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Ectopic foci and rotational activity as keys to atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia, but it is also mechanistically mysterious. Its onset is typically triggered by ectopic foci with short cycle length causing premature depolarization. These point sources are borne from a failure in the intracellular calcium handling system within individual cardiomyocytes. In contrast, AF drivers that perpetuate activity are often caused by rotational features (micro-reentrant circuits), thereby providing a continual source of substrate electrical activation. Newer techniques have created a window of opportunity to investigate the effect of both triggers and drivers in the onset and maintenance of AF. Newly developed Tau20-RETROmapping, a rule-based system using electrogram energy and percentage of sites exhibiting an increased energy level as metrics, identifies individual AF wavefronts and driver-like activation patterns with high sensitivity and specificity. Another novel technology, electrographic flow (EGF), discerns active point sources generating divergent, centrifugal flow from passive rotational patterns where wavefronts converge centripetally. It maps likely sources initiating and perpetuating AF, identifying both ectopic foci and rotational activity. Refractory gradients have been shown to be of importance in the onset of rotational activity in AF. An early prospective clinical study has demonstrated that strong refractory period gradients (SRG) are readily mapped during sinus rhythm, and that ablation there increases success rate for terminating AF. Minimal or no correlation was found between the hotspots versus low voltage or likely fibrotic areas. Understanding the mechanics of AF onset via these new techniques and technologies will likely lead to improved treatment efficacy.

Keywords: ablation, atrial fibrillation, electrographic flow, steep repolarization gradient, Tau20-RETROmapping

Introduction

Progress in understanding atrial fibrillation (AF) has been steadily improving [1]. Early maps and mapping techniques hinted at the chaotic electrical activity that occurred, but they were not yet sufficiently advanced to precisely define it. Assigning or pinning a local activation time (LAT) to AF electrograms was attempted, but difficulties were encountered due to the multitude of deflections caused by crosscurrents [2]. Initially, such maps of AF demonstrated chaotic wavelets traveling across the medium, which emerged and extinguished over brief moments in time. Older AF propagation videos were constructed using technology based on the electrogram deflections. However, during AF, the unfiltered electrogram signals are highly fractionated and of low voltage [3]. Initial software relied upon math interpolation to approximate voltage distribution between electrodes, which could erroneously cause the appearance of chaotic propagating wavelets. Artificial wavebreaks or false spinning loops were generated, particularly when catheters briefly lost contact with the substrate. Far-field background noise from the ventricles was also an issue at the thin-walled atria. More recently, Focal Impulse and Rotor Modulation (FIRM) technology used phase analysis to transform continuous voltage waves into a circle of phases (from 0 to 360 degrees, representing depolarization to repolarization) [4]. FIRM utilizes phase singularities, i.e., centers of mathematical pinwheels where all phases meet, to identify hotspots. Yet, this analysis is sensitive to noisy conditions. Simple collisions of two random waves, or a fast-firing point source, can be mistaken for a true spinning rotor core. Hence, false positive rotors were detected.

AF investigations have also focused on electrogram characteristics as a metric for identifying targets. Dr. Nademanee suggested the possibility of identifying hotspots via complex fractionated atrial electrograms beginning in 2004 [5]. His core hypothesis was that these morphologically distinct electrograms were harbingers of AF electrical activation sources. Though at the time the technology to distinguish true sources from random wavefront collisions was in its infancy, his basic hypothesis was valid. Other prominent biomarkers that were proposed for detecting hotspots included the dominant frequency (DF) metric [6]. The DF is measured from the frequency spectrum of an approximately 8sec electrogram sequence – being the largest peak not a harmonic in the physiologic range of interest of 3-12Hz [7]. Although with distance from the source, DF may diminish due to slowed and blocked conduction, swaths of the same or similar DF often occur over broad areas of the atrial chamber [8, 9]. Hence, although the DF, as well as the dominant amplitude (DA) which is the peak of the dominant frequency [10], are noted biomarkers, they are primarily useful to characterize different forms of AF, not for hotspot detection.

