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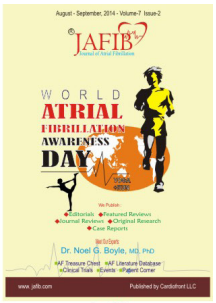

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Focal Impulse And Rotor Mapping (Firm): Conceptualizing And Treating Atrial Fibrillation

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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' AF[2] – 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.

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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 hypothesis[5] 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-

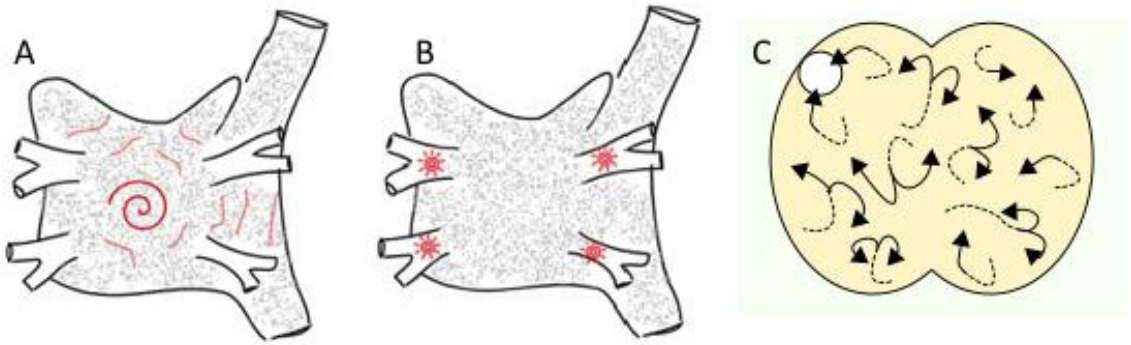

Figure 1: Proposed mechanisms in AF. A) spiral wave re-entry with peripheral fibrillatory conduction. B) focal discharges from the pulmonary veins. C) multiple wavelets. Adapted from.[12, 52]

semble macro-reentry – but are quite different. In macro-reentry, a stable circuit revolves around an inert obstacle. In AF, the rotor core ('singularity') is the primary mechanism, and emanating spiral waves rotate in variable fashion and break down into disorganized AF ('fibrillatory conduction'). In addition, the rotor core precesses ('wobbles'), as described by Davidenko and Jalife in animals in 1992[6] and recently in humans.[8]

Focal Discharges

Focal discharges were produced experimentally by Scherf by the application of aconitine[9] and implicated in atrial arrhythmogenesis, with the caveat that such discharges would have to sustain for years to drive persistent AF. The importance of focal beats to AF underwent a revolution in 1998 with the demonstration that pulmonary veins may harbor rapidly firing sources in patients with repetitive frequent paroxysms of AF,[10] contradicting the concept of multiple wavelets with no driver (see next section), in whom focal ablation could eliminate AF.[11] This work led to current approaches for pulmonary vein isolation for AF.[12]

Multiple Wavelets

In the late 1950s Gordon Moe used computational and canine models of AF to show that multiple small wavelets meandering through the atrium could sustain AF[13] given a minimum mass of tissue to propagate. He initially suggested the need for 20-30 wavelets, with trajectories based on regional refractory periods. Allessie subsequently reported multiple meandering wavelets in elegant animal and human studies, using high-density epicardial and endocardial mapping plaques,[5, 14–16] 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-

