Focal Impulse And Rotor Mapping (FIRM): Conceptualizing And Treating Atrial Fibrillation

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Abstract

Current approaches for the ablation of atrial fibrillation are often effective, but only partially rooted in mechanistic understanding. Accordingly, they are unable to predict whether a given patient will or will not do well, or which lesions sets should or should not be performed – in any given patient. This goal would require clearer mechanistic definition of what sustains AF after it has been triggered (i.e. electrophysiological substrates). There are two schools of thought. The first proposes disorganized activity that self-sustains with no ‘driver’, and the second describes drivers that then cause disorganization. Interestingly, these mechanisms can be separated in human studies by mapping approach – proponents of the disorganized hypothesis studying small atrial areas at high resolution, and proponents of the driver model studying wide fields-of-view at varying resolutions. Focal impulse and rotor modulation (FIRM) mapping combines a wide field of view with physiologically based signal filtering and phase analysis, and has revealed that human AF is often sustained by rotors. In the CONFIRM Trial, targeting stable AF rotors/sources for ablation improved the single-procedure efficacy for paroxysmal and persistent AF over conventional ablation alone, as now confirmed by independent laboratories. FIRM mapping gives a mechanistic foundation to predict whether any selected lesions should intersect AF sources in any given patient and which mechanisms may cause recurrence. Rotors of varying characteristics have now been shown by many groups. These insights have reinvigorated interest in AF mapping, and rationalizing these findings will likely translate into improved therapy for our patients.

Introduction

Atrial fibrillation (AF) is ‘the most common sustained arrhythmia’ with an increasing impact on global health.¹ Whatever the precipitant – and there is increasing opinion to refute ‘lone’ AF² – the consequences are severe, with thromboembolic disease in the form of strokes and death being the most devastating.

Catheter ablation promises durable elimination of AF, yet there is considerable room for improvement as single procedure success rates for paroxysmal AF are only 50-60% in recent multicenter trials and lower for persistent AF.³ Recent evidence suggests that this reflects incomplete understanding of ablation targets as well as ineffective delivery of ablation lesions or disease progression. In this review we shall outline mechanistic insights into AF guided by focal impulse and rotor modulation (FIRM), to address the question of whether this physiologically-tailored approach offers real progress over existing mapping approaches in the field.

Current Concepts in AF

The mechanisms underpinning AF have been the subject of speculation and intense research for well over a century. Classical teaching requires a trigger to encounter a substrate that sustains an arrhythmia, and this applies equally to AF. There are three main mechanistic theories for AF substrates (figure 1), discussed in chronological order:

Re-entry

The requirement of re-entry, or circus movement of an impulse to maintain AF was first suggested by Sir Thomas Lewis as early as 1920. Re-entry has certain pre-requisites, all of which are present in AF. Re-entry is affected by the nature of the obstacle circumscribed by the wavefront (anatomical or functional) and by the shape of the wavefront itself. Re-entry around an anatomical obstacle, such as in atrial flutter, is rarely if ever demonstrated in AF, and so it is unclear if ‘macro-reentrant’ circuits described in early human AF mapping are indeed anatomical.⁴ Functional reentry by the leading circle hypothesis⁵ suggests that a wavefront encircles a region of tissue that remains refractory because constant input from reentry keeps it continuously depolarized.

A rotor is a specific form of functional reentry, first shown in isolated fibrillating ventricular muscle using optical mapping,⁶ that pivots around a “core” with extreme conduction slowing. Jalife subsequently showed that AF in a sheep model can be caused by spiral wave re-entry around a central rotor that spins rapidly to produce complex fibrillatory patterns.⁷ Of note, rotors may superficially re-
mapping plaques, albeit of small atrial areas and without proving that this disorganization drives AF. Recent attempts to recreate Moe’s original work have questioned his original interpretation, suggesting instead that focal drivers may cause vagally induced AF in the canine heart.17 These possibly model-dependent results may explain the dichotomy of opinion that exists today for human AF.

**The Applicability of Existing Cardiac Mapping to AF**

Traditional mapping approaches have been applied to AF, but with often contradictory and often unsatisfying clinical results.

