UCLA

UCLA Previously Published Works

Title

Ablating atrial fibrillation: A translational science perspective for clinicians.

Permalink

<https://escholarship.org/uc/item/2721f44c>

Journal

Heart rhythm, 13(9)

ISSN

1547-5271

Authors

Weiss, James N

Qu, Zhilin

Shivkumar, Kalyanam

Publication Date

2016-09-01

DOI

10.1016/j.hrthm.2016.05.026

Peer reviewed

Ablating atrial fibrillation: A translational science perspective for clinicians

James N. Weiss, MD,^{*} Zhilin Qu, PhD,^{*} Kalyanam Shivkumar, MD, PhD, FHR[†]

From the ^{*}UCLA Cardiovascular Research Laboratory and [†]Cardiac Arrhythmia Center & Neurocardiology Research Center of Excellence, Departments of Medicine (Cardiology) and Physiology, David Geffen School of Medicine, University of California, Los Angeles, California.

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

(Heart Rhythm 2016;13:1868–1877) © 2016 Heart Rhythm Society. All rights reserved.

Introduction

Following the seminal 1998 study by Haissaguerre et al¹ 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 al⁷ 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

Supported by National Institutes Health/National Heart, Lung, and Blood Institute Grants P01 HL078931 to Drs. Weiss and Qu and R01 HL084261 to Dr. Shivkumar; and the Laubisch and Kawata endowments to Dr. Weiss. **Address reprint requests and correspondence:** Dr. James N. Weiss, Division of Cardiology, 3645 MRL Building, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095. E-mail address: jweiss@mednet.ucla.edu.

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 hearts¹⁵ 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.)

between isolated strands of myocytes.¹⁶ Anatomic reentry depends on the wavelength (product of action potential duration and conduction velocity) being shorter than the path length, such that the head of the wave (wavefront) does not collide with its tail (waveback) (i.e., an excitable gap must be present). By shortening wavelength, both slow conduction and shortened action potential duration increase the excitable gap, promoting and stabilizing anatomic reentry.

In functional reentry, on the other hand, the electrical wave circulates around an unexcited but excitable core (Figure 1, top middle and bottom panels). In other words, if functional reentry terminates, the next sinus beat propagates successfully through the region that previously served as the core (also called the pivoting point or the rotation center). The term *rotor* is most commonly used to refer to functional reentry. A variety of mechanisms have been proposed to underlie functional reentry, including leading circle reentry, anisotropic reentry, spiral wave reentry (in 2-dimensional [2D] tissue) and scroll wave reentry (in 3-dimensional [3D] tissue). Leading circle and anisotropic reentry are descriptive terms based on experimental observations. Spiral and scroll wave reentry, on the other hand, are generic terms derived from computer simulations of excitable media, of which cardiac tissue is just one example. The features of spiral/scroll waves in simulated cardiac tissue closely resemble the experimentally observed features of functional reentry. In our view, all of these terms are equivalent. For the purposes of this perspective, we use the term *rotor* to refer to any and all types of functional reentry, as distinguished from anatomic reentry.

Mechanisms of fibrillation

Cardiac fibrillation can involve reentrant, nonreentrant, and mixed reentrant/nonreentrant mechanisms (Table 1). Fibrillation mechanisms that have been characterized in atrial, ventricular, and/or simulated tissue include the following.

Multiple wavelet fibrillation

This purely reentrant mechanism, originally proposed by Moe et al,¹⁷ results from rotors that are inherently unstable

and spontaneously develop wavebreaks along the arm of the rotor. In simulated cardiac tissue, multiple wavelet (MW) fibrillation is equivalent to the unstable breakup regimen of spiral/scroll wave reentry (Figure 1, lower right panel), although in heterogeneous tissue, hypermeandering spiral waves (Figure 1, lower middle right panel) can break up to produce the same pattern. In this regime, factors such as steep action potential duration (APD) restitution slope and unstable Ca cycling cause oscillations in the waveback and wavefront of the spiral/scroll wave. As a result, the wavefront–waveback collisions along the arm of the spiral/scroll wave lead to spontaneous wavebreaks.¹⁸ The spontaneous wavebreaks then form daughter spiral/scroll waves. However, as these multiple spiral/scroll waves attempt to rotate, they collide with wavefronts and wavebacks from other spirals/scroll waves, such that full 360° rotations are rare once MW fibrillation has become established. In 3D tissue, activation patterns on the endocardial and epicardial surfaces can appear dissociated and asynchronous if scroll wave filaments are not aligned transmurally. Endo–epicardial asynchrony during human AF has been recently demonstrated by de Groot et al.¹⁹ These authors characterized the arrhythmia mechanism as multisite endo–epicardial reexcitation in which wavefronts propagating on 1 surface cross over and break through to excite recovered regions on the opposite surface, and vice versa in a reciprocating manner. Thus, the crossovers effectively represent the shifting antegrade and retrograde limbs of transmural reentry between the endocardial and epicardial layers. To us, this falls into the category of functional reentry with multiple shifting wavelets, that is, a variant of MW fibrillation.

