Is There Rule to the Chaos: Defining Stable Patterns in Atrial Fibrillation

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Treatment of persistent atrial fibrillation (AF) by elimination of pulmonary vein (PV) triggers alone with pulmonary vein isolation (PVI) has yielded poorer outcomes compared to the same treatment strategy in paroxysmal AF[1,2], consistent with the presence of additional substrate beyond the PVs. This has led to efforts to better understand the underlying mechanisms of persistent AF to devise a treatment strategy with improved outcomes over empiric PV trigger elimination. Animal studies over the past three decades suggest temporally and spatially stable organized activation patterns in atrial fibrillation[3,4]; which was validated in ex-vivo human tissue recently[5]. Clinical application of these findings has been challenging due to difficulty of using similar mapping techniques in-vivo. Ex-vivo optical mapping can visualise action potential propagation in tissues with high resolution; while clinical mapping of AF has been limited to marking activation times of electrograms as a surrogate for action potential propagation, which can be challenging to interpret in disorganized and very rapid rhythms due to low resolution compared to the multidirectional activation propagation of fibrillatory waves or unintentional far-field recording.[6]

Signal processing algorithms have been developed to overcome these challenges of working with atrial electrograms during fibrillatory conditions, which include FIRM (Abbott), ECGi (Medtronic), CARTOFINDER (Biosense Webster), electrographic flow mapping (Ablacon) and AcQMap (Acutus Medical), which have all

identified stable localized activation patterns during AF. Such patterns are most commonly categorized as sites of rotational activation or focal activation. Partial rotation patterns have been observed but have not commonly been targeted for treatment, nor have been linked strongly to a specific electro-architectural mechanism. AcQMap also described a new repetitive pattern which is an attempt to spatially localize fibrillatory conduction called localized irregular activation (LIA). In recent studies, this has been subdivided into four potentially underlying mechanisms based on propagation patterns **(Figure 1)**[7]. However much work needs to be done to better translate these studies into useful targets for additional ablation beyond the pulmonary veins. Uniting all the approaches is necessary to study stability of activation patterns and the duration of mapping required which once addressed will also provide indirect mechanistic insights to the persistence of human AF.

In this issue of the *Journal of Cardiovascular Electrophysiology,*Pope et al. studied the spatial stability of AF drivers and optimal duration of mapping while simultaneously mapping AF activation in both the left and right atria using the AcQMap system in 21 patients undergoing first time catheter ablation[8]. The wavefront patterns studied were localized rotational activation (LRA) - defined as a smooth depolarization wavefront rotating 360 degrees around a central point within 300mm^2, localized irregular activation (LIA) - defined as a difference in angle of more than 90 degrees between the entry and exit of a conduction from a confined region (200mm^2, and not meeting criteria for LRA), and focal firing (FF) - defined as a primary activation that extends centrifugally from its origin. In order to study spatial stability, frequency of these AF propagation patterns was correlated over two separate 30-second recordings that were taken prior to any ablation. LIA had the greatest spatial stability across each 30s recording with an R^2 value of 0.81 (0.75-0.88) in the right atrium and 0.84 (0.61-0.88) in the left atrium. LRA and low frequency FF were found to have low spatial stability. However, high frequency FF, defined as occurring >10 times in the 30s recording, had similar spatial stability to LIA with an R^2 of 0.83 (0.68-0.85). With regards to temporal stability and finding an optimal mapping duration, LIA was found to be most temporally stable with a kappa value of 0.8 reached by 12-seconds, LRA was the least temporally stable taking at least 22-seconds to reach a kappa value of 0.8 ($p<0.0005$), and it took 19-seconds for FF ($p<0.0005$). The authors found that there was no difference between the left and right atria. LIA stabilized earlier in patients with paroxysmal AF compared to persistent AF. High frequency FF stabilized earlier following PVI compared to readings taken prior to PVI suggesting more stability in non-pulmonary vein sites of focal activation.

The authors should be congratulated for adherence to a lengthy research protocol, systematic approach to bi-atrial mapping, data collection and rigorous analysis. There are only a handful of centres who have performed simultaneous bi-atrial mapping, either endocardially (FIRM) or epicardially (ECGi). Furthermore the authors aim to address questions such as stability of these patterns in humans as well as optimal duration of AF mapping to determine mechanistically relevant patterns, topics on which only limited knowledge exists.

This study integrates many previous attempts to address spatiotemporal stability of putative drivers. Using the same non-contact technology, Shi et al. showed preferential conduction areas on both posterior and anterior wall, with individual pattern repetition suggestive of spatiotemporal stability[7]. They also demonstrate how mechanisms are interchangeable at the same site, which confounds easy attempts to quantify spatial stability**(Figure 2)** .

Various other panoramic mapping algorithms also looked into the stability of activation patterns in AF. Our group has demonstrated that atrial sites where persistent AF terminated into normal sinus rhythm showed organized activation that temporally fluctuated, yet recurred in conserved spatial regions, with 2 different mapping algorithms using panoramic simultaneous mapping with basket catheters. Of 55 patients, 47 showed drivers for >50% of the time of the mapped interval over 1 minute. Optimal mapping duration depended on the prevalence of an AF driver, with > 66% prevalence requiring 23 s of mapping and smaller cutoffs requiring 4-8 s of mapping. In earlier studies where panoramic basket electrode catheters were left in place for extended periods of times with FIRM mapping, we have also found these localized sources to be stable over tens of minutes, with examples of source stability shown up to 90 minutes[9]. In subsequent studies, when patients returned for repeat ablation for recurrent AF (21±20 months later), spatially conserved localized

AF sources were shown in the repeat ablation procedure compared to the index procedure where mapping, but no ablation of these localized sources, was done[10].

