Ablation of Driver Domains During Persistent Atrial Fibrillation:

A Call for More Understanding

Running title: Kalifa et al.; A call for more understanding

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In this issue of Circulation, readers will find a fascinating study presented by Dr. Haissaguerre and several members of a promising and newly erected Institute for Cardiovascular Research located in Bordeaux (France): the LIRYC, (“L’institut de Rythmologie de Modélisation Cardiaque”, The Institute for Arrhythmia and Computer Modeling Research).1 This is yet another pioneering contribution from the Bordeaux group which, if confirmed, may improve the management of patients with persistent atrial fibrillation (AF). AF is commonly classified as paroxysmal (PAF) or persistent (PsAF), depending on the duration of the arrhythmic episodes, fewer or more than 7 days.2 PsAF may also be sub-classified as long-standing persistent (LPsAF) when fibrillation has been continuous for more than a year.2 In the late nineties, Dr. Haissaguerre and team’s seminal work indicated that, in patients with PAF, a catheter ablation procedure may be targeted at discrete pulmonary vein (PV) electrical foci and that PV electrical isolation from the remainder of the atrial muscle may prevent AF re-initiation.3,4 While the exact nature of PV foci has never been fully elucidated, this procedure proved successful in terminating AF, and in preventing its recurrence.5,6 Later on, a consensus emerged to propose PV isolation to patients with PAF, alone or in complement to an anti-arrhythmic drug therapy.2 Thereafter, many suggested that this procedure may also improve the outcome of patients with PsAF,7-9 with, however, the need for adjustments in the ablation strategy.8-11 Despite these efforts, the success rate of catheter ablation for patients with PsAF, let alone LPsAF, has remained substantially lower than that of PAF ablation.6,12 A nearly unanimous view is that ablation works well for PAF, but that the procedure is more tedious and the outcome less predictable for PsAF or LPsAF. Speculations as to what makes PsAF/LPsAF ablation less successful than PAF ablation could be summarized as follows: (i) Intensely remodeled and fibrotic atria are more difficult to ablate than normal atria. After an intense electrophysiological
and structural remodeling during the transition from PAF to PsAF, any region in the atrium is capable of maintaining PsAF. (ii) Ablation approaches, even if often extensive, miss key regions that mechanistically maintain the fibrillatory activity. Recently, the latter contention was propelled to the front scene after the presentation of an innovative ablation approach. In patients with PAF or PsAF, Narayan et al. mapped AF with a 64-pole basket mapping catheter positioned inside the atrium. After phase analysis of the signal obtained, these authors suggested that during AF, reentrant sources-a.k.a. rotors- may be localized and then targeted; and that ablation at regions harboring rotors is sufficient to increase the success rate of PsAF ablation procedures.

One of the ground-breaking aspects of these clinical contributions was that they were a resounding confirmation of the hypothesis that AF may be maintained by a single or a discrete number of reentrant sources. Initially hypothesized by Lewis in 1914, this mechanism of AF maintenance was subsequently described with high resolution optical mapping approaches in isolated hearts maintained in AF. Spiral waves were seen activating other atrial regions at a high frequency of excitation, and rotor parameters such as frequency of rotation, wavebreak formation and fibrillatory conduction indicated that rotors maintain fibrillation. Together with these experimental contributions, clinical studies described that high frequency regions may be successfully ablated. Still, human reports lacked direct evidence that such high frequency regions were indeed rotors. The successes of Narayan et al. in visualizing examples of rotors in patients in both PAF and PsAF then contributed to support the idea that relatively small rotor regions are key to AF maintenance. However, limitations inherent to the FIRM-guided approach proposed by Narayan et al., such as a relatively low mapping resolution and the need for a basket catheter positioned in the left atrium, were seen as a deterrent by some investigators. Although Narayan et al. were praised for their tour de force, it was unclear whether this could
durably change the therapeutic approach of patients with PsAF.

