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Mechanisms Underlying AF: Triggers, Rotors, Other?

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Abstract

Opinion statement

There is ongoing debate regarding the precise mechanisms underlying atrial fibrillation (AF). An improved understanding of these mechanisms is urgently needed to improve interventional strategies to suppress and eliminate AF, since the success of current strategies is suboptimal. At present, guidelines for AF ablation focus on pulmonary vein (PV) isolation for the prevention of arrhythmia. Additional targets are presently unclear, and include additional linear ablation and electrogram-guided substrate modification, without clear mechanistic relevance. PV and non-PV triggers are likely central in the first few seconds of AF initiation. Rapid activation from such triggers interacts with transitional mechanisms including conduction velocity slowing, action potential duration (APD) alternans, and steep APD restitution to cause conduction block and initiate functional reentry. However, complete suppression of potential triggers has proven elusive, and the intra-procedural mapping and targeting of transitional mechanisms has not been reported. A growing body of research implicates electrical rotors and focal sources as central mechanisms for the maintenance of AF. In several recent series, they were observed in nearly all patients with sustained arrhythmia. Ablation of rotor and focal source sites, prior to pulmonary vein isolation, substantially modulated atrial fibrillation in a high proportion of patients, and improved ablation outcomes versus pulmonary vein isolation alone. These results have subsequently been confirmed

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Conflict of Interest

Dr. David E. Krummen reports grants from National Institutes of Health and American Heart Association. Dr. Krummen reports EP Fellowship Support from Boston Scientific, Medtronic, St. Jude Medical, and Biotronik, and consultant fees from InsilicoMed and Topera Inc.

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Dr. Shrinivas Hebsur, Dr. Amir A. Schricker, Dr. Jon Salcedo, Dr. Gautam G. Lalani each declare no potential conflicts of interest.

Compliance With Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

in multicenter series, and the improved outcomes have been found to persist to a mean follow-up of 3 years. Recently, rotors have been observed by multiple groups using diverse technologies. These findings represent a paradigm shift in AF, focusing on sustaining mechanisms, as is currently done with other arrhythmias such as atrioventricular node reentrant tachycardia. Studies are currently underway to assess the optimal strategy for the application of rotor-based ablation in AF management, including clinical trials on the relative efficacy of rotor-only ablation versus PVI-only ablation, which will inform future practice guidelines.

Keywords

Atrial fibrillation; Mechanisms; Human; Multiwavelet reentry; Focal triggers; Ganglionated plexi

Introduction

Despite considerable technological advancement in mapping and ablation technologies, the success rate for atrial fibrillation (AF) ablation has remained suboptimal [1–3], reflecting uncertainty in underlying mechanisms. AF has been attributed to multiple wavelets [4], triggers [5], autonomic sources [6], and rotors [7•], and there is ongoing debate about the relative contribution of each [8, 9]. As a result, the optimal approach for modifying and preventing AF remains unclear [10•].

In this manuscript, we will discuss our current understanding of AF mechanisms, including insights from basic, translational, and clinical research, framed within the temporal evolution of the arrhythmia. We will highlight recent advances when applicable. We will also outline deficiencies in current models, and discuss ongoing studies to clarify remaining mechanistic questions.

Temporal evolution of AF mechanisms

Prior work has identified three distinct phases in establishing steady-state arrhythmia [11]: initiation, transition, and maintenance. In slow-fast atrioventricular node reentrant tachycardia (AVNRT), for example, the initiation phase often consists of rapid beats from pulmonary veins or other sites [12]. In the transition phase, this rapid activation impinges upon differential refractory periods in atrioventricular nodal tissue, and leading to unidirectional block [13]. AVNRT then enters the maintenance phase, characterized by classical reentry [14]. Clinically, catheter-based therapies for AVNRT target the maintenance phase of the arrhythmia via ablation of the slow pathway, resulting in excellent long-term success [15].

AF, similarly, has three phases. Importantly, mechanisms which play a central role in one phase may play a minimal or no role in another. Thus, a comprehensive understanding of the mechanisms underlying AF requires contextual placement in the temporal evolution of the arrhythmia.

Initiation of AF

There is general agreement that the initiation phase of AF consists of rapid activation from diverse sources including the pulmonary veins [5, 16], other venous structures [17], or non-venous sites [5, 18•]. However, there remains significant disagreement regarding the mechanism of such activation.

