HHS Public Access

Author manuscript

Circ Arrhythm Electrophysiol. Author manuscript; available in PMC 2017 June 21.

Published in final edited form as:

Circ Arrhythm Electrophysiol. 2015 October ; 8(5): 1296–1298. doi:10.1161/CIRCEP.115.003324.

Letter by Jalife et al Regarding Article, "Quantitative Analysis of Localized Sources Identified by Focal Impulse and Rotor Modulation Mapping in Atrial Fibrillation"

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Keywords

atrial fibrillation arrhythmia; mapping; rotor; dominant frequency; catheter ablation; phase mapping; basket catheter

"Nothing is more irredeemably irrelevant than bad science"

John C. Polanyi

German-Canadian chemist

Nobel Prize for Chemistry in 1986

In 1998 we introduced a unique phase mapping algorithm that markedly enhanced the characterization of complex spatiotemporal patterns of cardiac fibrillation.[1] We used a potentiometric dye and video imaging to record the dynamics of transmembrane potentials at many sites during fibrillation.[1, 2] Transmembrane signal at each site exhibited strong periodic components at 8-15 Hz and was seen as a quasi-closed trajectory in two-dimensional phase-space that could be represented by its phase around the circuit.[1] Spatial phase maps at each instant revealed the 'drivers' of fibrillation in the form of rotors displaying long-lasting topological defects, or phase singularity points at a few sites. We also demonstrated that such drivers are caused by a singularity event termed 'wavebreak'. Subsequently, the combined use of phase and dominant frequency (DF) maps of the optical movies led to the demonstration that atrial fibrillation (AF) in the isolated sheep heart was characterized by a hierarchy of DF domains where the highest domain (DF_{max}) corresponded to the location of the dominant rotor.[3-7] More recent data suggest that rotors may underlie both paroxysmal and persistent AF in humans.[8-12] Thanks to the recent introduction of mapping technology that utilizes a multielectrode basket catheter and is designed to identify highly localized drivers capable of maintaining AF, the field of AF ablation has begun to move away from purely anatomically based strategies. During the last

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Conflict of Interest Disclosures: J. Jalife is on the Scientific Advisory Board of Topera, Inc. O. Berenfeld is the Scientific Officer and has equity in Rhythm Solutions, Inc.

several years, ablation studies using novel mapping procedures specifically designed to assess the mechanism(s) underlying potential AF sources have been reported with very promising results. Such mechanistically based ablation techniques are a direct result of insights into the dynamic behavior of reentrant sources (rotors) derived from experimental optical mapping studies and computer simulations of AF dynamics.

A case in point is the work that has been published recently in a series of articles by Narayan et al,[9, 10] and others[13] who have offered a mechanistically-based tool that already has shown substantial practical application in the clinical electrophysiology laboratory, assisting in mapping and ablation of locally stable rotors in AF. The work of Narayan et al is perhaps one of the first examples of effective translation of numerical and experimentally derived data on arrhythmia mechanisms toward diagnosis and ablation therapy as demonstrated by the CONFIRM trial.[10] Recently, the results of an extended 3-year follow-up of the trial were reported.[14] Patients in the FIRM-guided ablation group maintained higher rates of freedom from AF than conventional therapy (78% vs. 36%) after a single procedure.

However, although an independent multicentric study has confirmed that FIRM-guided ablation is likely more effective than conventional ablation alone,[15] the FIRM-guided ablation protocol included not just the ablation of potential drivers, but also, PVI and other standard procedures.[14] In addition, the protocol is littered by issues that have contributed to raise skepticism in the minds of a few opinion leaders about its usefulness. In particular, the basket catheter system uses a proprietary algorithm (Rhythm View™; Topera Inc., CA, USA), which makes the methodology difficult to evaluate since the electrograms from which the color maps are obtained are not the primary display. Although not unique to the Rhythm View™ system, extracellular signals are subject to artifacts,[16] and ventricular activity often contaminates atrial recordings; thus appropriate location of the basket catheter and QRST subtraction are both paramount. Also the basket-catheter often provides far from optimal electrode-tissue contacts at many poles, and the splines are sometimes not equidistantly separated once they are deployed in the atria. Therefore, the raw inter-spline spatial resolution offered by basket-catheters is poor. Consequently, the amount of extrapolation when scarce or poor quality data are present is difficult to determine. Further, it should be considered that interpolation of phases is inherently biased toward detection of rotors as the algorithm is devised to demonstrate rotational activity. Thus, a focal activation might be displayed as rotational activity if the wavefront reaches the surrounding electrodes sequentially.[16] Nevertheless, although the FIRM-guided approach to AF ablation is not universally accepted, even with its inherent limitations, it is one of the first mechanistically based methodologies that have reported promising results in the long-term[8, 14] and after its first multicenter validation.[13]

The study by P. Benharash *et al,*[17] published recently in Circulation A&E, aimed at testing the FIRM procedure by quantifying the spectral properties and regularity of atrial electrograms recorded at rotors sites during atrial fibrillation ablation. The authors included a retrospective analysis of 24 consecutive patients undergoing AF ablation, with a significant percentage of patients having a previous history of multiple failed ablation procedures. Benharash *et al*[17] used the Topera system to determine the sites of rotor activity. Rotor sites were targeted for AF termination, slowing of AF cycle length or organization. Further

analysis included activation maps using unipolar signals from the basket catheter, Shannon entropy and dominant frequency.