Because MW fibrillation is purely reentrant, its initiation requires a trigger to create the original unstable spiral/scroll wave that subsequently breaks up to create daughter wavelets. Triggers can arise from automaticity, triggered activity, or phase 2 reentry as described in Brugada syndrome and acute ischemia,^{20,21} although the latter has not yet been documented in atrial myocardium. Once initiated, MW fibrillation can be either sustained or nonsustained, depending on factors such as tissue mass and excitation wavelength. If sustained, additional triggers are no longer required to

Table 1 Possible mechanisms of AF and their susceptibility to ablation and defibrillation

Possible AF mechanisms	Ablatable?		Defibrillatable?
	Focal*	MAZE†	
Sustained multiple wavelet fibrillation	No	Yes	Yes
Sustained mother rotor fibrillation	Maybe	No	Yes
Trigger-(re)induced nonsustained multiple wavelet fibrillation	Yes	Yes	Yes
Trigger-(re)induced nonsustained mother rotor fibrillation	Yes	No	Yes
Multifocal nonreentrant fibrillation	Yes	No	No
Mixed focal-reentrant fibrillation (early/delayed afterdepolarization mediated)	No	Yes	Yes

AF = atrial fibrillation.
*Focal refers to pulmonary vein isolation, complex fractionated atrial electrogram, focal impulse and rotor modulation–guided, or electrocardiographic imaging–guided ablation of localized atrial sites.
†MAZE refers to linear ablation lines emulating surgical MAZE, still a goal for catheter MAZE to achieve.
Yes and No refer to high or low probabilities rather than absolutes.

maintain fibrillation. If nonsustained, however, triggers arising from the PV or other locations, often promoted by rapid excitation during the period of fibrillation, can reinitiate fibrillation so that the arrhythmia appears to be sustained.¹⁴

Mother rotor fibrillation

In addition to the spiral/scroll wave breakup regime, spiral/scroll waves can also be intrinsically stable, meandering, or hypermeandering (Figure 1, bottom left and 2 middle panels).¹⁸ These other regimes are relevant to mother rotor (MR) fibrillation, characterized by Jalife et al,^{22,23} in which a fast stationary or meandering spiral/scroll wave in 1 region of the tissue develops peripheral wavebreaks as the spiral/scroll arm propagates into surrounding tissue with longer refractory periods, called fibrillatory conduction block.^{22,23} Thus, in MR fibrillation, the MR maintains fibrillation and the peripheral wavebreaks are noncausal epiphenomena (Figure 1, lower left panel). This feature distinguishes MR fibrillation from MW fibrillation, in which the functional reentry is inherently unstable, such that spontaneous wavebreaks due to wavefront–waveback interactions throughout the tissue play a causal role in both initiating and maintaining fibrillation (Figure 1, lower right panel). That is, MR fibrillation is driven by a localized source, whereas MW fibrillation is inherently nonlocalized. Activation patterns on the endocardial and epicardial surfaces can appear dissociated and asynchronous due to transmural fibrillatory conduction block, but a quasi-stable rotor should be present at some location.

Similar to MW fibrillation, MR fibrillation is purely reentrant and requires a trigger to initiate the original rotor. Once initiated, MR fibrillation can be sustained or nonsustained depending on tissue properties. If sustained, no further triggers are necessary to perpetuate fibrillation. However, the rapid excitation during the MR fibrillation may induce ongoing triggers that reinitiate the MR even if it is inherently nonsustained.

In diseased fibrotic atria (or atria with extensive ablation scars), it is also possible for multiple stable rotors to coexist in different regions, insulated by intervening tissue that cannot maintain 1:1 conduction.²⁴ This variant is equivalent to MR fibrillation with multiple stable MRs.

Nonreentrant fibrillation

Fibrillation can also involve nonreentrant mechanisms. One of the earliest examples used local injection of the drug aconitine into atrial tissue.²⁵ This drug interferes with Na channel inactivation, causing very rapid focal activity (equivalent to EAD-mediated triggered activity) that results in fibrillatory conduction block in surrounding tissue, similar to that in MR fibrillation. Although aconitine is not directly relevant to human AF, rapid focal activity arising from the PV and inducing fibrillatory conduction block in surrounding atrial tissue is conceptually analogous and is also consistent with the efficacy of PV isolation in terminating many cases of human AF. Alternatively, rapid focal activity in the PV due to triggered activity or microreentry may also

induce wavebreaks in the atria, which then initiate MW or MR fibrillation. In this case, MW or MR fibrillation would have to be nonsustained to explain the effectiveness of PV isolation in treating AF, which generally agrees with the observation that PV isolation has a higher success rate in paroxysmal than persistent AF. Sustained fibrillation due to purely nonreentrant unifocal or multifocal mechanisms, on the other hand, is unlikely, because most fibrillation episodes can be terminated at least transiently by electrical defibrillation. In contrast, nonreentrant activity is typically reset (phase-shifted) but not terminated by electrical defibrillation.