Here, Haissaguerre et al., with a distinct mapping approach, present a clinical study that confirms that small atrial regions harboring rotors are key to the maintenance of PsAF.1 The authors probed AF dynamics with a 252-electrode mapping vest that enables the non-invasive recording of unipolar surface torso potentials (ECVue™, Cardioinsight Technologies). From these torso potentials, biatrial inverse-reconstructed potentials were calculated according to measurements obtained from thoracic CT scan three-dimensional images of individual biatrial geometries.30, 31 This process, also known as electrocardiography imaging (ECGi) was developed by Yoram Rudy et al. for ventricular mapping, and later on adapted to atrial mapping.31 In Haissaguerre et al. study, electrograms were acquired in AF during long ventricular pauses - spontaneous or diltiazem-provoked. Then, phase maps and activation sequences were displayed on individualized atrial geometries. For the purpose of analysis, atrial geometries were divided into 7 domains, within which either rotors and/or spontaneous focal discharges (both named “drivers”) were localized. Also, fibrillation driver density maps were built to identify the atrial sites most likely to anchor such electrical sources of AF. Then, with the endpoint of terminating AF, point-by-point ablation was conducted sequentially in regions harboring the largest driver density, before it was done in other regions, following a decreasing order of arrhythmogenic density. Of note, this ablation strategy was completed with an ipsilateral PV isolation when the drivers were located within a PV. The authors report that the overall RF application duration was comparable with the one needed for the FIRM-guided ablation, approximately half an hour. Importantly, AF termination was seen after a significantly shorter RF application duration than the one needed to ablate AF in a control group, in which ablation was performed conventionally (PV isolation and electrogram-based lines). Also, most patients remained AF-free after 12
months, more so if their AF episode was terminated by driver-targeted ablation, but to a lesser extent if the patient was in LPsAF. The authors suggest that the increased difficulty in ablating LPsAF patients could be explained by one of the central observation of Haissaguerre et al.’s manuscript: PsAF is maintained by drivers mostly located in the PV-left atrium regions, but with continued AF maintenance, as in LPsAF patients, AF sources are found beyond the PV region. As also suggested by experimental and clinical studies\textsuperscript{28,32} this is another evidence that AF drivers’ atrial “estate” correlates with the duration of AF episodes, much wider in LPsAF than in PsAF.

Altogether, this work seems to corroborate the studies published by Narayan et al. In the human heart, small atrial regions are sites of rotor formation and are crucial to AF maintenance\textsuperscript{16,29,33} Also, Haissaguerre et al.’s results support the idea that the location and extent of rotor regions are distinct between PAF, PsAF and LPsAF. Overall, this manuscript presents a promising study, and one which further reconcile the many basic and clinical investigations conducted over the last decades. Still, the most fascinating aspects of this study are the questions that remain to be addressed.

First, the nature of AF drivers described by Narayan et al. with the FIRM mapping would appear to be entirely different from the one reported here. On the one hand, Narayan’s rotors are suggested to be stable and long-lasting, and on the other, Haissaguerre et al. describe iterative, re-nascent, 2-3 rotations rotors, which tend to drift over large distances. It is likely that technical limitations – mostly a relatively low mapping resolution – associated with both the FIRM-guided and ECGi mapping approaches could explain some of these discrepancies. However, it is important to mention that these observations are not necessarily mutually exclusive. As we have shown experimentally, the left atrium is a 3-dimensional (3D) synticium and atrial reentrant
impulses propagate in 3D. Rather than 2D entities, atrial rotors are in fact scroll waves, which span the thickness of the atrial muscle.\textsuperscript{23, 34} Often, a scroll wave appears as a rotor on the endocardium, but may be seen as a breakthrough wave on the epicardium.\textsuperscript{32} Possibly, the ECGi approach, which is an account of the overall atrial electrical activity, yields rotor visualizations different in nature from the mostly endocardial recordings of the FIRM technology. Instead, such discrepancies represent an opportunity to further investigate rotor dynamics during human AF, and they also illustrate the need for the development of technologies allowing for a higher mapping resolution.

Besides, there is still a lot of unknown on the precise dynamics of driver regions during PsAF. In the current study, as with the FIRM-guided approach, it is unclear whether the rotors, which were visualized and ablated, were activating the tissue at a faster frequency of excitation. Previously, the frequency of activation was shown to be a reliable surrogate for rotor detection.\textsuperscript{25, 28, 35} The general concept is that rotors driving fibrillation revolve at a faster frequency than the rest of the atrial muscle, and that fibrillation results from fibrillatory conduction of waves emanating from such rotors. An improvement in the assessment of the frequency of AF sources could prove important. Recent studies have indeed suggested that high frequency sites may be localized non-invasively.\textsuperscript{36} Therefore, one could assume that rotor visualization is not required to conduct a successful AF ablation procedure.

Finally, both the FIRM-guided and ECGi results question whether in PAF the PV region needs to be isolated because rotors anchor there, or instead because PV foci are key to AF maintenance. As Haissaguerre et al. found most of their rotors in the PV region during PsAF, one may wonder whether, in patients with PAF as well, the ablation of rotors may suffice.

In summary, Haissaguerre et al. present another key contribution to the field of AF
interventional therapy. Their results are an important indication that atrial regions, which mechanistically perpetuate AF, are reasonable targets for catheter ablation in patients with PsAF. At the same time, these results call for a more refined evaluation of AF dynamics and one that will further enlighten our understanding of AF. Readers of the Haissaguerre et al. manuscript may very well feel, as we did, that this work is a demonstration that translational research is one of the cornerstones of medical advances. As such, Haissaguerre et al. contribution is a call for more understanding.

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