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Ablating Atrial Fibrillation: A Translational Science Perspective for Clinicians

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Abstract

Although considerable progress has been made in developing ablation approaches to cure 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 non-reentrant, 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; arrhythmias; atrial fibrillation; fibrosis; ablation; rotor; triggered activity; automaticity

Introduction

Following the seminal 1998 study by Haissaguerre & colleagues [1] demonstrating that the pulmonary veins (PV) 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 world-wide 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

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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 (CFAE) 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 mos. 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 [5, 6]. Supporting the approach of identifying and ablating localized drivers of AF, Haissaguerre and colleagues [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 multi-center 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 non-paroxysmal AF, the rates of freedom for AF off antiarrhythmic drugs after 12 months were 14%, 52% and 76%, respectively [10]. Moreover, a spirited debate has arisen over FIRM technique itself, concerning both technical and mechanistic issues. The technical issue relates to whether the proprietary FIRM software algorithm (RhythmView™, Topera Inc.) 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 four-fold: 1) to review reentrant and non-reentrant 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 (Fig. 1). Automaticity is generally too slow to drive very rapid arrhythmias such

as AF, but can generate triggers such as premature atrial complexes (PAC's) that can initiate reentry leading to fibrillation. Triggered activity arising from early and delayed afterdepolarizations (EADs and DADs, respectively) can generate rapid non-sustained or sustained tachycardia and/or can serve as triggers to initiate reentry. Even if reentry is non-sustained, 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 for a focal source (Fig. 1, top right panel).

Reentry falls into two 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 (Fig. 1, top left panel). The path length can be large (macro-reentry on the centimeter scale) or small (micro-reentry on the sub-millimeter scale) depending on the electrophysiological characteristics of the tissue. Micro-reentry path lengths <1 mm (i.e. much smaller than the 3–4 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 between isolated strands of myocytes[16]. Anatomic reentry depends on the wavelength (the product of action potential duration times 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 (Fig. 1, top middle and lower 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 two dimensional (2D) tissue) and scroll wave reentry (in three 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, non-reentrant and mixed reentrant/non-reentrant mechanisms (Table 1). Fibrillation mechanisms that have been characterized in atrial, ventricular and/or simulated tissue include the following:

Multiple Wavelet (MW) Fibrillation

This purely reentrant mechanism, originally proposed by Moe [17], results from rotors that are inherently unstable and spontaneously develop wavebreaks along the arm of the rotor. In simulated cardiac tissue, MW Fibrillation is equivalent to the unstable breakup regime of spiral/scroll wave reentry (Fig. 1, lower right panel), although in heterogeneous tissue, hypermeandering spiral waves (Fig. 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 degree 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 one surface cross-over and break through to excite recovered regions on the opposite surface, and vice versa in a reciprocating manner. Thus, the cross-overs effectively represent the shifting antegrade and retrograde limbs of transmural reentry between the endo- and epicardial layers. To us, this falls into the category of functional reentry with multiple shifting wavelets, i.e. a variant of multiple wavelet fibrillation.

Since 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 from 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 non-sustained, depending on factors such as tissue mass and the excitation wavelength. If sustained, additional triggers are no longer required to maintain fibrillation. If non-sustained, however, triggers arising from the PV or other locations, often promoted by the rapid excitation during the period of fibrillation, can reinitiate fibrillation [14], so that the arrhythmia appears to be sustained.

Mother Rotor (MR) Fibrillation

In addition to the spiral/scroll wave breakup regime, spiral/scroll waves can also be intrinsically stable, meandering or hypermeandering [18] (Fig. 1, bottom left and 2 middle panels). These other regimes are relevant to MR Fibrillation, characterized by Jalife & coworkers [22, 23], in which a fast stationary or meandering spiral/scroll wave in one 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 mother rotor maintains fibrillation and the peripheral wavebreaks are noncausal epiphenomena (Fig. 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 (Fig. 1, lower right panel). That is, MR Fibrillation is driven by a localized source, whereas MW Fibrillation is inherently non-localized. 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 non-sustained 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 which re-initiate the Mother Rotor even if it is inherently non-sustained.