Mixed focal-reentrant fibrillation

Differing from the situation in which focal triggers emanating from fixed locations such as the PV keep reinitiating MW or MR fibrillation, mixed focal-reentrant fibrillation refers to types of fibrillation in which both triggers and electrical dispersion arise from a nonlocalized dynamical process that does not depend inherently on the presence of preexisting tissue heterogeneity. For example, under conditions in which reduced repolarization reserve promotes EAD-mediated triggered activity in ventricular tissue,²⁶ a process called regional chaos synchronization produces shifting EAD islands that markedly amplify dispersion of refractoriness. When some of these EAD islands develop triggered activity, the focal impulses propagate into adjacent EAD islands and develop wavebreaks initiating rotors. Moreover, the tissue becomes bi-excitabile under these conditions, such that rotors can propagate using either the Na current or the Ca current.²⁷ Recently, DAD-mediated triggered activity has been shown to cause a similar type of mixed focal-reentrant fibrillation in simulated ventricular cardiac tissue.²⁸ In this case, DAD-triggered activity arising from 1 region of tissue propagates into adjacent regions in which subthreshold DADs reduce excitability sufficiently to cause wavebreak. Neither EAD- nor DAD-mediated mixed focal-reentrant fibrillation has been conclusively demonstrated in atrial tissue, although mapping studies have frequently shown mixed focal-reentrant patterns during AF in human and animal studies consistent with this mechanism. EAD- and DAD-mediated mixed focal-reentrant fibrillation can be either sustained or nonsustained. Because the foci constantly shift location in the tissue, they are not stationary targets for ablation unless they emanate exclusively from a small confined region of tissue. Activation patterns on the endocardial and epicardial surfaces can appear dissociated and asynchronous. Mixed focal-reentrant fibrillation can be electrically defibrillated (at least transiently) because terminating the reentrant component often slows the rate sufficiently to suppress new EAD/DAD formation.

Arrhythmia mechanisms relevant to human AF

All of the fibrillation mechanisms listed in Table 1 have been demonstrated in either animal models or simulated cardiac tissue. However, which mechanisms are directly relevant to human AF remains controversial. Clues can be surmised

from the susceptibility of these various mechanisms to ablation and defibrillation, as summarized in Table 1. Because human AF can generally (at least transiently) be defibrillated, the fifth nonreentrant fibrillation mechanism is unlikely to be clinically important. The remaining mechanisms, however, could all be potentially relevant to different stages/settings of human AF. Indeed, different underlying mechanisms may explain why ablation is more effective in some settings (e.g., paroxysmal AF) than in others (persistent or long-standing AF, enlarged fibrotic atria, etc). Thus, different mechanisms may come into play at different stages (paroxysmal, persistent, long-standing) and clinical settings (structurally normal vs abnormal hearts).

Given the limited availability of intact human atria for detailed mapping studies with high-density electrode arrays or optical techniques, definitively elucidating the mechanisms relevant to human AF is challenging. Techniques for mapping human AF include (1) low density (i.e., widely spaced) electrode catheter mapping (mostly endocardial) or ECGI in the catheterization laboratory; (2) low- and high-density electrode mapping (mostly epicardial) during cardiac surgery; and (3) both high-density electrode and optical mapping in explanted human atrial tissue (endocardial and epicardial surfaces simultaneously). In the catheterization laboratory, low-density mapping using basket catheters with widely spaced electrodes (>1 cm between splines) has not been successful in detecting quasi-stable rotors when analyzed by standard activation timing. However, when analyzed by phase mapping using a proprietary software algorithm (RhythmView, Topera), phase singularities consistent with quasi-stable rotors have been consistently observed. In this method, a signal processing algorithm is applied to assign a phase, from $-\pi$ to π (-180° to $+180^\circ$), to each basket electrode signal in order to identify the cores (rotation centers) of rotors, which are called phase singularities (Figure 2). As with any signal processing algorithm, great care must be taken to avoid artifacts, especially in a situation in which signals from electrodes spaced >1 cm apart are being interrogated to identify the cores of rotors with diameters in the millimeter range. The controversy over whether the proprietary software algorithm used in the CONFIRM trial identifies true rotors or artifacts has been hotly debated. A recent analysis of basket electrogram characteristics at sites predicted to be near the phase singularities identified by the RhythmView phase-mapping algorithm failed to show usual ECG features associated with rotor cores.¹¹ Simulations have also shown the false-positive detection of phase singularities can be a significant problem.¹³ Although quasi-stable rotors have been observed during AF in some animal models, rotors that complete full rotations have only rarely been identified during AF in patients using high-density epicardial mapping during heart surgery.^{12,19,29–31} More commonly, focal excitations (target waves), breakthroughs, and multiple broken colliding waves have been described. On the other hand, ECGI, a different imaging technique also based on phase analysis, also identified unstable rotors that frequently recur

in the same “driver” regions during human AF.⁷ For the interested reader, a spirited debate arguing the pros and cons of whether rotors have been convincingly demonstrated to drive human AF has recently appeared.^{12,32–34} A possible resolution to the controversy has recently been proposed based on an optical mapping study of explanted human right atrial tissue.³⁵ In this study, both endocardial and epicardial activation patterns were analyzed simultaneously from 8 perfused lateral right atrial wall preparations from explanted human hearts. In 7 of 8 hearts, sustained AF required exposure to the ATP-sensitive K channel opener pinacidil, a class of drugs that shortens wavelength and stabilizes rotors.³⁶ Quasi-stable reentry anchored to microanatomic fibrotic regions on the endocardial surface was observed in all 8 cases, generally consistent with the FIRM (using endocardial basket catheters) and ECGI mapping results. Moreover, ablation of the subendocardial reentrant sites terminated AF. The epicardial surface, on the other hand, exhibited complex activation patterns consistent with breakthrough of intramural reentry, more closely resembling the patterns described in the intraoperative high-density electrode epicardial mapping studies. Although intriguing, the extent to which these findings from this study of AF induced by a rotor-stabilizing drug in denervated *ex vivo* human lateral right atrial wall preparations can be extrapolated to *in vivo* left and right atria in healthy patients at different settings/stages of AF remains to be established. Indeed, in contrast to the *ex vivo* study, the recent study by de Groot et al¹⁹ documenting endo-epicardial asynchrony with high-density electrode mapping during human AF failed to identify quasi-stable rotors or reentry on either the endocardial or epicardial surfaces.

