Review Article

The role of rotors in atrial fibrillation

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Abstract: Despite significant advances in our understanding of atrial fibrillation (AF) mechanisms in the last 15 years, ablation outcomes remain suboptimal. A potential reason is that many ablation techniques focus on anatomic, rather than patient-specific functional targets for ablation. Panoramic contact mapping, incorporating phase analysis, repolarization and conduction dynamics, and oscillations in AF rate, overcomes many prior difficulties with mapping AF. This approach provides evidence that the mechanisms sustaining human AF are deterministic, largely due to stable electrical rotors and focal sources in either atrium. Ablation of such sources (Focal Impulse and Rotor Modulation: FIRM ablation) has been shown to improve ablation outcome compared with conventional ablation alone; independent laboratories directly targeting stable rotors have shown similar results. Clinical trials examining the role of stand-alone FIRM ablation are in progress. Looking forward, translating insights from patient-specific mapping to evidence-based guidelines and clinical practice is the next challenge in improving patient outcomes in AF management.

Keywords: Atrial fibrillation (AF); ablation; rotors; substrate; phase mapping

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and case volume is expected to increase as the population ages (1). AF management consists of anticoagulation, rate control, and—for symptomatic patients—antiarrhythmic drugs and ablation to restore sinus rhythm (2). However, the efficacy of antiarrhythmic drugs remains poor, and recent trials challenge the use of pharmacologic therapy to maintain sinus rhythm (3,4). Ablation, too, remains suboptimal, given modest safety (5) and efficacy results (6), even in highly experienced centers.

Since the studies of pulmonary vein ectopy ablation in the treatment of AF (7), the pulmonary veins have been the focus of AF ablation therapy (8-11). Although effective, ablation response rate remains around 50% to 70% single to multi-procedure success rate at 1 year in paroxysmal AF patients (9,10,12) with lower success in persistent AF patients (8). This has prompted a search (8,13) for additional targets of ablation therapy including complex fractionated atrial electrograms (CFAE) (14), whose mechanistic significance remains unclear, or areas of high dominant frequency (15-17) and ganglionated plexus sites (18).

Recently, a growing body of work shows that rotors, identified using near-real-time mapping of AF (19), are both spatially and temporally conserved (20) and thus amenable for ablation (21). Mechanistic proof of concept is supported by the ability of brief targeted rotor ablation alone (22) to eliminate AF acutely (23) and on long-term follow-up in the precise trial. Clinically, Focal Impulse and Rotor Modulation (FIRM) has now been shown by many laboratories to substantially improve the results of AF ablation on long term follow-up in patients with paroxysmal and persistent AF (24,25). The purpose of this review is to discuss the conceptual basis for rotors, evidence for their existence, strategies and pitfalls of rotor mapping, and the role of rotors in guiding substrate-based ablation for AF.

Theory and evidence of rotors

The idea of functional reentry as the driver for AF was first proposed by Lewis in the 1920s (26). Allessie and colleagues

subsequently proposed the leading circle theory of reentry (*Figure 1A*) in the 1970s (27). Rotors altered this concept by proposing a region of extreme wave curvature as the center of reentry where conduction velocity approximates zero and detectable by phase mapping. The first experimental evidence of rotors was reported by Davidenko *et al.* in 1990 (28), subsequently supported by evidence from modeling and optical mapping of isolated animal heart preparations by Jalife and others (29-31).

With high temporal and spatial resolution, optical mapping and high-density epicardial electrode arrays (32) have been the principal methods by which rotors were explored. Subsequent work using these techniques in a canine model of AF found ablation of rotor sites suppresses subsequent AF inducibility (33). Unfortunately, these methods are impractical for clinical use, and evidence for rotors in human AF was scarce until recently.

Characterizing rotors: from the bench to the bedside

The term "rotor" is applied to a number of different concepts. One accepted definition from the basic literature is a phase singularity whose reverberations radiate "spiral waves" at high speed into surrounding tissue (34). Clinically, the most tangible feature of a rotor is repetitive, cyclic activation around a core (29,30), and while this is the simplest visual criterion for identifying rotors in phase maps (FIRM) or isochronal images, it does not capture the essence of detecting or defining a rotor.

