Thinking outside the Box: Rotor Modulation in the Treatment of Atrial Fibrillation

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Abstract
Ablation for atrial fibrillation (AF) is an important and exciting therapy whose results remain suboptimal. Although most clinical trials show that ablation eliminates AF more effectively than medications, it is disappointing that the continued single procedural success remains ≈50% despite the substantial advances that have taken place in imaging, catheter positioning and energy delivery. Focal impulse and rotor modulation (FIRM), on the other hand, offers the opportunity to precisely define and then ablate patient-specific sustaining mechanisms for AF, rather than trying to eliminate all possible AF triggers. For over a decade, electrophysiologists have described cases in which AF terminates after only limited ablation – usually that cannot be explained by ‘random’ meandering wavelets. Indeed, recent studies from several laboratories show that all forms of clinical AF are typically ‘driven’ by stable electrical rotors and focal sources, not by multiple meandering waves. FIRM mapping enables an operator to place a catheter at typically 1-3 predicted sites in the atria, and with <5-10 minutes of RF ablation, terminate AF and potentially render it non-inducible. Several independent laboratories have now shown that such FIRM ablation alone can terminate or substantially slow AF in >80% of patients with persistent and paroxysmal AF and increase the single procedure rate of AF elimination from 50% with PV isolation alone to >80%. Ongoing studies hint that FIRM only ablation, enabling ablation times in the range observed for typical atrial flutter, may also achieve these high success rates without subsequent trigger ablation. This review summarizes the current state-of-the-art on FIRM mapping and ablation.

Introduction
Atrial fibrillation (AF) is an epidemic both in the US1 and Europe, yet is poorly addressed either by pharmacologic rhythm control3) or rate control. Accordingly, ablation is increasingly recommended for symptomatic patients.5 However, even the most recent results from ablation continue to provide disappointing single procedure success of ≈50%6-8 and multi-procedure ceiling of ≈70%6,8,9 for paroxysmal AF, with lower results for persistent AF. What is remarkable, however, is that while this is better than anti-arrhythmic medications in patients who have previously failed such medications, ablation success has not increased in the past decade despite substantial improvements in anatomic map rendering, image integration, sheath and catheter design, and energy delivery.5,10 The precise mechanistic definition of the circuits that sustain arrhythmias has been the foundation of curative ablation for atrial flutter,11,12 AV node reentry,13 accessory pathways14 and even ventricular tachycardia. The mechanisms that sustain human AF, however, are not well defined15,16 and may represent fertile ground in improving patient outcomes.

Haïssaguerre et al. showed that ectopy from the pulmonary veins (PV) can trigger paroxysmal AF (PAF).17 However, triggers can arise outside the PVs in diverse bi-atrial locations,18 while, thus far, it remains very difficult to even achieve durable PV isolation.5 From these clinical facts alone, limitations to the success of PV isolation should not be surprising. Elimination of symptomatic AF is rather easier,5 but diverges from true AF elimination in part because ablation renders recurrent AF less symptomatic.19 Many have therefore called for work to better define the mechanisms for AF in patients.15,16

Key Words:
Atrial fibrillation, paroxysmal, ablation, therapy, rotor, focal source, spiral wave

Disclosures:
Dr. Sehra is the Chief Medical Officer of Topera, Inc. and holds equity in Topera.
Dr. Narayan reports being co-inventor on intellectual property owned by the University of California and licensed to Topera, Inc. Dr. Narayan holds equity in Topera.
Dr. Narayan also reports having received honoraria from Medtronic, St. Jude Medical and BIOTRONIK corporations.
Topera has not sponsored any research, including that presented here.

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Jun-Jul, 2013 | Vol-6 | Issue-1
What Mechanisms Sustain Clinical AF?

A number of mechanisms have been hypothesized over time to be those that sustain AF. Although the idea of local sustaining sources, such as focal rotors and/or discrete focal discharges, including those with variable epi-endocardial breakthrough, have been hypothesized, definitive evidence of these mechanisms in human AF remained elusive for many years.\(^{15,16}\) Therefore, for most of the last 1-2 decades, the multiple wavelet hypothesis, in contrast to localized sustaining sources, was assumed to explain human AF. However, outside of computer models\(^ {20}\) and studies in small atrial regions (typically <10% of atrial area\(^ {23}\)), evidence in support of the multiwavelet reentry hypothesis is sparse. Evidence from invasive EP studies for over a decade shows that AF can abruptly terminate by limited ablation,\(^ {17,18,22}\) that even persistent AF can terminate early during ablation,\(^ {22}\) and that AF patients exhibit localized regions of rapid rate\(^ {23,24}\) that remain stable over time.\(^ {25,26}\) These clinical facts are consistent with localized sustaining mechanisms rather than widely spread, chaotic, meandering wavelets. These facts are also consistent with mechanisms of AF in animal models such as electrical spiral waves (rotors)\(^ {25}\) or repetitive focal sources.\(^ {26}\) Nevertheless, as recently as 2010, human AF rotors were not considered a major mechanism for AF because they had not been clearly identified in humans using existing technologies of noninvasive body surface ECG imaging\(^ {29}\) or studies of small atrial patches.\(^ {21}\) These aforementioned studies question whether there is any role of rotors as a mechanism for the stability of AF because they could not reliably identify rotors when mapping human AF.\(^ {21,29}\) These approaches primarily utilized activation mapping, wavefront mapping, and, in the case of noncontact mapping, inverse solution computation that required generating a virtual electrogram (using predefined assumptions) derived from electrical patterns seen at the electrode on the body surface. One recent study proposed that stability of AF was correlated to dissociation and uncoupling of activation between epicardium and endocardium,\(^ {30}\) essentially creating substrate conditions for multiple wavelets to propagate. This was determined by measuring high density left atrial free wall potentials in goats simultaneously over the epi- and endocardial surfaces. Unfortunately, this high-density but narrow distribution recording method cannot visualize conduction over the panorama of the whole atrial chamber, potentially limiting its ability to detect large sources such as rotors that would encompass a large portion of the atrial tissue.