Panoramic mapping has also been conducted from bi-atrial simultaneous epicardial recordings of AF obtained during surgery. Lee et al. also noted focal activation patterns originating from spatially conserved sites with temporally variable behavior, with the duration of individually repetitive foci upto 19.7 seconds[11]. Non-invasive mapping of body surface potentials during AF with ECGi with duration of cumulative mapping windows was 9+1s, has shown the percentage of time without any driver was 38 + 22%[12]. Reentrant drivers tended to occur in the same region but not necessarily at the same discrete site, traveling a mean of 7 + 2cm^2. Our group has also shown correlation of temporal and spatial organization in reentrant AF activation patterns when simultaneous body surface mapping and intracardiac mapping during AF was performed, with the two mapping strategies reflecting epicardial and endocardial activation patterns respectively[13].

Sequential mapping confers differing definitions of stability, as by definition the whole atrium cannot be mapped simultaneously. However, a recent study using CARTOFINDER showed that sites of AF termination had temporal stability and were spatially conserved, with focal drivers having greater temporal stability than rotational drivers[14]. Another sequential method is STAR (Stochastic Trajectory Analysis of Ranked signals) mapping in which all 24 sites of early activation that were foci of AF termination were present in every segment of the 30 second mapping duration[15].

This study by Pope el al. and the previous ones mentioned above illustrate the challenges of classification and definition of stability. It is possible they are describing the same mechanisms, but with algorithm specific limitations on stability and discordance of classification as similarities exist between them. As cardiac electrophysiology is a multi-disciplinary effort, the field has differing perspectives on the relevance of stability. For example, should we classify per-patient (the clinician's perspective) or per source (the modeller's perspective) or per mechanism (the scientist's perspective)? Clinically, the field of relevance is within an ablation lesion (approx. 4mm), but scientifically this may seem arbitrary. Beyond the definition of stability, it is unclear what happens at areas where multiple mechanisms are displayed **(Figure 2)** . Is there a dominant mechanism based on occupancy percentage of the zone, or is it more important that the zone itself can support these? This leads onto the practical relevance of these sites - to target anything beyond PVs, it should firstly be stable enough to justify ablation, then show proof of disappearance when remapped that it has been treated. Arguably most importantly of all, how do these findings inform us of the pathophysiology of AF persistence in humans.

The increasing number of recent mapping studies, of which Pope et al. build upon, show repetitive patterns of organisations in both atria in AF persistence. As few centres have the resources or expertise to conduct simultaneous bi-atrial mapping, the findings from this study are of interest to all those in the field of AF mechanisms. The irregular substrate which was found to be most spatio-temporally stable (LIA) should now rank alongside rotational and focal activation as an important area of focus for future research studies. This will not only improve mechanistic understanding of AF beyond a simple 'trigger and substrate model' but may also lead to studies assessing clinical benefit from treating these areas with ablation and ultimately improved patient outcomes.

Figure Legends:

Figure 1 . Mechanistic subtypes of LIA and their frequency in LA of 25 patients with persistent AF (Shi et al J Arrhythmia 2020)[7] .

Figure 2 Preferential conduction zone on anterior wall of a patient with persistent AF. During a 520ms temporal window, LIA was detected on the mid-anterior wall with a combination of slow conduction and collision, followed by a LRA in the spatial region. From Shi et al. J Arrhythmia 2020.

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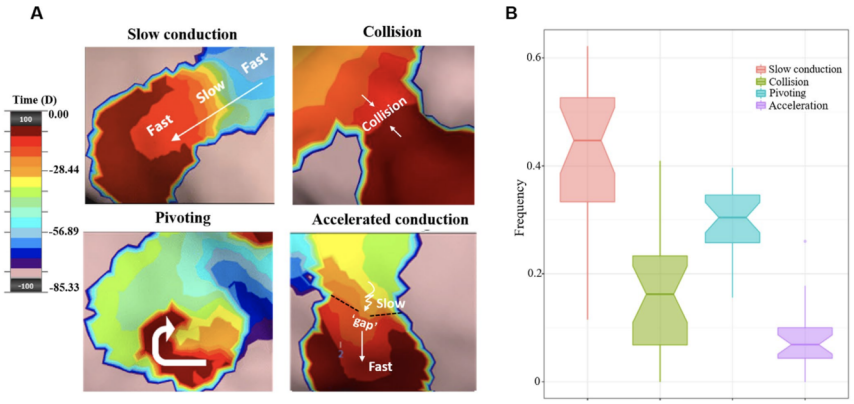

Figure 2 Preferential conduction zone on anterior wall of a patient with persistent AF. During a 520ms temporal window, LIA was detected on the mid-anterior wall with a combination of slow conduction and collision, followed by a LRA in the spatial region[7].