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Rotors as Drivers of Atrial Fibrillation and Targets for Ablation

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia targeted by catheter ablation. Despite significant advances in our understanding of AF, ablation outcomes remain suboptimal, and this is due in large part to an incomplete understanding of the underlying sustaining mechanisms of AF. Recent developments of patient-tailored and physiology-based computational mapping systems have identified localized electrical spiral waves, or rotors, and focal sources as mechanisms that may represent novel targets for therapy. This report provides an overview of Focal Impulse and Rotor Modulation (FIRM) mapping, which reveals that human AF is often not actually driven by disorganized activity but instead that disorganization is secondary to organized rotors or focal sources. Targeted ablation of such sources alone can eliminate AF and, when added to pulmonary vein isolation, improves long-term outcome compared with conventional ablation alone. Translating mechanistic insights from such patient-tailored mapping is likely to be crucial in achieving the next major advances in personalized medicine for AF.

Keywords

Atrial fibrillation; Ablation; Focal sources; Rotors; Substrate; Trigger

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the world, whose accelerating incidence and association with stroke, heart failure, dementia, and death make its management a top priority. However, recent clinical trials have questioned the value of pharmacologic agents both to limit ventricular rate [1] and to maintain sinus rhythm [2, 3•].

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Compliance with Ethics Guidelines

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Conversely, great strides have been made in nonpharmacologic therapies for AF. Catheter-based ablation has been shown to be more effective than medications in patients with paroxysmal AF [4•,5•] and persistent AF [6], although outcomes are suboptimal with multicenter randomized controlled trials showing 40 %–50 % single procedure to 70 % multiprocedure success rates at 1 year for paroxysmal AF [4•,5•,7, 8] and lower success in persistent AF [9, 10].

One major limitation to substantial advances in outcome is our incomplete understanding of the mechanisms that underlie AF. As with other arrhythmias, AF initiates when a “trigger” (eg, premature beat from the pulmonary veins or elsewhere) interacts with “substrate” (eg, atrial tissue with abnormal anatomic/functional characteristics that sustains AF). However, while it is well understood that AF is triggered from sinus rhythm by premature atrial contractions or rapid tachycardias [9], it is less well-understood what occurs next ie, what mechanisms initiate or sustain AF? As such, current catheter-based ablation strategies have been based on the elimination of potential triggers at the pulmonary veins. Although it is widely accepted that mapping the AF substrate is necessary for the next stages of catheter ablation [9, 11], this has not been easily accomplished.

In this section, we will review recent technical advances in mapping patient-specific electrical substrates, which in many patients comprise spiral waves (rotors) or focal sources. Such sources show parallels to AF-sustaining rotors shown for decades in animal models of fibrillation [12, 13, 14•] and, in patients, were identified using novel computational approaches [15–17] after defining the spatio-temporal dynamics of atrial repolarization and conduction [18–20]. Focal impulse and rotor mapping (FIRM) enables near-real time mapping of the atria at the time of electrophysiological study to identify rotors and other patient-specific AF mechanisms for ablation, then remapping to confirm elimination. In clinical trials, FIRM-guided ablation has been shown to eliminate AF on long-term follow-up with no other ablation [21], validating the physiological role of identified sources, and when combined with traditional pulmonary vein isolation [22••].

Mechanisms Driving Human AF

Mapping AF is challenging because its activation is complex with considerable spatio-temporal variability when assessed clinically. Paradoxically, AF also exhibits underlying spatial-temporal reproducibility or organization by many analyses [23–27]. Several mechanisms for AF have been proposed in the classical literature, highlighting a dichotomy between localized mechanisms (rapidly-firing ectopic atrial drivers or single-circuit reentry) or spatially nonlocalized mechanisms (multiple wavelet reentry) that have existed for over a century.