Clinically, while a rotor is superficially similar to reentry around a region of scar, the two mechanisms are quite different. In a reentry around a scar, the central obstacle is 'inert' and the surrounding reentrant circuit is the principal mechanism to which ablation is applied. Conversely, for a rotor, the singularity (or 'core') is the principal mechanism, while the surrounding 'spiral waves' disorganize and fuse passively with the milieu (fibrillatory conduction). Accordingly, therapy is directed to the core. This central difference summarizes why rotors are difficult to detect using approaches that do not take into consideration the impact of repolarization dynamics on wave break from a spiral wave and/or fusion of wavelets from the milieu with spiral waves.

Mechanistically, reentry in a rotor is functional (35) rather than anatomic, and has no [or a highly limited (36)] excitable gap. Because rotor cores exhibit functional reentry, rotors can precess (move) within a defined area as shown in animal models (37) and in 2-3 cm^2 areas humans (20). Such precession may contribute to the apparent global disorganization seen in AF.

Another property of rotors is that they are the source of fibrillatory wavefronts (29), and thus "control" surrounding tissue that activates passively, and often via fibrillatory conduction (*Figure 1B*, arrows to 1:1 breakdown). Such wavefronts can collide/fuse, and exhibit rotational activation within a variable and often small spatial domain. If multiple rotors are present simultaneously, distal wavefronts collide at varying locations, also contributing to the appearance of global disorganization.

Endocardial or epicardial rotors can be projected onto 2-dimensional (2D) movies, or isochronal maps for printed text. Such 2-D projections of rotors are termed spiral waves (38), and are characterized by a small, unexcited core termed a phase singularity. Phase singularities are sites about which all phases of the depolarization/repolarization cycle exist simultaneously, and are important because they identify tissue capable of supporting rotors. First demonstrated by computational modeling (39), 3D rotors are termed scroll waves (*Figure 1C*), and have recently been shown experimentally (40). In scroll waves, the phase singularity is a linear structure termed a filament (39), about which functional reentry occurs.

Filaments are typically discussed as spanning endocardium to epicardium (I type filaments, *Figure 1D*) (39), producing spiral waves observable on both surfaces. However, additional configurations are possible including U type filaments with both ends of the filament located on the same surface, and O type filaments in which the filament assumes a closed configuration completely within myocardial tissue (34). For U type and O type filaments, mapping of a surface without a filament terminus shows focal activity (39). Surfaces with two filament ends display contra-rotating spirals and figure-of-8 reentry.

Ionic and structural basis for rotors

A number of ionic changes have been shown to promote the development of rotors in experimental models. Atrial tissue from AF patients demonstrates an up-regulation in I_{K1} expression (41). Experimentally, transgenic mice overexpressing I_{K1} demonstrated rapid, stable rotors which were not present in control mice (42). Studies in transfected monolayers of cardiac cells have shown that I_{KS} plays an important role as well (43), promoting rotor formation. Other work has shown that the mild hyperpolarization from enhanced repolarization modifies I_{Na} availability (44), altering

