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Do Specific Connection Patterns of the Ligament Of Marshall Contribute Mechanistically to Atrial Fibrillation?

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The Ligament of Marshall (LOM) was first described in 1850 as a remnant of the embryonic left superior vena cava, consisting of fibrous bands, small blood vessels, and nerve elements[1]. Elegant canine[2] and human[3] studies have since shown that the vein (VOM) and LOM contain myocardial tissue, the Marshall Bundle (MB), which is electrically active and a potential cause of atrial fibrillation (AF) in canines.[4] Accordingly, a great deal of attention has focused on potential mechanistic contributions of the MB to human AF, given the central role of thoracic veins such as the pulmonary veins, coronary sinus and vena cava. Nevertheless, mechanisms linking the MB with human AF are unclear.

A priori, the MB possesses many attributes that may plausibly enable it to trigger and/or maintain AF. The LOM is a source of focal ectopy in humans[3] and tachycardia after isoproterenol infusion in dogs.[5] The LOM is also well-innervated, predominantly by sympathetic fibers at its pulmonary vein junction and parasympathetic ganglia at its coronary sinus junction,[6] which may explain AF initiation after rapid atrial or pulmonary vein firing[7, 8]. During AF, LOM electrograms may show shortest cycle-length, highest dominant frequency[9, 10] and complex fractionated atrial electrograms (CFAE)[10], all of which have been proposed as attributes of AF sustaining tissue. The LOM has also been targeted for clinical radiofrequency or ethanol ablation[11] for AF.

In this issue of *Heart Rhythm*, Han et al. present elegant data testing the hypothesis that the types of connections between the MB, coronary sinus and atria contribute mechanistically to AF in 64 patients undergoing catheter ablation for persistent AF.[12] Using direct LOM cannulation, adjacent endocardial and epicardial mapping and differential pacing, patients were grouped into those with single LOM connections (to the CS; n=11), double connections (between CS and left atrium; n=23), or multiple connections (n=30). This latter group exhibited variable LOM activation sequences in sinus rhythm, and CFAE in AF. After ablation at the atrial insertion site in some of these patients, maneuvers such as isoproterenol were able to elicit MB tachycardia with block to the atrium. The authors use these results to support their hypothesis that multiple connections between MB, left atrium and coronary sinus may create paths for reentrant excitation, leading to more complex and rapid activations that help maintenance of the AF.

The authors should be congratulated on their elegant and painstaking work that strengthens the mechanistic link between the MB and human AF. However, as expected in such a complex area, these results also raise many intriguing questions. While supporting the hypothesis that structural complexity may enable functional complexity (AF), these data stop short of actually

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defining how these LOM connections drive/sustain AF. In particular, it may have been useful (though challenging) to use incremental pacing to determine if the maximum rate at which the LOM can `drive' the atria before showing exit block, and the mode of block, differs between MB connection types due to wave collision, source-sink mismatch and other factors. Although the authors describe single LOM connections as slow, figure 4 illustrates LOM potentials during AF at a very short cycle length (≈100 ms), suggesting that LOM with single connections may also theoretically serve as `drivers' for AF. Thus, future work could be designed specifically to address the interplay between LOM activation rate and AF in terms of different connection types.

The results also address an important unknown in the link between CFAE in AF – whether CFAEs are rate-related[13–16] or caused by curved, colliding or other complex spatial activation paths[17, 18]. Figure 7 illustrates MB with multiple connections in which electrograms were fractionated in AF (CL ≈150 ms) and non-fractionated after ablation (CL ≈220 ms). It is not clear from these observations if the absence of CFAE represents slower rate, abolition of multiple MB connections, or autonomic denervation[19] post ablation. Other potentially useful data not included in the report include the presence of autonomic reflexes during LOM ablation, given recent data linking the LOM with cardiac autonomic reflexes.[6–8, 20]

The study is also limited by its retrospective nature, such that MB mapping and ablation were not standardized. Over half of the study population underwent epicardial mapping of the LOM because direct cannulation was not possible; in this group it may be difficult to validate MB potentials distinct from longitudinal dissociation along the lateral ridge. The authors deserve credit for using differential pacing to circumvent this limitation, despite the challenges of epicardial capture. Compelling examples of dissociated LOM potentials also mitigate this concern. Due to variations in recording technique, larger electrodes during epicardial mapping likely reduce the sensitivity for multiple connections. Results may also reflect structural heart disease in these patients (mean LVEF 46%), and may differ in other populations. These limitations, however, may affect the prevalence more than the substance of the authors' findings.

Lastly, the clinical implications of these findings remain to be defined. LOMs with double or multiple connections may clearly act as electrical conduits from the pulmonary veins, and potentially confound antral pulmonary vein isolation. However, this should be evident by activation sequences during pacing, and it is unclear what additional lesions are needed for each MB connection type. Endocardial lesions over the LOM may take the form of a mitral-isthmus line that in turn necessitates establishment of mitral isthmus block to avoid perimitral reentry[21]. It is unclear how often epicardial or coronary sinus[22] lesions will be needed. Assessment of clinical outcome after standardized ablation approaches in a larger series may address these issues.

In summary, Han et al. provide valuable human data addressing how the functional connections of the LOM affect its electrophysiology. These results shed new light on the pathophysiology of human AF, suggest that the number and type of LOM connections influence the genesis and maintenance of AF, and may help guide ablation to isolate the LOM. At this point, however, further studies are needed before concluding that the specific connections of the LOM connect it mechanistically with AF.

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