Localized sources for AF were postulated by Garrey, Mines, and Lewis in the early 20th century, and reported in seminal canine studies by Schuessler, Cox, and Boineau [13, 28] who showed that AF is often sustained by stable, relatively large drivers. Using optical mapping in sheep studies, Jalife et al [14•,29] for the first time revealed electrical spiral waves, or rotors that perpetuate fibrillation. In recent canine studies, direct ablation of rotors was shown to suppress AF [30•]. Clinically, although rotors had not been identified or

located until recently, multiple observations have strongly supported the existence of localized sources in patient subsets. These observations include the ability of a single ablation lesion to terminate persistent AF resistant to cardioversion [31] and recently various types of AF [22•, 31–33], and the ability of catheter pressure at a specific location to reproducibly terminate AF [32]. Indirect evidence for sources in human AF include reports of spatiotemporal stability [24], localized regions of stable high dominant frequency [23, 25, 26, 34], and reproducible vectors of AF propagation over time [35].

Multiple wavelet reentry, conversely, postulates that AF comprises meandering wavelets that collide and extinguish one another [36] and sustain AF without underlying driving sources. This hypothesis has become the prevailing conceptual model, but in many patients is unlikely to be the driving mechanism. For instance, nonlocalized mechanisms cannot readily explain clinical observations that favor localized sources including acute AF termination by single or very few ablation lesions at pulmonary veins (PVs) or other sites [22•, 31–33]. Moreover, while the Maze surgery is often taken as evidence in favor of nonlocalized mechanisms, Maze may also limit the tissue available for rotors or stable reentrant circuits as conceived by Cox, Schuessler, et al. at Washington University when developing the Maze procedure [13, 28]. Other limitations of work supporting nonlocalized mechanisms are that it mapped <10 % of atrial areas measured by MRI [37] in relatively few patients ($n=49$) [38, 39] and that recordings from many regions, when obtained, were not synchronized in time that limits spatial analysis. Perhaps most importantly, interventions to prove causality were not used so that disorganization could represent bystander activity. Finally, numerous groups have now shown organized ‘rotors’ of various durations in surgical [27] and electrophysiological [33, 40•, 41, 42•] studies of human AF.

Focal Impulse and Rotor Mapping (FIRM)

Rationale for Wide-Area Contact Mapping

One reason for our incomplete understanding of AF mechanisms lies in the challenges of mapping its complex spatio-temporal activity that varies on visual inspection, yet shows surprising spatiotemporal reproducibility on mathematical quantification. The major challenge has been to separate potentially reproducible elements (principal components) from disorganized activation in a clinically meaningful fashion.

Each of the existing mapping modalities has important limitations for AF. First, bipolar recordings may not accurately indicate local activation in AF, whether signals are fractionated or not (Figs. 1, 2 and 3 in [43•]), due to AF signal cancellation or augmentation between the poles of a bipole or between a unipole and its reference electrode. These issues may be compounded in mathematically inferred electrograms [44]. Surgical epicardial mapping is precise, but typically covers limited atrial areas [38] and may thus, miss organization outside a priori selected mapping regions. High-resolution optical mapping is theoretically ideal yet limited by dye toxicity in humans [11, 45•], and most maps have recorded for only short-durations that limits the ability to evaluate temporal and spatial stability or to remap after ablation to identify mechanism. Inability to separate bystander from mechanistic activation is well known to confuse the diagnosis and ablation of even simple electrophysiological disorders [46], and is likely just as relevant for AF.

We set out to map human AF using monophasic action potentials (MAPs), which may most faithfully represent local depolarization and repolarization than clinical alternatives, and thus, mitigate some of the above limitations [47]. A series of studies described the spatiotemporal dynamics of repolarization and conduction in human atria, and methods to physiological filter noise so to separate “principal components” of activation in AF from bystander disorganization. Features on resulting AF maps were then tested by ablation to prove whether they indicated AF- mechanisms (with improved patient outcomes) or bystanders.

Practical Approach to FIRM Mapping

Focal Impulse and Rotor Modulation (FIRM) mapping is a novel technique to identify patient-specific AF mechanisms, by recording AF electrograms in a wide field-of-view across the majority of both atria then using physiologically-directed computational methods to produce maps of AF propagation [16, 22••]. FIRM has revealed electrical rotors sustaining human AF for the first time, and has also enabled visualization of focal sources.