Early studies have suggested that such rapid activity is caused by triggered activity [19] due to increased delayed afterdepolarizations or other mechanisms for ectopy [20] that may reflect abnormal calcium handling as the mechanism of rapid activation. Interestingly, other investigators have reported data regarding the unique cellular architecture and electrophysiologic properties of pulmonary vein myocardium which are most consistent with localized reentry [21–23]. The autonomic nervous system has also been implicated as a mechanism of rapid activation; combined sympathetic and parasympathetic stimulation [24] has been shown to result in rapid firing from the ganglionated plexi near the pulmonary veins [25], leading to AF.

Figure 1a illustrates observations during the initiation phase of AF; sources of rapid activation were mapped to diverse locations during episodes of spontaneous AF in a patient during electrophysiology study. Such heterogeneity in AF triggers underscores the difficulty in comprehensively targeting AF triggers.

This rapid activation phase is of critical importance to arrhythmia initiation, since it results in calcium loading and amplifies abnormalities in calcium handling [26], and decreases activation latency [27], leading up to the transition phase of AF.

Presently, the precise duration of the initiation phase in spontaneous arrhythmia is unclear, although is likely to last from seconds to as long as 1–2 min. An upper limit for the initiation phase may be derived from the data during FIRM mapping performed in our lab [7•]; phase analysis of AF at 5–10 min after AF initiation shows conserved mechanisms compared with analyses done minutes to hours later [28], consistent with steady-state AF.

Unlike most other arrhythmias in clinical electrophysiology, the cornerstone of AF ablation consists of targeting the initiating mechanisms of AF via pulmonary vein isolation (PVI) [10•], which decouples the pulmonary vein triggers from the remaining atrium. Confusingly, however, strategies classified as PVI have progressively encompassed greater portions of the peri-venous myocardium [29], and include significant substrate ablation [30], and thus likely also affect transitional and sustaining mechanisms [31].

Transition phase: wavefront block and reentry

The transition phase of AF is characterized by functional wavefront block and the initiation of reentry, which may be facilitated by static and dynamic factors.

Static factors include fixed spatial dispersion of refractoriness, which mathematical and computational studies have shown may promote wavebreak and reentry [32] alone. Evidence exists for baseline intra-atrial differences in fibrosis [33] and density of the rapid

delayed rectifier current (I_{Kr}) [34], which may contribute such baseline heterogeneity. Atrial fibrosis, by altering normal atrial myocardial cell coupling, has been shown to result in discrete areas of slow conduction, favoring reentry [35]. In a recent study, atrial fibrosis burden was correlated to the probability of AF recurrence following ablation [36•]. However, static factors alone cannot fully account for AF initiation, since the majority of premature beats do not initiate fibrillation [32].

Rapid atrial activation causes alterations in atrial electrophysiology which favor AF including decreased atrial ERP [37], slowed conduction velocity [38], increased action potential duration (APD, i.e., refractory period) heterogeneity [39]. It also results in other dynamic, pro-arrhythmic conditions including steep APD restitution [40], action potential shape [41] and APD alternans [42], and dynamic conduction slowing [18•]. Autonomic modulation further steepens APD restitution [43] and decreases activation latency [27], promoting wavefront block and AF initiation.

An illustration of the transitional phase of AF, at which wavefront block occurs at a site of conduction slowing, is shown in Fig. 1b. Surprisingly, we have reported that sites of dynamic wavefront block were spatially conserved between inductions [18•], indicating spatial preferences which may allow targeting of such mechanisms for modification via ablation in the future.

Presently, the precise role of each factor, or combinations of factors described above, is unclear, and may be patient-specific, highlighting the need for individualized mapping and tailored therapy for AF. While the mechanisms active during the transitional phase of AF are not currently overtly targeted by catheter-based interventions, wide-area circumferential ablation (WACA) lesions [44] frequently encompass peri-venous locations of such mechanisms [40]. Additionally, they may be affected by current [45] and proposed pharmacologic therapies, as has been studied for ventricular fibrillation [46]. Ongoing work in transitional AF therapies is directed toward novel pharmacologic strategies [47, 48] to reduce the probability of wavefront block and initiation of reentry.