AF triggers and drivers

Ectopic foci, which randomly generate premature electrical impulses, are triggers that typically appear within the pulmonary veins, particularly during pre-AF and early paroxysmal AF [11]. In hearts compromised due to age or inflammation, calcium ions may leak into the cell during the Phase IV (diastolic) interval (i.e., the cellular resting phase) [12]. The sodium-calcium exchanger removes the excess calcium, but at the expense of adding more intracellular sodium, which may create an unprovoked positive voltage i.e., a delayed afterdepolarization or DAD [13]. If the voltage spike crosses threshold, it triggers a cellular action potential which forms a diverging premature activation wavefront, possibly leading to disorganized activity in the form of wavefront slowing and functional conduction block.

Rotational activity provides a consistent electrical source to perpetuate arrhythmia [14, 15]. For such reentry to occur, the presence of unidirectional conduction block followed by delayed propagation into the previously excited area is necessary. Unidirectional conduction block forms wherever the substrate is still refractory. It may also form at areas of source-sink (impedance-load) mismatch, whereupon the electrical current generated from preceding activating substrate (i.e., the source) is insufficient to activate the downstream substrate (the sink) [16]. This process is rate-dependent, and most often occurs during premature excitation [17]. Once unidirectional block forms, if there is a sufficient pause prior to wavefront arrival on the opposite side of the unidirectional block line, the wavefront reenters priorly activated tissue, forming a rotational activity source. Clinical examples include incomplete overlap of ablation lesions surrounding the pulmonary veins (PVs), so that a wave may circle around the outside, forming micro-reentry [15], and wavefronts blocking at one end of an incomplete roof line, then traveling all the way around the mitral valve or Bachmann's bundle, forming macro-reentry [18].

Modern mapping technologies

During recent years, several mapping techniques and technologies have become highly beneficial for arrhythmia analysis. High-resolution epicardial and endocardial AF mapping has revealed the presence of complex, disorganized propagation patterns with multiple, independently propagating wavelets colliding and disintegrating, supporting the multiple wavelet hypothesis [19-21]. Focal patterns are evident, some of which are transmural breakthroughs, yet sustained, stable rotors are uncommon. The recently developed Tau20-RETROmapping system is designed to detect and characterize the chaotic electrical waves, and it can also be used to create real-time endocardial activation maps during AF [22]. Advanced filters remove background noise and signals with poor electrode contact. The system marks electrogram activation time via a rule-based technology. The Threshold for Local Activation (TLA) calculates local electrogram energy as the squared voltage over a moving average window. The Threshold for Activation Wave (TAW) is a threshold percentage of closely spaced electrogram catheter recording sites (bipoles) that simultaneously detect a local electrical deflection. Visual maps of electrical pathways are then displayed for each beat of AF. The clinical statistical validation showed that using a threshold TLA of 75mV^2 and a threshold TAW of 12% (for example, activation of at least 6/48 bipoles in the grid) results in highest sensitivity and specificity for AF wavefront detection. When the thresholds are attained over a tight synchronized timeframe, the system uses the unipolar signals to determine the maximum negative slope ($-dV/dT_{max}$) as the actual local activation time (LAT) for each recording spot. A spatiotemporal coherence filter ensures that if many recording sites happen to randomly generate deflections at similar times, it will be rejected rather than being construed as a coherent wavefront, based on a very narrow time window, spatial adjacency, and physiological conduction velocity constraints required for acceptance. The system thereby improves AF activation mapping by enabling AF activation to be displayed in real time. The left atrial appendage in particular was found to possess driver-like activation patterns.

