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Rotor hypothesis in the time chain of atrial fibrillation

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Atrial fibrillation (AF) is the most prevalent arrhythmia in the aging population, with people over 75 years accounting for 70% of the AF population.[1] Over the past twenty years, despite tremendous progress has been made in catheter ablation for rhythm control of AF, we still cannot establish a reliable ablative target for non-paroxysmal AF. Part of the reason is an incomplete understanding of the mechanism underlying the progressive nature of AF. In the time chain of AF, AF burden increases, and the success rate of catheter ablation decreases as AF progresses from paroxysmal AF (PAF) to persistent AF (PerAF) and long-standing persistent AF (LS-PerAF) form. Recently, with the advance in mapping technologies combined with biophysical insight, a new concept of AF maintenance has been introduced--the rotor (spiral waves). Meanwhile, the concept of complete electrical left atrial (LA) isolation has been introduced for AF with extensive atrial fibrosis. These innovative ideas enriched our armamentarium to combat different AF subtypes. This article proposes a rotor hypothesis to illustrate the mechanism underlying AF progress and discuss the application of new strategies in different AF subtypes.

ROTOR HYPOTHESIS

The concept of rotors as a "spiral wave generator" was described by Winfree and first be demonstrated in *ex vivo* sheep hearts using optical mapping technology.[2] Rotor represents a specific form of functional re-entry; more specifically, it is a curved "vortex" formed by spin motion in the two-dimensional plane. Over the last two decades, with the introduction of more sophisticated signal analysis methods, the concept of rotors as drivers of AF has been gradually established. Until now, the mechanism underlying AF progression has not been fully understood. Here, we propose the rotor hypothesis to illustrate AF "evolution" mechanism.

A spiral-wave rotor is initiated and maintains AF when a wavefront encounters an inexcitable barrier and circulates around it. In the stage of PAF, rotors are unstable and may spontaneously terminate due to relatively normal atrial structural and electrophysiological properties. That is why PAF may self-terminate. As AF progresses, rotors may meander, resulting in the expansion of the rotor regions. When a rotor encounters an anatomical or functional barrier, wavebreak may occur, and the primary rotor splits into two or more daughter rotors.[3] Stable daughter rotors can continue to generate new daughter rotors. When the wavebreak rate is equal to or greater than the extinction rate of the primary rotor, AF sustains.[4] That is, the "rotor (driver) begets rotors (drivers)" hypothesis and may explain why AF progresses from a PAF form to a more stable and PerAF form. AF may induce atrial remodeling, which further provides substrate driving AF and creates a vicious circle, so-called "AF begets AF" theory. In the context of atrial remodeling, ion-channel alteration, connexin changes and tissue fibrosis may occur and further promote the stability and complexity of the rotors, leading PerAF to develop into LS-PerAF.

APPLICATION OF THE ROTOR CONCEPT

Strategy to identify rotors, named Focal Impulse and Rotor Modulation (FIRM) mapping technique, was first described by Narayan, *et al*.[5] and was applied in the CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without FIRM) trial. With FIRM-guided catheter ablation, rotors were detected in 98% of the study population, with an average of 1.9 ± 1.1 rotors per patient. Elimination of patient-

specific rotors achieved high rates of acute AF termination and less atrial tachycardia/AF recurrence.[5–7] Although other centers have reported inconsistent outcomes,[8] several factors should be considered when interpreting these discrepancy results, including the complicated properties of rotors, inadequate resolution of mapping techniques for rotor identification and a steep operator-dependent learning curve required for rotor ablation.

