EDITORIAL COMMENT

Targeting Atrial Fibrillation Rotors
Does Being Close Count?

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The hypothesis that rotors or areas of rapid reentry are critical to maintenance of atrial fibrillation (AF) has gained considerable currency with clinical data supporting enhanced efficacy when targeting these sites in AF ablation (1-3). Regions bordering AF rotors have been shown to generate high wavebreak density (HWD) that corresponds to complex fractionated atrial electrograms (CFAEs). CFAE ablation does not appear to be helpful in the elimination of AF, yet the mechanistic reason for this is poorly understood. In this issue of JACC: Clinical Electrophysiology, Yamazaki et al. (4) examine the underlying spatial distribution of AF rotors in comparison to regions of HWD/CFAE and the response of AF to ablative and modeled influences on these substrates. Langendorff-perfused sheep hearts underwent induction of sustained AF using an acetylcholine (ACh)/atrial stimulation model. Optical mapping of endocardial and epicardial patterns of electrical impulse propagation throughout the corresponding left atrium was undertaken. Construction of dominant frequency (DF) and HWD maps and phase movies allowed delineation of the DFmax/rotor regions versus neighboring sites where rotor-generated wavefronts experienced HWD and CFAE formation. The study consists of 2 parts, which we address sequentially. First, the response of AF to ablation of DFmax/rotor versus HWD/CFAE regions is examined. Subsequently, the authors investigated the regional response of DFmax/rotors to stretch and ACh influences.

The authors present an examination of AF dynamics before and after ablation of DFmax/rotor sites versus HWD/CFAE sites that are anatomically adjacent. This small distance between targeted ablation sites resulted in very different outcomes. DFmax/rotor ablation either terminated or evolved AF into a much slower atrial arrhythmia (from ~19 Hz to ~15 Hz), whereas ablation of adjacent HWD/CFAE sites resulted in anatomic relocation of the primary rotor, while maintaining similar frequency (~15 Hz). Thus it appears that ablation of rotor adjacent HWD/CFAEs may lead to ablation procedures that are potentially more complex and lengthy.

Preliminary findings on ex vivo diseased human hearts suggest that the response to “on-target” transmural ablation of rotor sites is similar, whereas “off-target” ablation (not adjacent to the leading reentrant driver) does not change either frequency or AF pattern (5).

The findings are also consistent with clinical outcomes observed using a CFAE ablation strategy. In the Star AF2 trial, patients with persistent AF were randomized to pulmonary vein isolation (PVI) alone, PVI + CFAE, or PVI + lines ablation (6). Freedom from AF after 1 procedure was reached in 59% of patients in the PVI-alone group, 48% in the PVI + CFAE group, and in 44% of the PVI + lines group. Although the numerical superiority of PVI alone did not reach statistical significance, the trends support the findings of Yamazaki et al. that ablation of HWD/CFAEs may not be helpful.

The correlation of these findings with endocardial focal impulse and rotor modulation (FIRM) (3) is more complicated. Narayan et al. (7) undertook contact
mapping using biatrial multipolar basket catheters and found AF rotors or focal sources that were targeted for ablation. AF acutely terminated or organized with ablation of the primary source. Source regions showed CFAE grades that did not differ from surrounding atrium, and AF sources were not consistently surrounded by CFAEs. Thus, these findings support the idea that HWD/CFAE sites are not adequate AF source targets but conflict with the isolated heart study’s findings that the sites are adjacent. This may reflect a lack of electrode density in FIRM mapping or the requirement of DFmax regions as a prerequisite to qualifying as an AF source region in the Yamazaki et al. study (4). Although regions of DFmax may harbor rotors, other mechanisms such as wavefront collisions may also generate a DFmax region (7). Nonetheless, analysis of electrograms at successfully targeted rotor sites support the absence of HWD/CFAE in these locations and the contention that CFAE cannot, at this time, be used to target AF rotors.

There are limitations to the first part of this study. The authors speculate that when DFmax/rotor ablation did not terminate AF (5 of 7 hearts), the initial AF driving rotor was eliminated and a second, slower rotor perpetuated AF (blamed as a failure of ablation to cover an area sufficient to eliminate the dominant rotor), but this may not be the case. The authors also hypothesize that HWD/CFAE ablation results in rotor relocation from the left atrial appendage/free wall (LAA/LAFW) to the pulmonary vein (PV) region and identify this as rotor drift (Figure 5 in the article by Yamakazi et al. [4]). However, it is possible that the initial AF driver was eliminated and a secondary driver was uncovered. These discrepancies may only be resolved by a simultaneous panoramic and transmural optical mapping view of the atrium that can track the drift or termination of AF drivers. Further limitations include an unexplained higher baseline DF before DFmax targeted ablation compared with hearts used for HWD/CFAE ablation.

Subsequent to the ablation experiments, the authors presented a second set of experiments in which they used a stretch-related AF model and increased ACh concentration to 0.05 μmol/L ACh (n = 6) or 0.1 μmol/L ACh (n = 6). After a larger ACh concentration (0.1 μmol/L), the DFmax domain relocated from the pulmonary vein-posterior LA (PV-PLA) region to the LAA/LAFW. Whether this model accurately mimics the atrial electrophysiology after ablation of HWD/CFAEs is unclear given that ablation caused rotors to drift from LAA/LAFW toward the PV-PLA region while ACh administration caused drift away from the PV-PLA. Nevertheless, these observations highlight the potential for cholinergic stimulation to alter the driver sites of AF and raise the worrisome possibility that this occurs during clinical radiofrequency ablation.

Further examination of 3-dimensional rotor dynamics in the PV-PLA versus LAA/LAFW suggests a correlation between rotor locations and underlying atrial wall structure. The many pectinate muscles’ thin-thick transitions (wall thickness gradient) appear to provide a substrate for large rotor drifts. Although these findings are based on ex vivo studies in healthy animal hearts, they are supported to some degree by ex vivo studies in the right atria from diseased human hearts (8). Their results suggest that the anatomic structure of some sites is more prone to sustaining rotors than others, but direct structural data are lacking to confirm this claim.

Lastly, the study was performed ex vivo on sheep hearts, which begs the question as to whether these findings can be confirmed in vivo in AF patients. Animal AF models provide a wealth of information on AF pathophysiology, but they have many limitations that have been emphasized in recent reviews (9).

Overall, this significant contribution by Yamakazi et al. (4) furthers our appreciation that widely different results can occur with point ablations close in proximity. The study gives us insight into mechanisms through which AF ablation of non-PV targets such as rotors or CFAEs may succeed or fail. These findings also speak to the need to be able to target and ablate sites accurately based on patient-specific mechanisms of AF. More translational experimental-clinical studies must be done to identify mechanisms and target specific regions that are critical to maintaining AF.

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**REFERENCES**


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