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Rotors: How Do We Know When They Are Real?

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A spiral wave is a common macroscopic behavior of excitable media observed in biological, chemical, and physical systems.[1, 2] In cardiac tissues, spiral wave re-entry occurs when a wavefront of electrical propagation encounters functionally inexcitable tissue and rotates around it in a vortex-like fashion.[3] A '*rotor*' of a spiral wave is a rotation center from which a two-dimensional spiral wave of excitation rotates outward. Phase mapping has been the *de facto* standard method to identify rotors and to track their trajectories in animal models of fibrillation.[4] On phase maps, a rotor is defined as a phase singularity point around which the phase transitions through a complete cycle from $-\pi$ to $+\pi$.[3, 5] Phase mapping can falsely detect phase singularities in the absence of rotors,[6] and spiral waves can exist without phase singularities.[7] Rotors and focal impulses have been proposed to be the underlying drivers of atrial fibrillation (AF) in human.[3, 8, 9] This *localized source hypothesis* has resulted in utilization of phase mapping in clinical practice, mainly in two settings: invasive focal impulse and rotor modulation (FIRM) and noninvasive electrocardiographic imaging (ECGI).

FIRM uses phase mapping to locate stable rotors based on endocardial unipolar electrograms acquired by a 64-lead basket catheter.[9] ECGI utilizes phase mapping to locate rotors based on unipolar electrograms acquired by ~250 body surface electrocardiographic leads, which are back-projected onto the epicardial surface, using a technique called 'inverse solution'. FIRM and ECGI have several limitations, in addition to the intrinsic limitations of phase mapping. FIRM may not show consistent results when compared to other methods of rotor detection. FIRM-detected rotors were confirmed by an independent phase-based mapping method[10], but were not reproduced by a different mapping method.[11] FIRM-mapping may relect endocardial activation more than epicardial or intramural activation. ECGI is limited by a relatively large localization error, up to 4 cm, and may not reflect

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endocardial activation patterns. A significant proportion of this error is introduced by the 'inverse solution' methodology.[12]

Early clinical studies using FIRM-guided AF ablation showed promising results.[9, 13, 14] However these results are variable in more recent studies.9 Likewise, although ECGI-guided driver ablation terminated 75% of persistent AF and 15% of long-standing persistent AF,[20] in a different study that used the same ECGI technology, only rare rotor activity was described in AF.[21] It is possible that technical limitations in rotor mapping (Figure 1) are solely responsible for the conflicting clinical evidence described above. However, the contradictory clinical evidence has led to a growing skepticism in the electrophysiology community, about the presence and role of rotors in AF.[22] The *localized source hypothesis* is currently in jeopardy, while alternative -but not mutually exclusive- hypotheses of AF mechanisms are being developed.[23-25] Nevertheless, a scientific hypothesis should not be rejected on the basis of technical limitations, but rather be tested by transparent and carefully designed studies, which are essential for improving our understanding of the true mechanism underlying human AF.

In elegant work published in this issue of the *Journal*, Rodrigo *et al.*[6] made a large stride to address the technical limitations associated with rotor mapping using ECGI. Rotor mapping is a complex multi-step process that involves data acquisition, filtering, phase mapping, and rotor detection algorithms (Figure 1). The authors use *in silico* simulations of AF, (a) to develop a phase mapping-based method for rotor detection with optimal sensitivity and specificity, and (b) to assess the effect of highest dominant frequency (HDF) filtering on the accuracy of rotor identification. The authors demonstrate that the activation phase calculated for tissue in a circle of radius 1.5 cm, concentric to a phase singularity identified as a potential rotor, should progress monotonically and linearly from $-\pi$ to $+\pi$. A deviation from linearity greater than 0.4 rads is suggestive of a wavebreak and thus should not be identified as a rotor. In addition, only phase singularities that exhibit a rotational pattern lasting at least 2 complete rotations should be identified as stable rotors. These two simple criteria alone could achieve an optimal balance between sensitivity and specificity in rotor detection. Furthermore, unipolar cardiac electrograms directly measured at the endocardium, or estimated with ECGI can be used in phase mapping without additional filtering, with good sensitivity and specificity for rotor detection. HDF filtering should be avoided in endocardial and ECGI-derived unipolar signals as it greatly decreases specificity for rotor detection. Moreover, bipolar electrograms and body surface potential mapping have inadequate sensitivity in detecting rotors. The sensitivity of bipolar electrograms and body surface potential mapping can be improved with the application of an HDF filter but this comes with a significant decline in specificity, and inappropriate identification of false rotors.

The authors should be congratulated on their robust contribution to address the technical limitations associated with rotor mapping. The authors used an AF model with a realistic human atrial geometry, as well as noise added to the recorded signals to mimic real-life signal acquisition conditions. The constraints that they apply in rotor identification are physiologically plausible. Their rotor detection algorithm is easy to implement, computationally efficient, and significantly improves sensitivity and specificity in rotor identification. Importantly, the authors also demonstrate that HDF filtering of endocardial or

ECGI-derived unipolar electrograms is unnecessary, and that bipolar electrograms or body surface potential signals are not ideal for rotor detection. Future studies should validate the results of this *in silico* study in more realistic conditions such as *ex vivo* torso tanks or *in vivo* large animals.

