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Mapping for Non-Pulmonary Vein Atrial Fibrillation Sources: The Road to Improved Ablation Outcomes

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Abstract

Since the publication of seminal work demonstrating ablation of AF triggers within the pulmonary veins, significant focus has been placed upon finding adjunctive AF mapping and ablation strategies to improve the targeted treatment of this arrhythmia. Presently, wide-area circumferential ablation to achieve pulmonary vein isolation has become the standard of care for catheter-based management. However, despite significant work, a comprehensive mechanistic understanding of the sustaining mechanisms of AF remains elusive. The present study from Nagase and colleagues provides important insight derived from a multielectrode catheter-based mapping algorithm regarding the spatial relationships between identified targets, regions of low voltage, and complex fractionated atrial electrograms. Being spatially distinct and distributed in both atria, they may represent novel targets for ablation therapy. Additional studies are required to better assess the impact of elimination of such foci.

Editorial

"The Road goes ever on and on / down from the door where it began. / Now far ahead the Road has gone, / and I must follow, if I can, / pursuing it with eager feet, / until it joins some larger way, / where many paths and errands meet." -J.R.R. Tolkien

Nearly 25 years have passed since Prof. Haissaguerre's seminal AF study[1] ushered in the era of catheter-based nonpharmacologic therapy of AF. The core findings from that work, that the pulmonary veins (PVs) frequently harbor the triggers for AF, remain the central tenet upon which current ablation therapies are based. A significant amount of research has been conducted since that time in the basic science, translational, bioengineering, and clinical settings to improve our understanding of this common arrhythmia and improve the delivery of ablation. But questions regarding the optimal targets and strategies to map these phenomena remain.

In this issue, Nagase and colleagues report the results of their mechanistic study of multielectrode catheter mapping of AF drivers. The study enrolled 20 patients with persistent AF undergoing AF ablation. The authors meticulously evaluated the relationship between potential AF drivers identified by Cartofinder, regions of low voltage, and areas

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with complex fractionated atrial electrograms. Notable findings include the following: AF drivers were found in both atria; were predominantly focal according to this mapping technology; and AF drivers did not co-localize with complex fractionated atrial electrograms (CFAE) or low volage regions. These findings add to the growing body of literature regarding the spatial relationships between regions of interest identified by various analysis techniques and provide a unique perspective regarding the current state of the art in AF driver mapping.

Following the report of PV triggers for AF[1], many attempts have been made to improve the detection of AF-sustaining sites outside the pulmonary veins, particularly in patients with persistent or recurrent AF. In these populations, regions of diseased myocardium outside of the PV ostial areas may harbor substrates capable of initiating and sustaining AF, negatively impacting the procedural success of pulmonary vein isolation alone. Some of the first attempts at improving AF ablation success focused upon linear ablation lesions at the mitral isthmus[2] and other sites. Complex, fractionated atrial electrograms (CFAE) were also proposed as markers of AF drivers[3]. Despite promising early reports, the randomized, multicenter STAR AF II trial demonstrated that neither approach provided improvement in arrhythmia-free survival compared with pulmonary vein isolation. Furthermore, a strategy of defragmentation (combination of PVI, linear lesions, and extensive CFAE ablation) also did not improve arrhythmia-free survival[4] in a multicenter clinical trial. Relevant to the present study, however, CFAE identification algorithms remain within the clinical armamentarium and are commonly employed given the convenience of using such algorithms and the lack of more definitive AF driver surrogates.

The next mechanistic insights into AF were provided by dedicated, multielectrode basket catheter (FIRMap, Abbott, Chicago, USA) recordings during AF. Employing phase analysis, this process identifies repetitive rotational drivers during AF within the left and right atria. Mechanistically consistent with prior studies of cardiac fibrillation[5], this approach resulted in high rates of AF termination during ablation and improved AF-free survival[6] in initial reports. However, a multicenter trial of this technique was negative (REAFFIRM trial; NCT02274857) and subsequent studies failed to demonstrate significant benefit in repeat ablation procedures[7]. More recently, an emerging technology also employing a dedicated mapping catheter (AcQMap, Acutus Medical, Carlsbad, USA) has been studied. In a large, single arm, multicenter study the technology demonstrated high single and multi-procedure arrhythmia-free survival[8] with high rates of AF slowing and termination. Additional, randomized studies are required to assess the precise impact of this technology compared with PVI alone.

