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Two Independent Mapping Techniques Identify Rotational Activity Patterns at Sites of Local Termination during Persistent Atrial Fibrillation

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Abstract

The mechanisms for atrial fibrillation (AF) are unclear in part because diverse mapping techniques yield diverse maps ranging from stable organized sources to highly disordered waves. We hypothesized that AF mechanisms may be clarified if mapping techniques were compared in the same patients, and referenced to a clinical endpoint. We compared 2 independent AF mapping techniques in patients in whom local ablation terminated persistent AF before pulmonary vein isolation (PVI).

Techniques and Results—We identified 12 patients with persistent AF (61.2±10.8 years, 4 female) in whom mapping with 64 pole baskets and technique 1 (activation/phase mapping, FIRM) identified rotational activation patterns during at least 50% of the 4-second mapping interval and targeted ablation at these rotational sites terminated AF to sinus rhythm (n=10) or atrial tachycardia. We analyzed the unipolar electrograms of these patients to determine phase maps of activation by an independent technique 2 (Kuklik, Schotten et al., IEEE Trans Biomed Eng 2015). Compared to technique 1, technique 2 revealed a source in 12/12 (100%) cases with spatial concordance in all cases ($p<0.05$) and similar rotational characteristics.

Discussion—At sites where ablation terminated persistent AF, 2 independent mapping techniques identified stable rotational activation for multiple cycles that drove peripheral disorder. Future comparative studies referenced to a clinical endpoint may help reconcile if discrepancies between AF mapping studies reports represent techniques, patient populations or models of AF, and improve mapping to better guide ablation.

Keywords

atrial fibrillation; catheter ablation; FIRM; phase mapping; rotor mapping; human

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Introduction

Therapy for persistent atrial fibrillation (AF) is limited by uncertainty in its mechanisms, and even extensive ablation may not improve the moderate success of pulmonary vein isolation (PVI)[1]. However, mechanistic uncertainty stems in part from studies in diverse populations, using diverse mapping techniques with varying technical or clinical validation. For arrhythmias such as atrial macroreentry, the accuracy of mapping can be gauged by its ability to identify sites where arrhythmia terminates by ablation. Conversely, in AF, few studies have compared AF mapping techniques in the same patients, and even fewer are referenced to a defined clinical endpoint.

Some recent mapping studies[2, 3] propose that rotational or focal drivers in localized regions maintain AF, with promising results by ablating such sites at independent centers[4–8]. This concurs with optical mapping of AF in human atria[9]. However, other studies disagree. First, AF mapping historically shows disorganized waves with no[10] or very few[11] drivers, typically in patients with accepted permanent AF at non-arrhythmia surgery. Second, some studies show organized drivers on dominant frequency analysis[12] that may be unstable by activation[13] or phase[14–16] mapping. Third, AF-driver ablation outcomes are disappointing at some centers[17–19]. It is unresolved if conflicting results reflect patient selection, methodology or inter-center variations in the results of any approach to AF ablation[20].

We hypothesized that AF mechanisms may be clarified if independent mapping techniques were compared in the same patients, referenced to the endpoint of AF termination. We report on an early cohort of patients at our Institution in whom limited ablation guided by one mapping technique (Focal Impulse and Rotor Mapping, FIRM) terminated persistent AF prior to pulmonary vein (PV) isolation, and compared the results with a distinct second mapping technique applied to the same clinical data.

Methods

Study Design

We studied patients ≥ 21 years of age referred for ablation of drug-refractory persistent AF to Stanford University. This report analyzes an early cohort of n=12 such patients in whom activation/phase (FIRM) mapping was performed in real-time, revealed rotational activity patterns for ≥50% of mapped periods (‘epochs’), and targeted ablation terminated AF before PVI commenced. We compared rotational activity in patients at first ablation, and those with prior PVI[21] and PV reconnection. This study was approved by the Institutional committee on human research at Stanford University.

