Rotors and Focal Sources for Human Atrial Fibrillation
– Mechanistic Paradigm With Direct Clinical Relevance –

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Outcomes for patients with atrial fibrillation (AF) have changed little despite many advances in technology. In large part, this reflects fundamental uncertainty about the mechanisms for AF in humans, which must reconcile diverse observations. Despite the complexity of AF, many electrophysiologists have witnessed modulation of ‘chaotic’ AF after the first few ablation lesions, or before lines are complete or trigger sites are isolated, and numerous analyses demonstrate temporospatial stability in AF. These common observations challenge the concept that AF is driven by spatially disorganized, widespread mechanisms. Using mathematical techniques applied to other complex systems, evidence is rapidly accumulating that human AF is largely sustained by localized rotors and focal sources. Elimination of sources by Focal Impulse and Rotor Modulation (FIRM)-guided ablation has been shown by independent laboratories to substantially improve success compared with pulmonary vein isolation alone. These data advance our mechanistic understanding of AF. Randomized trials are underway to verify the relative efficacy of ablation at AF sources (substrate) vs. conventional trigger ablation. The renewed focus on AF substrates is a paradigm shift, but also a re-alignment of concepts for AF towards those for other cardiac arrhythmias that are generally defined by sustaining mechanisms (substrates). (Circ J 2014; 78: 2357–2366)

Key Words: Atrial fibrillation; Multiwavelet reentry; Phase mapping; Rotors; Substrate

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia in the world, leading to hospitalization, heart failure, thromboembolic complications and mortality. However, with the exception of stroke prevention, AF outcomes have improved little in recent decades. Many trials challenge the efficacy and safety of pharmacologic therapy to maintain sinus rhythm, while others question its role in rate control in AF. Although ablation for AF shows promise, it has modest single-10–13 and multi-11–13 procedure efficacy, with safety concerns even at experienced centers. Many limitations in the risk stratification, prognostication and therapy for AF can be traced to uncertainty about its mechanisms. AF is initiated by “triggers” and then sustained by “substrate”, similar to other arrhythmias whose substrates are therapeutic targets. Uncertainty about the AF substrates has until recently required us to focus on eliminating AF triggers. However, it has been uncertain whether AF substrates comprise multiwavelet reentry16,17 or localized sources that cause disorganization, and how they interact with the autonomic nervous system19,20 fibrosis,21 heart failure, obesity22 or other predictors of clinical outcome.3

In this review, we propose that greater mechanistic clarity for AF will enable truly personalized therapy, that may lead to eventually catalyzing a mechanistic AF classification to predict “responders” or “non-responders”. Our synthesis will include the rapidly growing body of evidence that AF is sustained by localized rotors and focal sources23–29 that can be targeted for precise patient-specific therapy (Table). We summarize multicenter clinical trials in which AF source ablation improved outcome,23,26,28,29 even in patients with ‘adverse’ comorbidities,30 and propose directions for future research.

AF Mechanisms: What Explains Clinical Observation?

In 1964, Moe et al proposed in computer simulations that disorganized activity drives AF, but to date mapping studies to support this hypothesis have examined small areas and may miss small regions harboring a localized driver, and have not used interventions to prove that disorganization causes AF (ie, is a mechanism) and is not a bystander. Conversely, AF may be caused by localized AF sources as suggested by a parallel body of clinical and basic studies. Anecdotally, many electrophysiologists have witnessed modulation of “chaotic” AF by few,23 or even a single33 ablation lesion, even in patients resistant to electrical cardioversion, or by pressure at 1 site.34 Reports have also been made of stable high-frequency sites inside and outside the pulmonary veins,35–39 reproducible spatial vectors, and other spatiotemporal consistency in AF. These observations support localized sources as the mechanism (Figure 1).
Localized Electrical Rotors and Focal Sources

Sir Thomas Lewis proposed that functional reentry may drive AF. Rotors are localized functional reentrant circuits that sustain AF in animal models and are defined as a phase singularity whose reverberations radiate “spiral waves” at high speed into surrounding tissue. Rotors differ from leading circle reentry by exhibiting a central zone of extreme wave curvature that causes very slow conduction, allowing precession into excitable tissue, with emanating spiral waves that disorganize (“fibrillatory conduction”; Figure 2). Conversely, leading circle reentry requires an unexcitable/refractory core that fixes reentry, which conceptually differs from a rotor, with outward activation of peripheral tissue.

