CONTEMPORARY REVIEW

Ablating atrial fibrillation: A translational science perspective for clinicians

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Although considerable progress has been made in developing ablation approaches to cure atrial fibrillation (AF), outcomes are still suboptimal, especially for persistent and long-lasting persistent AF. In this topical review, we review the arrhythmia mechanisms, both reentrant and nonreentrant, that are potentially relevant to human AF at various stages/settings. We describe arrhythmia mapping techniques used to distinguish between the different mechanisms, with a particular focus on the detection of rotors. We discuss which arrhythmia mechanisms are likely to respond to ablation, and the challenges and prospects for improving upon current ablation strategies to achieve better outcomes.

KEYWORDS Reentry; Arrhythmia; Atrial fibrillation; Fibrosis; Ablation; Rotor; Triggered activity; Automaticity

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Introduction

Following the seminal 1998 study by Haissaguerre et al[1] demonstrating that the pulmonary veins (PVs) are a common site of triggers that initiate and/or maintain atrial fibrillation (AF), the era of AF ablation therapy was inaugurated and has been embraced enthusiastically on a worldwide scale. An overall ~80% multiple procedure success rate reported in patients with paroxysmal AF has been an impressive achievement. Results with persistent (>1 week) or long-standing persistent (>1 year) AF, however, remain less impressive, with an overall ~50% success rate. To improve upon these results, a variety of refinements beyond PV isolation have been explored, which include creating linear ablation lines across the left atrial roof and mitral valve isthmus emulating the surgical MAZE procedure, using atrial catheter mapping to identify and ablate complex fractionated atrial electrograms (CFAEs) reflecting regions with slow conduction and, most recently, utilizing phase mapping analysis such as focal impulse and rotor modulation (FIRM) or electrocardiographic imaging (ECGI) to target quasi-stable rotors for ablation. The eagerly awaited STAR-AFII study,[2] in which 589 patients with persistent AF were randomized to PV isolation alone or in combination with the creation of linear ablation lines or CFAE ablation, failed to show that adding the latter techniques to PV isolation improved outcomes after 18 months. On the other hand, the CONFIRM study,[3] which randomized 92 patients with paroxysmal or persistent AF to PV isolation without or with FIRM-guided ablation, reported significantly better outcomes in the PV isolation + FIRM group after 9 months (82% vs 45% success rate), which was maintained at 3-year follow up (78% vs 39% success rate).[4] Two subsequent studies of 79 and 80 patients treated with paroxysmal and persistent AF treated with PV isolation + FIRM-guided ablation reported similar high efficacies at 12 and 24 months, respectively.[5,6] Supporting the approach of identifying and ablating localized drivers of AF, Haissaguerre et al[7] used ECGI to image regions with frequent unstable reentry whose ablation, combined with linear ablation lines if needed, terminated AF acutely in 80% of patients. At 12 months, 85% remained free from AF. However, a similar high efficacy (87%) was achieved in a control group treated with PV isolation and linear ablation lines without ECGI-guided ablation, although total ablation time was twice as long.

On the other hand, the excitement generated by the CONFIRM study has been tempered by several new studies. A multicenter study of 43 patients treated with PV isolation + FIRM for paroxysmal or persistent AF reported a success rate of only 47% after 18 months,[8] and in 29 patients with persistent AF treated with FIRM alone, without PV isolation, the success rate after 6 months was only 28%.[9] In the first randomized trial (OASIS) comparing FIRM alone, PV isolation + FIRM, and PV isolation + posterior wall and non-PV trigger ablation in 113 patients with nonparoxysmal AF, the rates of freedom for AF off antiarrhythmic drugs after 12 months were 14%, 52% and 76%, respectively.[10]

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Moreover, a spirited debate has arisen over the FIRM technique itself, concerning both technical and mechanistic issues. The technical issue relates to whether the proprietary FIRM software algorithm (RhythmView, Topera Inc, Palo Alto, CA) actually identifies bona fide rotors.[11–13] The mechanistic issue relates to whether rotors are intrinsically susceptible to elimination by ablation. Should the effectiveness of FIRM-guided (or ECGI-guided) ablation, either alone or in combination with PV isolation, be substantiated by future studies, these issues will be important to resolve. In this context, the purpose of this perspective is 4-fold: (1) to review reentrant and nonreentrant arrhythmia mechanisms relevant to AF; (2) to describe the techniques for distinguishing rotors from other arrhythmia mechanisms; (3) to discuss which arrhythmia mechanisms are reasonable targets for ablation therapy; and (4) to assess the prospects for improving upon current ablation strategies to prevent AF.

