underwent transesophageal echocardiogram. Patients were excluded if thrombus was detected, if ablation was not pursued, or if data could not be analyzed due to technical limitations.

Procedural details

Patients were brought to the electrophysiology laboratory in a fasting state. Under general anesthesia catheters were introduced via the femoral veins. After transseptal cannulation of the left atrium (LA), heparin was administered to maintain an activated clotting time (ACT) >350 s. A linear decapolar catheter (Inquiry, St. Jude, St. Paul, MN) was placed in the coronary sinus (CS). A circular duodecapolar catheter (Reflexion Spiral, St. Jude Medical, St. Paul, MN, or LASSO, Biosense Webster, Diamond Bar, CA) and a 3.5-mm irrigated tip ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA) were placed in the LA. While in AF, high-density 3D electro-anatomic LA maps were created with the Ensite Velocity mapping system (St. Jude) using the circular mapping catheter. An average of 16.1 ± 5.7 distinct LA locations were sampled with the circular catheter per patient. At each location, simultaneous CS and circular catheter electrograms were recorded for 30 s.

Ablation was performed in a power-controlled mode at 20–40 watts and 40°C. All patients underwent wide-area circumferential ablation (WACA) of the PVs, with subsequent step-wise linear ablation until organization into atrial tachycardia, atrial flutter, or sinus rhythm. CFAEs and/or continuous local electrograms were targeted at the operator’s discretion. Subsequent atrial tachycardias or flutters were mapped and targeted. Patients who remained in AF after extensive ablation were cardioverted to achieve sinus rhythm.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. The chi-square test was applied to analyze categorical variables, and p < 0.05 was considered statistically significant. CMA identified CS, and circular catheter phase correlations are given as a percentage of signal alignment, 0% corresponding to no alignment and 100% complete alignment.

Panoramic correlation of CS phase map

CMA-derived maps were created via post-processing of raw data collected during AF before ablation allowing for reconstruction of integrated 3D panoramic unipolar AF maps post procedure. LA activation times from all near- and far-field unipolar electrograms were determined by peak dV/dt and filtered to eliminate high- and low-frequency noise. CMA was used to detect correlations between activation times from the “near-field” (LA) circular catheter and the “far-field” (CS) catheter. As depicted in Figure 1a-c, processed signals from the CS catheter (spatial domain) were placed in a matrix consisting of a 3-5-beat overlapping window (time domain). Using a roving window, matrices were analyzed for repeating spatiotemporal patterns in the CS catheter. A distinct CS catheter spatiotemporal activation pattern that recurred at every 30-s circular catheter recording location within the LA was defined as a CS phase. On average, 10.8 ± 3.1 distinct AF phases were observed per patient.

In Figure 1a, the green shaded rectangle highlights a single CS phase (“CS phase green”) identified by the CMA from a 3-beat matrix of CS catheter signals. Notably, this identified CS phase occurred three times (Figure 1a, red, blue, and green electrograms) while the circular catheter was at the LA position marked by the green triangle in Figure 1g. Comparing the red, blue, and green electrograms highlighted by the green rectangle in Figure 1a, it is evident that the general spatiotemporal activation pattern is preserved in the CS. For each instance where CS phase green repeated itself on the CS catheter (Figure 1a), the electrograms that occurred simultaneously on the circular LA catheter (near field) were evaluated and noted to be conserved.
Figure 1: (a–c) Coronary sinus electrograms in human atrial fibrillation (AF) (cycle length (CL) 180 ms) depicting computational mapping algorithm (CMA) matching. (d–f) Corresponding circular catheter electrograms demonstrating repeating AF patterns. (g–i) Schematic representation of circular catheter and CMA vector map technique.