Which arrhythmia mechanisms are ablatable?

The underlying clinical motivation for identifying localized drivers of human AF, whether due to quasi-stable rotors, anatomic microreentry, or triggered foci, is to ascertain whether they can serve as ablation targets. In this context, it is useful to review the potential for catheter ablation to terminate the various arrhythmia mechanisms listed in Table 1.

Mechanism 1: Sustained MW fibrillation

In this purely functional reentry fibrillation mechanism due to the spiral/scroll wave breakup (or multisite endo-epicardial reexcitation), every wavebreak generates new wavelets that are “wannabe” rotors, although they rarely have the opportunity to make full 360° rotations due to interference by other nearby wavelets. Thus, new rotors are constantly appearing and extinguishing by fusing with other wavelets or running into nonexcitable borders. On phase maps, phase singularities can originate anywhere in the tissue and then meander transiently before disappearing. In electrophysiologically heterogeneous tissue, regions with shorter refractory periods will exhibit a higher dominant frequency, but there is no discrete stationary rotor site that can be ablated to

Figure 2 Principles of phase mapping and dominant frequency determination. **A:** Optically recorded trace of voltage fluorescence [$F(t)$] from a point on the surface of the heart during a tachyarrhythmia. **B:** Transformation of the voltage trace in **A** to a time delay plot, in which $F(t)$ at time t is plotted against $F(t+\tau)$ (i. e., voltage fluorescence at a later time $t+\tau$). When τ is chosen properly, this produces a circular pattern. The phase at any given time is then defined as the angle (from $-\pi$ to π) of a line drawn from the center of the circle (red dot) to the position on the circular pattern at that point in time (analogous to time on a clock face). **C:** Angles are color-coded corresponding to the different phases of action potential recorded by the voltage fluorescence at that location. **D:** Snapshot of the color (phase) at each location over the surface of the heart at a given time point generates a phase map. **E:** Rotation centers (cores) of rotors have small voltage oscillations (corresponding to low-amplitude double potentials on extracellular electrograms). Because phase is indeterminate, they are called phase singularities (PS). They appear as the rotation centers of color wheels on the phase map (white circles in **D**). In contrast, a focal source emanating from automaticity or triggered activity appears as a target wave of colors (phases), analogous to Figure 1C. **F:** Alternatively, the fluorescence trace in **A** can be converted from the time domain to the frequency domain using a Fourier transform. The largest peak is called the dominant frequency (DF). (Panels A, B, and D–F adapted with permission from Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. *Nature* 1998;392:75–78.)

terminate fibrillation. However, MW fibrillation is a contest between the rates of rotor formation and rotor extinction, and requires a critical tissue mass to be sustained. Below this critical mass, the rate of new rotor formation (proportional to volume of excitable tissue) falls below the rate of rotor extinction (proportional to the surface area of nonexcitable borders), such that MW fibrillation terminates spontaneously.³⁷ Thus, sustained MW fibrillation can be prevented by creating ablation lines that effectively create new borders to increase the rate of rotor extinction, which is the rationale behind both the surgical and catheter MAZE procedures. The ablation lines do not necessarily need to connect to tissue borders. Partial lines or discrete obstacles also increase the rate of rotor extinction by anchoring new wavebreaks and causing them to collide and annihilate each other (Figure 3).³⁷ By this mechanism, extensive focal ablation sites may cause MW fibrillation to become nonsustained even when lines of block between borders are incomplete.

Mechanism 2: Sustained MR fibrillation

In this second type of purely functional reentry fibrillation mechanism, a region of heterogeneous tissue with appropriate electrophysiologic characteristics harbors a rapid quasi-stable rotor that is too fast for the surrounding tissue

to sustain 1:1 conduction, resulting in fibrillatory conduction block. Ablating the functional core of an MR will replace the excitable but unexcited tissue with a nonexcitable obstacle. In this case, the MR may become attached to the obstacle, converting functional reentry to anatomical reentry, usually

Figure 3 Focal ablation lesions accelerate termination of multiple wavelet fibrillation. Simulation in 2-dimensional tissue (10×10 cm) illustrating multiple wavelet fibrillation before (left) and after (right) an obstacle (ablation lesion, black circle) is created. The obstacle anchors 2 of the rotor tips, causing them to collide and annihilate (arrows), whereas the remaining rotor tips self-extinguish at the tissue borders, terminating multiple wavelet fibrillation. (Adapted with permission from Qu Z. Critical mass hypothesis revisited: role of dynamical wave stability in spontaneous termination of cardiac fibrillation. *Am J Physiol* 2006;290:H255–H263.)