FIRM records AF in both atria using direct contact electrodes, the gold standard particularly for low-amplitude AF electrograms, in the form of 64-pole basket catheters each of 8 splines containing 8 electrodes. Basket catheters are advanced from the femoral vein into the right atrium (RA) or, transseptally, to the left atrium (LA). Recordings are made sequentially using 1 basket in each atrium in turn. Electrodes are separated by 4–6 mm along each spline and by 4–10 mm between splines. Catheters are manipulated to ensure good electrode contact and electrode locations are verified within the atrial geometry using fluoroscopy or electroanatomic mapping [22••]. It was predicted [48] and recently demonstrated [17] that human atria can support 1:1 activation in a shortest reentrant path of ~5 cm, requiring a minimum electrode spacing of ~10 mm for which these clinical catheters should be sufficient.

AF is recorded for 1 minute then exported for analysis using RhythmView (Topera, Palo Alto, CA). Native AF is mapped when possible, but when required, induced by burst pacing from the coronary sinus using a continuous incremental pacing protocol from cycle lengths 500 ms, continuously decrementing to 450 ms, 400 ms, 350 ms, 300 ms, then in 10 ms steps to AF. If required, isoproterenol is infused and pacing repeated. Recent data has shown that induced and spontaneous AF show very similar intra-atrial rates [49] and spatial propagation patterns [16] in the same patient.

Interpretation of FIRM Computational Maps of AF

Traditional a priori rules to include electrograms based on presumed minimum F-F intervals [50] or signal shape [39] are not clearly tailored to human atrial physiology. Therefore, computational mapping (FIRM) examines patient-specific AF electrograms based upon rate-dependent refractoriness (“restitution”) [51, 52] and conduction slowing [20]. AF electrograms resulting from such physiological filtering are used to construct propagation paths across both atria. Phase mapping is applied to identify regions that activate coherently (ie, together).

FIRM mapping results in movies of AF propagation that are the primary diagnostic tools in a case. Such movies are summarized in this manuscript as isochronal maps [19, 51, 53, 54]. An example isochronal map of a sinus beat is shown in Fig. 1, which also illustrates the nomenclature of FIRM maps. The LA is opened at its “equator” through the mitral valve, and the RA is opened along a central meridian through the tricuspid valve.

Rotors are defined as phase singularities with emanating spiral waves that disorganize in surrounding tissue. The core is often not precisely resolved, but bracketed between surrounding electrodes as one would clinically bracket an accessory pathway between adjacent coronary sinus electrodes. Repetitive focal drivers, the other AF-sustaining mechanism identified by FIRM mapping, are defined as activation emanating centrifugally from a source region. Multiple 1-minute epochs are typically analyzed over 5–10 minutes.

Clinically, rotors or focal drivers observed in FIRM maps are diagnosed as AF sources only if they lie in a spatially reproducible location (ie, showing spatial stability) for minutes (ie, showing temporal stability) [55]. This definition excludes transient or migratory activity that would be difficult to target for ablation. Figure 2a demonstrates an AF rotor in the low posterior LA, with disorganized and fibrillatory conduction in the RA.

FIRM-Guided Ablation and Clinical Outcomes

Direct Ablation at AF Sources Identified by FIRM Maps

The spatial and temporal stability of sources makes them suitable ablation targets. Once rotors or focal sources are identified, they are directly targeted for ablation energy using any clinically indicated catheter. The rationale for localized ablation has been analogous to ablation of microreentrant focal atrial tachycardia, for which localized ablation is highly successful. In multicenter studies, FIRM ablation has been accomplished with a 3.5 mm tip irrigated catheter (Thermocool, Biosense-Webster, Diamond Bar, CA), an 8 mm tip nonirrigated catheter (Blazer, Boston Scientific, Natick, MA), or cryoablation. The ablation catheter is maneuvered to the location of the rotor core, as identified by fluoroscopy and/or electroanatomic mapping.