(Figure 1d). The red, blue, and green electrograms on the CS in Figure 1a correspond in time to the red, blue, and green electrograms recorded on the spiral mapping catheter in Figure 1d. All recordings from Figure 1a,d were obtained over a single 30-s time period. Importantly, each time CS phase green was seen in Figure 1a, the corresponding activation pattern on the near-field circular catheter in Figure 1d was conserved for the LA location highlighted by the triangle in Figure 1g. These correlations were maintained at different locations within the LA for the same CS phase. Figure 1b,e shows the CS and circular catheter electrograms, respectively, when the circular catheter was moved to the position depicted by the square in Figure 1h. The same far-field CS pattern or, CS phase green, that occurred while the circular catheter was in the triangle location in Figure 1g recurred while the circular catheter was in the square location in Figure 1h, evident by comparing the corresponding CS electrogram patterns in Figure 1a,b. For every CS phase green that was observed at distinct and separate time points (Figure 1b, red, blue, and green electrograms), a unique corresponding spatiotemporal electrogram pattern was observed in the near-field circular catheter (Figure 1e, red, blue, and green electrograms). The circular catheter activation patterns at different LA locations were noted to be different for the same CS phase green (Figure 1d–e), while those at the same location within the LA were conserved for a given CS phase.

CMA identified a second recurring CS phase on the CS catheter, highlighted by the yellow rectangle in Figure 1c (“CS phase yellow”). The red, green, and blue electrograms in Figure 1c all occurred while the circular catheter was positioned in the area of the LA depicted by the square in Figure 1i. CS phase yellow was significantly different from CS phase green, which can be seen by contrasting unipolar CS electrograms patterns in Figure 1a to those in Figure 1c. Figure 1f shows local unipolar electrograms recorded from the circular LA mapping catheter at position square when CS phase yellow occurred on the CS catheter in Figure 1c. Notably, correlations between the spatiotemporal activation patterns on the CS catheter and circular LA catheter were conserved and these correlations were repeatable for CS phase yellow (Figure 1c,f).

Similar correlations between conserved local circular LA catheter spatiotemporal electrogram patterns and recurring CS spatiotemporal electrogram patterns were observed for multiple CS phases. These observations demonstrate that different CS phases from the far-field CS catheter correspond to unique and reproducible near-field circular catheter activation patterns for a given location in the LA, as noted in Figure 1. The spatiotemporal electrograms on
the CS were noted to be conserved and have a phase correlation factor of 90% ± 6% for a given CS phase across all CS phases identified. The correlation between conserved circular catheter electrograms at a given anatomical LA location for an identified CS phase was 80% ± 2.7%. The near-field–far-field correlations were reproducible 1) at different LA locations and 2) across different CS phases.

Creation of panoramic 3D conduction vector maps

Having established that a given far-field CS phase corresponds to a specific and reproducible near-field local LA electrogram activation pattern on the circular catheter, we created a global LA conduction vector map for a single recurring CS phase by “stitching together” the corresponding near-field spatiotemporal patterns observed on the circular catheter electrograms from each LA location. Conduction vectors were calculated from circular catheter electrodes as noted from the x–y–z position obtained from 3D mapping. Conduction vectors for areas between circular catheter electrode positions were interpolated from the adjacent circular catheter electrodes recordings. Next, the 3D geometry of the LA was used as a surface upon which the CS phase-specific conduction vectors were projected. The result of this process is shown in Figure 2. The two 3D panoramic conduction vector maps in Figure 2a,b correspond to the two distinct CS phases shaded by the green and yellow rectangles in Figure 2c,d, respectively. A single circular catheter location (grey dots) and the corresponding local unipolar electrograms (insets) are shown in Figure 2a,b. Notably, the global conduction vector map revealed areas of transient spiral wave-like or rotor-like conduction patterns in one AF phase (Figure 2a, mid-LA roof and below the left inferior PV) that were absent in the second AF phase (Figure 2b).

Figure 2: (a,b) Computational mapping algorithm maps for two different phases of human atrial fibrillation. Circular catheter electrograms insets demonstrating (a) rotational direction of “green” phase corresponding to circular pattern of white arrows and (b) non-organized phase “yellow”. (c,d) Coronary sinus electrograms corresponding to phase “green” and “yellow” of (a) and (b) respectively.

Results

Patient characteristics

Patient age ranged from 51 to 78 years, with a mean of 66.9 years (Table 1). The majority of the patients had persistent or longstanding persistent AF (38/40). Prior ablation was noted in 12.5% (5/40), and 35% (14/40) were noted to have failed antiarrhythmic drugs.