Electrophysiology Study

Electrophysiology (EP) study was performed after discontinuing antiarrhythmic medications for 5 half-lives. Catheters were advanced transvenously to the right atrium, coronary sinus and transseptally to left atrium. A 64-pole basket (FIRMap, Abbott Electrophysiology, Menlo park, CA) was advanced through an 8.5Fr SL1 sheath to map AF in right then left atria. Multiple basket positions were used routinely to cover the atria in successive mapping periods ('epochs') (figure 1). Electroanatomic shells were created (NavX, St Jude Medical, Sylmar, CA or Carto, Biosense-Webster, Diamond-Bar, CA) to relate basket electrodes to anatomic regions (Figures 2–4).

We exported the electrograms used for prospective mapping by technique 1 (FIRM, duration 1 minute) from our electrophysiological recorder (Prucka, GE Marquette, Milwaukee, WI), filtered at 0.05–500 Hz for independent mapping analysis by technique 2.

Index Mapping Approach (FIRM)

Real-time mapping in these cases was Focal Impulse and Rotor Mapping (FIRM)[22], which was used as the index (technique 1) and served to generate cases with AF termination by localized ablation. Unipolar AF electrograms were recorded from multipolar basket catheters, with electroanatomic localization (e.g., NavX) inactive to avoid signal interference. FIRM creates maps of activation sequence which, for non-complex electrograms, may identify rotational activation[23]. However, AF electrograms often show far field deflections marked by traditional dV/dt criteria,[24] which will alter map. FIRM filters out far-field activation using rate-related repolarization[25, 26] and conduction[27] to create activation maps, and also applies action potential data for phase analysis[22]. AF activation maps (gray scale maps) and singularities (colored rotational activity profiles, RAP) are used to identify organized regions during AF.

AF maps from FIRM were used prospectively to guide ablation. Rotational activation was defined as a stable spiral wave that drives disorder. A focal impulse was defined as an origin from where activation emerged centrifugally to cause disorder. Both patterns were used to guide ablation in this series if present for >50% of the mapped 4-second period (i.e., >10 cycles) within a limited spatial region (< 2–3 cm^2) [28]. Rotational activity profile (RAP) was used as an adjunct.

Ablation

Radiofrequency energy was delivered via an irrigated catheter (Thermocool™ or Smart-Touch™, Biosense-Webster; or Tacticath™, St Jude) at 25–35 Watts (10–15 Watts on posterior left atrium). FIRM-guided lesions were each applied for 15–30 seconds, typically requiring 10–20 lesions to cover each source area bounded by the projection of each electrode onto the shell.

This report focuses on cases in which AF terminated by targeted ablation alone. We excluded patients in whom PVI, FIRM or other ablation lesions were intermixed, for reasons of workflow or study protocol. Patients proceeded to wide area circumferential ablation of left and right PV pairs with verification of entrance and exit block by pacing without adenosine.

Independent AF Mapping Approach

Unipolar electrograms in AF from the precise segments used by technique 1 (FIRM) were exported for analysis by technique 2, an independent published algorithm[14–16]. Technique 2 differs from FIRM in several key respects. First, technique 2 does not create activation maps of AF, which is the principal output from FIRM (gray scale maps). Second, technique 2 does not apply algorithms to filter far-field timing data using action potential duration or conduction restitution, unlike FIRM. Third, unlike FIRM, technique 2 reconstructs AF signals using sinusoids[14]. We selected technique 2 because it shows very few (<1%) rotational sites in different patients and sheep models of AF[14–16], i.e. it does not appear to falsely create rotational activation[29].

We implemented this algorithm directly from its reports using the steps of Kuklik et al[14–16] as follows. First, the QRS complex is removed on each channel by computing an average QRS complex and subtracting it from electrograms. Next, we applied a 1–30 Hz fourth-order Butterworth band pass filter and computed the dominant cycle length of each electrogram from the Welch Power Spectrum Density estimate of the signal, with a window size of 2000 ms, overlap of 1000 ms, and a cycle length cutoff between 130 and 280 ms. Finally, the recomposed signal was constructed as a sum of single-period sinusoidal waves with frequency equal to the computed dominant frequency and amplitude equal to the negative slope of the electrogram. For display we interpolated these recomposed signals to a grid, and applied the Hilbert Transform to compute phase maps (figures 2–4, even-numbered movies).