**Activation Mapping**

This approach maps activation across the heart, identified when voltage or another parameter (e.g. its first derivative) crosses a threshold. The speed and direction of wavefront propagation can be inferred from these maps, but only when wavefronts are spatially coherent. Notably, varying activation of any given electrode by multiple, possibly colliding and varying wavefronts, as in AF, limits the insights available from activation mapping. Activation mapping from clinical electrograms is also problematic, whether the electrogram is complex or not, because it is sensitive to errors in assigning ‘local activation time’ in AF from far field activity or missed local activity.18 Accordingly, maps based upon action potentials often show considerable organization,19 while maps based upon unipolar or bipolar electrograms often show highly complex patterns that have been used as evidence in support of multiple wavelet re-entry.20

**Entrainment Mapping**

Entrainment mapping is specifically designed to reveal and pen-
contrast to prior mapping of 1-10 cm
ly-based noise filtering. First, we mapped human AF globally, in
to identify AF rotors or focal sources, enhanced by physiological
missing localized regions of interest, with sufficient spatial resolution
herent milieu. Seminal work by Gray, Jalife et al.
regions of tissue based on their spatial and temporal periodicity, and
and has been used to construct dominant frequency (DF) maps in
often reveal stable gradients that track the natural histo-
disease. Notably, animal models of AF exhibit stable drivers
simultaneous and atrial flutter.22 This approach is of lim-
ated value in AF, since functional reentry or rotors have no excitable
gap per se.
Frequency Mapping
As opposed to time domain analyses (voltage and activation map-
ing), frequency domain analysis uses approaches such as the Fast
Fourier Transform to reveal the frequency content of signals a sur-
rogate of rate. This approach can deal with complex electrograms,
and has been used to construct dominant frequency (DF) maps in
AF that often reveal stable gradients that track the natural history
of disease.21 Notably, animal models of AF exhibit stable drivers
with a high DF,24 and similar spatial gradients have been observed in
human AF that may be successful ablation targets.25 Again, DF
analysis may be less affected by noise and artifact if applied to action
potentials rather than clinical bipolar signals,26,27 and thus may be
combined with other methods to probe the AF substrate.
Phase Mapping
Phase mapping is a specific mathematical approach that identifies
regions of tissue based on their spatial and temporal periodicity, and
can identify periodic rotations (i.e. rotors) even in a complex non-co-
herent milieu. Seminal work by Gray, Jalife et al.28 used this approach
to greatly enhance the detection of rotors from optically mapped
atrial fibrillation in the sheep. Whilst rotors were first demonstrated in
AF using this approach in animal models (figure 2), the toxicity of
potentiometric dyes and mechano-electric uncouplers – both prereq-
usities for optical mapping – currently preclude their use in humans.
However, FIRM mapping was based upon the insights derived from
optical mapping applied to human AF.
FIRM – A New Approach to Map Human AF
Development of FIRM
FIRM mapping provides panoramic mapping of the atria, to avoid
missing localized regions of interest, with sufficient spatial resolution
to identify AF rotors or focal sources, enhanced by physiologically-
ly-based noise filtering. First, we mapped human AF globally, in
contrast to prior mapping of 1-10 cm² areas29,30 that were assumed to
represent the entire atrial surfaces (areas of 110-138 cm²). Rather
than use non-contact systems32 we selected contact recordings.
Basket catheters map the majority of each atrium, at 4-10 mm resolution
that is theoretically capable33 of mapping the smallest human reen-
trant circuits of 4-5 cm perimeter.14,34 Clinically, ablation lesions of
≈7 mm diameter also provide a relevant ‘resolution’ requirement.
Second, in developing FIRM we used monophasic action potentials (MAP),35 since AF signals are poorly represented by bipolar
signals36 due to potential AF signal cancellation or artifact between
non-coherent waves on each pole of a bipole or between a unipolar
recording and its indifferent pole. MAPs represent local activation
and recovery more accurately than clinical alternatives. Third, we
developed signal processing methods to filter AF signals based on
the dynamics of repolarization and conduction in human atria.26,37-39
Practical Approach
A commercially available basket catheter (FIRM, Topera, Palo Alto,
CA; Constellation, Boston Scientific, MA) is used to map
AF. Ideally, the basket covers >80-90% of the atria, and typically
the basket catheter is sized to cover the left atrium. Suboptimal bas-
te deployment (electrode non-contact) may cause AF sources to be
missed. Mapping is performed first in right atrium, followed by
FIRM-guided elimination of rotors/focal sources. This process is
then repeated in the left atrium.
FIRM mapping produces movies of AF propagation that are the
primary tool during a case. Snapshots (isochrones) shown in manu-
scripts are for illustration, and are not used to target ablation since
they do not depict rotor precession during and between cycles nor
the complexity of the fibrillatory milieu. In FIRM maps, the LA is
opened at its “equator” through the mitral valve, and the RA opened
along a central meridian through the tricuspid valve (figure 3).
Clinically, AF rotors or focal drivers observed in FIRM maps are
diagnosed as sources and targeted for ablation only if they remain in
reproducible locations (i.e. spatial stability) for minutes (i.e. temporal
stability). This definition excludes transient activity that we consid-
ered would be difficult to ablate. This observation also increases our
confidence in FIRM maps, as it corroborates data showing spatially
stable gradients and propagation patterns in several studies of human
AF.
The total FIRM-guided ablation time for the typical 2-3 sources in
any given patient is 15–20 minutes. Ablation is performed over each
source precession area of ≈2–3 cm² on phase mapping, requiring an
average of 5-10 ablation lesions.40 The endpoint of FIRM-guided
ablation is source elimination on repeat FIRM-maps. Once all right
atrial rotors or focal sources are eliminated, this process is repeated
in left atrium.
Clinical Outcomes of FIRM Guided Ablation
Confirm
The scientific proof of any mechanism requires intervention to
eliminate said mechanism. The CONFIRM trial (CONventional
ablation with or without Focal Impulse and Rotor Modulation)41 en-
rolled 92 subjects undergoing 107 consecutive ablation procedures
for drug-refractory AF under an IRB-approved protocol. Cases were
prospectively enrolled in a two-arm design: FIRM-guided patients
underwent ablation at 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. This was a tertiary care AF population,
roof regions. RA sources included the inferolateral, posterior, and septal regions typically away from the superior vena cava.