Rotors were shown experimentally by Davidenko et al in 1990, then supported by modeling and optical mapping of isolated animal hearts. Sources are often spatially and temporally stable but precess (“wobble”) in small regions related to tissue anisotropy or other discontinuities. In a recent canine model, ablation of AF rotors prevented subsequent inducibility of AF, while other studies show focal sources in AF.

The cellular mechanisms enabling AF source formation are incompletely defined, but may include upregulation in $I_{K1}$ expression, changes in $I_{KS}$ and modifications in $I_{Na}$ that slow conduction velocity.

Determining if Rotors and Focal Sources Drive Human AF

Starting in 2001, we set out to study both sides of the disorganized/organized source debate for human AF. This required tools suited to mapping either mechanism – wide-area mapping to avoid missing a localized source, with sufficient spatial resolution and tools to filter signal from noise and either identify or exclude AF rotors or focal sources.
Rotors and Focal Sources in AF

First, we mapped human AF globally within both atria. Most prior human studies assumed that AF is uniform, by extrapolating from small plaques of 1–10 cm² area,31,32 to the entire atrium with areas >100 cm² (by MRI in AF patients).57 Rotor circuits detected using small plaques in the operating room33 or electrophysiology laboratory38 will not appear stable if they process outside the array. We abandoned early attempts using non-contact systems because of inaccurate inverse-solution electrograms.59 We selected basket catheters that map the vast majority of each atrium with resolution sufficient to map the smallest theoretical human reentrant circuits86 of 4–5 cm perimeter,60 which requires a minimum electrode spacing of =1.1 cm,56

Second, we used monophasic action potentials to validate AF signals.61 Routinely acquired signals poorly indicate activation in AF, even in non-fractionated signals (see figures 1–3 in Narayan et al62), because of AF signal cancellation and double counting between non-spatially coherent waves.

Third, we developed signal processing methods to map human AF based on our studies of repolarization,63–66 conduction,65,67 and electrogram phase68–71 in relation to AF.64,72 These studies led to the development of Focal Impulse and Rotor Modulation (FIRM) mapping, which identifies rotors, as phase singularities in noise-filtered electrograms,61,73 and focal sources in human AF.

Distinction Between Mapping Human AF Rotors vs. Reentrant Atrial Tachycardias

Despite superficial similarities, an AF rotor differs substantially from macro-reentry. Reentry in atrial tachycardia is relatively fixed in location and rate from cycle to cycle and rotates around an “inert” obstacle. Conversely, the AF rotor core precesses and is not fixed, which changes the electrograms ahead vs. those behind the direction of precession because of the Doppler effect,46 with spiral waves that rapidly disorganize and fuse with the milieu from fibrillatory conduction. Thus, human AF rotors were undetected for decades.74

Figure 3 shows a human left atrial AF rotor detected by FIRM. The isochronal (contour) map (Figure 3A) shows a clockwise spiral wave (arrow) whose electrograms at fixed sites E3–F3 show rotation for this cycle (core at EF4, rotor cycle length 180 ms; Figure 3B), which may be obscured with fibrillatory decay and rotor precession, as shown in the movies used to guide ablation (see online supplementary files23,75). Figure 3C shows a focal AF source.

Figure 4 details the effect of rotor precession in an 81-year-old man with persistent AF. Rotor precession shown in Figure 4B for approximately 4 cycles (900 ms) is sufficient to obscure “simple” rotation on sites 1–8 and produce irregular electrograms.48 In Figure 4C, the core (point of phase singularity) starts at point α, passing point β to γ, all within 190 ms, largely outside sites 1–8. Recent approaches identify AF rotors in this complex milieu using physiological noise-reduction algorithms with phase mapping.