Multiple ablation lesions are placed typically over the source for ~2–3 cm² of atrial tissue, via 5–10 ablation lesions each ~0.25 cm² in area. This covers the area of rotor or focal source precession (Fig. 2c shows that this area can be quantified by phase mapping). These areas are small relative both current ablation approaches, and current estimates of atrial area from MRI of >100 cm² [37]. The endpoint of FIRM guided ablation is elimination of all AF rotors/focal sources remapping, which is performed after each set of lesions.

Typically, 2–3 concurrent rotors are identified in each patient, requiring a total FIRM ablation time of ~15–20 minutes and ~5 cm² ablation. FIRM ablation is commonly added to PV isolation, but if performed alone as recently demonstrated [21], results in a small ablated areas compared with conventional AF ablation.

The CONFIRM Trial

The CONFIRM trial was performed to test whether human AF may be sustained by localized sources—either electrical rotors or repetitive focal drivers—the elimination of which by FIRM ablation would improve outcomes compared with conventional AF ablation [22••].

For this study we recruited 92 subject undergoing 107 consecutive ablation procedures for drug-refractory AF, who were referred for ablation to the Veterans Affairs and University of California Medical Centers in San Diego, under IRB-approved protocol. Cases were prospectively enrolled a 2-arm design: FIRM-guided patients underwent ablation sources followed by conventional ablation ($n=36$), whereas FIRM-blinded patients underwent conventional ablation only ($n=71$) with FIRM mapping performed off-line and not used to guide ablation.

Patients had symptomatic AF, either paroxysmal or persistent, and by design, we included patients both at first ablation and a minority with prior unsuccessful conventional ablation. The goal of broad inclusion was to test how AF-sustaining mechanisms (substrates) differ in patients with and without prior ablation, and with various presentations. The only exclusion criterion was an unwillingness or inability to provide informed consent. Supplemental Table 1 displays the clinical characteristics of the patient populations. Of note, persistent AF was present in 81 % of the FIRM-guided group, and 66 % of the FIRM-blinded group.

The primary long-term endpoint was defined as freedom from AF for up to 2 years after a single procedure, defined <1 % burden using continuous implanted ECG monitors, AF <30 seconds on quarterly event monitors (ie, monitoring for 28 days or 7.8 % of the year). The safety endpoint was comparison of adverse events between groups.

CONFIRM Results

Localized Sources are Highly Prevalent in Human AF

We found AF sources in 97 % of cases (98 of 101) with sustained AF, each subject demonstrating 2.1 ± 1.0 sources (median 2, interquartile range [IQR] 1–3), of which 70 % were rotors and 30 % focal drivers. The number of simultaneous AF sources was higher in persistent than paroxysmal AF (2.2 ± 1.0 vs 1.7 ± 0.9 ; median 2.0 vs 1.0; $P=0.03$). Source numbers were unrelated to duration of AF ($r=0.13$; $P=0.20$) or whether patients did or did not have prior conventional ablation (2.0 ± 0.8 vs 2.1 ± 1.1 ; $P=0.71$).

Stable AF sources lay at diverse patient-specific locations in the LA (76 %) and RA (24 %). Left atrial sources were found at widespread locations, including sites outside the PVs, as well as the posterior, inferior, and roof regions. RA sources included the inferolateral, posterior, and septal regions but lay away from the superior vena cava.

Total FIRM-guided ablation time at all sources was 16.1 ± 9.8 minutes (median 18.5, IQR: 7.9–24.5). Total ablation time was similar in both arms since FIRM-ablation time lay within the typical variation of a conventional ablation procedure.

Long-Term Results

By intention-to-treat analysis, freedom from AF after a single procedure was higher for FIRM-guided than conventional ablation (82.4 % vs 44.9 %; $P=0.001$) after median 273 days (IQR: 132–681 days). Freedom after a single procedure from any atrial tachyarrhythmia was also higher in FIRM-guided than FIRM-blinded cases (70.6 % vs 39.1 %; $P=0.003$). These results were achieved despite more rigorous follow-up (implantable loop recorders in 88.2 % vs 26.1 %) and more persistent AF (81 % vs 66 %) in FIRM-guided than FIRM-blinded patients.