Nevertheless, activation-dependent changes in bipolar voltage and electrogram morphology remain a limitation of substrate interpretation in platforms such as Tau20, and sequential contact mapping cannot simultaneously establish the relationship between activation patterns at widely separated atrial sites. Its implementation is rule-based rather than AI-based; operating thresholds are optimized against manually annotated electrograms rather than adaptive learning. The TLA and TAW parameters are optimized based on the sensitivity and specificity for identifying organized AF wavefronts across various cardiac rhythms. A two-part clinical validation standard served as the

ground truth: 1. Electrophysiologists searched for a high degree of temporal and spatial organization, defined as a uniform, non-fractionated electrical sweep that sequentially propagated across adjacent bipoles on the multielectrode grid. 2. The algorithm's automated maps were then cross-referenced against the electrophysiologists' manual annotations. One limitation of surface mapping techniques, however, is endocardial–epicardial dissociation. Activation at the two atrial surfaces can become asynchronous, particularly with advanced remodeling, so that a breakthrough appearing focal on the endocardium may in fact reflect transmural or epicardial propagation. Simultaneous endocardial-epicardial mapping and integration with three-dimensional anatomical information may ultimately be required to resolve such ambiguity.

ElectroGraphic Flow (EGF) is another recently developed medical imaging technique and it translates electrical signals from the heart into visible space-domain flow vectors to track endocardial wavefront propagation during complex arrhythmias including AF [23]. By comparing spatial and temporal gradients, it checks for voltage space transitions along the X- and Y-axes, and time-transitions between time points. The EGF velocity vectors grow longer and more defined wherever voltage is shifting rapidly, often along the electrical wavefront leading edge. The technology thereby detects and localizes point sources, rotational drivers, and divergent electrical activations (singularities) which sustain abnormal heart rhythms. Clinical trials including the randomized FLOW-AF and the observational RESOLVE-AF results have shown that targeting EGF-identified sources significantly reduces AF recurrence as compared to imparting standard ablation lesions alone [24-26]. Based on EGF mapping, focal hotspots, which are active sources exhibiting centrifugal propagation, and passive rotational patterns, characterized by centripetal flow convergence, typically number 1 to 2 in paroxysmal AF, 2-5 in persistent AF, and 5+ in longstanding or permanent AF [27]. Recent EGF studies suggest that focal activity accounts for approximately 25% to 40% of all hotspots, while rotational activity comprise approximately 60% to 75% of hotspots. An important discovery from panoramic contact mapping is that the rotational hotspots tend to meander within a stable architectural zone of ~ 1-2 cm^2 [28]

At issue with EGF and many new technologies is the 'whack-a-mole' or 'hydra-with-seven-heads' phenomenon - if an operator successfully ablates Hotspot A and Hotspot B, the global electrical dynamics of the chamber shift dramatically [29]. With the original dominant anchors eliminated, chaotic wavefronts may find new patches of abnormal tissue on which to anchor, creating a Hotspot C and Hotspot D during the same procedure, or causing subsequent reentrant atrial tachycardia. Furthermore, missing electrode contact with atrial surfaces at portions of the chamber having complex geometry causes data gaps, potentially leading to a mislocation of the true hotspot core [30]. As a result, currently only the most stable, dominant, and persistent extra-pulmonary vein hotspots are ablated. Focal activity, which requires minimal ablation lesioning to eliminate, are prioritized over the presence of more spatially extended and meandering rotational activity [31]. The pulmonary veins are the ultimate point source locations, particularly in paroxysmal AF, and their isolation is therefore a priority [32]. Focal sources also provide premature excitation resulting in remodeling, so that rotational activity more readily forms, which adds to the urgency of their ablation [33]. After severe structural remodeling causing interstitial fibrosis and scarring, any rotational activity may become self-sustaining, particularly in persistent and longstanding persistent AF, and must be targeted for success even after eliminating focal activation sources [34, 35].

For further improvements in technology, it should be noted that although AF activation patterns often vary beat-to-beat, substrate properties, including spatial refractoriness and conduction

characteristics, are probably relatively stable over electrophysiologic mapping time scales [36]. Repolarization heterogeneity is likely important in establishing sources of micro-reentrant activity, whereas fixed conduction barriers and scar assume greater importance in established macro-reentry.