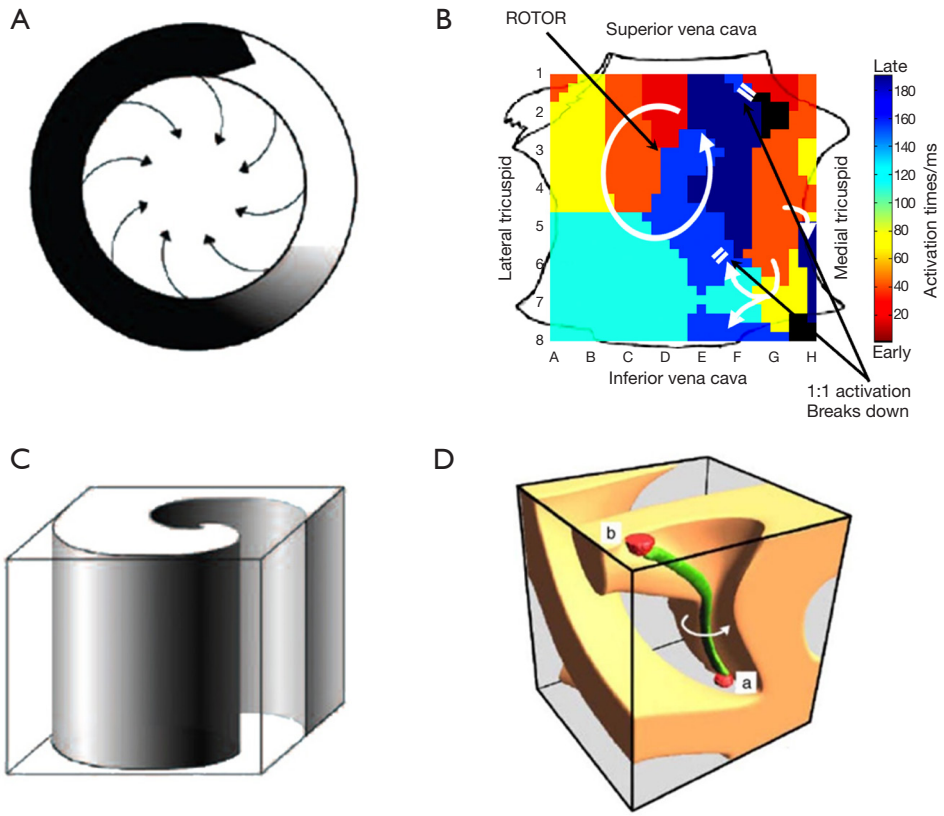

Figure 1 Rotor mechanisms and representations. (A) The first theory of functional reentry was leading circle reentry. In this model, reentry occurs about a functionally refractory core, which is in contrast to our current understanding of rotors which revolve around a small, unexcited, but not refractory core. (B) Isochronal plot of a right atrial rotor (arrow) detected by endocardial basket catheters and phase-mapping. Orientation: The right atrium is opened along its meridian, with the lateral tricuspid annulus folded laterally and medial annulus medially. (C) The 3 dimensional scroll wave in a computational model. (D) Filament (green curve) between endocardial and epicardial termini (red points) about which functional reentry occurs in a 3 dimensional simulation of a rotor.

wavefront conduction. Abnormal calcium dynamics have been implicated in the initiation of torsades des pointes (45), but the precise relationship between I_{Ca} and AF rotors remains controversial (46).

Structurally, delayed gadolinium enhancement magnetic resonance imaging (DE-MRI) studies show that scar burden predicts AF recurrence post ablation (47,48), suggesting that AF in patients with atrial scar reflects mechanisms outside the pulmonary veins. Indeed, areas of patchy fibrosis are sites of slow conduction and altered repolarization dynamics that may form and stabilize rotors; in explanted hearts, rotors are predominantly associated with areas of scar and microfibrosis (49) identified histologically. Ongoing clinical studies are examining the relationship between AF rotors identified by FIRM and other techniques and areas of fibrosis on DE-MRI (50).

AF rotor mapping: techniques

The conventional ablation with or without Focal Impulse and Rotor Modulation (CONFIRM) trial, presented in 2011 (24), demonstrated that rotors and focal sources were present in nearly all patients with paroxysmal, persistent, and long-standing persistent AF, and that ablation of these sources nearly doubled the single-procedure ablation freedom from AF at 1 year (51) and now shown to be durable at 3 years (52). Rotors were identified in near real-time using multielectrode contact basket catheters to record AF (*Figure 2*) then phase-based algorithms incorporating the dynamic response of repolarization (53-55) and conduction (54,56,57) in these patients to abrupt and gradual changes in rate.

