What is atrial fibrillation? A RETRO-spective analysis

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Ideally, before implementing any treatment as standard of care, pathophysiological mechanisms need to be identified in order to elaborate and define potential therapeutic targets. Philosophy of science described the fundamental role of categories for components of biological mechanisms: entities and activities. In this regard, activities between different entities are considered to establish a specifically organized biological phenomenon (1).

More than six decades ago, pioneer research on mechanisms of atrial fibrillation (AF) by Moe and co-workers introduced the "multiple wavelet hypothesis" (2). It was not until the mid 1980s that a group of researchers led by Allessie performed high-density atrial mapping in the canine heart and demonstrated multiple wandering wavelets with a continuous beat-to-beat change in activation pattern (3). Based on this concept,

the surgical MAZE procedure developed by Cox et al. aimed at creating anatomical barriers for multiple reentrant wavefronts by means of surgical incisions transecting the atria into separated areas was introduced (4). The identification of focal repetitive electrical discharges arising from the pulmonary veins by Haissaguerre and colleagues in the late 1990s ushered in a new era in the interventional treatment of AF (5). This new pathophysiological concept not only provided a fundamentally new target for the interventional treatment of AF, it also shifted the focus of research from the perpetuating substrate to initiating triggers. However, while patients with "short-lived" episodes of AF typically respond well to pulmonary vein isolation, efficacy of catheter ablation is limited in many patients with persistent AF. This led researchers to re-appraise mechanisms of the atrial arrhythmogenic substrate. Using computational mapping of AF models, several mathematical methods for signal processing (e.g., dominant frequency, Hilbert transformation, etc.), optical mapping, non-invasive panoramic mapping and rotational activity mapping were investigated in the pre-clinical and clinical setting for characterization of electrophysiological mechanisms during electrically established AF (6). Interestingly, there is one specific key feature collectively described: activation patterns of consecutive phases during AF demonstrate spatiotemporal organization with varying stability. Thus, accumulating data derived from contemporary AF mapping studies challenge the concept of a global randomly meandering atrial activation causing different phenotypes of AF.

In this issue of the *Journal* , Smith and colleagues (9) report from a prospective, observational study on a novel, computationally acquired and algorithm-based AF mapping technology developed in conjunction with a proprietary software (MATLAB). This mapping tool has been previously introduced by the same group and is called RETRO-Mapping (7). RETRO-Mapping is a technological expansion of RIPPLE-Mapping, an algorithm that is independent of time-window settings, also developed by the group of Linton et al (8). The basic principle of RETRO-Mapping is an analysis of cross-referenced electrode activation derived from a multi-polar catheter in the surface-covered area during AF. The current study was designed as a proof-of-concept investigation aimed at the evaluation of patterns of AF activation. A 20-pole spiral double loop catheter (AF Focus II, St. Jude Medical) was placed at the posterior left atrium. After stabilization, local electrograms during AF >30 seconds were obtained. Anatomical positions of the catheters electrodes were visualized with the NavX Ensite X system and exported into the RETRO-Mapping software along with their corresponding electrophysiological data. The algorithm calculated three parameter of wavefront propagation: cycle length, conduction velocity, and wavefront direction. The midpoint between two adjacent electrodes of the loop catheter corresponds to the position of bipolar electrograms. Through a process called triangulation, midpoints were used to define corners for the segmentation of the left atrial posterior wall into triangles. The idea of triangulation of the covered area is to obtain the most appropriate position of two adjacent midpoints for further comparison of two local electrograms connected by the edge of a triangle. The geometric and activation properties of connected electrograms allowed for further analysis used for calculation of cycle length. A dichotomization of tissue excitability (depolarized myocardial tissue was coded as 1, and repolarized tissue was coded as 0) was used to create binary images. The Euclidean distance transform algorithm calculated the distance of pixels with a value of 0 to the nearest pixel with a value of 1. Incorporating distance information and the sampling frequency of the mapping algorithm as a marker of time, conduction velocity is calculated. Smith and colleagues used the Sobel operator for image processing to analyze wavefront direction. This mathematical filter calculates the gradient of image intensity at each point. These data are then used to detect areas where the intensity changes rapidly, which helps to identify edges of an image. The activation edge direction was derived from these edges and was used to calculate the overall wavefront direction. The researchers were interested in (1) whether an advancing wavefront maintained its direction and (2) whether the plane wavefront would be predictive of the subsequent wavefront direction.