Figure 4 Ablatability of mother rotor fibrillation. **A:** Ablation (Abl) converts the mother rotor from functional reentry (left) to slower anatomic reentry around the ablation lesion (right, white arrow). **B:** Ablation creates a lesion extending from the mother rotor core to a border, interrupting the reentrant circuit (left). **C:** Ablation creates a lesion in the central common pathway of a figure-of-8 mother rotor. **D:** The mother rotor is not true functional reentry but anatomic microreentry dependent on slow conduction through a channel (right), which is interrupted by the ablation lesion (left).

at a slower rate (Figure 4A). This is because the core of a functional rotor is the shortest possible path length than can support reentry and is replaced by a longer path length around the circumference of the obstacle. If the rate is sufficiently slowed, however, the surrounding tissue may regain the ability to maintain 1:1 conduction, such that the fibrillatory conduction block resolves, converting fibrillation to tachycardia. It is not uncommon for ablation to convert AF to atrial tachycardia, consistent with this mechanism. Alternatively, if the anatomic reentry has a large enough excitable gap, it is possible that other fibrillatory wavefronts could invade and then terminate the anatomic reentry (although this implies that fibrillation continues in the distant regions so that termination of anatomic reentry does not equate to termination of fibrillation). There are other possible ways in

which ablation might terminate an MR. If the MR is located close to a border, an ablation lesion extending from the core of the MR to the border could prevent the return pathway for reentry (Figure 4B). If the MR has a figure-of-8 (Figure 4C), then creation of an ablation lesion in the central common pathway can terminate reentry. Likewise, if the MR really is microreentry dependent on a slowly conducting channel, ablation might disrupt the channel (Figure 4D). However, in this case, special conditions would have to be present for a slow conducting channel to appear as a phase singularity rather than a target wave emanating from the exit site of the channel. Finally, simulations have also shown that when the regions harboring the MR core and surrounding tissue have different excitability characteristics, ablating the core region can cause the rotor to self-terminate or detach and collide with a border.³⁸

An important point regarding all of these mechanisms is that *terminating the MR is not equivalent to terminating MR fibrillation*. Even if ablation is successful in terminating the MR, the peripheral wavebreaks due to fibrillatory conduction block at distant sites can form new rotors. If 1 of these new rotors becomes anchored, then fibrillation may continue with a new MR. Alternatively, if the new rotors are unstable in the spiral/scroll wave breakup regimen, then MR fibrillation may be converted to MW fibrillation.

Mechanisms 3 and 4: Trigger-(re)induced nonsustained MW or MR fibrillation

If atrial tissue cannot support sustained MW or MR fibrillation, triggers emanating from the PV or other locations can immediately reinitiate reentry once it self-terminates.^{14,39} In this case, silencing of triggers by PV isolation or targeted focal ablation will prevent fibrillation from reinitiating. On the other hand, if the trigger initiating either MW or MR fibrillation is caused by phase 2 reentry, these sites can potentially shift in location on a beat-to-beat basis.⁴⁰ Therefore, there may not be a localized site that can be ablated to prevent phase 2 reentry from recurring and reinitiating fibrillation.

Mechanism 5: Nonreentrant fibrillation

As noted earlier, this mechanism is unlikely to be an important cause of AF because AF can almost always at least transiently be terminated by electrical defibrillation. However, if this mechanism were to occur, ablation or electrical isolation of sites of the nonreentrant focal activity, if accessible and not overly numerous, should terminate AF.

Mechanism 6: Mixed focal-reentrant fibrillation (EAD/DAD mediated)

In this type of fibrillation, EAD or DAD islands arise spontaneously in different regions of the tissue and shift location on a beat-to-beat basis. Therefore, there is generally no localized site that can be ablated to eliminate the EAD- or DAD-mediated triggered beats perpetuating reentry. Only if all of the triggered activity arises from a confined region that

Figure 5 Conventional ablation targets in structurally normal and abnormal hearts. **Left panels** show histology of pulmonary vein (PV) sleeves near the PV–left atrial junction (PV–LAJ), with cardiac myocytes strands (red) separated by collagen bundles (blue) and vascular tissue, from which triggers emerge to initiate atrial fibrillation (AF). **Right panels** show histology of remodeled atrial tissue, with myocyte strands (red) interdigitated with collagen bundles (top) and dense fibrosis (bottom), promoting both triggers and slow conduction. Both cardiovascular (CV) diseases and persistent AF promote remodeling. AAD = antiarrhythmic drug. (Histology panels on the left reproduced with permission from Mueller-Hoecker J, Beiting F, Fernandez B, Bahlmann O, Assmann G, Troidl C, Dimomeletis I, Kaab S, Deindl E. Of rodents and humans: a light microscopic and ultrastructural study on cardiomyocytes in pulmonary veins. *Int J Med Sci* 2008;5:152–158; and panels on the right from McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. *Circ Arrhythm Electrophysiol* 2014;7:23–30.)

can be ablated or electrically isolated is ablation likely to be successful at terminating fibrillation.

What are the challenges?

Taking all the information into consideration, what can be said about the prospects and barriers toward further refining catheter ablation as a definitive treatment of AF? Because some of the mechanisms listed in Table 1 are more amenable to ablation than others, the strategy depends on which mechanisms are operating in various settings and stages of human AF (Figure 5).

