ATRIAL FIBRILLATION

REVIEW ARTICLE

Focal Impulse and Rotor Modulation for Paroxysmal Atrial Fibrillation

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ABSTRACT. Therapy for atrial fibrillation (AF) remains suboptimal, largely because of uncertainty in its mechanisms. While the “triggers” versus “substrate” debate continues to rage, it is not clear that this is central. All supra- and ventricular arrhythmias are initiated from sinus rhythm by “triggers,” and successful therapy targets their sustaining mechanisms rather than triggers. Paroxysmal AF, moreover, often sustains for hours or days after it is triggered, longer than many presenting supraventricular tachycardias. Accordingly, refocusing therapy on sustaining mechanisms for paroxysmal AF may improve upon the results of recent multicenter trials, in which trigger elimination yields a single procedure success rate of less than 50–60%, compared with more than 80–90% for other supraventricular arrhythmias. Wide-area (panoramic) contact mapping now shows that paroxysmal AF, and persistent AF, is maintained by a small number of stable rotors or focal sources that lie widely in both atria often remote from pulmonary veins. Mechanistically, targeted ablation at sources alone (focal impulse and rotor modulation, FIRM) has proven able to acutely terminate AF and render it non-inducible, often with very brief energy delivery (<5–10 min). Clinically, abolition of rotors and focal sources substantially improves the results from conventional pulmonary vein ablation alone. This review focuses on the evidence that stable rotors and focal sources drive clinical paroxysmal AF, and discusses their role as ablation targets either with trigger elimination or as solitary therapy.

KEYWORDS. ablation, atrial fibrillation, focal source, human, paroxysmal, spiral wave therapy, rotor.
multiwavelet hypothesis proposed that spatially meandering waves actually sustain AF, but cannot explain how AF may terminate by localized ablation. The alternative localized source hypothesis is supported by elegant experiments in which activation from localized spiral waves (rotors) or focal sources sustains AF, so that disorganization is an epiphenomenon. Until recently, however, there had been little or no evidence to support stable sources for human AF.

Recent studies from our group and independent laboratories show that paroxysmal and persistent AF is sustained by a small number of rotors or focal sources. Using wide-area contact mapping techniques, but not non-contact methods, sources are remarkably stable over time, enabling targeted source ablation (focal impulse and rotor modulation, FIRM) to rapidly terminate and render AF non-inducible, and greatly improve AF elimination on long-term follow-up in the CONFIRM (Conventional Ablation with or without FIRM) trial. Initial reports of stable human AF rotors have now been validated by at least eight independent groups worldwide.37

This review summarizes the evidence for stable electrical rotors and focal sources for human paroxysmal AF, and their role as targets for ablation to achieve long-term maintenance of sinus rhythm.

Contact panoramic mapping: approach

We recently mapped human AF sources using contact electrodes in a wide field of view (Focal Impulse and Rotor Mapping, FIRM) at clinical electrophysiology study. A commercially available basket catheter (Constellation, Boston Scientific, Boston, MA) is advanced first into the right atrium for mapping and ablation; then this process is repeated in the left atrium as shown in Figure 2. In the right atrium, signals are recorded from 64 poles and exported for analysis to a computational system (RhythmView, Topera Medical, San Diego, CA). Analyses use physiologically adaptive algorithms to analyze AF in terms of biatrial action potential duration restitution and oscillations and conduction velocity restitution. These analyses are concordant with the facts that paroxysmal AF and even lone AF patients exhibit the “substrates” of conduction slowing, repolarization abnormalities, and scar on delayed enhancement magnetic resonance imaging. In early studies, we attempted to use virtual (reconstructed) electrograms from the inverse solution, but found that their modest correlation with real (contact) AF electrograms prevented the detection of stable rotors amidst transient fibrillatory conduction (e.g., one to two spins) and abandoned that approach.

Animated movies (isopotentials) are created and used to identify AF mechanisms in any individual. Ablation (FIRM) is targeted at sources as described below, then the process is repeated in the left atrium. Anticoagulation is maintained with heparin for standard target activated clotting time (ACT), and, to date, there have been no complications during contact panoramic mapping. In the work flow illustrated in Figure 2, FIRM mapping and ablation time is <1 h after gaining intravenous and left atrial access. In published studies, PV isolation is then performed, although in our preliminary studies the procedure concludes after FIRM ablation alone.