A growing body of work shows rotors and focal sources in human AF using FIRM76 and other methods.25,26,58 Using FIRM, AF sources are spatially and temporally stable in limited 2–3 cm² areas,77 amenable for targeted ablation.23 Mechanistic proof that these sources sustain human AF is provided by the ability of FIRM-targeted rotor ablation alone, without pulmonary vein isolation (PVI), to eliminate AF acutely and, on long-term
that FIRM-guided ablation provided substantially higher late freedom from AF than trigger-based ablation alone (Figure 5).

Results from FIRM-guided mapping and ablation have been verified by multiple centers in the United States and Europe.24,27,80,81 The first independent report of AF termination by FIRM-guided ablation was by Shivkumar, Miller et al in 2012.24 One-third of AF sources lie in the right atrium away from the superior vena cava, and in other bi-atrial regions that would ordinarily not be targeted by conventional ablation. External studies confirm that FIRM-mapped AF sources are spatially stable for hours or even days,61,82 providing a rationale for targeted ablation.

follow-up in the multicenter PRECISE trial, even in patients with paroxysmal AF.78 Table summarizes the current literature on FIRM.

Clinical Relevance of Detecting Stable AF Rotors

In 2011, the CONFIRM trial (CONventional ablation with or without Focal Impulse and Rotor Modulation)79 reported that FIRM mapping revealed 2.1±1.0 concurrent rotors and focal sources in nearly all (97%) of 107 consecutive cases of paroxysmal and persistent AF in 92 patients. Ablation of sources raised single-procedure freedom from AF at 1 year to 82.4% from 44.9% for trigger-based ablation alone (PVI) alone.23 This benefit has been shown to be durable at 3 years,28 confirming

Figure 3. Detecting atrial fibrillation (AF) rotors in complex fibrillatory milieu. (A) Spiral waves emanating from a left atrial (LA) AF rotor (labeled) vary from fibrillatory breakdown (labeled), fusion with the milieu (arrows/double lines) and precession of the core. (B) Electrograms for this single cycle (core at EF45) show rotational activity on electrodes E3–F3 (highlighted), but this will move as AF rotor cores precess and drag the spiral waves, in addition to fibrillatory decay. AF spiral waves thus typically require dynamic signal processing for detection (adapted with permission from Narayan SM et al85). (C) Focal source driving AF (adapted with permission from Narayan SM et al86). Orientation: the left atrium is opened horizontally through the mitral valve (MV), and its superior and inferior halves folded upwards and downwards, respectively.
A commercially available contact catheter (FIRMMap, Topera, Menlo Park, CA, USA; Constellation, Boston Scientific, MA, USA) is advanced to the right atrium to record AF during electrophysiological study. Optimal contact is important. RhythmView™ (Topera) is used to generate diagnostic movies of AF.

Ablation is then performed over the source precession area of 2–3 cm² on phase mapping, requiring an average of 5–10 ablation lesions. Many ablation catheters have been successfully used, including irrigated and non-irrigated radiofrequency and cryoablation. Once all the right atrial rotors or focal sources are eliminated, FIRM-guided ablation is repeated in the left atrium. Occasionally, the ablation of a dominant AF rotor or focal source may unmask a secondary source at repeat FIRM mapping. The endpoint of FIRM-guided ablation is source(s) elimination on repeat FIRM maps. Typically, >2–4 repeat FIRM maps are performed in each atrium following source ablation to reassess for elimination of all sources. The time taken to export data and create each FIRM-map is <2 min and total FIRM-guided ablation time (for 2–3 sources) is 15–20 min. Additional ablation, including PVI, has been performed in some studies, but omitted in other protocols.