Phase maps generated by technique 2 were analyzed by 3 operators (MAH, GM, CK), blinded to clinical data. The number of rotations at each site and the location of these sites was compared to numbers and locations using technique 1. Rotational activity determined by both techniques were considered spatially concordant if locations differed by ≤1 electrode.

Statistical Analysis

Continuous data are represented as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate. Comparisons between 2 groups were made with Student's t-tests and summarized with means and standard deviations for independent samples if normally distributed or, if not normally distributed, with the Mann-Whitney U test and summarized with medians and quartiles. Nominal values were expressed as n (%) and compared with chi-square tests or the Fisher exact test when expected cell frequency was < 5. Multi-rater agreement was assessed using Fleiss' Kappa score. A probability of < 0.05 was considered statistically significant throughout all analyses.

Results

Table 1 provides clinical details for patients in this cohort, in each of whom targeted ablation guided by mapping terminated persistent AF prior to PVI.

Mapping At Sites of AF Termination By Ablation

Index mapping using technique 1 detected 5.9±1.4 organized regions per patient (LA 3.4±1.2, RA 2.5±1.1). This report focuses on the region where targeted ablation (<2–3 cm^2) terminated AF in each patient, which was the first source in 4 patients and the $2.1±1.0^{th}$ source overall. All sources were ablated before PVI commenced in this series, and in no case did FIRM-guided ablation isolate a PV.

Figure 2 illustrates a 78-year-old man in whom targeted ablation (A) at the inferior septal left atrium (B) terminated persistent AF to sinus rhythm. A right atrial source had previously been ablated without termination. (C) AF maps from technique 1 show clockwise rotation at this site (coordinate GH7). Movie 1 shows that rotational activation (in white) was sustained for 18 cycles in 4 seconds, with rotational activity confirmed by phase analysis (colored repetitive activity profile, RAP). (D) AF maps using mapping technique 2 also showed clockwise activation at this site (GH7), sustained for many rotations (movie 2). Both techniques confirmed complex activation surrounding the rotational site of termination. AF continued until ablation at this site terminated AF to sinus rhythm.

Comparison of Mapping Techniques 1 and 2

Technique 1 and 2 both produced AF maps showing regional organization and surrounding disorder. As summarized in table 2, each site of termination by ablation exhibited rotational activation by index mapping and also by technique 2 ($p<0.05$).

Figure 3 illustrates persistent AF in 72 year old man in whom prospective ablation (A) at the carina of left superior pulmonary vein (B) terminated persistent AF to sinus rhythm prior to PVI. This was the first site targeted for ablation. (C) AF maps from technique 1 show counterclockwise rotation at this site, which are sustained for many cycles at site CD2 (movie 3; most apparent in second half). (D) AF maps from technique 2 also show counterclockwise activation, sustained in movie 4. Movies of both techniques show complex surrounding activity with competing wavefronts, and technique 2 showed slightly greater precession of rotational activation. AF continued until ablation at this site terminated AF to sinus rhythm.

Figure 4 illustrates AF in a 67 year old woman in whom prospective targeted ablation (A) on the left atrial roof (B) organized then terminated persistent AF to sinus rhythm prior to PVI. A right atrial source had previously been ablated. (C) AF maps from technique 1 show counterclockwise rotational activation around a pivot (rotor precession area) that was targeted for ablation. In movie 5, rotational activation sustained for >10 cycles (19 cycles) in 4 seconds at site CD45, indicated by a computational index for rotational activity (colored markings, RAP). Applying mapping technique 2 to these data also shows (D) counterclockwise rotation at this location which, in movie 2, was sustained for >10 cycles at site CD45. Maps from technique 2 showed greater complexity than technique 1, with greater precession of the dominant rotation to locations CD67, intermittent foci and greater complexity of fibrillatory conduction surrounding the organized rotational site. AF continued until ablation at this site terminated AF to sinus rhythm.