This experimental approach was chosen for a number of

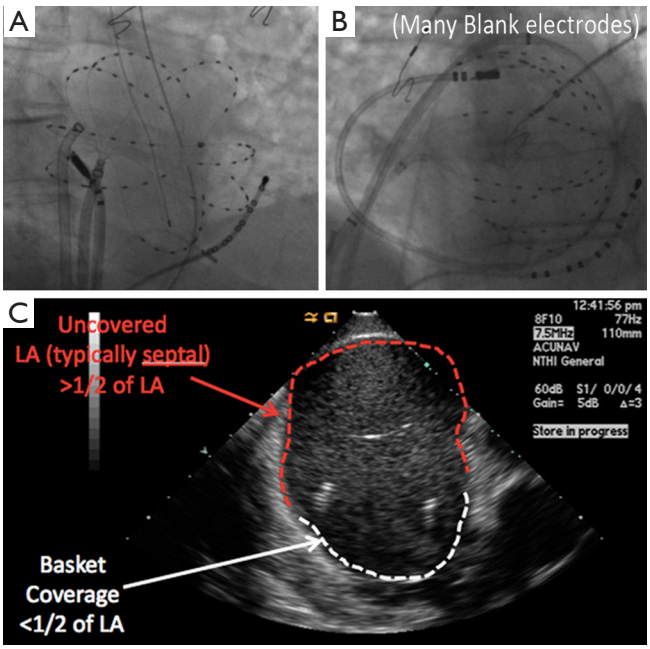

Figure 2 Strengths and Limitations of Contact Mapping for Focal Impulse and Rotor Mapping (FIRM). Broad coverage of the atria can reveal rotors in variable patient-specific regions easily overlooked by limited mapping at pre-determined sites. (A) Fluoroscopy of basket catheter in left atrium with good contact. Analysis will have high confidence except for electrodes near tricuspid or mitral annuli, where rotors are unlikely to form (34). (B) Fluoroscopy of basket catheter with poor contact particularly near septal left atrium. (C) Intracardiac Echocardiogram of Basket catheter in a patient with LA diameter 8.4 cm. In cases (B) and (C), results of FIRM will be suboptimal. Electrodes of poor contact reduce the confidence of maps, and so FIRM mapping is less satisfactory in atria larger than the current >55 mm diameter of the largest baskets.