Recent work shows that the benefits of FIRM-guided over conventional ablation are maintained over 3–4 years of follow-up, as FIRM-guided ablation may prevent late AF recurrence [56].

Finally, multicenter experiences of FIRM ablation in >200 patients at >10 independent laboratories have recently confirmed the acute results of FIRM and long-term results from FIRM-guided ablation [40••, 57].

Relationship of Rotors to Ablation Lesions

Importantly, freedom from AF was higher in patients in whom ablation passed through sources—whether directly or coincidentally—than in those in whom ablation missed all sources. Upon analysis of electroanatomic and FIRM maps in each patient, ablation lesions were deemed to pass through an AF source if ablation lesion markers on the mapping system lay within one-half interelectrode spacing of the electrode targeted as the rotor core. “Source ablation” was defined if 1 source was ablated, whether directly by FIRM-guided ablation or coincidentally by anatomic lesion sets (eg, PVI), and assignments were performed independently and blinded to outcomes. Long-term efficacy was higher for patients in source ablation groups than in nonsource ablation groups ($P<0.001$) [58•]. Freedom from AF was highest when all sources were eliminated, intermediate when some were eliminated, and lowest when all sources were missed (Fig. 3).

This concept was recently tested prospectively in the PRECISE trial (Precise Rotor Elimination without Concomitant pulmonary vein Isolation for the Successful Elimination of Paroxysmal AF), a multicenter single-arm trial of FIRM ablation at sources only (ie, without trigger ablation (PVI)) in patients with paroxysmal AF. Preliminary results from PRECISE showed that FIRM-only ablation provided >80 % elimination of paroxysmal AF [21]. These results strongly support localized sources as a primary mechanism for AF, and provide an alternative paradigm for clinical ablation that is currently being tested in randomized multicenter trials.

Finally, sites of localized rotors/sources do not show a specific electrogram fingerprint, with an inconsistent relationship to complex fractionated atrial electrograms (CFAE) sites [59•]. Even in cases where rotors overlay CFAE, additional sites of more marked CFAE were frequently noted at distant locations.

Limitations of FIRM Mapping and Ablation

CONFIRM and recent confirmatory multicenter studies of FIRM ablation were not randomized, although patients were enrolled, mapped, and treated prospectively for prespecified endpoints. In CONFIRM, the FIRM-guided group had more patients with persistent AF, higher comorbidities, and more intense monitoring than FIRM-blinded patients, thus, potentially underestimating the benefit of FIRM-guided ablation. Second, current baskets may map large atria suboptimally—specifically the septal aspect of the large LA—and it is possible that improved designs may reduce this technical limitation. Third, as with any new technology, interpreting FIRM maps requires a learning curve, although this was relatively short in the recent multicenter experience [57]. Finally, the mechanism(s) by which targeted ablation eliminates rotors is unclear; however, it likely involves the alteration of functional or anatomic tissue properties.

Clinical Implications and Future Studies

The identification of stable rotors in human AF reconciles several clinical observations in the context of previously proposed AF mechanisms. First, despite its complexity AF can be terminated by targeted interventions [31, 32], which supports localized mechanisms in a majority of patients. Second, the observation that human AF is sometimes terminated by anatomic lesions before they are complete, such as pulmonary vein isolation (PVI) or a left atrial roof line, is consistent with stable sources, and is supported by the on-treatment analysis of CONFIRM [58•]. In persistent AF, the diversity of AF source locations provides a mechanism for the efficacy of extensive ablation [58•] that eventually ‘hits’ a source, as opposed to the often cited “reduction in critical mass”, which does not explain AF termination early during ablation.

Conclusions

The AF epidemic necessitates dramatic improvements in treatment and ultimately prevention, which can be achieved only by a thorough understanding of arrhythmia mechanisms. A rapidly growing body of evidence shows that wide field-of-view, physiologic-based mapping (ie, FIRM) identifies electrical rotors in diverse, stable, and patient-specific locations. Ablation of these locations with or without conventional ablation substantially increases single procedure success. These data establish rotors as sustaining mechanisms and, most importantly, show that patient-tailored mechanistic ablation can improve outcomes while reducing unnecessary ablation. Patient-specific mapping of AF-sustaining mechanisms (substrates) is likely to become the future cornerstone of AF therapy, as it has become for essentially all other arrhythmias.