Paroxysmal AF

Because paroxysmal AF is by definition nonsustained, the high success rate of PV isolation in structurally normal hearts suggests that focal impulses arising intermittently from the PV are the drivers responsible for inducing nonsustained MW or MR fibrillation in most of these cases. Why are the PVs so important? The formation of EADs or DADs in tissue is highly sensitive to electrotonic loading (source-sink) conditions, such that EAD- or DAD-mediated triggered activity is favored in 1-dimensional (1D) over 2D over 3D cardiac tissue.⁴¹ The structure of PV sleeves (Figure 5, left panels), with quasi-1D atrial muscle strands interdigitated with strands of vascular connective tissue, is conducive to both the emergence of triggered activity and the initiation of microreentry between adjacent muscle strands. Myocytes in PV sleeves have been shown to be intrinsically susceptible to

EAD-mediated triggered activity.⁴² If the atrial muscle strands in the PV sleeves from which these triggers originate are interconnected, they can potentially provide discrete anterograde and retrograde channels for anatomic microreentry, especially if poor connectivity between channels promotes slow or discontinuous conduction. Other structures, such as the venae cavae or ligament of Marshall, can exhibit similar structural features promoting triggered activity and slow conduction and are likewise feasible targets for electrical isolation when PV isolation alone is ineffective.

Although a goal of ablation is to achieve permanent electrical isolation of PV and other arrhythmogenic structures from the bulk atrial myocardium, failure to achieve this endpoint does not always mean that AF will recur. For example, Jiang et al⁴³ found that in 32 patients who underwent PV isolation and were still AF-free 12 months later, 90% demonstrated PV electrical reconnection in at least 1 PV, and 52% showed reconnection in at least 3 PVs. Because triggered activity is often sensitive to parasympathetic/sympathetic tone, ablation-induced damage to autonomic ganglia at the PV–left atrial junctions has been proposed as 1 potential explanation, and ablation-mediated neuromodulation is an interesting avenue to pursue.

In structurally abnormal hearts resulting from cardiovascular disease, hemodynamic stress and/or inflammatory processes result in Ca^{2+} cycling protein, ion channel, structural, neural, and vascular remodeling in the atria.⁴⁴ As a component of structural remodeling, fibrosis creates regions in which collagen bundles are interposed between strands of atrial myocytes (Figure 5, right panels), effectively generating a network of interconnected quasi-1D cables analogous to the interconnected myocyte strands in the PV sleeves described earlier (Figure 5, left panels). Not only does this create a substrate for anatomic microreentry, but the altered source-sink relationships in quasi-1D cables also favor the emergence of EAD- and DAD-mediated triggered activity.⁴¹ Thus, in addition to the PV, fibrotic atrial myocardium can develop sites for triggered activity or microreentry to initiate and maintain for AF. The type of fibrosis plays an important role.⁴⁵ Dense fibrosis provides obstacles for anatomic reentry but otherwise is less arrhythmogenic than moderate fibrosis (30%–50%), which produces quasi-1D tissue strands (Figure 5, right panels) promoting triggers, slow conduction, and wavebreak. However, moderate fibrosis can be below the spatial resolution of current imaging techniques to detect. Improvements in imaging resolution and refined mapping techniques will be required for targeted ablation to succeed in this setting.

Persistent and long-lasting persistent AF

In persistent and long-lasting persistent AF, the chronic arrhythmia itself induces electrical and structural remodeling, a phenomenon originally described by Allessie and colleagues as “AF begets AF.”⁴⁶ As a result, initially structurally normal atria become abnormal when AF persists for more than a few weeks (Figure 5).⁴⁷ Ca^{2+} cycling protein

remodeling promotes triggers and electrical remodeling shortens wavelength, making reentry more easily sustainable, and also flattens action potential duration restitution,⁴⁸ which stabilizes rotors and promotes MR over MW fibrillation. Structural remodeling promotes fibrosis, producing the same profibrillatory consequences described earlier. Thus, in addition to the PV, fibrotic regions of atrial myocardium become potential sources of triggered activity or micro-reentry initiating and maintaining AF,¹⁴ making ablation more challenging. In structurally abnormal hearts, both disease-related remodeling and AF-related remodeling combine to create a tissue substrate enhancing both nonreentrant and reentrant arrhythmia mechanisms. This setting is particularly challenging because with diffuse fibrosis, the entire atria, from endocardium to epicardium, can harbor potential arrhythmogenic sites that may be inaccessible or simply too numerous to neutralize by catheter ablation. Even if ablation is initially successful, progressive disease may continuously create new arrhythmogenic sites. Such factors may have played a role in the failure of CFAE ablation, when added to PV isolation, to improve long-term success rates in patients with persistent AF in the STAR-AFII trial.² Fibrosis also promotes both sustained MW and MR fibrillation by enhancing wavebreaks and anchoring rotors as well as mixed focal-reentrant fibrillation, in which the locations of triggers maintaining fibrillation shift from site to site.

The alternative to ablating individual arrhythmogenic sites is to electrically isolate them from the rest of the atria by creating encircling lesions or linear ablation lines emulating the surgical MAZE procedure. Surgical MAZE has an overall success rate of approximately 75% in persistent and long-standing persistent AF.⁴⁹ Unfortunately, catheter MAZE has yet to achieve comparable efficacy, as demonstrated in the STAR-AFII trial,² in which linear ablations lines did not improve success over PV isolation alone. Even if catheter MAZE can be refined to be as effective as surgical MAZE, however, it still is unlikely to be successful in more than 75% of patients.