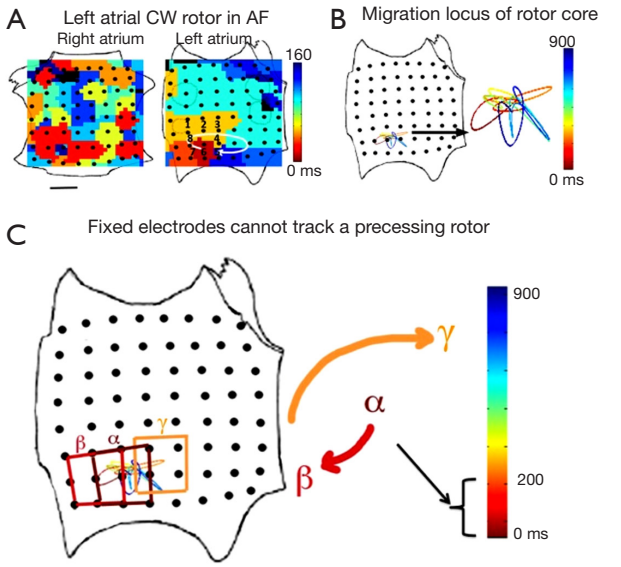

Figure 3 Rotor core precession ('wobble') obscures detection of rotors by activation mapping at fixed electrodes. (A) Clockwise rotor in the inferior left atrium, computed by phase mapping of multiple cycles (FIRM movies). This isochronal (contour) map of 1 cycle superficially resembles macro-reentry, and rotation may be expected on electrodes 1-8. However, (B) Rotor Core Precesses ('Wobbles') rapidly on Phase mapping (FIRM) during and between cycles. Fixed electrodes 1-8 are thus unlikely to track rotation. (C) Expanded view: as the rotor core precesses from the red location (α) to brown (β) in 100 ms, to orange (γ) at 200 ms, electrodes 1-8 would have to track this rapid trajectory to see rotation. FIRM mapping includes phase mapping to track this trajectory with analyses of repolarization/conduction restitution to account for disruption of spiral waves by fusion from the fibrillatory milieu (*Figure 1B*) [modified, with permission from Narayan *et al.* (20)]. Orientation: The right atrium is opened along its meridian, with the lateral tricuspid annulus folded laterally and medial annulus medially. The left atrium is opened horizontally through the mitral valve, and its superior and inferior halves folded upwards and downwards.

reasons. First, although it is theoretically possible to map stationary rotational cycles (e.g., in macro-reentry) with a minimal number of (approximately 4) electrodes (58), fibrillatory rotors precess (i.e., wobble) over time in animal models (37) and humans (20). *Figure 3A,B* shows the location of the AF rotor core as it precesses in a complex path within a stable region bounded by limited numbers of electrodes. Thus it is necessary to map panoramically (20) to encompass rotor trajectories as completely as possible (*Figure 3C*).

Second, a major obstacle to AF mapping has been separating near field activation from far-field noise in atrial signals. This is particularly important for noncontact mapping, in which electrogram reproducibility decreases with distance from the mapping catheter (59). Earlier work using monophasic action potential catheters demonstrated the importance of accurately determining local activation (60), and thus, biatrial contact mapping was chosen to improve the probability of good quality signals encompassing a significant proportion of the atrial surface (61).

Following signal recording, electrograms are exported to a commercially available computational system (RhythmView, Topera Medical, Palo Alto, CA, USA),