Identification of AF drivers

For each unique CS phase, a conduction vector map was created and visually inspected by two operators to identify putative AF drivers. FIs were predefined as a single point from which all conduction vectors pointed outwards. A rotor was defined as a point around which a circular or semicircular (>75% of a complete circle) pattern of conduction vectors appeared to rotate. Hilbert transformation was applied to raw unipolar electrograms from CS phase-specific maps before projection of conduction vectors. Examples of a rotor and FI for two different patients are shown in Figure 3, along with corresponding reconstructions of the Hilbert transformation. Hilbert maps (Figure 3a,c) correlated with drivers that were identified by CMA-created conduction vector maps containing rotors (Figure 3b, yellow arrows) and FIs (Figure 3d, yellow arrows).

Overall, 172 drivers were identified in the 40 patients in this series (4.3 ± 2.2 drivers/patient). Seventy percent of drivers were rotors (120/172) and 30% were FIs (52/172). One or more rotors were detected in all patients (mean 3.0 ± 1.7). A FI was detected in 75% of patients (mean 1.3 ± 1.1). FIs were observed predominantly within or near PV–LA junctions, while rotors were noted to have a wide spatial distribution within the LA (Online Supplementary Figure 1). Forty-eight percent of drivers (38 rotors and 44 FIs) were noted to occur on or within traditional WACA lines.

Table 1: Patient characteristics for patients undergoing atrial fibrillation ablation

<table>
<thead>
<tr>
<th>Patient characteristics (n = 40)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 9 (51–78)</td>
</tr>
<tr>
<td>Male</td>
<td>27 (68%)</td>
</tr>
<tr>
<td>Classification of AF</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>28 (70%)</td>
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<tr>
<td>Longstanding persistent</td>
<td>10 (25%)</td>
</tr>
<tr>
<td>Co-morbid conditions</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &lt; 50%</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>34.3 (20–53)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Failed antiarrhythmic drugs</td>
<td>14 (35%)</td>
</tr>
<tr>
<td>Previous pulmonary vein isolation ablation (PVI/ablation)</td>
<td>5 (13%)</td>
</tr>
</tbody>
</table>
Classification of identified rotors

After being identified from conduction vector maps, rotors were characterized based on their electrophysiological and underlying atrial substrate properties, such as voltage transition during AF, proximity to CFAEs, whether the rotor was consistently observed in multiple CS phases (stability), and whether the rotor was fixed or precessed in space. A voltage transition zone was defined as an area with $DV > 0.23$ mV based on combined cardiac magnetic resonance imaging (MRI) and in vivo electro-anatomic mapping studies correlating voltage gradients in AF between regions of dense delayed enhancement (DE) and patchy/non-dense DE regions. Specifically, each rotor was evaluated for 1) proximity and relationship to voltage transition zones, 2) proximity and relationship to areas of CFAEs, and 3) stability, defined as recurrence of the rotor in at least 30% of the total CS phases observed in that patient. After analysis, 68% (82/120) of rotors were found to occur along voltage transition zones ($DV > 0.64$ ± 0.77 mV) in AF ($p<0.00001$). In contrast, only 22% (26/120) of rotors were noted to occur in areas of CFAEs ($p=NS$). Forty-six percent (55/120) of rotors were considered stable while 54% were considered unstable and transient in nature. Of the stable rotors identified, 64% (35/55) were noted to precess within a localized anatomical region, and 36% (20/55) were noted to be fixed within an anatomical region. We hypothesized that electrophysiological properties and underlying atrial substrate might provide information to distinguish between whether observed rotors were true drivers of AF or simply bystander phenomena. A RCA was developed to classify each rotor using a weighted scoring system. Rotors that occurred along voltage transition zones ($DV > 0.23$ mV), existed in areas devoid of CFAEs, and were present in >30% of total CS phases were designated as SBRs, while those lacking these characteristics were designated NSBRs. Examples of rotors classified as SBR and NSBR on the basis of these criteria are shown in Figure 4. The SBR located on the left inferior portion of the posterior wall (Figure 4a, yellow arrows) was stable, occurring in both CS phases shown (Figure 4a,b), and five of 15 total CS phases in this patient. When evident, it precessed along a voltage transition zone (Figure 4c, white rectangle), and occurred in an area devoid of CFAEs (Figure 4d, white rectangle). In contrast, the NSBR rotor located just below the LIPV (Figure 4b, black arrows) occurred in only one of 15 total CS phases, was located in an area with minimal voltage transition (Figure 4c, white circle), and occurred next to an area of high CFAEs (Figure 4d, white circle). A summary of RCA classification of all rotors is shown (see Figure 7a).