In diseased fibrotic atria (or atria with extensive ablation scars), it is also possible for multiple stable rotors to co-exist in different regions, insulated by intervening tissue which cannot maintain 1:1 conduction [24]. This variant is equivalent to MR Fibrillation with multiple stable mother rotors.

Non-reentrant Fibrillation

Fibrillation can also involve non-reentrant 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 micro-reentry 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 non-sustained 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 non-reentrant unifocal or multi-focal mechanisms, on the other hand, is unlikely, since most fibrillation episodes can be terminated at least transiently by electrical defibrillation. In contrast, non-reentrant 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 re-initiating MW or MR Fibrillation, Mixed Focal-Reentrant Fibrillation refers to types of fibrillation in which both triggers and electrical dispersion arise from a non-localized dynamical process which does not depend inherently on the presence of pre-existing 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 which 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-excitable 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 one 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 non-sustained. Since 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. Which mechanisms are directly relevant to human AF, on the other hand, remains controversial. Clues can be surmised from the susceptibility of these various mechanisms to ablation and defibrillation, as summarized in Table 1. Since human AF can generally (at least transiently) be defibrillated, the fifth non-reentrant 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 versus 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: i) low density (i.e. widely-spaced) electrode catheter mapping (mostly endocardial) or ECGI in the catheterization laboratory, ii) low and high density electrode mapping (mostly epicardial) during cardiac surgery, and iii) 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-space electrodes (>1 cm between splines) have not been successful at detecting quasi-stable rotors when analyzed by standard activation timing. However, when analyzed by phase mapping using a proprietary software algorithm (RhythmView™, Topera Inc.), 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°), to each

basket electrode signal in order to identify the cores (rotation centers) of rotors, which are called phase singularities (Fig. 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 about >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 mapping algorithm failed to show usual electrocardiographic 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 one or many 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 also 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 micro-anatomic 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 sub-endocardial reentry 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 al [19] 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 micro-reentry or triggered foci, is to ascertain whether they can serve as ablation targets. In this context, the potential for catheter ablation of the various arrhythmia mechanisms in Table 1 is useful to review.

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 degree rotations due to interference by other nearby wavelets. Thus new rotors are constantly appearing and extinguishing by fusing with other wavelets or running into non-excitable 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 DF, but there is no discrete stationary rotor site that can be ablated to 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, rate of new rotor formation (proportional to volume of excitable tissue) falls below the rate of rotor extinction (proportional to the surface area of non-excitable 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 a 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 (Fig. 3) [37]. By this mechanism, extensive focal ablation sites may cause MW Fibrillation to become non-sustained 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 electrophysiological 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 a Mother Rotor will replace the excitable but unexcited tissue with a non-excitable obstacle. In this case, the Mother Rotor may become attached to the obstacle, converting functional reentry to anatomical reentry, usually at a slower rate (Fig. 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 the termination of the anatomic reentry does not equate to termination of fibrillation). There are other possible ways in which ablation might terminate a Mother Rotor. If the Mother Rotor is located close to a border, an ablation lesion extending from the Mother Rotor’s core to the border could prevent the return pathway for reentry (Fig. 4B). If the Mother Rotor has a figure of eight configuration (Fig. 4C), then creation of an ablation lesion in the central common pathway can terminate reentry. Likewise, if the Mother Rotor is really micro-

reentry dependent on a slowly conducting channel, ablation might disrupt the channel (Fig. 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 region harboring the Mother Rotor 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].

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

Mechanisms 3 and 4

Trigger-(re)induced Non-Sustained MW or MR Fibrillation. If atrial tissue cannot support sustained MW or MR Fibrillation, triggers emanating from the PV or other locations [14, 39] can immediately reinitiate reentry once it self-terminates. In this case, silencing of triggers by PV isolation or targeted focal ablation will prevent fibrillation from re-initiating. 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 re-initiating fibrillation.

Mechanism 5

Non-Reentrant Fibrillation. As noted above, this mechanism is unlikely to be an important cause of AF, since 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 non-reentrant 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 can be ablated or electrically isolated is ablation likely to be successful at terminating fibrillation.