Quantitative Comparison Between Techniques

Table 2 details activation at the site of AF termination by technique 1 (index approach) and technique 2 (validation method). Rotational activation was identified at each site of AF termination by technique 1 and by technique 2 ($p<0.05$) with a spatial concordance of less than 1 electrode (100% concordance, $p<0.05$) as illustrated in movies 1–6. The number of cycles detected in 4 seconds trended higher for technique 1 than technique 2 (14.7 ± 2.8 versus 12.2 ± 3.9, $p=0.087$).

Visual inspection uncovered qualitative differences between techniques, with technique 2 maps showing greater precession of rotational activation at sites of AF termination than technique 1, with greater surrounding complexity. Organized sites were intermittently obscured by competing wavefronts, either from another organized site or from disorganized waves ('fibrillatory conduction'), before resuming in a very similar location. This phenomenon can be observed in movies 1–6.

Discussion

In this cohort of patients in whom localized ablation terminated persistent AF before pulmonary vein isolation, 2 independent mapping techniques revealed rotational activity at the site of AF termination for several cycles with surrounding complex fibrillatory activation. The approach of comparing mapping techniques referenced to a defined clinical endpoint provides a novel platform to study AF mechanisms. Future studies should investigate whether specific techniques under- or overestimate the presence of organized drivers in AF, referenced to sites of termination, to define the sensitivity and specificity of several methods for each endpoint, and finally examine sites where AF does not terminate by ablation.

Defined Clinical Endpoint

This study uses acute termination of persistent AF by targeted intervention as a reference for AF mapping – just as termination of atrial flutter by mapping-guided ablation can be used to validate that mapping. We acknowledge that acute AF termination is not equivalent to long-term freedom from AF, just as acute termination of atrial flutter is not equivalent to long-term freedom from atrial flutter, and may reflect the facts that mechanisms addressed acutely are not durably eliminated or because AF is later sustained by other mechanisms. In the absence of a clinical reference, it is possible that mapping of patients at non-arrhythmia surgery with permanent AF[10, 11, 13] did not map regions of importance that were not identified, or studied patients whose mechanisms differ from patients referred for ablation because mapped patients did not receive AF therapy.

Alternative clinical reference endpoints that prove helpful for comparative mapping include AF termination to atrial tachycardia versus sinus rhythm, termination near versus remote from PVs, or sites where ablation terminates AF prior to isolation of PVs during ongoing PV ablation.

Comparative Mapping Techniques

The index method used to generate cases prospectively, method 1 (FIRM), and method 2 (Kuklik)[14–16] produced similar maps in this cohort of patients with acute AF termination, showing organized rotational activity at sites of termination with peripheral disorder. This was true in patients at first and repeat ablation, suggesting similar AF mechanisms.

Despite showing similar results in this cohort, the mapping methods compared in this study are quite different. Method 1 (FIRM) creates activation maps of AF, using repolarization and conduction data to filter far-field, with additional phase mapping to reveal singularities[22]. Method 2 (Kuklik)[14–16] avoids the proprietary algorithms used by FIRM and, while it uses phase, does not appear to create ‘false’ rotations because it showed only foci and conduction block and rare short-lived rotations in sheep AF[16].

Method 1 (FIRM) has recently been correlated with optical mapping of human AF, with preliminary studies showing concordant rotational activity by both methods[30]. The spatiotemporal dynamics of sources in those human optical studies are similar to maps of AF termination sites by both methods in our patients: stable endocardial rotations intermittently obscured by competing waves[31].

It is not clear why some techniques do not show rotational patterns in AF. In some cases, this may reflect epicardial-endocardial differences shown by bi-surface optical imaging of human atria, which may explain less stable drivers in body surface mapping[3] or surgical[13] studies of the epicardium. Other differences may reflect patient populations, differences between animal models (e.g., sheep) and human AF or algorithmic implementation.

Further studies comparing methodologies in the same patients with a defined clinical endpoint are required.

Inferring Mechanisms for Persistent AF

The current study provides a clinical reference of AF termination. However, studies are still needed to define how ablation at a rotational site may terminate AF[32] or, by mapping techniques that do not show drivers at sites of AF termination, how ablation at disordered sites or sites with transient conduction block may terminate AF. Studies are needed to clarify if the lack of success of extensive ablation[1], which limits critical mass, argues against the disordered wave hypothesis for AF.