In 2011-2012, Narayan et al.\(^ {31}\) and several independent laboratories\(^ {32}\) reported, using, in contrast to previous techniques, patient-specific computational phase analyses of data from wide-area contact AF recordings (Focal Impulse and Rotor Mapping, FIRM) (RhythmViewTM, Topera, Inc., San Diego, CA), that paroxysmal AF and persistent AF were typically sustained by a small number of rotors or focal sources. This diagnostic technology enabled guidance for direct ablation at identified bi-atrial sources (Focal Impulse and Rotor Modulation, FIRM). FIRM mapping allowed electrophysiologists to terminate and render AF non-inducible prior to any PV ablation, and greatly improved AF elimination on long-term follow-up in the CONFIRM (Conventional Ablation with or without FIRM) trial.

**Focal Impulse and Rotor Mapping**

FIRM mapping analyzes data acquired from a 64-electrode basket catheter (Constellation, Boston Scientific, Natick, MA) that is placed sequentially into right then left atria (Figure 1) that achieves acceptable endocardial contact unless the atrium is larger than the largest basket currently available (55 mm deployed diameter).\(^ {33}\) Anticoagulation with heparin is titrated to achieve routine ACT targets, and no complications from FIRM mapping have been reported in >100 patients.\(^ {31,32}\) Data are exported for analysis to RhythmView\(^ {TM}\) (Topera, Inc., San Diego, CA), the details of which have been published elsewhere.\(^ {34-37}\)

RhythmView\(^ {TM}\) outputs patient-specific electrophysiologic videos\(^ {33}\) showing, among other things, 3D activation patterns throughout the chamber being mapped. From these videos, patient-specific AF mechanisms can be identified. FIRM mapping takes ≈1 hour for both atria after IV and left atrial access. This includes the time taken to manipulate the basket catheter and mapping time (10 minutes per map, for 2-3 maps per atrium) (figure 2). Newer versions of RhythmView\(^ {TM}\) will produce maps in <2 minutes, thus greatly speeding FIRM mapping.

FIRM is a three-dimensional mapping system, since all atrial regions are depicted. For ease of interpretation, projection onto grids...
enables both atria to be visualized without having to repeatedly rotate and angle the atria to fully identify the mechanistic circuits (figure 3). The right atrium basket representation is typically displayed as a vertical basket catheter with the splines spanning lateral and medial aspects of the tricuspid valve at the left and right edges of the grid. The left atrium basket representation is typically displayed as a horizontal basket (as it crosses the atrial septum) with the top and bottom of the grid representing the superior and inferior aspects of the mitral valve. These representations are interchangeable based upon the actual basket catheter positioning in the chamber of choice. Figure 3A shows an AF rotor in which rotational activity was consistent for hours. Consistent rotation is noted for thousands of cycles (>10 minutes during FIRM mapping) in order to diagnose a rotor source. Transient rotors\(^\text{39}\) are discarded as representing fibrillatory conduction or noise as these would be considered bystander waves rather than mechanisms that could sustain AF over time. Focal impulses are identified as consistent, sustained, centrifugal activation from a point of origin.

In Figure 3A, the left atrial AF rotor (red-to-blue rotation) shows activation around a “core” that “wobbles”, or precesses, (Figure 3B) within a small local area, rather than remaining at a single focal point. Such rotor precession is predicted in animal models of rotors.\(^\text{38}\) There is evidence for the stability of rotors as sustaining mechanisms of AF. In a subset of subjects FIRM maps were acquired at the time of the initial failed conventional ablation. The patients were subsequently re-mapped later for FIRM. AF rotors were found to be stable for months with ablation at these rotors terminating the AF both short and long-term.\(^\text{39}\) Several groups have found stable rotors or focal
sources in all paroxysmal AF and most persistent AF patients (98% in CONFIRM,30 100% in independent labs31). Paroxysmal AF may differ from persistent AF in showing fewer sources (1.7 ± 0.9 vs. 2.2 ± 1.0; p = 0.03). Sources lie in both atria (24% in right atrium).31,32