Employing a non-invasive, inverse-solution mapping vest technology, significant work has demonstrated the ability to identify focal and rotational drivers in AF[9]. A multicenter study found high rates of AF termination[10] but also demonstrated recurrent atrial tachycardia. This approach remains a topic of ongoing research interest, with a more recent single-arm study also demonstrating good clinical results in a persistent AF population[11].

Leveraging imaging-based technology, prior work has demonstrated that increased atrial fibrosis burden was associated with greater risk of AF recurrence after AF catheter ablation.

To test the hypothesis that targeting of such regions may improve AF ablation success, the multicenter, randomized DECAAF-II study was performed[12]. The study results were negative for improved freedom from AF in the MRI-guided limb.

Finally, focus has shifted to more spatially limited, multielectrode catheter mapping. Technologies include Cartofinder (Biosense-Webster, Carlsbad, CA), the RADAR mapping system, and the VX1 mapping system. Prior work with Cartofinder has shown promising initial results in identifying intra-pulmonary vein[13] and non-pulmonary vein[14] AF targets. The RADAR system (AFTx, Inc, Westminster, CO) recently demonstrated clinical feasibility in a persistent AF population[15]. The rate of AF termination with ablation was 55%, with a 74% freedom from atrial arrhythmias on or off antiarrhythmic drugs at an average of 1 year follow-up. In the VX1 system (Volta Medical, Marseille, France), an artificial intelligence-based mapping algorithm has been developed to assist in identifying AF drivers. A multicenter, single arm study showed promising procedural results which were consistent between centers[16]; randomized multicenter studies are ongoing.

In this context, the present study provides important perspective with respect to the relationship between AF targets identified by spatially limited multielectrode mapping catheters and other markers of potential AF drivers – notably regions of low voltage and CFAE. Prior work has shown that AF drivers identified by Cartofinder are distinct from low voltage areas[17]. The present study adds to the current body of knowledge in that AF targets identified by the Cartofinder technology are also spatially distinct from regions of CFAE. This is notable given the mixed results seen with ablation of abnormal electrograms in prior work[18] and the need to identify mechanistically important AF sustaining sites.

A second notable finding regarding in this study is that most non-PV AF drivers identified with this technology were characterized as focal. This differs from some prior work but agrees with the work by Unland and colleagues[14]. From a mechanistic standpoint, characterization as rotor, suggesting functional reentry, or focal, consistent with triggered activity or endocardial-epicardial breakthrough, is important for a better understanding of the precise mechanism of fibrillatory activation. In the context of catheter ablation, this distinction may be less important than the sensitivity and specificity to truly identify AF-sustaining regions, and may be dependent to some degree upon the computational mapping methodology, spatial resolution, and layout of the mapping electrodes themselves.

One limitation of the present work was the fact that AF termination was rare. While the importance of AF termination is debatable[19], other studies in AF ablation studies have reported significantly greater rates of AF interruption[10, 15, 16, 20]. It remains to be seen whether this lack of AF termination is related to shortcomings in the mapping system or ablation strategy, and whether the therapy at such locations impacts AF outcomes.

A second limitation was that the study did not provide a control group by which to assess AF ablation success in a cotemporaneous cohort. Of course, this hypothesis-generating study was not powered to assess ablation outcomes; larger, randomized clinical trial of this approach are required.

A third limitation of the study is that the mapping process requires deliberate placement of the multielectrode catheter sequentially at sites throughout the atria. This process is likely to add time significant time and potentially increase complications related to catheter manipulation. Potential combination of this technology with extant[10] and emerging[21] regionalization technologies may permit more focused mapping to expedite this process.

In summary, the authors of this work deserve considerable congratulations in presenting their detailed study. Because of these and other ongoing efforts in the field, the prospect of improved AF targeting and ablation strategies moves steadily closer. Indeed, these and other studies are converging “where many paths and errands meet” at an improved understanding of the optimal treatments for atrial fibrillation, bringing hope to the many patients with this common, debilitating arrhythmia.

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