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 a median of 273 days follow-up censored at first recurrence (IQR: 132–681 days). Freedom after a single procedure from any atrial tachyarrhythmia was also higher in FIRM-guided than FIRM-blinded cases. These results were achieved despite more rigorous follow-up in FIRM-guided than FIRM-blinded patients (figure 5).

Very long-term analysis of all patients in CONFIRM recently showed that the benefits of FIRM plus PVI are maintained at 3 years (median follow up 873 days) compared to the expected attrition in success with PVI alone (figure 6).

**On-Treatment Analysis of CONFIRM**

The mapping of rotors and focal sources in all patients in CONFIRM enabled an on-treatment analysis of AF source ablation, i.e. to determine outcome when sources were ablated by any means (directly by FIRM or coincidentally by anatomical lesions) or not. In this on-treatment analysis, freedom from AF was highest when all sources were eliminated, intermediate when some were eliminated, and lowest when all sources were missed. This study suggests that rotor elimination was the key to successful AF ablation. This mechanistic concept was tested prospectively in early data from 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 (without PVI). Preliminary results from PRECISE showed that FIRM-only ablation provided >80% elimination of paroxysmal AF. These results support FIRM-mapped AF rotors and focal sources as a primary mechanism for AF.

**Multicenter FIRM Registry**

Independent centers have now confirmed acute and long-term outcomes from FIRM-guided ablation. In a recent prospective evaluation, Miller et al. examined the first n=78 consecutive patients undergoing FIRM guided ablation for AF with >1 year follow-up at 10 centers, excluding the original San Diego center. The population had age 61±10 years, n=23 had paroxysmal AF, n=48 had persistent AF and n=7 had longstanding persistent AF. All patients exhibited AF sources, for an average of 2.3±0.9 concurrent AF rotors or focal sources per patient. Patients were treated by ablation of all sources, requiring a total of 16.6±11.7 minutes, followed by conventional ablation. On >1 Year follow up with a 3 month blanking period and no repeat procedures (median time to 1st recurrence: 245 days, IQR 145–354), single-procedure freedom from AF was 80.5%, similar for persistent and paroxysmal AF (p=0.89). The authors concluded that FIRM-guided ablation has a short learning time, and that elimination of AF rotors and focal sources produced freedom-from-AF of ≈80% at 1 year at centers new to FIRM. No safety issues were identified, with no reported cases of thromboembolism or perforation related to basket catheters.