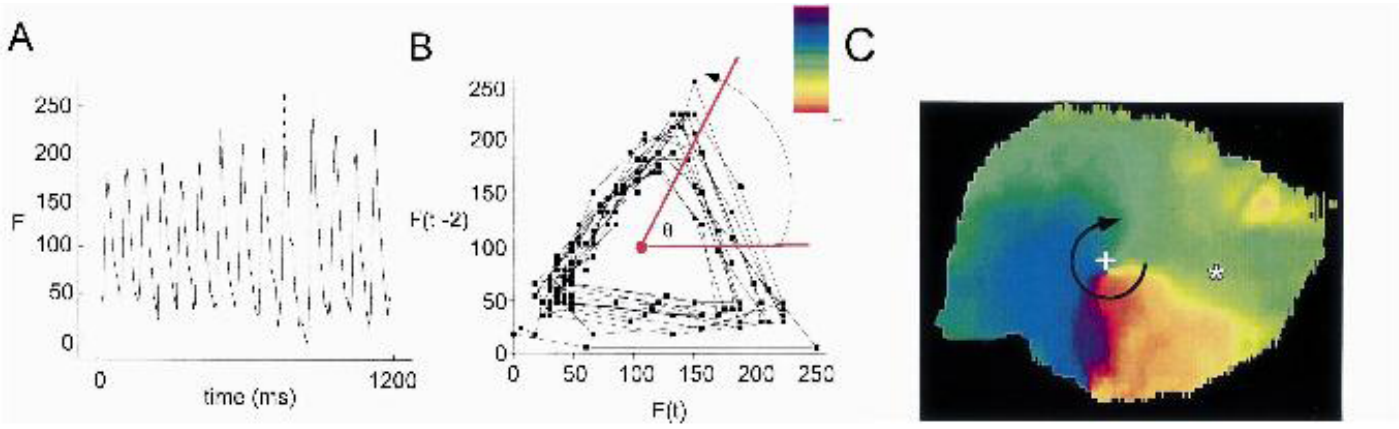

Figure 2: Phase mapping from an isolated sheep heart. A) Optical action potentials recorded using voltage sensitive dyes. B) Phase plots of F(t-2) vs. F(t), where time, t, is the frame number and 2 is the number of lagging frames. The colorbar represents the variation in phase. Two-dimensional phase map of a clockwise rotor during AF. From.[53]

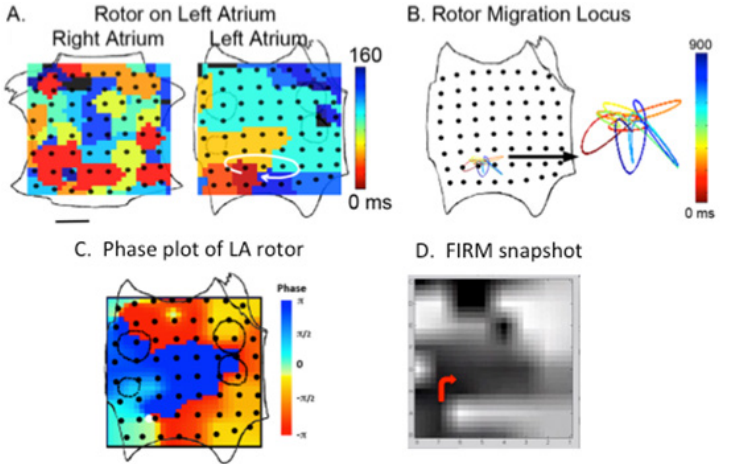

Figure 3: **Stages in FIRM mapping. Right atrium basket is opened vertically on tricuspid valve and left atrium is opened horizontally along mitral valve. A) Rotor in left atrium visualized with isochrones. B) Clockwise rotation and precession of rotor over a small locus. C) Phase plot of same rotor showing convergence of phase at rotor core. D) Snapshot from FIRM movie depicting phase and direction of rotor in red. From.[36]**

etrate an excitable gap in stable re-entrant tachyarrhythmias, as in ventricular tachycardia[21] and atrial flutter.[22] This approach is of limited 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 mapping), frequency domain analysis uses approaches such as the Fast Fourier Transform to reveal the frequency content of signals a surrogate 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.[23] 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-coherent 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 prerequisites 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-based noise filtering. First, we mapped human AF globally, in contrast to prior mapping of 1-10 cm^2 areas[29,30] that were assumed to represent the entire atrial surfaces (areas of 110-138 cm2[31]). Rather than use non-contact systems[32] we selected contact recordings. Basket catheters map the majority of each atrium, at 4-10 mm resolution that is theoretically capable[33] of mapping the smallest human reentrant circuits of 4-5 cm perimeter.[34, 35] Clinically, ablation lesions of ≈7 mm diameter also provide a relevant 'resolution' requirement.

Second, in developing FIRM we used monophasic action potentials (MAP),[36] since AF signals are poorly represented by bipolar signals[18] 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.[37] 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 (FIRMap, 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 basket 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 manuscripts 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 considered 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] enrolled 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,