What are the challenges?

Taking the above information into consideration, what can be said about the prospects and barriers towards further refining catheter ablation as a definitive treatment for AF? Since

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 (Fig. 5).

Paroxysmal AF

Since paroxysmal AF is by definition non-sustained, 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 non-sustained MW or MR Fibrillation in most of these cases. Why are the PV so important? The formation of EADs or DADs in tissue is very sensitive to electrotonic loading (source-sink) conditions, such that EAD- or DAD-mediated triggered activity is favored in 1D over 2D over 3D cardiac tissue [41]. The structure of PV sleeves (Fig. 5, left panels), with quasi-1D atrial muscle strands interdigitated with strands of vascular connective tissue, is conductive to both the emergence of triggered activity and the initiation of micro-reentry 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 antegrade and retrograde channels for anatomic micro-reentry, especially if poor connectivity between channels promotes slow or discontinuous conduction. Other structures, such as the vena 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 al. [43] 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 PV. Since triggered activity is often sensitive to parasympathetic/sympathetic tone, ablation-induced damage to autonomic ganglia at the PV-LA junctions has been proposed as one potential explanation, and ablation-mediated neuromodulation is an interesting avenue to pursue.

In structurally abnormal hearts due to 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 (Fig. 5, right panels), effectively generating a network of interconnected quasi-1D cables analogous to the interconnected myocyte strands in the PV sleeves described above (Fig. 5, left panels). Not only does this create a substrate for anatomical micro-reentry, 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 also can develop sites for triggered activity or micro-reentry 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 (Fig. 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 (Fig. 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 pro-fibrillatory consequences described above. Thus, in addition to the PV, fibrotic regions of atrial myocardium become potential sources of triggered activity or micro-reentry initiating and maintaining for 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 non-reentrant and reentrant arrhythmia mechanisms. This setting is particularly challenging, since 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 is still unlikely to be successful in more than 75% of patients.

In 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 non-sustained 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 or 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 (Fig. 5). Development of new pharmacological and biological approaches to slow or reverse remodeling processes that promote AF recurrence may ultimately be critical for long-term success, with therapies directed to prevent or reverse fibrosis holding particular promise. Neuromodulation, either by more selective catheter-based ablation of cardiac autonomic gangliated plexi or by device-based autonomic neurostimulation are also promising novel directions 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.

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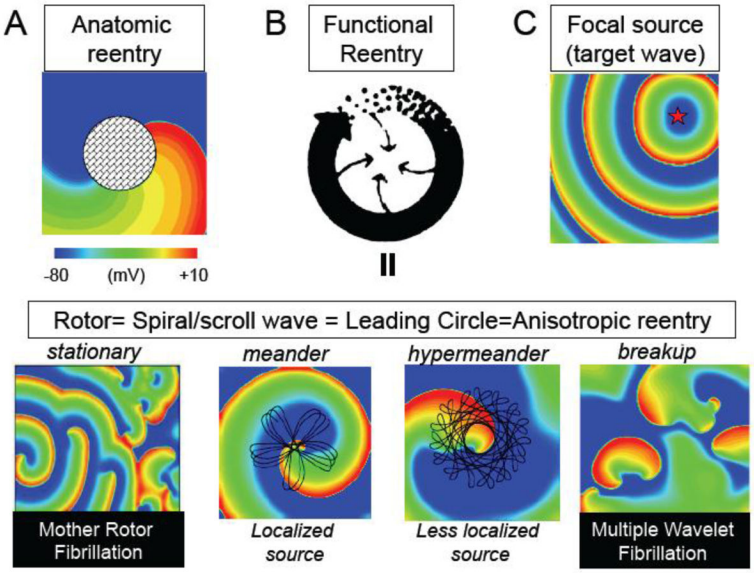