AF maintenance

The central issue of AF maintenance remains the subject of ongoing debate [8, 9]. Candidate mechanisms include multiwavelet reentry, PV triggers, autonomic sources, and rotors/focal sources.

Multiwavelet reentry

Multiwavelet reentry, first proposed by Moe in 1964, postulates that, during ongoing AF, a sufficient number of randomly propagating wavefronts exist such that spontaneous termination of AF is unlikely [49]. In this model, wavefronts continually interact with preexisting electrophysiological heterogeneity, with wavebreak occurring at discrete points of local refractoriness [32]. Additionally, AF is maintained if sufficient tissue is available, and occurs without spatial preference. Experimental work consistent with multiwavelet reentry was subsequently reported [50], as has more recent work in patients with longstanding AF, which appears consistent with this model [51]. In this study, epicardial

focal activation was found to be due to breakthrough activation from deeper myocardial layers, without observation of a focal driving mechanism.

While the multiwavelet reentry appears to account for the disordered activation present in AF, it does not account for observations in which limited ablation terminates AF reported by several groups [7•, 52–54]. More importantly, research on multiwavelet reentry lacks data showing that intervening on this mechanism alters AF, and thus has not been able to establish causality. Thus, while AF is clearly a disorganized rhythm, whether multiwavelet reentry actually is the driver of AF or is secondary to other mechanism(s) remains unclear at this time.

Pulmonary vein triggers

While experimental evidence shows a role for pulmonary vein triggers during the initiation phase of AF, their role in AF maintenance is uncertain. Prior arguments in favor of an ongoing role often cited the relative success of PVI as evidence for this hypothesis [55, 56]. However, as monitoring intensity post-ablation improved, the true success rate for PVI-based procedures has been shown to be modest [1–3]. Furthermore, intervention targeted at PV triggers has evolved from segmental PVI to WACA [44], which likely disrupt other mechanisms [29].

Interestingly, ablation strategies have been proposed in which the pulmonary veins are intentionally not isolated [57]. Such approaches showed success equivalent to PVI-based strategies [58]. A potential advantage of such strategies includes the safety of avoiding ablation on the posterior left atrium that should decrease the risk of esophageal injury, and avoiding ablation near the right phrenic nerve that should decrease the risk of injury to that structure.

Furthermore, the role of the PVs has been directly evaluated; in many studies they were found to activate passively during ongoing AF, in that their rate was slower than the remaining left atrium with activation into the veins rather than out of the veins (as would be expected for an active mechanism) [59]. Overall, the role of the PVs likely diminishes with time [60], consistent with their accepted role as a trigger but with a less clear role beyond the initiation phase.

Autonomic sources

The heart is the site of extensive autonomic innervation [61], which alters heart rate and contractility via humoral and neural routes. Sites of dense autonomic innervation of the atria occur at ganglionated plexi [62], located at characteristic sites throughout both atria. Mechanistic studies have found that such sites may serve as high-frequency AF sources as a result of autonomic remodeling [63]. Such sites may be localized by high-frequency pacing and the observation of a stimulated vagal response, defined as either atrioventricular block, asystole, or an increase in the mean RR interval of greater than 50 % [6].

Understanding the precise role of such sites has proved challenging. Mechanistic studies in animal models have shown that vagal-nerve stimulation promotes long-lasting AF by shortening the atrial effective refractory period in a spatially heterogeneous manner [64].

Computational studies proposed that autonomic stimulation could stabilize fibrillatory rotors [65], and experimental validation of this hypothesis is awaited.

Interventionally, prior studies have shown that PVI also denervates atrial tissue [66, 67]. Recent evidence from a randomized trial found that the addition of GP ablation to pulmonary vein isolation increases procedural success [68, 69]; these findings await confirmation in multicenter trials.

While autonomic sites are increasingly recognized for their role in AF initiation and maintenance, the link between such sites and other mechanisms, such as rotors (discussed below) is uncertain. Future studies are required to determine whether GP and rotors co-localize or are spatially independent.

Rotors and focal sources

While rotors had been observed in animal models [70, 71] and human VF [72–74], until recently [75, 75–78, 79] there was little or no evidence for rotors in human AF. Several features of human AF may have contributed to difficulties in arrhythmia mapping, including low-amplitude signals [80], the practice of recording from a limited number of simultaneous electrodes during AF despite its spatial heterogeneity, the use of clinical bipolar signals during AF [81], and dependence upon activation-based analysis of AF, rather than phase mapping [82].