Figure 3 shows illustrative FIRM maps. The three-dimensional atria are projected onto grids, with the right atrium opened vertically through the tricuspid valve and lateral and medial halves opened. The left atrium is opened horizontally through the mitral valve, and its superior and inferior halves folded upwards and downwards.
AF rotors were identified as rotational activity around a center. Focal impulses were identified as centrifugal activation from a point of origin. Rotors and focal sources are diagnosed if consistent for hundreds to thousands of cycles over multiple epochs spanning 10–20 min. This excludes transient or unstable activation that likely represents passive “fibrillatory conduction.”

Contact panoramic mapping: results

Figure 3a illustrates a right atrial AF rotor (same patient as the fluoroscopy in Figure 1a), showing head-to-tail (red-to-blue) activation in its organized domain with fibrillatory conduction causing disorganization and/or collision. Figure 3b illustrates a left atrial AF rotor (same...
patient as the fluoroscopy in Figure 1b). Each rotor activates sequentially (arrowed), precessing in an area \( \approx 1-2 \text{ cm}^2 \) to lie over slightly varying electrodes from cycle to cycle.\(^{39}\) Notably, on detailed analysis\(^{39}\) we have found no relationship between AF rotors/focal sources and complex fractionated electrograms or low electrogram amplitude in patients with paroxysmal AF or persistent AF.

Stable sources were observed in all patients during paroxysmal AF and nearly all with persistent AF (98% in CONFIRM,\(^{24}\) 100% in recent external validation\(^{25}\)). AF sources were stable for thousands of cycles\(^{24}\) and, in a subset of subjects who failed conventional ablation then remapped for FIRM-guided ablation, for months.\(^{40}\) Fewer sources were observed in patients with paroxysmal than persistent AF (1.7 \(\pm\) 0.9 vs 2.2 \(\pm\) 1.0; \(p = 0.03\)). Sources lay in both atria, surprisingly with 24% in right atrium. The ratio of rotors to focal sources is approximately 4:1.\(^{24,25}\)

Focal impulse and rotor modulation ablation: approach

Stable rotors or focal sources are targeted directly for ablation (FIRM). Any clinical energy source can be used, and CONFIRM\(^{24}\) and external studies\(^{25}\) used irrigated and non-irrigated radiofrequency catheters and cryoaiblation. As recently described,\(^{24,25}\) the catheter is maneuvered to electrode(s) subtending each source on fluoroscopy (Figures 1 and 3); then energy is applied. The acute endpoint is “hyperacute” AF termination or 5–10 min ablation during FIRM ablation, whichever comes first. If AF terminates, then vigorous attempts are made to reinuce AF (using burst pacing). If AF is non-inducible, then the event is classified as “AF termination/non-inducible” (Figure 4). The composite acute endpoint is AF termination (with non-inducibility), or AF slowing >10% that indicates elimination of a secondary AF source in our studies (and computer simulations with a less stringent 3–4% cutpoint).\(^{41,42}\) Since 2.1 \(\pm\) 1.0 sources were observed per patient in the CONFIRM trial, typical total FIRM ablation time is 15–20 min. In CONFIRM, FIRM-guided patients then went on to conventional ablation. FIRM-blinded patients received only conventional ablation.

FIRM only ablation: acutely terminates and renders AF non-inducible

Figure 3 shows AF termination by FIRM ablation at (a) a right atrial AF rotor, (b) a left atrial rotor, prior to any other ablation. Figure 4 shows AF termination by FIRM alone, prior to any other ablation. In each case, multiple and vigorous attempts at reinitiation showed that burst pacing was able to trigger AF but that the atria were no longer capable of sustaining AF after burst pacing stopped (<2.9 s in Figure 4c). This strict endpoint of termination/non-inducibility predicts freedom from AF for conventional\(^{43}\) and FIRM\(^{24}\) ablation.