Basic arrhythmia mechanisms

Tachyarrhythmia mechanisms fall into 3 general categories: automaticity, triggered activity, and reentry (Figure 1). Automaticity is generally too slow to drive very rapid arrhythmias such as AF but can generate triggers such as premature atrial complexes, which can initiate reentry leading to fibrillation. Triggered activity arising from early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) can generate rapid nonsustained or sustained tachycardia and/or can serve as triggers to initiate reentry. Even if reentry is nonsustained, recurrent triggered activity can reinitiate reentry and thereby synergistically maintain fibrillation that would otherwise self-terminate.[14] On activation mapping, automaticity and triggered activity appear as target waves emanating from a focal source (Figure 1, top right panel).

Reentry falls into 2 general categories: anatomic reentry and functional reentry. In anatomic reentry, the electrical wave circulates around an inexcitable obstacle such as a scar or valvular annulus (Figure 1, top left panel). The path length can be large (macroreentry on the centimeter scale) or small (microreentry on the submillimeter scale) depending on the electrophysiologic characteristics of the tissue. Microreentry path lengths < 1 mm (i.e., much smaller than the 3- to 4-mm-tip diameter of an ablation catheter) have been observed in embryonic hearts[15] and may also be possible in diseased atria in which fibrosis causes slow discontinuous conduction

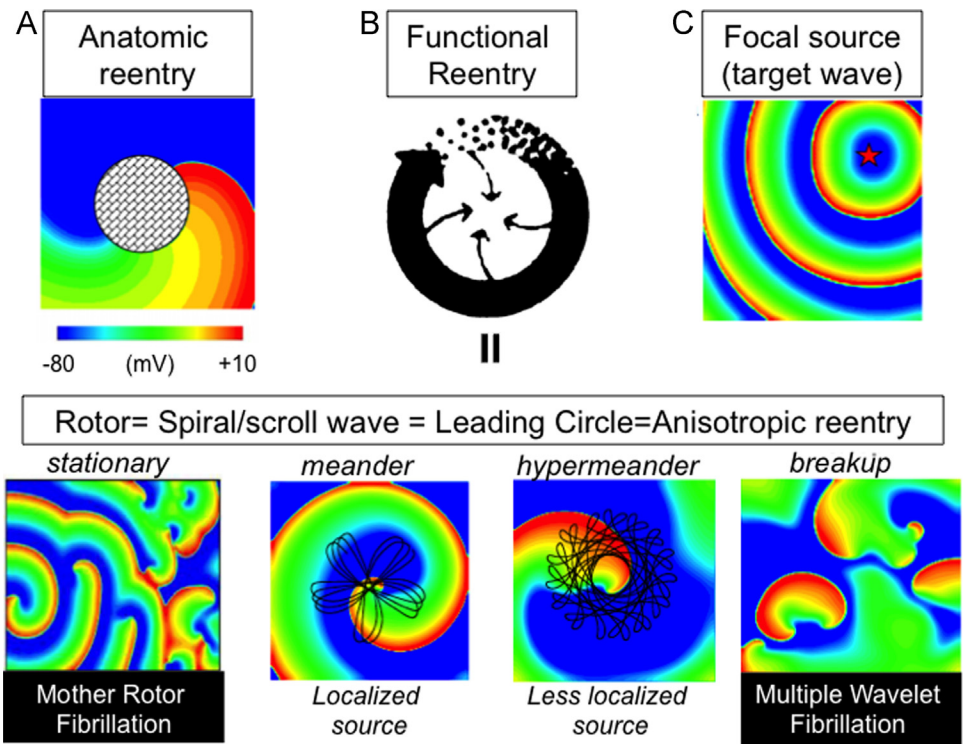

Figure 1 Basic arrhythmia mechanisms relevant to fibrillation. **A:** Anatomic reentry in which the wavefront rotates around an inexcitable anatomic obstacle. **B:** Functional reentry (leading circle = anisotropic = spiral/scroll wave), in which a rotor rotates around a core of excitable, but unexcited, tissue. Depending on the electrophysiologic characteristics of the tissue, the rotor can be stable **(bottom left panel)** with peripheral wavebreaks (fibrillatory conduction block) if the surrounding tissue has a longer refractory period, meandering **(bottom left middle panel),** hypermeandering **(bottom middle right panel),** or in an unstable breakup regime **(bottom right panel).** A stable or meandering rotor with peripheral wavebreak is equivalent to mother rotor fibrillation, whereas spiral wave breakup is equivalent to multiple wavelet fibrillation. **C:** Focal sources due to automaticity or early afterdepolarization– or delayed afterdepolarization–mediated triggered activity produce a target wave pattern of concentric wavefronts. Except for the middle upper panel, all other panels show color-coded voltage (blue = repolarized, red–green = depolarized) snapshots. The temporal trajectories of the rotor tips are shown in *black lines* for the meandering and hypermeandering rotors. (Panel B adapted with permission from Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res 1977;41:9–18.)