Formation of rotational activity

Bidirectional conduction block occurs wherever there is a no-flux boundary, such as is caused by fibrosis, calcification, or the presence of fat globules [37]. It provides circuitous pathways for activation wavefront travel; however, the pathway by itself cannot form a reentrant circuit [14]. Circuit onset often occurs following premature excitation and the resulting functional conduction block that may occur [38, 39]. Once unidirectional block forms, a long and/or slow propagation pathway around the blocked area delays wavefront arrival on the opposite side, so that it can reenter the previously activated region, initiating reentry [40]. The presence of a refractory patch can result in unidirectional conduction block, as illustrated via an automaton simulation in Figure 1 [41]. Activation time is shown early-to-late (red-to-blue). The stimulation site is at the lower right corner of the grid. 2:1 anisotropy is added (2× faster conduction velocity vertically along the grid versus horizontally). A refractory patch is noted by the rectangular region not activated during S2 in panel A (arrow). There is also a minute, simulated ablation lesion (small black rectangle) below it, through which electrical activation does not occur. The S2 premature wavefront arrives while the patch is refractory; hence the wavefront blocks there and travels around. Once recovery of excitability occurs, the wave enters the refractory patch to generate rotational activity (panels B-C). The simulated ablation lesion did not prevent onset of rotational activity. Additional simulated fibrotic discontinuities within the substrate delay the rotational activity around the refractory patch and also cause frittering along S1S2 wavefront leading edges (panels D-F).

Presence of a refractory gradient can also contribute to unidirectional conduction block formation, as in Figure 2 [42]. When the S2 wavefront impinges upon a uniform gradient at the point where the refractory period RP = S1S2 interval, it blocks and does not reenter (panels A-C). However, if random perturbations alter refractoriness along the boundary, then the wavefront, although blocked at RP = S1S2, can travel around wherever RP < S1S2, and if there is sufficient delay it will reenter the previously excited area, establishing a micro-reentrant circuit. This process can be aided by the presence of fibrosis or other impediments to conduction, including prior ablation-mediated scar, which enable the pathway to lengthen, providing additional delay for recovery of excitability.

Source-sink mismatch – defined as a low source electrical current versus a high required sink current during activation wavefront propagation – may also occur, the effect of which is magnified by a short coupling interval [39]. When unidirectional conduction block forms during source-sink mismatch, if the wavefront can travel around to the opposite side, it will conversely be propagating from a high source current region to a low required sink current region, whereupon it can proceed, establishing a micro-reentrant circuit.