Limitations

This study design used ‘true positives’ – cases in whom ablation terminated AF – and does not comment on sites where ablation does not terminate AF. Such studies are ongoing. Subjects in this study were enrolled on different protocols, but long-term outcomes studies in each protocol are ongoing. The method 1 algorithm has been described scientifically[22, 26, 33] although its precise steps are undisclosed, but this limitation may be circumvented in this study because a second method showed similar results and AF termination provided a clinical reference to interpret mapping. Delayed termination of AF after ablation is an emerging concept, but may not alter our conclusions that ablation prior to PVI terminated AF at sources that appeared similar by both mapping techniques. Source ablation in this series typically preceded PVI by many minutes, giving time for delayed termination to occur. Patients with prior ablation were included by design to assess whether sources differed between groups. Finally, we did not perform concurrent epicardial mapping.

Conclusions

We demonstrate convergence of mechanisms in a cohort of patients with persistent AF, in whom 2 independent mapping techniques revealed rotational activity at sites where ablation terminated AF prior to PVI. The novel approach of comparing mapping techniques referenced to a defined clinical endpoint may provide a robust platform for future advances in AF mapping.

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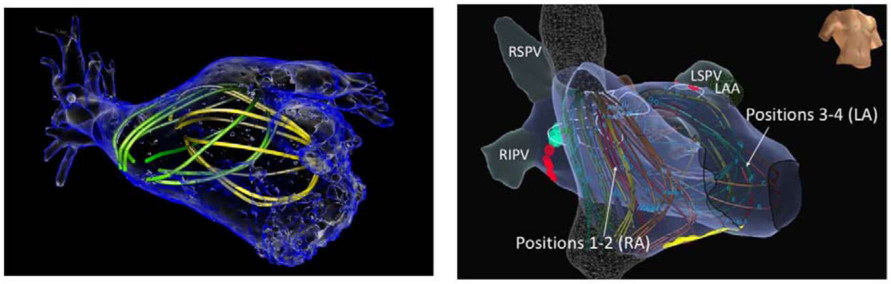

Figure 1. Multiple basket positions in each atrium

are used to ensure that AF signals are recorded from the majority of both chambers, reconstructed here within (A) atrial computed tomography; (B) anatomic shell.

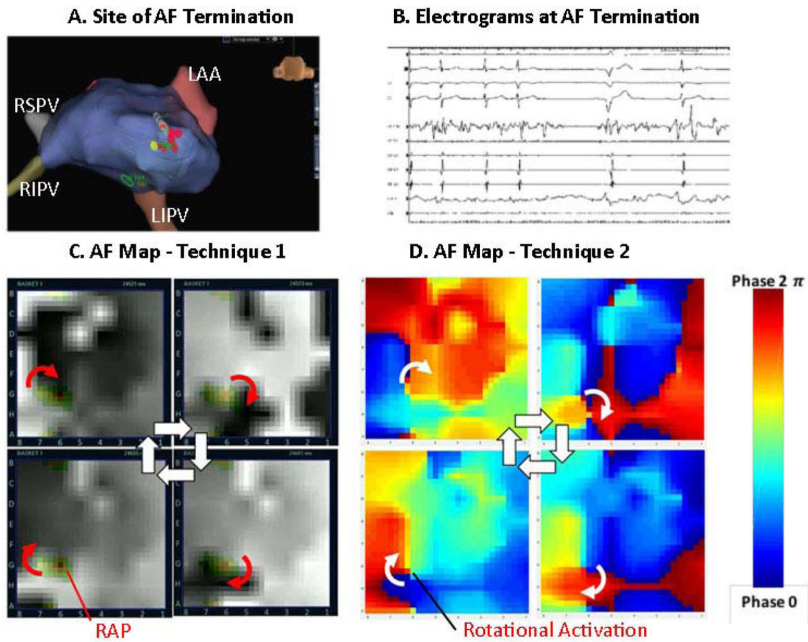

Figure 2. Identification of Rotations At Site of AF Termination Between Techniques (patient ID 1)

in a 78-year-old man with persistent AF. (A) Ablation at the inferior septal left atrium near the mitral annulus; (B) terminated AF. (C) Snapshots of AF map from technique 1 show clockwise activity for numerous cycles in 4 seconds at termination site (GH7; movie 1). (D) Snapshots of AF map from method 2 also show sustained clockwise activation at this AF termination site (movie 2). Both maps show fibrillatory complexity outside these sites.