Last, another technical limitation associated with rotor mapping is inter-electrode distance of signal measurements. Roney *et al.* report that the 64-lead basket catheter, routinely used in clinical practice, fails to accurately localize rotors due to a high inter-electrode distance (>9-11 mm).[26] In addition, King *et al.* demonstrate that a higher inter-electrode distance lowers both sensitivity and specificity of rotor detection.[27] They also report that a band-pass filter falsely increases the temporal and spatial stability as well as the persistence of rotors. Furthermore, Kuklik *et al.* showed that rotor detection is most accurate with a double-ring electrode configuration, comprising of 2×2 and 4×4 electrodes,[28] suggesting that rotor detection also depends on electrode configuration. The simulated left atrium of Rodrigo *et al.*[6] contains a total of 2,048 electrodes over the epicardial surface with an inter-electrode distance of 1 mm. Unfortunately, a technology providing such high-density, high-resolution mapping is not available in clinical practice at this point. There is an urgent need for readily available, high-resolution mapping technologies.

With the work of Rodrigo *et al.*[6], we are one step closer to testing the *localized source hypothesis* as a potential mechanism of human AF. Future studies to address other aspects of technical limitations associated with rotor detection (Figure 1) would further advance our understanding of human AF and help expand our therapeutic armamentarium.

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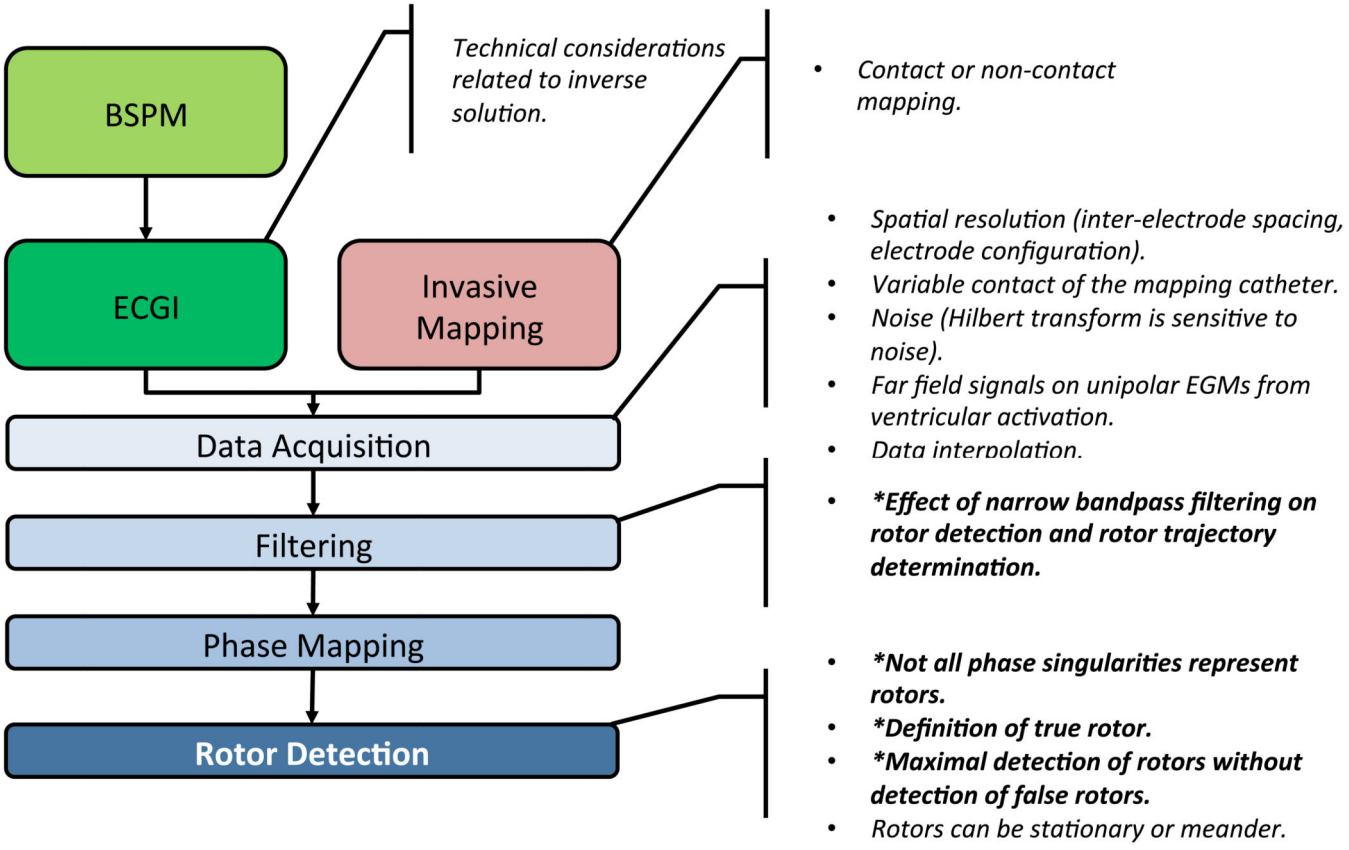

Figure 1.

Schematic summary of the steps involved in rotor identification as well as the relevant technical considerations for each step. Highlighted with an asterisk (*) are the considerations that the current work of Rodrigo et al. successfully addressed as described in the main text.