Summary

The prospects for long-term AF control with ablation continue to be bright for structurally normal hearts in which triggers emerge from discrete anatomic locations such as the PV or venous structures to induce nonsustained MW or MR fibrillation. If AF persists long enough to cause irreversible structural remodeling, however, new arrhythmogenic sites are likely to develop throughout the atria, particularly in regions of moderate fibrosis. With remodeling, MW and MR fibrillation are also more likely to become sustained. Accurately mapping and ablating focal arrhythmogenic sites in this setting becomes more challenging and less likely to achieve long-term AF control. Catheter MAZE techniques hold promise if future refinements allow the procedure to achieve technical equivalence to surgical MAZE. The same issues apply to cases in which the heart is already structurally abnormal before the onset of AF. In this setting,

hemodynamic and inflammatory stressors related to conditions such as hypertension, coronary artery disease, diabetes, and/or valvular dysfunction cause disease-related remodeling, which combines synergistically with AF-induced remodeling to accelerate the creation of new arrhythmogenic sites and sustained reentry (Figure 5). Development of new pharmacologic and biologic approaches to slow or reverse remodeling processes that promote AF recurrence may ultimately be critical for long-term success, with therapies directed at preventing or reversing fibrosis holding particular promise. Neuromodulation, either by more selective catheter-based ablation of cardiac autonomic gangliated plexuses or by device-based autonomic neurostimulation, is another promising novel direction worthy of further exploration. Given the multiplicity of arrhythmic mechanisms likely to be present in different settings/stages of AF, antiarrhythmic drugs are likely to remain an adjuvant therapy tailored to individual patients rather than a universal cure.

References

- Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–666.
- Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–1822.
- Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel WJ, Miller JM. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J Am Coll Cardiol* 2012;60:628–636.
- Narayan SM, Baykaner T, Clopton P, Schriker A, Lalani GG, Krummen DE, Shivkumar K, Miller JM. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). *J Am Coll Cardiol* 2014;63:1761–1768.
- Miller JM, Kowal RC, Swarup V, et al. Initial independent outcomes from focal impulse and rotor modulation ablation for atrial fibrillation: multicenter FIRM registry. *J Cardiovasc Electrophysiol* 2014;25:921–929.
- Tomassoni G, Duggal S, Muir M, Hutchins L, Turner K, McLoney AM, Hesselton A. Long-term follow-up of FIRM-guided ablation for atrial fibrillation: a single center experience. *J Innov Card Rhythm Manage* 2015;6:2145–2151.
- Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:530–538.
- Buch E, Share M, Tung R, Benharash P, Sharma P, Koneru J, Mandapati R, Ellenbogen KA, Shivkumar K. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. *Heart Rhythm* 2016;13:636–641.
- Gianni C, Mohanty S, Di Biase L, et al. Acute and early outcomes of focal impulse and rotor modulation (FIRM)-guided rotors-only ablation in patients with nonparoxysmal atrial fibrillation. *Heart Rhythm* 2016;13:830–835.
- Mohanty S, Gianni C, Mohanty P, et al. Impact of rotor ablation in non-paroxysmal AF patients: results from a randomized trial (OASIS). *J Am Coll Cardiol* 2016. [In press] <http://dx.doi.org/10.1016/j.jacc.2016.04.015>.
- Benharash P, Buch E, Frank P, Share M, Tung R, Shivkumar K, Mandapati R. Quantitative analysis of localized sources identified by focal impulse and rotor modulation mapping in atrial fibrillation. *Circ Arrhythm Electrophysiol* 2015;8:554–561.
- Allessie M, de Groot N. CrossTalk opposing view: rotors have not been demonstrated to be the drivers of atrial fibrillation. *J Physiol* 2014;592:3167–3170.
- Kuklik P, Zeemering S, van Hünnik A, et al. Identification of rotors during human atrial fibrillation using contact mapping and phase singularity detection: technical considerations. *IEEE Trans Biomed Eng* 2016; [In press] [10.1109/TBME.2016.2554660](https://doi.org/10.1109/TBME.2016.2554660).
- Burashnikov A, Antzelevitch C. Reinduction of atrial fibrillation immediately after termination of the arrhythmia is mediated by late phase 3 early after-depolarization-induced triggered activity. *Circulation* 2003;107:2355–2360.