Focal Impulse and Rotor Modulation (FIRM Ablation)

As with any stable arrhythmia source, rotors or focal sources can be targeted for ablation (FIRM). In the CONFIRM trial31 and studies from labs independent of CONFIRM,32 ablation was delivered to the tissue adjacent to electrodes surrounding each source (rotor core or focal source). FIRM mapping is agnostic to an ablation catheter guidance method, as fluoroscopy appears just as effective as electroanatomic mapping. The procedural flow dictates that FIRM-guided ablation is applied before any other ablation (e.g. PV isolation) to achieve the acute endpoint of AF termination or typically 5–10 minutes ablation, whichever comes first. For example, in Figure 3C, FIRM alone terminated AF to sinus rhythm in <1 minute.

Notably, it has recently been shown that AF rotors/focal sources are poorly related to CFAE.39 This is shown in figure 3D, in which the left atrial rotor is marginally associated with CFAE, but most CFAE regions are distant (and even contralateral) to the successful AF rotor site. This finding agrees with clinical experience that CFAE ablation entails considerable atrial destruction, and is relatively non-specific.

In these trials when FIRM terminates AF, the FIRM mapping/ablation protocol requires attempts to reinduce AF using burst pacing. Only if AF is non-inducible is the event classified as “AF termination/non-inducibility” (Figure 4). The composite acute endpoint of all FIRM clinical studies is AF termination/non-inducibility, or AF cycle length prolongation by >10% (indicating elimination of a secondary AF source).41 If FIRM terminates AF but AF is then reinduced at a slower cycle length, the event is classified as ‘AF slowing’. Induction protocols entail rapid atrial pacing to at least 200 msec (or faster if AF was induced with a faster cycle length at the beginning of the case), along with IV isoproterenol infusion if used initially for sustained AF induction.

Patients in the CONFIRM trial exhibited 2.1 ± 1.0 sources, with a total FIRM ablation time of 15–20 minutes. Notably, this was achieved with less than 4–6 cm² of bi-atrial ablation (<5% atrial ablation), in contrast to all other ablation approaches that involve a considerable footprint of atrial ablation. In CONFIRM, FIRM-guided patients went on to conventional ablation while FIRM-blinded patients received only conventional ablation.

Figure 4 shows AF termination and non-inducibility by FIRM prior to any other ablation. Vigorous burst pacing was able to trigger AF, but the atria were no longer capable of sustaining AF when pacing stopped (<2.9 seconds in Figure 4C). This endpoint of termination/non-inducibility has been shown to predict very high freedom from AF after conventional34 and FIRM31 ablation.

In all AF patients, FIRM ablation alone terminates and renders AF non-inducible in 56%31 and 67%32 of patients before PV isolation. The composite acute endpoint (termination/non-inducibility and slowing) was achieved by FIRM alone in 86% patients in the FIRM-guided limb of CONFIRM31 and all patients in the first series from other independent sites.32 A detailed example of the FIRM-guided ablation workflow has been recently published as a video case demonstrating acute AF termination to sinus rhythm with non-inducibility.44

Long-Term Outcome After FIRM-Guided Ablation at AF Sources: The CONFIRM Trial

As alluded to above, CONFIRM (CONventional ablation with or without Focal Impulse and Rotor Modulation) was a prospective case cohort trial31 enrolling 92 patients at 107 consecutive AF ablation procedures, the majority (n = 61) of whom had nonparoxysmal AF. For all patients, single-procedure AF elimination in CONFIRM was higher for FIRM-guided than FIRM-blinded (conventional ablation only) cases (82.4% versus 44.9%; p < 0.001) after 273 days (median; IQR 132–681).

Figure 5 illustrates the Kaplan-Meier curve from CONFIRM, in which FIRM-guided ablation showed significantly more success than FIRM-blinded ablation for patients off anti-arrhythmic medications (p < 0.001). CONFIRM is among the largest AF trials to compare a novel ablation strategy to state-of-the-art conventional ablation, rather than just to failed anti-arrhythmic medications.6,45,46

Although CONFIRM was non-randomized, subjects were enrolled consecutively and treated prospectively for pre-specified endpoints. Moreover, FIRM-guided subjects had more comorbidities and more rigorous follow-up (implanted ECG monitors in 88.2%
Conclusions:
Atrial fibrillation is triggered then sustained by patient-specific mechanisms, in accordance with the mechanisms for other arrhythmias. Stable rotors and focal sources have been shown to sustain paroxysmal and persistent AF at a number of independent centers. Ablation of patient-specific sources by FIRM can terminate AF and render it non-inducible prior to PV isolation, and FIRM-blinded therapy in patients undergoing their first ablation (dashed lines). Intention-to-Treat Analysis, and p-values reflect the complete follow-up period. (Adapted from Narayan et al with permission)

References:


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