Pulmonary veins isolation (PVI) is still the cornerstone of catheter ablation since a landmark study by Haissaguerre's group confirmed pulmonary veins as major sources of AF. AF began with paroxysmal episodes, PVI alone yielded 60% to 79% success rates in this stage.[9] Is PVI alone sufficient for PAF? Our recent work showed that PVI alone was insufficient to terminate AF for up to 60% of patients with PAF due to rotors outside the pulmonary veins.[10] In comparison, PVI plus rotor ablation increased the long-term success rate by 15% compared with PVI alone. Similar findings have been echoed by the recent IU-FIRM (Indiana University FIRM) study, 95% of PAF patients were free of AF recurrence in one-year post-ablation when FIRM-guided catheter ablation was combined with PVI.[7]

8%−22% of patients with PAF progressed to PerAF one year after the first diagnosis.[11] In this stage, AF may represent more a state of atrial arrhythmogenic substrate sustaining AF than just the consequence of pulmonary vein triggers. As shown in our previous work, the complexity of rotors and rotor regions outside the pulmonary veins increases as AF progresses and, therefore, gradually attenuates the efficacy of PVI alone in PerAF.[12] Hence, adjuvant substrate modification is often required in PerAF. Disappointedly, the STAR AF II trial (The Substrate and Trigger Ablation for Reduction of AF Trial Part II) did not show any superiority of additional empiric linear ablation or ablation of complex fractionated electrograms over PVI alone.[13] In our experience, regions that exhibit spatio-temporal dispersion are optimal targets site for PerAF. In our recent study, PVI plus dispersion area ablation achieved a higher rate of AF termination and better outcome than the stepwise approach.[14] In fact, rotor (driver) areas often anchor to regions with density fibrosis,[15] suggesting that rotor (driver) ablation may modify the arrhythmogenic substrate to prevent future AF recurrence. The ongoing RECONFIRM trial (NCT02456233) and REDO-FIRM trial (NCT02799043) will provide more evidence regarding the efficacy of rotor ablation.

CONFINED AF TO THE ISOLATED LEFT ATRIUM

The efficacy of ablation is further impacted in LS-PerAF compared with PAF and PerAF. This subset of patients is characterized by advanced atrial remodeling with a more diffuse abnormality of the atrial substrate and conventional ablative strategy has limited efficacy. In the DECAAF study, up to 69% of AF recurrence was documented when the area of LA fibrosis quantified by delayed enhancement magnetic resonance imaging was greater than 30%.[16]

The concept of electrical LA isolation was proposed 40 years ago as a surgical technique for managing atrial arrhythmia and is limited by a high risk of thrombosis and decreased LA function.[17] Recently, this strategy was applied in the field of interventional electrophysiology. LA isolation is achievable by catheter ablation and therefore makes AF confined to the left atrium while restoring sinus rhythm in the remainder of the heart. Gautam, *et al.*[18] reported the first case of inadvertent complete isolation of the left atrium after multiple ablation procedures for AF. After that, the methodology of electrical LA isolation was refined and combined with LA appendage occlusion by Zedda, *et al.*[19] for rhythm and stroke control in patients with extensive atrial fibrosis and 76% (70/92) of them were in sinus rhythm at 12-month without detrimental hemodynamic effect despite LA transport function being impacted. In our most recent experience, we carried out ten cases of LA electrical. We selected patients with severe atrial fibrosis who experienced at least two prior failed ablations while antiarrhythmic drugs were insufficient for rate control. Complete LA isolation was achieved in six patients by endocardial ablation only, while the electric connection along the Bachmann bundle was hard to isolate for the other four patients. For safety reasons, we did not perform epicardial ablation. An optimal approach should be established to improve such therapeutic strategies' success rate and safety.

CONCLUSIONS

Advanced mapping technology and translational

research innovations have inspired new ideas and paved the way toward novel treatment strategies. The rotor hypothesis comprehensively explained the evolution of AF and renewed our understanding of the mechanism underlying AF. Due to the progressive nature of AF, a patient-tailored ablation strategy is warranted in different AF subtypes. Our experience indicated that patients-specific rotors ablation is promising, although some inconsistent results have been reported. A more precise phase-mapping technique should be developed to improve the accuracy of identifying rotor regions. The efficacy of rotor ablation is being tested in ongoing trials. Data from the single-center experience of electrical LA isolation is encouraging, more robust studies would be desirable to testify the safety and efficacy of LA isolation.

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