In 2012, we published the results of the CONFIRM trial [79], a study of 92 patients undergoing 107 ablation procedures for drug-refractory AF; demographics of study patients are shown in Table 1. In both arms, 64-contact electrode basket catheters were advanced to both atria and AF recorded [77]. In the experimental arm, AF was mapped and sustaining sites were targeted for ablation; in the control arm, mapping was performed off-line. We found AF-sustaining sources in 97 % of cases with sustained AF, with each patient displaying 2.1 ± 1.0 sources.

Although the majority of sources were located in the left atrium (76 %), a significant fraction lay in the right (24 %). Within the left atrium, sources were found at diverse locations including the posterior, inferior, and roof regions in addition to sites near the pulmonary veins. RA sources were commonly found in the inferolateral, posterior, and septal regions.

Identified rotors (Fig. 1c to d) were ablated in the experimental arm using 16.1 ± 9.8 min of radiofrequency energy. Importantly, ablation time was similar in both arms because the relatively modest FIRM ablation time was within the variation of energy delivery for a conventional ablation procedure. PVI was performed in all patients using right and left WACA lesions, with a roof line in patients with persistent AF.

The study showed an improvement in procedural success from 45 % in the control arm to 82 % in the FIRM+PVI arm at a median follow-up of 273 days (Fig. 1e). Notably, a significant proportion of patients in this study had modulation of AF by rotor-based ablation alone with FIRM ablation alone. Follow-up in this study was more rigorous than guidelines; 88 % of patients in the FIRM plus PVI arm had continuous monitoring from an implanted device.

These provocative results have subsequently been confirmed in independent studies of acute outcomes [83] and long-term follow-up [84•] (Fig. 1f). In the multicenter study, results from 10 centers new to the technique of FIRM ablation are reported. In 78 patients, a median of 6 patients per center, single procedure freedom from AF was 80.5 % in all patients, and was 87.5 % in patients with no prior ablation. This study is particularly notable because the high success rate was seen in patients early in the “learning curve,” reinforcing the robust nature of the results. In separate analyses, the benefits of FIRM ablation have been shown to extend to high-risk patients [85], and persist through 3 years follow-up [86•].

To further establish the rotor-hypothesis of AF, preliminary results from the PRECISE trial [87] showed that elimination of patient-specific rotors and focal sources alone, without any PVI, demonstrated excellent short-term outcomes. Several randomized clinical trials are using this proof-of-principle to test the efficacy of FIRM-only compared to traditional ablation.

Prior work has attempted to find AF-sustaining sources using electrogram characteristics such as complex fractionated atrial electrograms (CFAE) [88]. Subsequent investigations have shown mixed results [89–91]. We [92] and others [93] have found little correlation between rotor sites and CFAE. Instead, directed or coincidental rotor ablation predicted ablation success [31].

Recently, evidence for the presence and importance of rotors and focal sources in AF has been published by other groups using FIRM [94, 95] and alternative methods. In a recent clinical trial, an array of 252 body surface electrodes was used to map atrial activation during AF [96•]. Ablation of driver sites alone modulated AF and shortened procedural time. Procedural success was 85 %, compared to 87 % in the control population. Similarly, another study found evidence of high-frequency AF rotors using surface potentials recorded using a 67-lead recording system [97•].

Conclusions and future directions

When framed within the complete context of AF, PV and non-PV triggers have a role in the initiation phase of AF, spanning the first few seconds of the arrhythmia. Next, AF transitions to steady-state arrhythmia via diverse mechanisms including as conduction velocity slowing, steep APD restitution, AP and APD alternans resulting in conduction block and reentry.

A growing body of evidence, first from San Diego and more recently from other centers, demonstrates that human AF maintenance is predominantly due to rotors and focal sources (Table 2). These findings represent a paradigm shift in AF management, focusing on sustaining mechanisms, as is currently done with other arrhythmias such as AVNRT or AFL, and demonstrating that they are not random and located in limited regions of the atria in each patient. Clinical trials are currently underway to assess the relative importance of rotor-only ablation versus PVI-only ablation in AF management, which will further establish this mechanism and potentially inform future practice guidelines.