In eight patients with three types of AF (paroxysmal, persistent without amiodarone and persistent under amiodarone treatment), more than 34.000 activation edges of plane wavefronts (i.e., linear wavefront activations of the mapping field) were detected. With increasing intervals between new wavefront activations, the difference of wavefront directions also increased in a linear relationship. Smaller direction changes were observed in patients with persistent AF with amiodarone as compared to those with persistent AF with-

out amiodarone. However, the greatest variability in activation changes was observed in paroxysmal AF. Activation direction consistency, indicated by small variations between wavefront directions, was highest in persistent AF with amiodarone and lowest in paroxysmal AF. More than half of all wavefront activation patterns predicted the pattern of the subsequent wavefront. In this context, the highest predictive value of activation patterns for subsequent wavefronts was found in persistent AF without amiodarone (the AF type with the shortest cycle length).

With the presented study, Smith and colleagues shed some light on the complexities surrounding AF activation patterns. Gleaned from human high-density contact mapping of electrophysiological features during AF, data were processed with a dedicated software in order to transform AF activation patterns into a color-coded two-dimensional model. This novel software package may provide real-time calculation of conduction velocity and cycle length during a mapping/ablation procedure and could potentially be incorporated into existing 3-dimensional mapping systems. The authors are to be commended for providing a potential solution for processing electrophysiological activation data of AF with the potential to include this information into the ablation procedure. Furthermore, the data of this study reinforce the paradigm that AF perpetuation follows an organized and repetitive activation pattern (10).

While the study has a clear scientific basis, there are some practical issues to be considered. First, the current technology is limited by the apparent inapplicability to fibrotic atrial tissue which may represent an anatomical substrate in patients with more advanced types of persistent AF. Second, the algorithm characterized paroxysmal AF by features indicating more "disorganized" patterns as compared to the persistent AF types. The reasons for this observation currently remain unclear since paroxysmal AF with focal triggering (and maintaining) sources predominantly located within the pulmonary veins (and not the atria) and longer AF cycle lengths appears to represent a more organized type of AF. Third, with the current type of visualization of activation patterns, focally activated wavefronts cannot be distinguished from rotor activity or even passively activated areas. Fourth, only a small area covered by the double-looped mapping catheter can be mapped at a given time. However, even with larger high-density contact mapping catheters (e.g., the basket catheter), it still remains impossible to simultaneously cover the entire surface of the left atrium. In this context, the data of the presented study also may help to overcome this limitation since they revealed that a preceding wavefront predicted the subsequent activation pattern, potentially indicating similar wavefront configurations in neighboring areas. Sixth, calculation models used in this study are evaluated with a limited number of electrodes. Thus, it needs to be determined if larger areas represented by considerably more electrodes (and data) can undergo computational analysis in the same way (and in real-time). Finally, further and much larger studies are needed to determine how best to incorporate information on AF mechanism and visualization of atrial activation during AF in the clinical setting. Thus, next steps of research may include characterization of appropriate targets for the interventional treatment.

At the end of the day, the clinical electrophysiological community should welcome efforts aimed at improving our understanding of the underlying mechanisms of particularly non-pulmonary vein dependent AF. This seems critical in order to define a tailored approach to the individual patient. The alternative is a continued focus on "empirical" ablation without fully appreciating the underlying pathophysiology. For now, durable pulmonary vein isolation is the only pathophysiologically established treatment in AF ablation, but hopefully will not remain the only in the future.

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