Figure 1. Basic arrhythmia mechanisms relevant to fibrillation

A. Anatomic reentry (A), 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 electrophysiological characteristics of the tissue, the rotor can be stable (lower left panel) with peripheral wavebreaks (fibrillatory conduction block) if the surrounding tissue has a longer refractory period, meandering (lower left middle panel), hypermeandering (lower middle right panel), or in an unstable breakup regime (lower right panel). A stable or meandering rotor with peripheral wavebreak is equivalent to Mother Rotor Fibrillation, whereas spiral wave break-up is equivalent to Multiple Wavelet Fibrillation. **C.** Focal sources due to automaticity or EAD- or DAD-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) voltage snapshots. The temporal trajectories of the rotor cores are shown in black lines for the meandering and hypermeandering rotors. Panel B was adapted from Allessie et al [50] with permission.

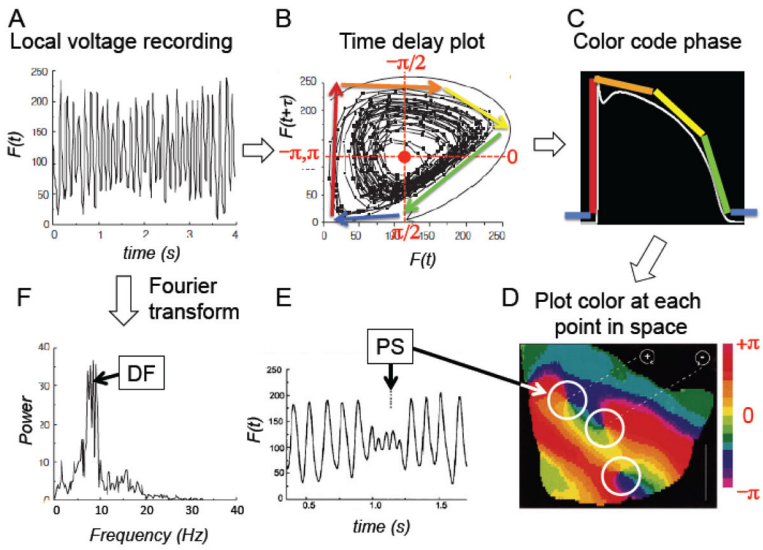

Fig. 2. Principles of phase-mapping and dominant frequency (DF) determination

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+τ)*, i.e. the voltage fluorescence at a later time *t+τ*. When *τ* is chosen properly, this produces a circular pattern. The phase at any given time is then defined as the angle (from **-π** 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 clockface). **C.** The angles are color-coded corresponding to the different phases of action potential recorded by the voltage fluorescence at that location. **D.** A snapshot of the color (phase) at each location over the surface of the heart at a given time point generates a phase-map. **E.** The rotation centers (cores) of rotors have small voltage oscillations (corresponding to low amplitude double potentials on extracellular electrograms). Since their 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 Fig. 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, D–F were adapted from Gray et al [51], with permission.

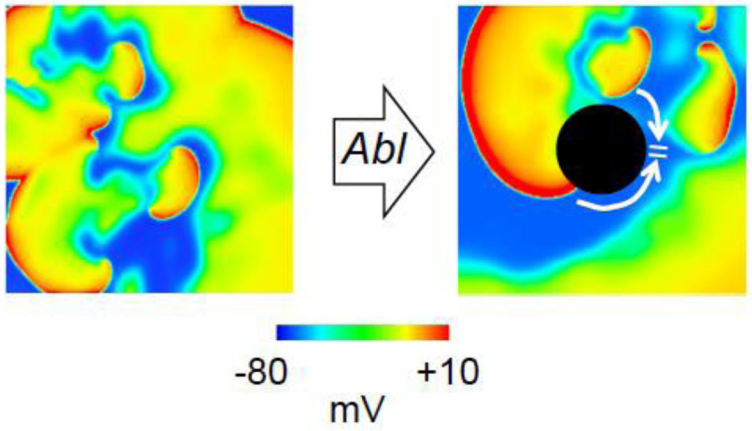

Fig. 3. Focal ablation lesions accelerate termination of MW Fibrillation

Simulation in 2D tissue (10×10 cm) illustrating MW Fibrillation before (left) and after (right) an obstacle (ablation lesion, black circle) is created. The obstacle anchors two of the rotor tips causing them to collide and annihilate (arrows), while the remaining rotor tips self-extinguish at the tissue borders, terminating MW Fibrillation. Adapted from Qu et al. [37], with permission.