**Limitations of FIRM Mapping**

FIRM mapping requires a learning curve to interpret the visual propagation videos which are the primary guide to ablation targets, although in a multicenter study centers were early in their experience. Whilst the basket catheter is typically stable within the atria, registration errors if the basket moves between mapping and ablation...
analyses of contact mapping including traditional activation mapping – despite its caveats in AF. It is not surprising that these divergent approaches different characteristics of rotation, including case reports of rotors\(^1\) which repeatedly return to spatially circumscribed areas in the atria. Other groups have detected only focal sources.\(^1\) As with FIRM, validation of each new tool will require mapping before/after each localized ablation set to confirm that the feature was abolished. This introduces an unanticipated limitation of the use of AF termination during non map-guided ablation. Without defining a mechanistic target or mapping it pre/post ablation, it is unclear if AF termination after potentially widespread and lengthy ablation (>40-50 minutes) reflects just the last lesion(s) or some cumulative aspects of prior atrial modification. Such termination is thus difficult to compare to results from driver-focused localized intervention. Studies comparing these strategies – by continuous mapping – are needed. Such studies are ongoing.\(^5\)

Integrating FIRM with existing concepts of AF

The identification of stable rotors in human AF by FIRM mapping reconciles diverse clinical observations. How do these ideas fit with existing models? What role is there for other substrate and trigger based methods of AF ablation? If rotors are a prevalent mechanism for AF maintenance, then there should be a more robust electrogram surrogate for these initiating processes than currently proven. In particular, this may be based on stereotypic changes in conduction and wavefront propagation that appear to precede AF rotor formation. However, in CONFIRM there was no relationship between rotor sites and electrogram fractionation (figure 7), and so novel electrogram indices of AF driver sites are needed.

There are numerous other putative stabilizing mechanisms in human AF,\(^2\) which likely have relevance in relation to the driver/disorganization debate – autonomic innervation, fibrosis, connexin distribution and cellular calcium handling are a few examples of mechanisms that are currently being related to regions of relative or ganization (possible AF drivers) or disorganization in various studies. It is likely that many of these concepts will converge in the near future – for instance, the locations of autonomic ganglia coincide with some areas ablated during PVI and WACA, and their resultant shortening of action potential duration locally but also widely within the atria may stabilize localized reentry.\(^5\) Clearly, further studies are needed to better link these mechanistic schools of thought.

Contact of the basket with the atrial wall is a major concern, and must be optimized prior to FIRM mapping that may require basket repositioning or even resizing. Many authors\(^46, 47\) recognize that atria >55–60 mm diameter currently pose a problem (this is the current size of the Constellation basket). New basket designs may reduce this limitation. We use fluoroscopy, intracardiac echo (if already used) and electrogram quality to determine contact. Basket coverage may under-represent certain areas, notably inter-atrial septum, appendage and vena cava, due to splaying of the splines and unequal electrode spacing, that can also be accommodated by repositioning the basket.

Future Directions

Comparison With Non-FIRM Methods ToDetect Rotational Circuits In AF

Since CONFIRM was reported, several groups have shown rotational activity and rotors in human AF.\(^30, 48, 49\) These reports used various mapping techniques, some using non-contact body surface electrodes to create virtual electrograms\(^30\) and others using various can affect results and so steps must be taken to track position (e.g. biplane cineangiography or electroanatomic mapping).

Figure 5: Cumulative freedom in CONFIRM from atrial fibrillation, in all cases and in those at first ablation for (A) the entire population and (B) the population off anti-arrhythmic medications. From.\(^43\)

Figure 6: Very long term results from CONFIRM trial. From.\(^42\)

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Conclusion:
Focal Impulse and Rotor Modulation (FIRM) mapping provides a mechanistic approach to map and ablate AF. Demonstration of rotors and focal sources in AF by FIRM builds upon decades of bench-to-bedside studies, and explains divergent clinical results that are difficult to explain by other hypotheses. The preliminary results of FIRM-only ablation in the PRECISE trial confirm that stable AF rotors are important mechanisms for human AF, and provide a framework to predict which lesion sets may or may not be effective in each individual. The results of the CONFIRM trial and multicenter registry show that adding AF source elimination to trigger ablation provides high single-procedure efficacy on term follow-up. Future studies should explain why FIRM-guided ablation is not always effective, and whether this reflects undetected sources, suboptimal source elimination or other mechanisms. Ongoing randomized clinical trials will define the efficacy of FIRM-guided ablation versus conventional ablation. We are hopeful that renewed focus on the mechanisms of human AF will accelerate progress in our understanding and rapidly translate into better therapies for our patients.

References:


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