15. Valderrabano M, Chen F, Dave AS, Lamp ST, Klitzner TS, Weiss JN. Atrioventricular ring reentry in embryonic mouse hearts. *Circulation* 2006;114:543–549.
16. Spach MS, Dolber PC, Heidlage JF. Influence of the passive anisotropic properties on directional differences in propagation following modification of the sodium conductance in human atrial muscle. A model of reentry based on anisotropic discontinuous propagation. *Circ Res* 1988;62:811–832.
17. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. *Am Heart J* 1964;67:200–220.
18. Qu Z, Xie F, Garfinkel A, Weiss JN. Origins of spiral wave meander and breakup in a two-dimensional cardiac tissue model. *Ann Biomed Eng* 2000;28:755–771.
19. de Groot N, van der Does L, Yaksh A, Lanfers E, Teuwen C, Knops P, van de Woestijne P, Bekkers J, Kik C, Bogers A, Allesie M. Direct proof of endocardial asynchrony of the atrial wall during atrial fibrillation in humans. *Circ Arrhythm Electrophysiol* 2016;9:e003648.
20. Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. *Cardiovasc Res* 1996;32:593–603.
21. Antzelevitch C, Yan GX. J-wave syndromes: Brugada and early repolarization syndromes. *Heart Rhythm* 2015;12:1852–1866.
22. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res* May 2002;54:204–216.
23. Zaitsev AV, Berenfeld O, Mironov SF, Jalife J, Pertsov AM. Distribution of excitation frequencies on the epicardial and endocardial surfaces of fibrillating ventricular wall of the sheep heart. *Circ Res* 2000;86:408–417.
24. Xie F, Qu Z, Weiss JN, Garfinkel A. Coexistence of multiple spiral waves with independent frequencies in a heterogeneous excitable medium. *Phys Rev E Stat Nonlin Soft Matter Phys* 2001;63:031905.
25. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J* 1959;58:59–70.
26. Weiss JN, Garfinkel A, Karagueuzian HS, Chen PS, Qu Z. Early afterdepolarizations and cardiac arrhythmias. *Heart Rhythm* 2010;7:1891–1899.
27. Chang MG, Sato D, de Lange E, Lee JH, Karagueuzian HS, Garfinkel A, Weiss JN, Qu Z. Bi-stable wave propagation and early afterdepolarization-mediated cardiac arrhythmias. *Heart Rhythm* 2012;9:115–122.
28. Liu MB, de Lange E, Garfinkel A, Weiss JN, Qu Z. Delayed afterdepolarizations generate both triggers and a vulnerable substrate promoting reentry in cardiac tissue. *Heart Rhythm* 2015;12:2115–2124.
29. Lee S, Sahadevan J, Khrestian CM, Cakulev I, Markowitz A, Waldo AL. Simultaneous biatrial high-density (510–512 electrodes) epicardial mapping of persistent and long-standing persistent atrial fibrillation in patients: new insights into the mechanism of its maintenance. *Circulation* 2015;132:2108–2117.
30. de Groot NM, Houben RP, Smeets JL, Boersma E, Schotten U, Schalij MJ, Crijns H, Allesie MA. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation* 2010;122:1674–1682.
31. Lee G, Kumar S, Teh A, et al. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J* 2014;35:86–97.
32. Allesie M, de Groot N. Rebuttal from Maurits Allesie and Natasja de Groot. *J Physiol* 2014;592:3173.
33. Narayan SM, Jalife J. CrossTalk proposal: rotors have been demonstrated to drive human atrial fibrillation. *J Physiol* 2014;592:3163–3166.
34. Narayan SM, Jalife J. Rebuttal from Sanjiv M. Narayan and Jose Jalife. *J Physiol* 2014;592:3171.
35. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–2401.
36. Garfinkel A, Kim YH, Voroshilovsky O, Qu Z, Kil JR, Lee MH, Karagueuzian HS, Weiss JN, Chen PS. Preventing ventricular fibrillation by flattening cardiac restitution. *Proc Natl Acad Sci U S A* 2000;97:6061–6066.
37. Qu Z. Critical mass hypothesis revisited: role of dynamical wave stability in spontaneous termination of cardiac fibrillation. *Am J Physiol* 2006;290:H255–H263.
38. Rappel WJ, Zaman JA, Narayan SM. Mechanisms for the termination of atrial fibrillation by localized ablation: computational and clinical studies. *Circ Arrhythm Electrophysiol* 2015;8:1325–1333.
39. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. *Circ Res* 1986;58:356–371.
40. Weiss JN, Garfinkel A, Karagueuzian HS, Nguyen TP, Olcese R, Chen PS, Qu Z. Perspective: a dynamics-based classification of ventricular arrhythmias. *J Mol Cell Cardiol* 2015;82:136–152.
41. Xie Y, Sato D, Garfinkel A, Qu Z, Weiss JN. So little source, so much sink: requirements for afterdepolarizations to propagate in tissue. *Biophys J* 2010;99:1408–1415.
42. Patterson E, Jackman WM, Beckman KJ, Lazzara R, Lockwood D, Scherlag BJ, Wu R, Po S. Spontaneous pulmonary vein firing in man: relationship to tachycardia-pause early afterdepolarizations and triggered arrhythmia in canine pulmonary veins in vitro. *J Cardiovasc Electrophysiol* 2007;18:1067–1075.
43. Jiang RH, Po SS, Tung R, Liu Q, Sheng X, Zhang ZW, Sun YX, Yu L, Zhang P, Fu GS, Jiang CY. Incidence of pulmonary vein conduction recovery in patients without clinical recurrence after ablation of paroxysmal atrial fibrillation: mechanistic implications. *Heart Rhythm* 2014;11:969–976.
44. Schotten U, Dobrev D, Platonov PG, Kottkamp H, Hindricks G. Current controversies in determining the main mechanisms of atrial fibrillation. *J Intern Med* 2016;279:428–438.
45. Nguyen TP, Xie Y, Garfinkel A, Qu Z, Weiss JN. Arrhythmogenic consequences of myofibroblast-myocyte coupling. *Cardiovasc Res* 2012;93:242–251.
46. Wijffels M, Kirchhof C, Dorland R, Allesie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;92:1954–1968.
47. Eckstein J, Verheule S, de Groot NM, Allesie M, Schotten U. Mechanisms of perpetuation of atrial fibrillation in chronically dilated atria. *Prog Biophys Mol Biol* 2008;97:435–451.
48. Allesie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230–246.
49. Phan K, Xie A, Tian DH, Shaikhreza K, Yan TD. Systematic review and meta-analysis of surgical ablation for atrial fibrillation during mitral valve surgery. *Ann Cardiothorac Surg* 2014;3:3–14.