Analysis of rhythm changes after ablation of drivers

Having classified rotors as SBR or NSBR, we asked whether incidental ablation of SBRs versus NSBRs resulted in different outcomes with respect to rhythm changes. Ablation lesion sets were superimposed on the
reconstructed panoramic conduction vector map to identify incidentally ablated FIs and rotors. A driver was considered ablated if 1) 4-mm ablation lesion markers traversed the driver core(s) and 2) more than one ablation lesion was present at the ablated driver site. When ablated drivers were found, surface and local electrograms were analyzed before, during, and for 30 s after radiofrequency energy was delivered for rhythm changes. Rhythm change was defined as a $6 \times$ frequency resolution shift in fast Fourier transform (FFT), or conversion to atrial tachycardia, atrial flutter, or sinus rhythm.

An example of incidental ablation of two SBRs and one NSBR is shown (Figure 5a,b, yellow versus black arrows, respectively) for two different CS phases. While all three rotors were ablated (red dots in Figure 5b), significant rhythm change was only observed with ablation of the SBRs in this case. Ablation of the SBR located near the LA roof–left superior PV junction was associated with a rhythm change as noted by change in FFT (data not shown). Ablation of the second SBR at the base of the left atrial appendage (LAA) terminated AF with organization into atrial tachycardia (Figure 5e).

Interestingly, in this series, the LAA and areas directly adjacent to the LAA were noted to support rotor activity. CMA–RCA identified and classified seven SBRs and one NSBR in or near the LAA. One patient in our series underwent extensive ablation of the LA and right atrium without appreciable rhythm change (Figure 6). CMA–RCA identified and classified a SBR in the LAA that was present in multiple CS phases (Figure 6a,b, yellow arrows), located in an area of significant voltage

Figure 5: (a) Anterior view of left atrium identifying one non-substrate-based rotor (NSBR) (black arrows) and two substrate-based rotor (SBRs) (yellow arrows). Electrograms in the inset demonstrate a circular pattern of atrial fibrillation (AF) corresponding to computational mapping algorithm (CMA) phase vectors. (b) A second CMA phase identifying two SBRs, and no NSBRs. (c) Voltage transition zone as measured in AF. (d) Areas of low to moderate complex fractionated atrial electrograms. (e) Global organization to atrial tachycardia occurred during ablation inferior to the left atrial appendage (ablation region within yellow arrows, b) as observed in coronary sinus electrograms.
transition (Figure 6c, white square) and an area of predominately low CFAEs (Figure 6d, white square). During the case, interrogation of the LAA revealed continuous electrograms that were targeted with radio-frequency energy. Ablation lesions superimposed on the conduction vector map reveal that when the SBR was incidentally ablated (Figure 6b), conversion to sinus rhythm occurred (Figure 6e). CMA identified 120 rotors in total, and RCA classified 67% as SBR and 33% as NSBR. Sixty-nine percent of all SBRs and 53% of NSBRs were incidentally ablated (Figure 7). Notably, 91% of ablated SBRs resulted in measurable rhythm change, while only 24% of ablated NSBRs resulted in rhythm changes (p<0.0001). Non-ablated SBRs were found in 75% of patients where ablation did not terminate AF, and patients had to be cardioverted. Together, these results suggest that classifying rotor activity based on atrial substrate and electrophysiological properties such as voltage transition, areas of low CFAEs, and reproducibility over multiple CS phases may distinguish between rotors that are responsible for maintenance of AF versus bystander rotor-like wavefronts that may not require ablation.