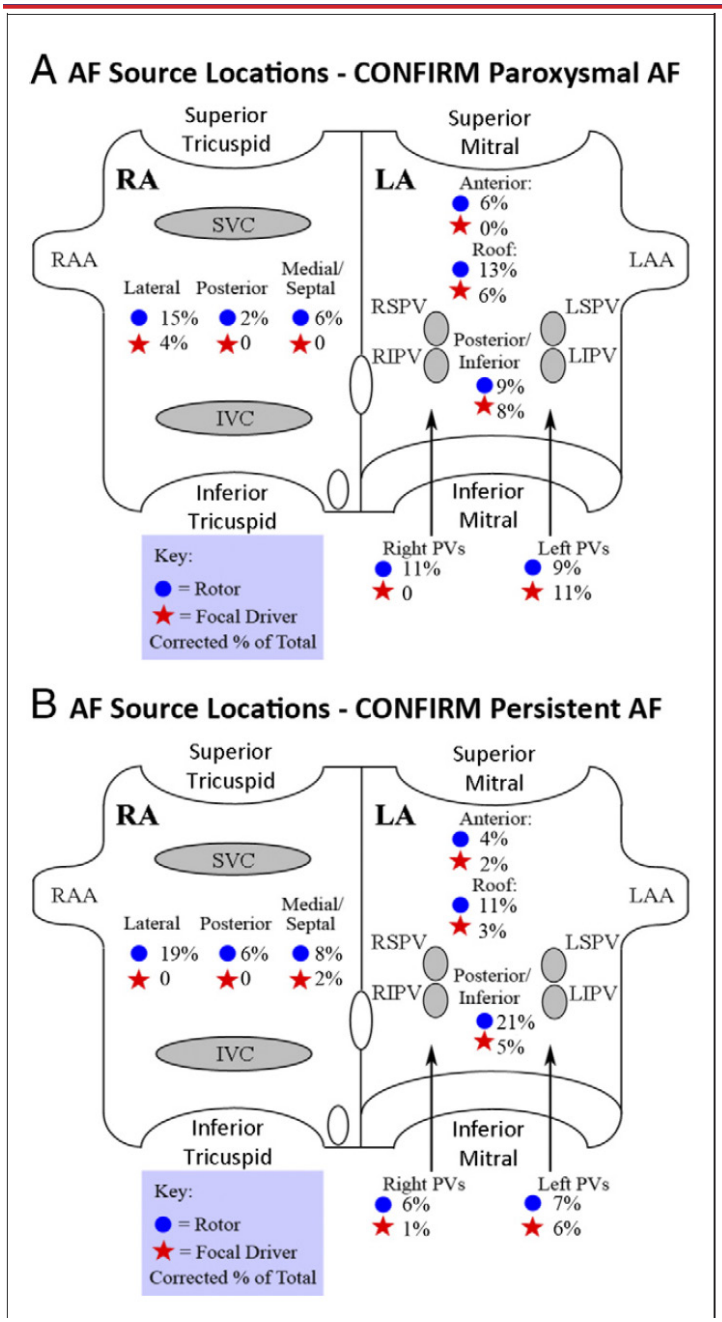

Figure 4: Location of focal sources and rotors in patients enrolled in the CONFIRM trial in A) paroxysmal and B) persistent AF. From.[41]

with persistent AF present in 81% of the FIRM-guided group, and in 66% of the FIRM-blinded group. The primary long-term endpoint was defined as freedom from AF for up to two years after a single procedure, defined as <1% burden using continuous implanted ECG monitors (monitoring 100% of 1 year), or AF <30 seconds on quarterly event monitors (monitoring 7.8% of 1 year).

AF sources were documented 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). 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). Notably, stable AF sources lay at diverse patient-specific locations (figure 4) 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 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).[42]

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.[43] 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.[44] 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[45] and long-term outcomes from FIRM-guided ablation. In a recent prospective evaluation, Miller et al.[40] 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.[45] Whilst the basket catheter is typically stable within the atria, registration errors if the basket moves between mapping and ablation