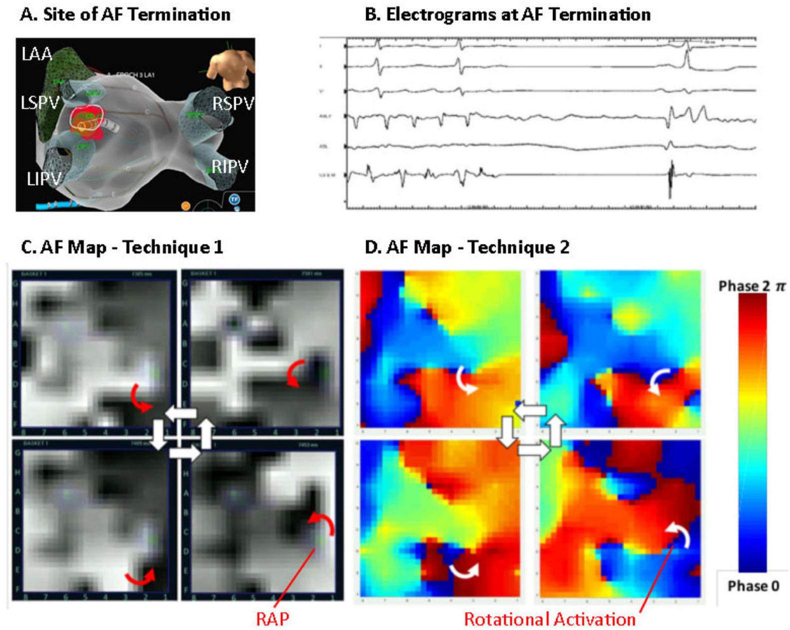

Figure 3. Identification of Rotations at Site of Termination by Both Techniques (patient ID 2)
in a 72-year-old man with persistent AF. (A) Prospective guided ablation at the carina of left pulmonary vein (B) terminated persistent AF prior to PVI. (C) AF snapshots from technique 1 show counterclockwise rotation at termination site CD2 for > 10 cycles particularly in the second half of movie 3. (D) AF snapshots from technique 2 also show counter clockwise activation at this termination site (movie 4). Complex fibrillatory activity and competing wavefronts are also seen.