Discussion
This study relays the following observations: 1) repeating electrical activation patterns during AF are observed in the majority of patients with AF undergoing ablation, 2) these patterns can be identified by activation patterns observed from a stable reference point. 3) local activation patterns at multiple anatomical locations within the LA that are obtained with circular mapping catheters are noted to be reproducible and consistently correlate with an identified CS pattern or CS phase. These observations have the following implications: if a CS phase has a high correlation of reproducible local electrograms at any given anatomical site within the LA, then one can construct a 3D electro-anatomical map utilizing the correlation of identified AF phase(s) in the CS with...
corresponding local electrograms within the LA. Given this, panoramic 3D LA conduction maps can be constructed for each of the multiple CS phases identified. Based on this observation we created multiple 3D panoramic AF conduction maps per patient, depending on the number of AF patterns or “CS phases” present, and used these maps to identify drivers of AF. Recent clinical studies have relayed improved outcomes with targeting AF drivers as identified with panoramic mapping achieved with either high-density body surface mapping, requiring CT, or an intracardiac basket. The CS phase-mapping approach is unique as it allows for the creation of accurate integrated 3D panoramic conduction vector maps from which drivers of AF can be easily and directly visualized. This approach requires only a circular mapping catheter, a CS catheter, and a 3D electro-anatomic mapping system, all of which are commonly used for standard radiofrequency ablation for AF.

Using this approach, AF drivers were identified utilizing conduction vector analysis, Hilbert transformation, and local electrograms. Identified AF drivers were noted to have similar anatomic distributions within the LA as noted previously by other groups utilizing panoramic AF imaging modalities. Interestingly, in this study, rotors were also identified within and around the LAA, and may provide mechanistic insight and rationale for success observed by some groups with isolation or ablation of the LAA in AF patients (Figures 5 and 6). Rotors observed by imaging modalities including that described in this study may differ in their ability to maintain AF. This study characterized AF drivers with respect to their association with AF voltage transition zones, CFAEs, and stability. Rotors that were considered stable by virtue of being reproducible across multiple CS phases of AF were located near and/or precessed along voltage transition zones in AF. As previously described in both computational and animal models, fibrosis is thought to play a role in atrial fibrillation and with respect to rotor facilitation and propagation. Voltage transition zones in AF may play a role with respect to rotor stability and propagation based on the observations in this study. These areas may highlight regions of local tissue anisotropy secondary to fibrosis and/or tissue orientation predisposing these regions to rotor initiation, propagation, and maintenance.

Given the associations noted with CFAEs, stability across CS phases of AF, and voltage transition zones, rotors were specifically sub-categorized as SBR and NSBR based on a weighted association of these variables. Interestingly, SBRs were associated with a rhythm change compared with NSBRs when incidentally ablated (p < 0.00001). Analyzing rotors in the context of these variables may help differentiate true drivers of AF that should be pursued versus bystander rotor wavefronts that merely are a product of local conduction properties, transient in nature, and byproducts of AF. These associations may provide insight into the mechanism of AF with respect to local substrate, and highlight regions in the atria more likely to be vital for success with termination of AF with ablation.

Limitations

While this study provides a novel approach to panoramic mapping based on the identification of “CS phases” and subsequent correlation of local electrograms that allows for the construction of a 3D AF maps, its usefulness as a tool to improve AF ablation requires further validation. Right atrial maps were not created in this study and need to be validated to identify right atrial drivers. The overall sample size in this study is small and rhythm changes that did occur after incidental atrial ablation were analyzed post-procedure. Future prospective studies will be needed with bi-atrial mapping, as well as identification of AF drivers prior to ablation with
consequent prospective targeting and follow-up for near-term and long-term efficacy.

Conclusion

AF is noted to have reproducible AF patterns, referred herein as CS phases. This study describes the use of this phenomenon to enable the creation of panoramic 3D maps using only commonly employed high-density mapping catheters and 3D electro-anatomic mapping systems. This approach enabled the identification and characterization of AF drivers in the form of rotors and FIs. Further characterization of rotors into SBR versus NSBR differentiated ideal target sites versus bystanders for AF ablation, a distinction that may provide a tailored substrate-based approach for patients undergoing ablation for persistent AF. This approach may ultimately improve procedure times, decrease unnecessary ablation, and improve AF ablation outcomes.

References