In a recently presented multicenter FIRM experience\(^{44}\) (\(n = 201\) patients with CPM, \(n = 136\) with FIRM-guided ablation), termination and non-inducibility was achieved in 92% of \(n = 38\) patients with paroxysmal AF after a median of 6 min (interquartile range (IQR) 2–10 min) of FIRM ablation at the primary source, or 11 min (IQR 8–22 min) total FIRM ablation (Figure 2). By comparison, Jais et al\(^{45}\) reported that PV isolation terminated and rendered paroxysmal AF non-inducible in 57% of patients using 36 \(\pm\) 13 min of ablation. Additional linear lesions (20 \(\pm\) 8 min ablation) at the left atrial roof and/or mitral isthmus increased the rate of AF termination and non-inducibility.\(^{43}\)

In persistent as well as paroxysmal AF patients, FIRM ablation caused AF termination and non-reinducibility in 56%\(^{24}\) and 67%\(^{25}\) of patients before PV isolation. The composite acute endpoint (termination/non-inducibility and slowing) was achieved by FIRM alone in 86% (31/36) of patients in the FIRM-guided limb of the CONFIRM trial\(^{24}\) and 100% (12/12) of mapped patients in an external series.\(^{25}\) Notably, AF termination by FIRM was predominantly to sinus rhythm (23/28 terminations in both pooled studies, 82%\(^{24,25}\)) unlike prior studies in which conventional (non-FIRM guided) ablation terminates non-paroxysmal AF typically to atrial tachycardia.\(^{42}\)
A videotaped case of FIRM-guided ablation demonstrating acute AF termination to sinus rhythm with non-inducibility is available as an online video report. 45

Long-term outcome after firm-guided ablation at AF sources: the CONFIRM trial

We hypothesized that abolition of patient-specific AF sources by FIRM would portend long-term maintenance of sinus rhythm. The CONFIRM trial (CONventional ablation with or without Focal Impulse and Rotor Modulation) was a prospective case cohort study24 that enrolled 92 patients at 107 consecutive AF ablation procedures, of whom 31 had paroxysmal AF. In patients with paroxysmal AF, freedom from AF (or atrial tachycardia) after a single procedure was 83.3% in those receiving FIRM-guided ablation compared with 59.1% in those receiving conventional ablation alone (FIRM-blinded) after a median of 470 days of follow-up. Although FIRM ablation is being performed in larger cohorts, these indicate that a single FIRM-guided procedure provides a higher elimination of paroxysmal AF on rigorous follow-up than PV isolation alone.3–5 For comparison, FIRM-blinded paroxysmal AF patients (PV isolation) had similar success to the 60% single procedure freedom from paroxysmal AF reported by Jais et al43 after AF termination with non-inducibility.

For all patients (2/3 persistent AF, 1/3 paroxysmal AF), single-procedure AF elimination in CONFIRM was higher for FIRM-guided than conventional FIRM-blinded cases (82.4% vs 44.9%, p<0.001) after 273 days (median; IQR 132–681). Figure 5 illustrates a Kaplan–Meier curve showing benefit for FIRM-guided versus FIRM-blinded cases for patients off antiarrhythmic medications (p<0.001). CONFIRM is among the largest AF trials to compare a novel ablation strategy to state-of-the-art conventional ablation46,47 rather than to failed antiarrhythmic medications.4,48,49

The main limitation of CONFIRM is that it was non-randomized, although subjects were enrolled consecutively and treated prospectively for prespecified end-points, and FIRM-guided subjects had more comorbidities and more rigorous follow-up (implanted electrocardiogram monitors in 88.2% vs 26.1%; p<0.001) than FIRM-blinded patients. Although CONFIRM included patients with prior ablation, FIRM-guided ablation maintained its benefit over FIRM-blinded therapy in patients at first ablation, and in all prespecified subgroups.

Conclusions

Paroxysmal atrial fibrillation, like other supraventricular tachycardias, is sustained by patient-specific mechanisms after it has been initiated from diverse triggers. Independent laboratories now show that localized stable rotors and focal sources sustain AF across a wide-range
of clinical presentations. In paroxysmal AF, FIRM mapping shows stable rotors and focal sources in patient-specific locations in both atria. Abolition of all patient-specific sources (FIRM-guided ablation) can terminate AF and render it non-inducible prior to any other ablation, and increase single-procedure freedom from conventional ablation by >70% in patients with paroxysmal AF. Ongoing studies will determine the efficacy of FIRM ablation alone (to eliminate sustaining mechanisms rather than other eliminating triggers) in patients with paroxysmal AF.

References

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