Importantly, data discussed in this review establish rotors as sustaining mechanisms and show that targeted ablation of AF sources can improve outcomes while reducing

nonspecific, and potentially hazardous [98], non-targeted ablation. We believe that patient-specific mapping and ablation of the sustaining mechanisms of AF will become the cornerstone of AF therapy, as it is for essentially all other arrhythmias.

While these advances represent significant improvements in the mechanistic understanding of AF, several important questions remain including mechanisms for AF rotor formation in localized atrial regions, how activation disorganizes from rotors into the familiar “chaos” of AF, and how best to target rotors to treat patients. Ongoing studies by many groups will address these questions in the near future.

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Fig. 1.

a Diverse locations of rapid triggers (*red stars*) in a patient with three spontaneous episodes of AF. Note that location of subsequent rotor (*gray circle*) is conserved. **b** Rapid activation causes slow conduction, wavefront block, and functional reentry (*white arrow* along numbered isochrones). **c** Isochronal left atrial map during sustained AF shows 2 rotor sites (*curved arrows*). **d** Ablation of all rotor sites terminates AF to sinus rhythm, rendering AF non-inducible. **e** Procedural results of the CONFIRM trial at a median of 273 (IQR: 132 to 681) days, showing improvement in AF-free survival from 45 to 82 % with the addition of FIRM-guided ablation. **f** Long-term follow-up results showing durable benefit to FIRM-guided ablation at a median of 890 (IQR: 224 to 1563) days. Figures 1a, b adapted with permission from Schricker et al. [18]. Figure 1e adapted with permission from Narayan et al. [7]. Figure 1f adapted with permission from Narayan et al. [86].

Table 1

Characteristics of patients in the CONFIRM trial

Characteristics	Conventional ablation (n=71)	FIRM-guided ablation (n=36)	p value
AF presentation			0.12
Paroxysmal	24 (34 %)	7 (19 %)	
Persistent	47 (66 %)	29 (81 %)	
Age (y)	61±8	63±9	0.34
Gender (male/female)	68/3	34/2	1
Nonwhite race	9 (13 %)	6 (17 %)	0.57
History of AF (months)	45 (18–79)	52 (38–110)	0.04
Left atrial diameter, mm	43±6	48±7	0.001
LVEF (%)	55±12	53±15	0.59
CHADS2 score			0.09
0–1	38 (54 %)	13 (36 %)	
2 or more	33 (46 %)	23 (64 %)	
Hypertension	50 (70 %)	31 (86 %)	0.07
Diabetes mellitus	22 (31 %)	12 (33 %)	0.81
Previously failed >1 AAD	16 (23 %)	16 (44 %)	<0.05

Table 2

Timeline of selected works in rotor and focal source research in human AF

Year	Reference	Study type	Description
2011	[78]	Dual-center clinical trial	Late-breaking clinical trial presentation: FIRM-guided ablation vs. conventional ablation
2012	[7•]	Dual-center clinical trial	CONFIRM trial: FIRM-guided ablation vs. conventional trigger ablation
	[75]	Mapping, mechanisms	Physiologic basis of FIRM mapping
	[76]	Mapping, mechanisms	Physiologic basis of FIRM mapping
	[77]	Case report	Videotaped FIRM ablation case
	[83]	Multicenter case series	Multicenter case series of FIRM mapping and ablation of AF, atrial tachycardia
2013	[31]	Mapping, mechanisms	Success of AF ablation can be explained by ablation of AF sources
	[92]	Mapping, mechanisms	AF sources are unrelated to sites of complex fractionated electrograms or low voltage
	[85]	Single-center clinical substudy	FIRM-guided ablation is effective in high-risk groups
	[79•]	Mapping/algorithms	Biophysical analysis of spatial resolution, with modeling
	[95]	Clinical case	FIRM mapping of atypical atrial flutter
2014	[84•]	Multicenter clinical trial	Multicenter registry shows similar outcomes to CONFIRM trial
	[86•]	Single-center clinical trial	Very long-term results of the CONFIRM trial
	[28]	Mapping, mechanisms	Spatial stability of rotors
	[94]	Clinical case	Robotic ablation and FIRM mapping
	[96•]	Single-center clinical series	Rotor and source mapping and ablation using surface ECG mapping
	[97•]	Mapping study	Independent validation of rotor mapping using surface ECG data