EDITORIAL COMMENTARY

Ligament of Marshall arrhythmogenesis and vein of Marshall ethanol: A problem with a solution

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The ligament of Marshall (LOM) and vein of Marshall (VOM) have fascinated cardiac electrophysiologists for decades. Initially described by the British surgeon John Marshall in 1850[1] as the normal involution of the left cardinal vein, the role of the LOM in electrophysiology was first unveiled by Benjamin Scherlag, PhD, in 1972,[2] who showed evidence indicating the existence of functional atrial muscle within the ligament of Marshall that formed part of an "interatrial conduction pathway." More interestingly, Scherlag showed that stimulation of the left cardiac sympathetic nerves led to the induction of an ectopic atrial rhythm arising from the LOM, thus providing a first proof of the LOM's arrhythmogenic potential of neurogenic origin. Decades later, work in Peng-Sheng Chen's laboratory confirmed the LOM's role in adrenergic atrial tachycardia,[3] delineated its myocardial architecture,[4,5] demonstrated the role of LOM-pulmonary vein (PV) connections in complex activation patterns in atrial fibrillation (AF),[6] and showed LOM triggers in certain cases of paroxysmal AF.[7] As a source of ectopic beats that could initiate AF[8] and of dual sympathetic[4] and parasympathetic[9] innervation of arrhythmogenic potential, these data suggested that the LOM could become a therapeutic target in its own right. In addition, the VOM anatomical location—connecting the coronary sinus with the PVs—coincides with the typical location of the mitral isthmus, commonly ablated to treat perimitral flutter. The LOM/VOM arrhythmogenic mechanisms are summarized in Figure 1.

The LOM's mechanistic role in clinical arrhythmias beyond animal studies has been more elusive. Hwang et al[8] were the first to cannulate the VOM with a microelectrode catheter to record LOM electrograms in humans and showed the first convincing evidence that AF could have LOM triggers. Using a similar technique, Dave et al[10] studied systematically 54 patients with recurrent AF after prior PV isolation. Of note, all 54 patients had robust VOM electrograms, even those with prior extensive endocardial ablation. Direct VOM electrogram recordings and differential pacing for the first time demonstrated that VOM-mediated connections with the left inferior PV could bypass previous PV isolation lesions, as predicted by animal studies.[6] These were, however, rare—present in 5 of 32 patients with left inferior PV reconnection. VOM focal activity was rare.

Therapeutic targeting of VOM electrical activity was limited to radiofrequency (RF) delivery in its neighborhood, either endocardially or epicardially, which lacked therapeutic specificity. VOM ethanol infusion allowed for specific ablation of the VOM, its intrinsic electrical activity,[11,12] the neighboring myocardium and associated PV connections,[10] the mitral isthmus,[13] and the associated parasympathetic innervation.[14] Although these data had been confirmed in anecdotal case reports by other groups beyond its original proponents,[15,16] the therapeutic value of VOM ethanol needed validation.

In this issue of **Heart**Rhythm, Chugh et al[17] report on 56 patients in whom LOM was considered to be a legitimate therapeutic target on the basis of pacing data suggesting LOM-mediated left atrium–PV connections or mapping data suggesting LOM-mediated macroreentrant or focal tachycardias. The mechanistic involvement of the LOM was not confirmed with direct VOM recordings. In patients with LOM-mediated PV connections, the authors were able to use RF targeting the LOM to successfully achieve PV disconnection in 15 of 18 patients. The remaining 3 were successfully disconnected using VOM ethanol. A total of 13 patients had LOM-mediated tachycardia (9 macroreentrant and 4 focal). RF targeting the LOM was successful in all but 2 patients. In 31 patients with perimitral atrial flutter, venography showed a suitable VOM in 23, and 16 of them received VOM ethanol, which led to perimitral conduction block—with or without added RF—in 15 (94%).