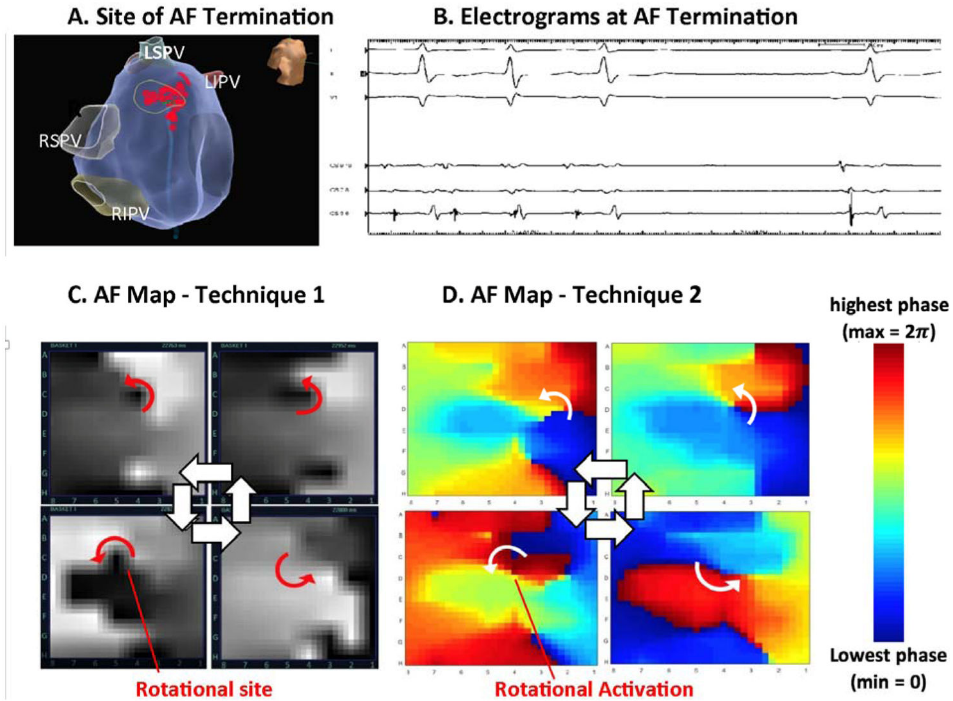

Figure 4. Identification of Rotational Activity at Site of AF Termination by Both Techniques (patient ID 3)

in a 67-year-woman with persistent AF. (A) Ablation site on posterior left atrial roof; (B) terminated AF. (C) Snapshots of AF map from technique 1 show a counterclockwise activation sequence (movie 5) and other CW rotations. (D) Snapshots of AF map from technique 2 also show counterclockwise rotation (movie 6) at termination site.

Table I

Characteristics of Cohort

ID	Age	Gender	Left atrial Size	LVEF	Prior Ablation	Terminate To	Where Ablated
1	78	M	40	60	Redo	Sinus Rhythm	Mitral Isthmus
2	72	M	36	62	1st Ablation	Sinus Rhythm	Left PV Carina
3	67	F	55	36	Redo	Sinus Rhythm	Posterior LA Roof
4	66	M	47	59	Redo	Sinus Rhythm	Near LIPV
5	53	M	52	36	1st Ablation	Atrial Tachycardia	Ant Septal Mitral
6	50	F	40	59	1st Ablation	Sinus Rhythm	Near LA Appendage
7	56	M	47	60	Redo	Sinus Rhythm	Near LIPV
8	49	M	53	51	Redo	Sinus Rhythm	Post Lateral LA
9	57	M	67	55	1st Ablation	Sinus Rhythm	Near RSPV
10	79	F	47	69	Redo	Sinus Rhythm	Near LA Appendage
11	52	M	45	58	Redo	Sinus Rhythm	Left PV Carina
12	55	F	45	60	1st Ablation	Atrial Tachycardia	Infero-posterior to the LIPV
	61.2±10.8	4F	47.8±8.2	55.4±10.0	7 Redos	2 Atrial Tachycardia	

Table 2

Comparative Mapping in All Patients

ID	Technique 1 (Index Mapping)		Technique 2	
	No. cycles (4 seconds)	**Comments**	**No. cycles (4 seconds)**	**Comments**
1	18	Figure 2, Movie 1. CW rotation at term site, minimal precession	12	Figure 2, movie 2. CW rotation with some precession; some foci
2	12	Figure 3, Movie 3. CCW rotation at term site; other transient rotations	8	Figure 3, Movie 4. CCW rotation at term site (2nd half), other rotations
3	18	Figure 4, Movie 5. CCW rotation at term site, also CW rotation sites.	19	Figure 4, movie 6. CCW rotation at term site, other rotational sites.
4	19	CCW rotation at term site, other transient rotations	16	CCW rotation at term site, other transient rotations
5	12	CCW rotation at term site	12	CCW rotation at term site
6	13	CCW rotation at term site	9	CCW rotation at term site with some precession
7	18	CCW rotation at term site, other transient rotations	15	CCW rotation at term site, other transient rotations
8	15	CW rotation at term site, other transient rotations	12	CW rotation at term site, other rotations
9	11	CCW rotation at term site	5	CCW rotation at term site, other transient rotations
10	14	CW rotation at term site	10	CW rotation at term site
11	13	CCW rotation at term site, other transient rotations	16	CCW rotation at term site, other transient rotations
12	13	CW rotation at term site, other transient rotations	12	CW rotation at term site, foci, other transient rotations
	14.7±2.8		12.2±3.9	