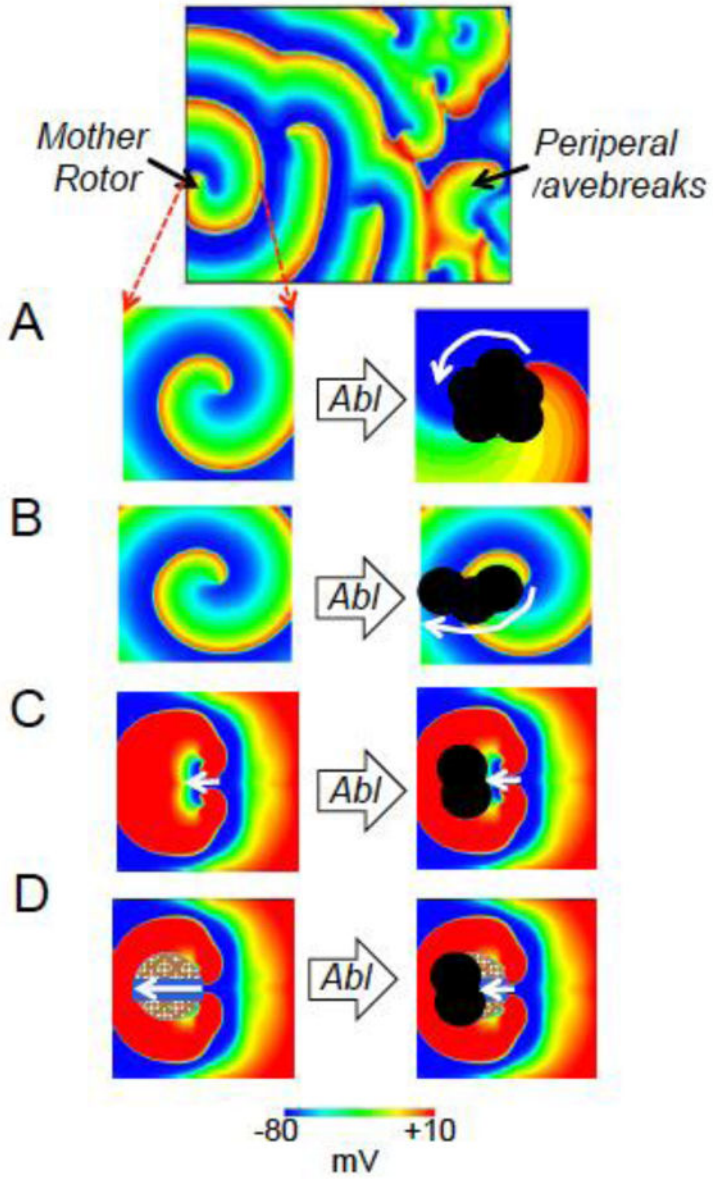

Fig. 4. Ablatability of MR Fibrillation (upper panel)

A. Ablation (Abl) converts the Mother Rotor from functional reentry (left panel) to slower anatomic reentry around the ablation lesion (right panel, red arrow). **B.** Ablation creates a lesion extending from the Mother Rotor core to a border, interrupting the reentrant circuit (left panel). **C.** Ablation creates a lesion in the central common pathway of a figure of eight Mother Rotor. **D.** The Mother Rotor is not true functional reentry, but anatomic micro-reentry dependent on slow conduction through a channel (right panel), which is interrupted by the ablation lesion (left panel).