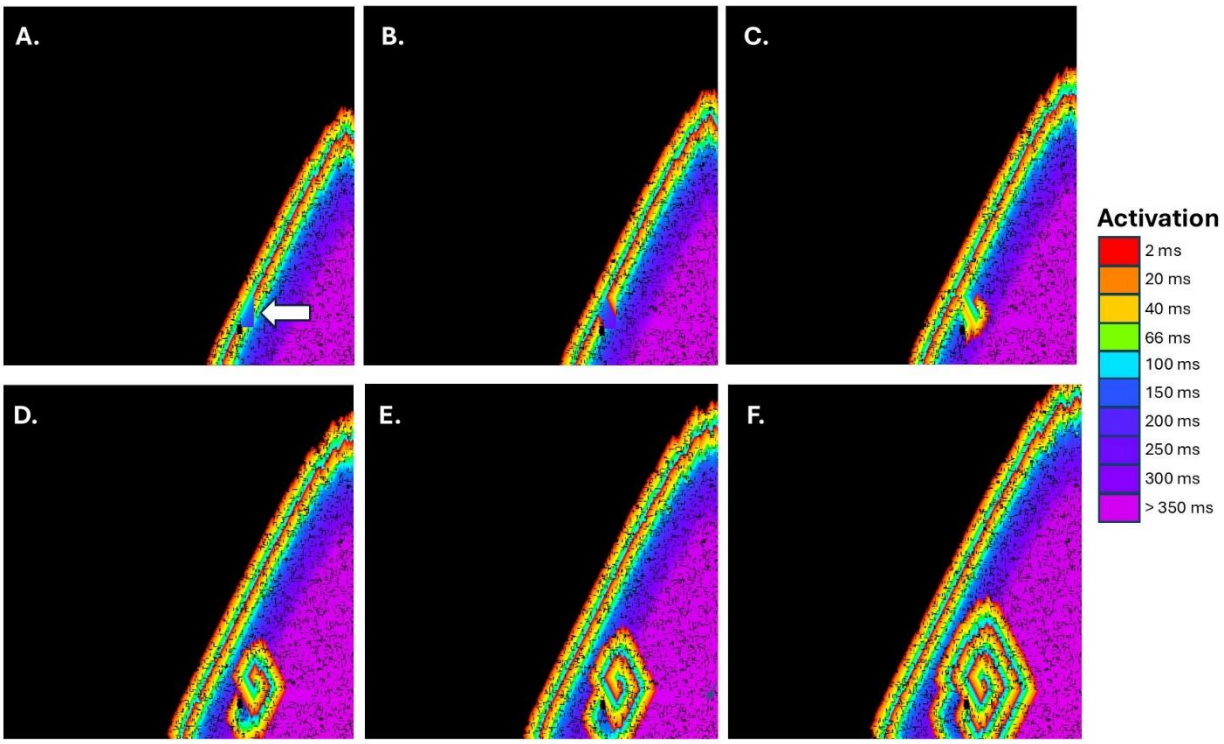

Figure 1 Using an automaton model for illustration: A. presence of a refractory patch (small blue partial rectangle) at S2 stimulation (arrow). B. The S1 and S2 wavefronts proceed from lower right. Included in the model are fibrosis (small black lines) and anisotropy (2x conduction velocity vertically versus horizontally). There is a uniform refractory period throughout. C. Rotational activity begins when the refractory patch recovers excitability, causing the wavefront to turn. A small, simulated ablation lesion (black rectangle just below the refractory patch in panel A) has no evident effect on the rotational activity. D-F. Due to the presence of simulated fibrosis causing wavefront block, frittering occurs along the S1S2 wavefront leading edges.

Refractory gradients

In a recent landmark clinical study, Dr. Anter and his group investigated refractory gradients in AF patients [43]. They showed that steep repolarization (i.e., refractory) gradients (SRG) coincided with regions arrhythmogenic for AF initiation, that when ablated prevented AF reinduction [44, 45]. The repolarization maps were rendered by measuring atrial effective refractory periods (ERPs) at predefined atrial locations based on the longest S1S2 coupling interval failing to capture [46]. SRGs were defined as ERP differences ≥50msec over ≤10 mm. Temporal reproducibility required AF induction during at least two separate stimulation attempts at 3–5-minute time intervals. Reentry was identified based on predefined electrophysiological features including vulnerability window and stimulation directionality. Discrete regions with SRG were demonstrated in 91.7% of patients with AF versus 8.3% of control subjects. The AF initiation sites were typically distributed along a refractory gradient, short-to-long, within approximately 20msec of the RP = S1S2 interval, and initiation was wavefront direction-dependent. Low bipolar voltage was not a distinguishing feature of AF initiation sites, though microscopic fibrosis, fiber architecture, and wall-thickness transitions remain possible contributors.

The procedural endpoint in the study was elimination of local repolarization gradient and abolition of AF inducibility using the preablation stimulation protocol. Following ablation, single-procedure freedom from AF without antiarrhythmic drugs was observed in 87.5% of patients over a