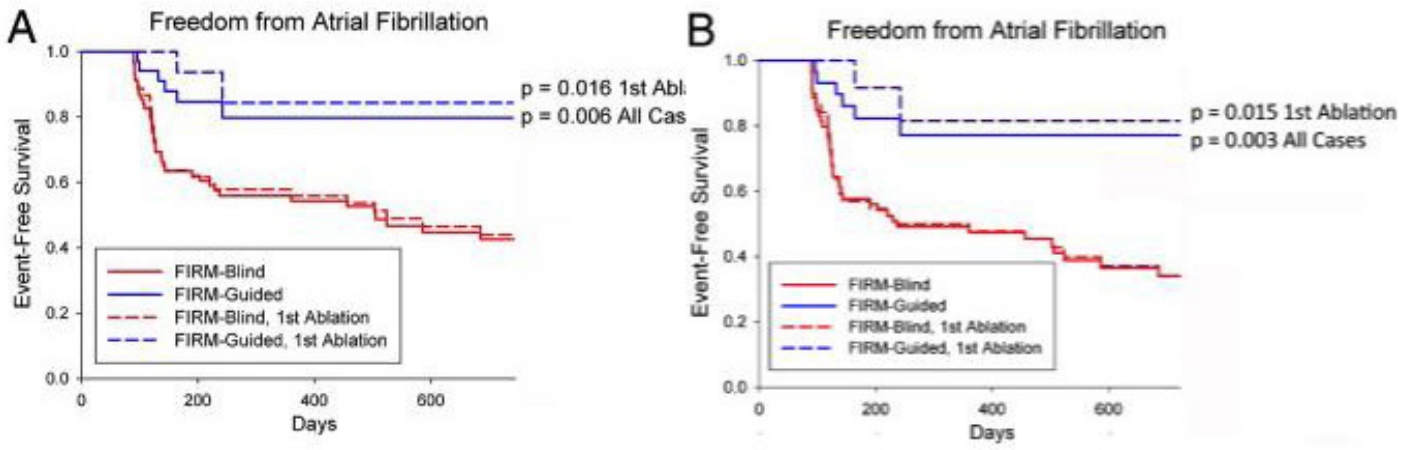

Figure 5: **Cumulative freedom in CONFIRM from atrial fibrillation, in all cases and in those at first ablation for (A) the entire population and (B) the population off anti-arrhythmic medications. From.[43]**

can affect results and so steps must be taken to track position (e.g. biplane cineangiography or electroanatomic mapping).

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[48] and others using various 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[48] which repeatedly return to spatially circumscribed areas in the atria. Other groups have detected only focal sources.[47] 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.[50]

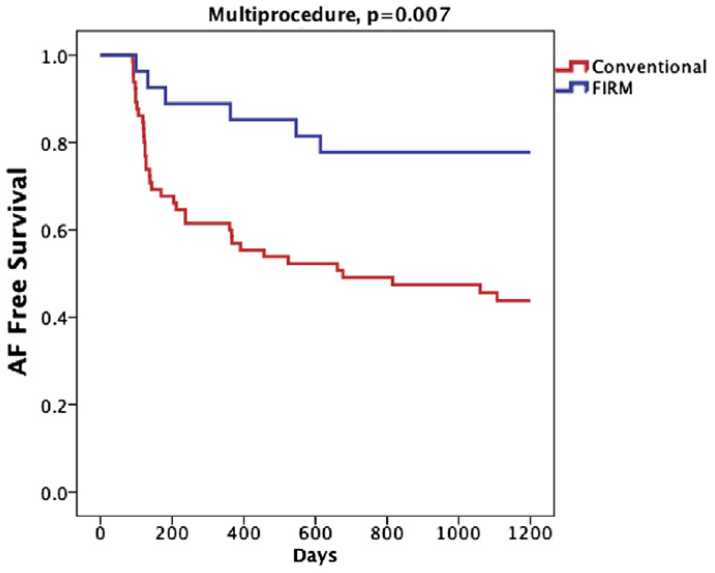

Figure 6: **Very long term results from CONFIRM trial. From.[42]**

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 organization (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.[51] Clearly, further studies are needed to better link these mechanistic schools of thought.

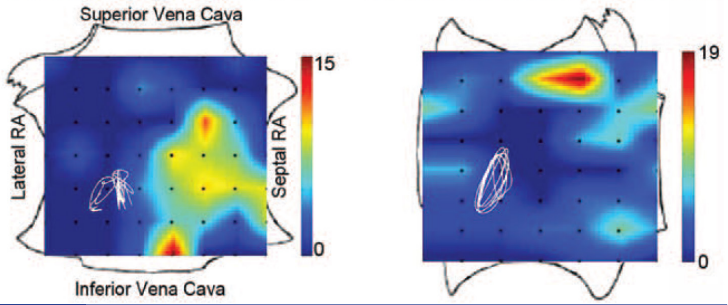

Figure 7: Rotor precession (white) in right (A) and left (B) atrium does not overlap with CFAE areas on NavX map. From.[8]

Summary of Conventional vs. FIRM Mapping

Table 1. FIRM – Real progress over conventional techniques.

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.

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Table 1: FIRM – Real progress over conventional techniques.

	Conventional	FIRM
Single procedure success, 1 year	≈50%	≈80%
Proof of success	Some implanted ECG Intermittent Holter recording	Many (majority) implanted ECG
Multicenter	✓	14 centers, ~200 reported cases
Ability to predict who will do well/recur?	X	✓
Ability to explain why patients do well/recur?	X	✓
Defined patient specific mechanism	Triggers – Sometimes defined Sustainers – rarely defined	Defined consistently. Validated by mapping pre/post ablation.
Basic science supports mechanisms	✓/X	✓
Future work	1.PV reconnection 2.Other triggers, whether PVs isolated or not? 3.Other sustainers?	1.Fibrillatory conduction from rotors (i.e. why do patients do well even if AF does not terminate procedurally?) 2.Why do rotors form where they do?

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