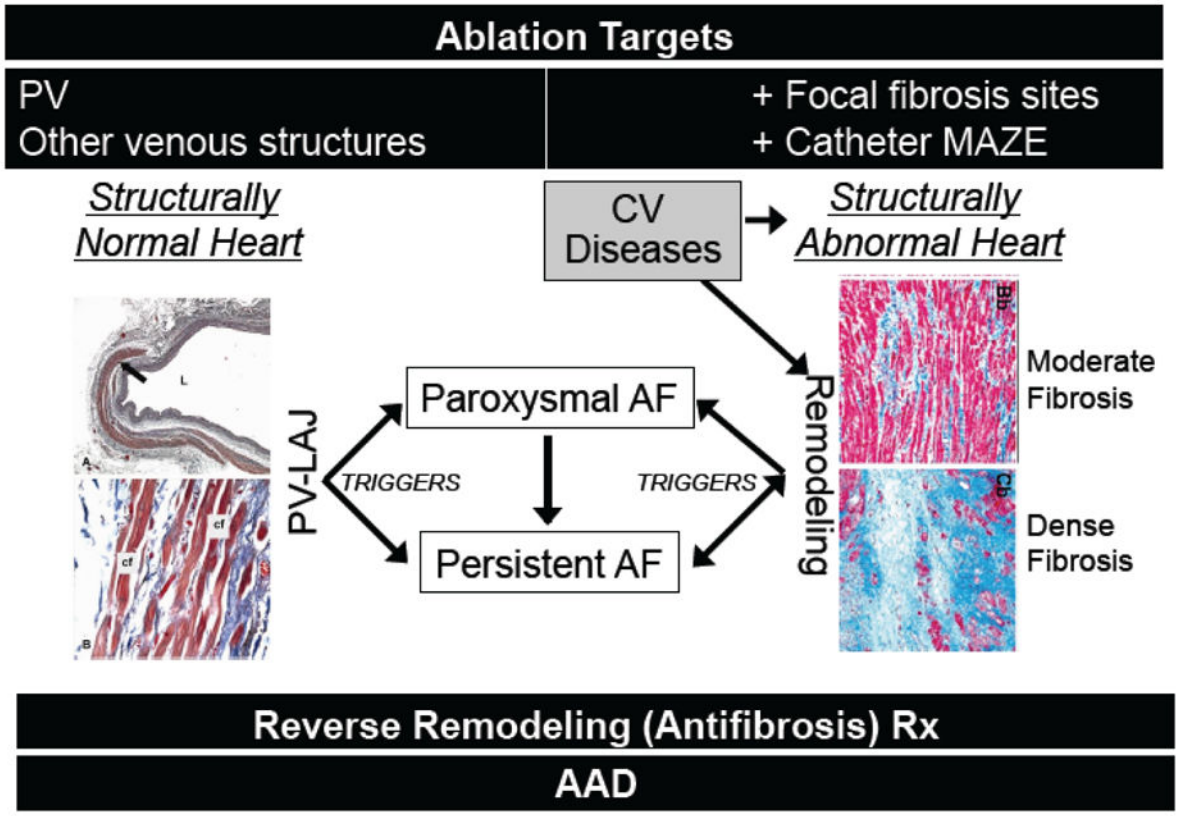

Fig. 5. Conventional ablation targets in structurally normal and abnormal hearts

Left panels show histology of PV sleeves near the PV-LA junction (PV-LAJ), with cardiac myocytes strands (red) separated by collagen bundles (blue) and vascular tissue, from which triggers emerge to initiate AF. Right panels show histology of remodeled atrial tissue, with myocyte strands (red) interdigitated with collagen bundles (upper) and dense fibrosis (lower), promoting both triggers and slow conduction. Both CV diseases and persistent AF promote remodeling. Histology panels reproduced with permission from [52 and 53]. AAD, antiarrhythmic drugs

Table 1

Possible mechanisms of AF and their susceptibility to ablation and defibrillation

"Focal" refers to PV isolation (PVI), CFAE, FIRM-guided or ECGI-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.

Possible AF Mechanisms	Ablatable?		Defibrillatable?
	Focal*	MAZE	
Sustained Multiple 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
Multi-focal Non-Reentrant Fibrillation	Yes	No	No
Mixed Focal-Reentrant Fibrillation (EAD/DAD-mediated)	No	Yes	Yes

*PVI, CFAE, FIRM- or ECGI-guided