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Fig. 1.

Mapping of the human atria. (a) Basket catheter splines are represented as colored lines within the right atrium (blue) and left atrium (grey) in the left anterior oblique and (b) right anterior oblique projections. For clarity, only alternate splines are shown. (c) Schematic representation of both atria as if opened through its poles (RA) or its equator (LA), with black dots representing electrode positions. (d) ECG leads and electrograms of 1 sinus rhythm beat (red box) recorded by baskets in the right and left atrium. (e) Isochronal maps of sinus rhythm activation, originating in the high right atrium (sinus node) and propagating to the lateral left atrium. Adapted with permission from: Narayan SM, Krummen DE, Enyeart MW, Rappel WJ. Computational mapping identifies localized mechanisms for ablation of atrial fibrillation. *PloS One*. 2012;7:e46034) [60]

Fig. 2.

Stable left atrial fibrillation (AF) rotor overlying minimal complex fractionated atrial electrograms (CFAE). **(a)** Left atrial rotor during AF (time bar=1 second), which **(b)** controls the direction of activation in surrounding atrium. **(c)** The path (locus) undertaken by rotor precession, with a color-coded time line. **(d)** Electrograms showing low CFAE score (=6) at the rotor site, referenced to **(e)**. **(e)** Locus of AF rotor precession superimposed upon a CFAE map, demonstrating that the rotor overlies only a low-grade CFAE (yellow, 4–6). Adapted with permission from: Narayan SM, Shivkumar K, Krummen DE, Miller JM, Rappel W-J. Panoramic electrophysiological mapping but not individual electrogram morphology identifies sustaining sites for human atrial fibrillation (AF rotors and focal sources relate poorly to fractionated electrograms). *Circ Arrhythm Electrophysiol.* 2013;6 [59•]

Fig. 3.

Cumulative freedom from AF, based on whether (a) ablation did (blue) or did not (red) pass through AF sources, or whether (b) source ablation was direct (FIRM-guided, blue) or coincidental (FIRM-blinded, red). Solid lines represent entire populations and dashed lines first-ablation patients only. (c) Elimination of all (green), some (yellow), or no (red) stable AF sources, in patients with bi-atrial baskets. P values reflect the complete follow-up periods. (Adapted with permission from: Narayan SM, Krummen DE, Clopton P, Shivkumar K, Miller JM. Direct Or Coincidental Elimination of Stable Rotors or Focal Sources May Explain Successful Atrial Fibrillation Ablation: On-Treatment Analysis of the CONFIRM

(CONventional ablation for AF with or without Focal Impulse and Rotor Modulation) Trial.
J Am Coll Cardiol. 2013) [58•]

Table 1

Clinical characteristics of patients in the CONFIRM trial

Characteristic	Conventional ablation (n=71)	FIRM-guided ablation (n=36)	P
AF presentation			0.12
Paroxysmal	24 (34 %)	7 (19 %)	
Persistent	47 (66 %)	29 (81 %)	
Age (y)	61±8	63±9	0.34
Gender (male/female)	68/3	34/2	1.00
Non-white race	9 (13 %)	6 (17 %)	0.57
History of AF (mos)	45 (18–79)	52 (38–110)	0.04
Left atrial diameter (mm)	43±6	48±7	0.001
LVEF (%)	55±12	53±15	0.59
CHADS2 score			
0 or 1	38 (54 %)	13 (36 %)	0.09
2 or more	33 (46 %)	23 (64 %)	
Previously failed >1 AAD	16 (23 %)	16 (44 %)	<0.05

Values are number (%), mean±SD, or median (interquartile range)

Adapted with permission from: Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, Miller J. Treatment of Atrial Fibrillation by the Ablation of Localized Sources: The Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation: CONFIRM Trial. *J Am Coll Cardiol*. 2012;60:628–36. [22••]