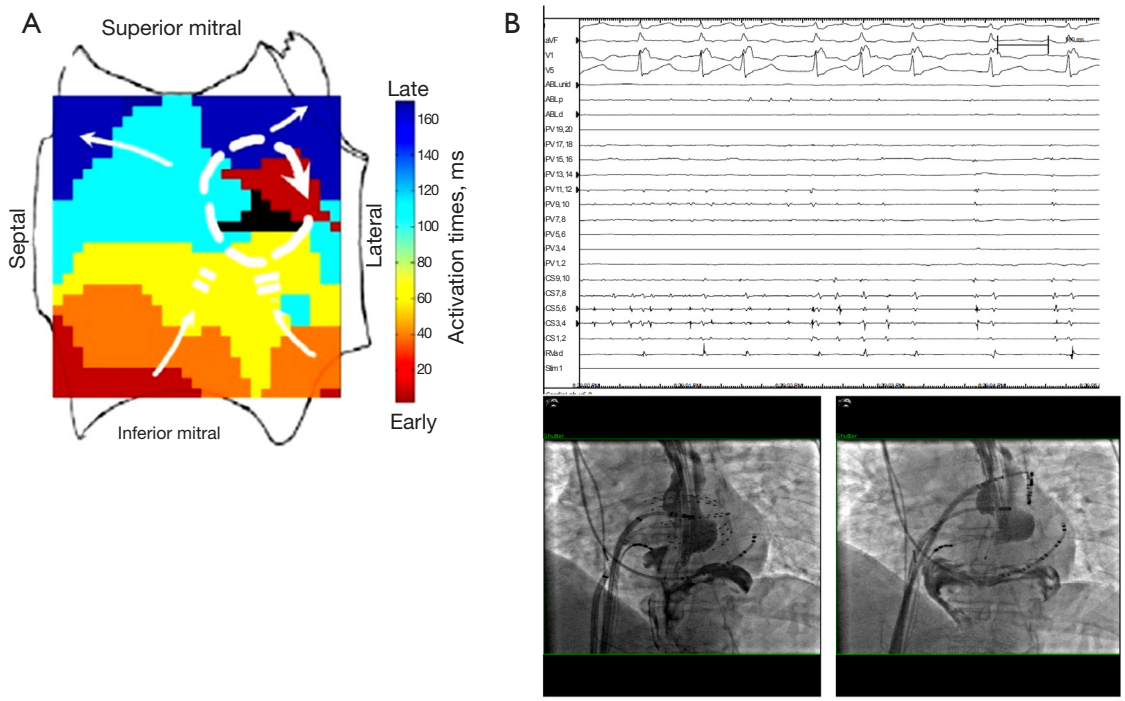

Figure 4 AF termination to sinus rhythm by FIRM-guided ablation at the high lateral left atrium. The FIRM map (A) shows a clockwise rotor (arrow) with fusion/collision of spiral arms by fibrillatory waves (block/arrows). Ablation at this rotor terminated AF to sinus rhythm (B, top), with corresponding fluoroscopic images in the bottom panels (B, bottom) showing coronary sinus catheter and barium in the esophagus [from Shivkumar *et al.* (64)]. Orientation: As in *Figure 1B*. AF, atrial fibrillation; FIRM, Focal Impulse and Rotor Modulation.

which uses phase-based algorithms in conjunction with computational algorithms incorporating repolarization dynamics (54,57,62), conduction dynamics (54,56), and compensation for AF rate oscillations (53) to determine wavefront propagation. Diagnostic movies are then created for physician interpretation and ablation planning. Physician training for movie interpretation is moderate, and includes practice case review and interpretation such that good clinical results can be achieved with a rapid learning curve (25).

Clinical approach and results of FIRM mapping of AF

FIRM mapping identified an average of 2.1±1.0 concurrent rotors or focal sources in the CONFIRM trial (24), that has increased slightly to ≈2.5 sources per patient in recent studies with better basket placement and repeated FIRM maps (25) that were not possible in CONFIRM. In a population of whom two thirds had persistent AF, approximately one-third of sources lie in the right atrium away from the superior vena cava, and hence in regions that would normally not be targeted for ablation. AF rotors and focal sources identified by FIRM are spatiotemporally stable for periods of hours or even months, as described in our early work (61) and in recent external reports from Miller *et al.* (63). Stability provides a rationale for limited ablation that is less clear for targets that migrate throughout the atria.

FIRM-guided therapy targets each rotor and focal source for ablation, with the endpoint of rotor/source elimination on repeated FIRM mapping. In the CONFIRM trial (24) and independent external laboratories, elimination of FIRM-sources takes 5-10 minutes per source, for an average of 15-20 minutes FIRM-guided ablation time per case (25). FIRM-guided ablation may terminate AF, typically to sinus rhythm (*Figure 4A,B*) as first shown outside San Diego by Shivkumar *et al.* (64) and in a larger series by Kowal *et al.* (65). However, results of the on-treatment analysis of CONFIRM (21) and the PRECISE trial (22) show that elimination of AF rotors/sources on repeat FIRM mapping is a more effective endpoint. *Figure 5A,B* shows the 3Y very long term outcome in the CONFIRM trial, in which FIRM + PVI ablation provided substantially higher freedom from AF than conventional ablation after multiple and a single procedure.