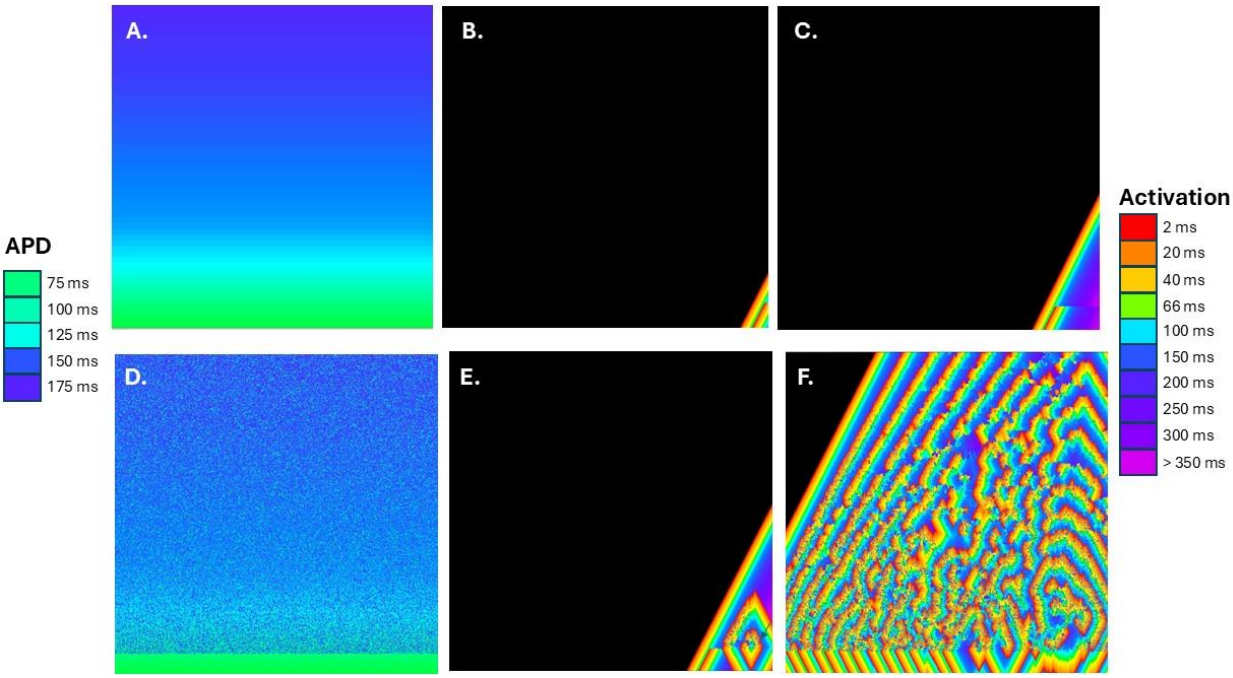

Figure 2 In this version of the automaton model, a refractory gradient rather than fibrosis is added to the substrate, shown in panel A with color code to the left. B. S1S2 begins from lower right. C. Although there is a gradient, the lack of variability in the refractoriness causes S2 to block where the refractory period RP = S1S2 interval, and no rotational activity occurs. D. A spatially random refractory component is added to the refractory gradient. The refractory patch of Figure 1 is absent. E. Onset of S1S2 shows it to arrive at discontinuities in the refractory period, and conduction block partially occurs where RP = S1S2. F. However, due to the random perturbations in the refractory period, a path is present for the wavefront to continue and reenter previously excited areas (wherever RP < S1S2). F. Because such random perturbations occur throughout the region, additional wavebreaks and rotational activity occur.

median follow-up of 489 days in an exploratory cohort of 24 redo patients with durable pulmonary vein isolation. Regions where SRGs were detected included the pulmonary veins, the atrial appendages, and the posterior wall [47]. Pulmonary vein-associated SRGs predominated in paroxysmal AF, with increasing non-pulmonary vein substrate being present in persistent AF and in redo patients with durable pulmonary vein isolation. Women more frequently harbored right atrial SRG substrate not targeted by standard pulmonary vein isolation, which may contribute to the persistently lower procedural success rates reported in female patients [48]. The study concluded that AF onset arises from substrates capable of supporting reentry, identified by sharp refractory gradients detected with programmed electrical stimulation during sinus rhythm.