FIRM-guided ablation may terminate AF typically to sinus rhythm (Figure 6), as first shown outside San Diego and now in larger series. Nevertheless, there is debate whether AF termination by conventional ablation, does or does not predict outcome. For FIRM, the PRECISE and on-treatment analyses of the CONFIRM trials show that AF source elimination on repeat FIRM maps is a more effective endpoint than AF termination. Among several theoretical reasons, a practical reason is that AF termination and non-inducibility prevent repeat FIRM mapping to confirm that all sources are eliminated during AF.
of triggers and substrates are thus complementary.\textsuperscript{85} Eliminating pulmonary vein triggers remains central to many approaches to AF ablation,\textsuperscript{9,11,36,87} although with single to multiprocedure success rate at 1 year of 50–70% for paroxysmal

Integrating FIRM Into Current Ablation Paradigms

Like all arrhythmias, AF is initiated by “triggers” then sustained by electrophysiological substrates. Mechanistically, ablation

Figure 5. (A) Very long-term freedom from atrial fibrillation (AF) in the CONFIRM trial for FIRM-guided ablation (blue) and conventional ablation (red; P=0.003) after 1.2±0.4 procedures. (B) Very long-term single-procedure freedom from the AF for FIRM-guided ablation (blue) and conventional ablation (red) in the CONFIRM trial. Data show all cases (solid lines, P=0.002) and patients undergoing their first ablation (dashed lines, P=0.002). Reproduced with permission from Narayan SM et al.\textsuperscript{28} FIRM, Focal Impulse and Rotor Modulation.

Figure 6. Atrial fibrillation (AF) termination to sinus rhythm by FIRM-guided ablation at the left atrial AF rotor in the first external multicenter experience of FIRM. This snapshot shows a clockwise spiral wave (arrow) with fusion of spiral arms with fibrillatory waves (block/arrows). FIRM-guided ablation terminated AF to sinus rhythm (adapted with permission from Shivkumar K et al.\textsuperscript{24}). Orientation: as in Figure 3. FIRM, Focal Impulse and Rotor Modulation.
AF patients, and lower success in persistent AF patients.5
Substrates were previously emphasized only in persistent AF, but are increasingly revealed in paroxysmal AF by low voltage, conduction slowing, and fibrosis, and electrophysiologically by FIRM-mapped rotors and focal sources whose ablation alone (without PVI) can eliminate AF long-term.78 Other substrates include complex fractionated atrial electrograms (CFAE), which correlate poorly to FIRM-mapped AF sources and have unclear mechanisms, areas of high dominant frequency that may indicate rotor locations, and gan glionated plexus sites.20

AF Rotor Mapping: Limitations and Future Directions
A technical limitation of FIRM is electrogram contact.76 FIRM mapping is not ideal in patients whose atria are larger than available basket catheters, as illustrated by Shivkumar et al24 and Miller et al.29 FIRM can still be effective if rotors happen to lie at the subset of electrodes that contact the atria (Figure 7), although basket manipulation is then needed to serially sample the atria. New basket designs may reduce this limitation. Another limitation is the interpretation of complex FIRM maps, and although this learning curve was rapid in a recent external series by Miller et al., automated rotor detection algorithms may further assist this process.
Mechanistically, studies are needed to define why AF sources precess, and what mediates fibrillatory conduction to the disorganized phenotype. Clinically, multicenter studies show that FIRM-guided ablation increases the success of trigger-based ablation alone, but ongoing randomized trials will verify this in various populations. In addition, AF rotational activation has recently been described using alternative approaches that should be compared with FIRM in terms of mechanism and clinical results.

Conclusions
AF is a highly prevalent disease with considerable morbidity, for which greater mechanistic clarity has the potential to greatly improve therapy. A rapidly growing body of literature shows that human AF is sustained, after it has been triggered, by rotors and focal sources that are spatially stable and amenable to targeted ablation. Ablation of AF sources identified by FIRM has been shown in several centers to improve ablation outcome vs. trigger elimination alone. Such data provide a unique platform to re-examine patient-specific physiological, structural and genetic mechanisms for AF, and to translate these into clinical classification and therapy.

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