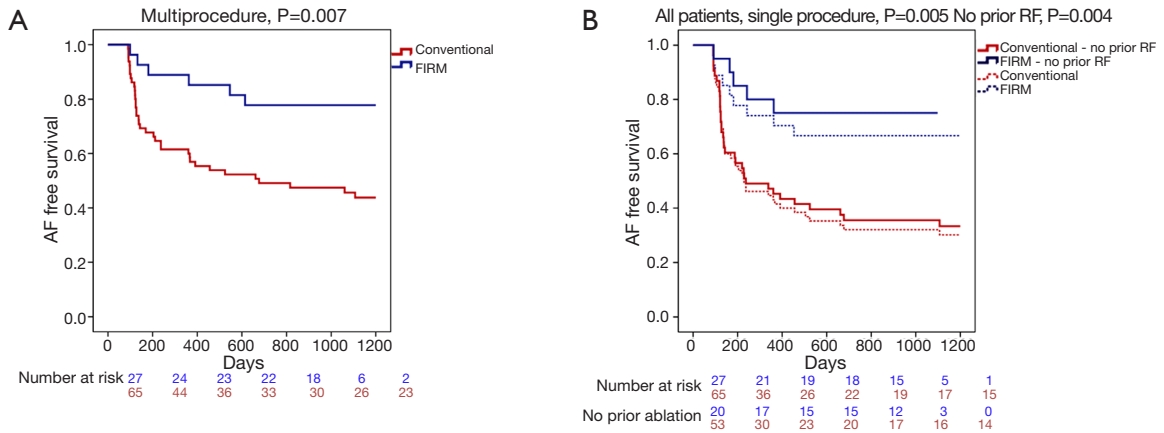

Figure 5 (A) Very Long-Term from atrial fibrillation in the CONFIRM trial for FIRM-guided ablation (blue) and conventional ablation (red; P=0.003) after 1.2±0.4 procedures; (B) very Long Term Single-Procedure freedom from the AF for FIRM-guided ablation (blue) and conventional ablation (red) in the CONFIRM trial. Data shows all cases (solid lines, P=0.002) and those undergoing their first ablation (dashed lines, P=0.002). AF, atrial fibrillation; FIRM, Focal Impulse and Rotor Modulation.

AF rotor mapping: pitfalls

A clear technical limitation to AF mapping is electrogram contact as we have reported (19), particularly in atria whose dimensions exceed the size of commercially available basket catheters (*Figure 2B*) as included in external reports by Shivkumar *et al.* (64) and Miller *et al.* (25). While not recommended, successful ablation in such patients is possible when rotor locations coincide with areas of good electrode-tissue apposition—although electrodes opposite these sites will typically then show marginal or poor contact. Multiple basket manipulations can then theoretically be used to sequentially sample regions of the atrium. A second related limitation is poor electrode coverage in the septal aspect of the left atrium (*Figure 2C*). Future improvements in basket design and maneuverability are required to fully exploit current rotor mapping technology. A final consideration in FIRM ablation is the learning curve for reading the potentially complex maps, although this was relatively rapid in the recent series by Miller *et al.* (25). Automated detection algorithms are being developed that may further help this process.

Relationship of rotors to CFAE and ganglionated plexi (GP)

There has been a significant amount of interest in CFAE as markers of AF drivers (14). CFAE have multiple definitions, include electrograms with multiple deflections, very short cycle length (<120 ms) (14), or continuous activation (66). Although results using this technique are mixed (67,68), it is frequently considered in patients with persistent or ablation-refractory AF (8). However, the mechanisms of fractionation may be diverse, and a recent study showed poor correlation of AF sources to CFAE (20). This is in agreement with earlier work (69), showing that rotors did not co-localize with regions of fractionation.

Also of interest as potential AF-sustaining sites, GP are regions of autonomic innervation to the atria (18). Prior work has shown that such areas may serve as high frequency AF sources as a result of autonomic remodeling (70). Procedurally, they may be localized by high frequency stimulation and the appearance of a stimulated vagal response, defined as either atrioventricular block, asystole, or an increase in the mean RR interval of greater than or equal to 50% (71). Notably, a randomized clinical trial found that the addition of GP ablation to PVI improved procedural success (72). However, the link between GP and rotors is presently unclear.

Conclusions

Rotors are regions of functional reentry which drive AF. Ionic remodeling, fibrosis, and structural features have been shown to facilitate and stabilize rotor formation, which precess in the midst of complex fibrillatory dynamics making their detection difficult. Confirmation of the existence and importance of rotors in human AF has emerged only

recently, with the advent of appropriate procedural and computational techniques. A rapidly growing body of literature shows that rotors are spatially conserved and amenable to ablation. Clinically, studies from multiple independent laboratories shows that rotor elimination via FIRM substantially improves AF freedom compared to conventional ablation alone. Future clinical studies should confirm these promising results in multicenter randomized trials, which are underway. Mechanistically, studies should define how rotors anchor in human atria, and the mechanisms for fibrillatory conduction.

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