Reconciliation of SRGs with other observations

The SRG study focused on AF initiation rather than perpetuation, wherein the latter scar and conduction abnormalities may play a larger role, particularly in persistent AF [49]. It is believed that roughly 15–20% of paroxysmal patients fail standard pulmonary vein isolation because of a hidden point source firing from another position, such as from the posterior wall or the septum, instead of localizing within the veins [50]. Although SRG hotspots did not correlate with low bipolar voltage, macro-catheters (with 1 mm or 2 mm electrode spacing) suffer from a limitation: when a microscopic cluster of collagen threads is interspersed with healthy, hyper-excitable muscle cells, the healthy cells will still generate a robust voltage signal [51]; thus hidden microscopic fibrotic boundaries can be missed [52]. SRGs may therefore result from microscopic interstitial or endomysial fibrosis, creating

lateral uncoupling and zig-zag conduction, so that the incoming wave splits and stalls. Furthermore, wherever muscle fiber bundles merge or change orientation abruptly, local impedance mismatch occurs [53]. The unique mechanical stretch and the increased electrical load can cause heart muscle cells to downregulate so that specific ion channels are altered, creating a SRG [54]. Mismatch also occurs at architectural transitions, with differences in electrical current loading altering speed of repolarization [55]. Moreover, cholinergic stimulation via acetylcholine, wherever it may occur, opens potassium channels, causing large alterations in refractoriness [56]. Steep spatial refractory gradients can therefore be present at ganglionated plexi, which are heavily clustered near the pulmonary vein ostia; hence refractory patches can appear virtually out of nowhere [57]. Finally, stimulation and short coupling intervals created by focal ectopic sources may cause a sharp local decrease in refractory period [11], which may diminish with distance as discontinuities delay the wavefront and slow conduction. Hence, ectopic sources may cause refractory gradients leading to rotational features.

Conclusions

AF is a complex arrhythmia more efficaciously analyzed with new techniques and technology. Arrhythmogenic sources vary, and are not necessarily generated via priorly conceived notions regarding structural and electrical substrate properties. Fibrosis may play a role in reentry formation, but it is not a required precursor; rotational activity may also form in younger patients lacking evident fibrosis. Additionally, micro-fibrosis when present is undetectable via standard catheter acquisition, and may contribute to arrhythmogenicity. For reentry onset, a unidirectional block line with sufficient path length and delay are needed for recovery of excitability from the opposite side. Refractory patches, refractory gradients with random perturbations, and source-sink mismatch are all capable of forming unidirectional conduction block, a precursor, along with sufficient pathlength for delay, for onset of rotational activity. There are a multitude of ways to form refractory gradients along short spatial intervals that can be involved in reentry induction. Intermittent focal ectopic sources caused by action potential alterations at ion channel levels may act as premature excitation triggers during onset, and they may also be in part responsible for rapid tissue remodeling causing strong refractory gradients. Rotational activity tends to form consistent AF drivers, which promotes AF perpetuation.

New tools for mapping and analysis have added to the electrophysiologist's armamentarium. Using rule-based Tau20-RETROmapping, it is now possible to accurately detect LAT and map AF wavefronts to provide a clear picture of electrical activity sources. EGF mapping identifies hotspots and can distinguish focal sources from micro-reentry, although it ideally requires the clinical AF rhythm to be present during measurement. Mapping refractory gradients is useful to identify rotational activity even when clinical AF is uninducible during study. It is now possible to identify the triggers and drivers of AF in real time so that significant improvements in ablative therapy are within reach.

The future of AF mapping may include a combination of functional interrogation and artificial intelligence (AI)-assisted data integration. Functional measurements, including refractory gradients, direction-dependent conduction, response to premature stimulation, activation stability, and vulnerability windows, provide mechanistic information not available from static voltage maps alone. AI may become particularly useful as an integrator of these dynamic electrophysiological measurements with high-density electrograms, atrial anatomy, wall architecture, and structural imaging to identify patient-specific vulnerable substrate.

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Conflicts of Interest

Dr. Angelo B. Biviano serves as a member of the medical Advisory Board for AltaThera Pharmaceuticals. The remaining authors declare no conflicts of interest.

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Data availability

No biological data was generated or analyzed during this study. The computer simulations were performed using a program that is publicly available as described in [58].

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