Contrary to what has been shown by others[13, 18] the report by Benharash et al[17] did not observe any significant differences between rotor sites and atrial areas without rotors. Neither DF analysis nor Shannon entropy analysis showed any differences between sites. There was a low rate of AF termination using FIRM-guided ablation. Notably, atrial unipolar signals were poor in all cases and only an average of 20 signals was suitable for analysis. Further, a substantial area of the left atrium was not considered for analysis due to inability of the basket catheter to cover the entire endocardial surface. These authors concluded that, in conjunction with pulmonary vein isolation, catheter ablation at FIRM-identified rotor sites resulted in AF termination or organization to atrial tachycardia in only four out of 24 patients. Such outcomes were so remarkably poor that the paper prompted an editorial that called for additional studies to better understand persistent AF mechanisms.[19]

Close examination of the data presented by Benharash et al[17] reveals that, in their attempt to test the validity of FIRM-guided analysis they committed an unsettling array of mistakes that likely contributed to their failure, which unfortunately has become a source of confusion for readers of Circulation A&E who are unfamiliar with the topic of rotor mapping. Clearly, rigorous and detailed analysis of their results raises significant concerns about the scientific validity and integrity of the overall study.

Of greatest concern in the Benharash *et al*[17] report are the ostensible difficulties they had in properly deploying the basket catheter, which certainly may explain their poor signal recordings. For example, they use Figures 6 and 7 as evidence supporting their contention that even using the NavX electroanatomic mapping system they were unable to annotate activation times automatically because of poor signal quality of the basket catheter. This is precisely why phase mapping should have been performed. The lack of identifiable activations is what is actually expected at the core region of rotors. By excluding these electrodes the authors basically eliminated the possibility of finding what they were looking for. A more appropriate approach would have been to quantify where those low-amplitude signals were located; if they were at FIRM-based rotor sites then the data would have been consistent with the presence of a rotor. Unfortunately, QRS subtraction images were not shown for Figure 6 that may have revealed that atrial signals may be detected unimpinged. Therefore, unless otherwise revealed, the best interpretation one can give to the data in Figure 6 is that basket positioning was poor, as reflected by electrograms that often displayed more ventricular than atrial signals! Indeed, figures 1B and C show cases selected by the authors where baskets are placed in the left ventricle based on published studies on the pitfalls of basket placement (compare with figure 1, panels H, I of Narayan et al,[20]) while in figure 1A the basket was undersized and floated in the atrium (compare with figure 1 panel J of Narayan et al,[20]). Similarly, unless otherwise demonstrated, the apparent change in the chirality of the rotation in Figure 7 of Benharash et al[17] was most likely the result of inappropriate marking of the activation timing, which in unipolar recordings should be the most negative slope rather than the peak as the authors mistakenly have done. Again, phase analysis would have helped here. Phase analysis gives no particular weight to the activation timing and considers as equally important all the phases of the action potential.

An additional limitation that affected the results of Benharash et al[17] is their lack of attention to detail in the electrophysiological approach they have used to generate their phase maps. Narayan et al complemented their development of FIRM mapping from basket catheters with monophasic action potential (MAP) catheter recordings to define action potential duration (APD) and regional conduction restitution,[9] which were essential to identify rotor activity and slow conduction areas. The latter was completely missed by Benharash et al.[17] As such, their results can hardly be compared with those generated by others using the Firm-guided approach.

Dominant frequency is yet another example of poor signal analysis in Benharash et al.[17] The authors report in Figure 5 and Table 2 no differences in DF or Shannon entropy distributions between rotor sites and other regions; by itself this similarity in distributions doesn't preclude the presence of a driving rotor and seems to demonstrate that their 'rotor' sites were probably fibrillatory activity rather that the dominant rotor at the highest DF site. In addition, the data presented as evidence for FIRM rotor identification do not display anything that may suggest the presence of a rotor by FIRM or any method. In fact, no single FIRM map or electrogram is provided to verify that DF is measured correctly from the appropriate location at the precise time period analyzed, which is critical since rotors meander in space.[21, 22] Even if their DF measurements (by FIRM) are correct, a frequency of 3.6 Hz is not particularly high (reflecting a cycle length of 278 ms), and probably resulted in 1:1 propagation to large areas as suggested by the relatively homogeneous DF map in their Figure 4, and may reflect atrial tachycardia without fibrillatory conduction. Further, while Shannon entropy has been previously used to detect rotors using bipolar signals, the use of Shannon entropy to detect rotors with unipolar signals has not been validated. Therefore, it is unsurprising that so-called "rotor identification" in the article by Benharash et al failed to terminate AF.

In conclusion, although skepticism facing FIRM mapping and ablation is healthy and necessary, the paper by Benharash et al[17] does not have the material or the scientific quality to counter the claims of the FIRM approach. Clearly, ablation failure does not mean that there are no rotors/foci driving AF. We submit that the battery of mistakes committed in the design, conduction and interpretation of the results contributed more than anything to such a failure. Therefore, while we agree that on available evidence, the relative contribution of sustained or transient rotors to the mechanism of human persistent AF remains uncertain[19] and requires further support, we firmly propose that the evidence provided by Benharash et al[17] should not be taken as contributing constructively to such an uncertainty.

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