Their data are important because they represent a real-life account of clinical situations where VOM and its associated myocardium play a role in challenging ablation cases. Although the data supporting the VOM/LOM mechanistic involvement in clinical arrhythmias was purely inferential given the lack of VOM multipolar recordings or VOM pacing as reported by Dave et al,[10] most laboratories do not have or use microelectrode catheters in the VOM routinely and are limited to the same kind of inferential approaches. This may account for the lesser incidence of VOM-mediated PV connections reported in previous descriptions,[10] which included a highly selected research patient population. However, the rigor at attributing a mechanistic role of VOM/LOM connections seems of little practical value beyond that of academic pontification: what the clinician needs

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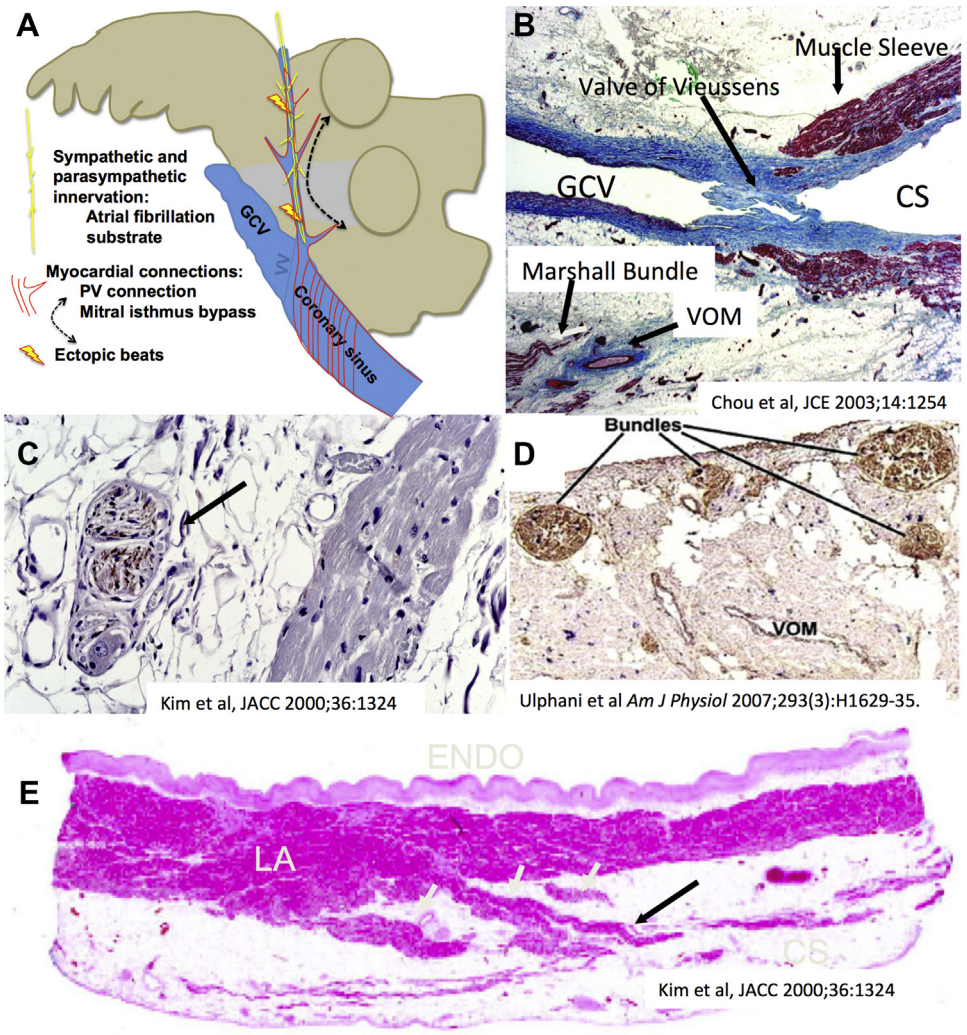

Figure 1 Ligament and vein of Marshall (LOM/VOM) arrhythmogenesis. **A:** Schematic of the VOM arrhythmogenic mechanisms: (1) sympathetic and parasympathetic innervation, which can generate a profibrillatory substrate and ectopic beats; (2) myocardial bundles, which can lead to epicardial connections with the pulmonary veins (PVs) and atrial tissue and can bypass ablation lesions created in the mitral isthmus (shaded gray area). **B:** Histology of the coronary sinus (CS) and VOM takeoff, showing the CS myocardial sleeve ending at the valve of Vieussens (VV) and the great cardiac vein (GCV) without myocardial sleeve. **C:** Sympathetic innervation (tyrosine hydroxylase staining, arrow) and adjacent myocardial tract in the LOM. **D:** Parasympathetic innervation bundles (acetylcholinesterase staining) adjacent to the VOM. **E:** Myocardial connections (arrow) between the LOM and the atrial myocardium. LA = left atrium.

is a tool to solve the problem when standard RF fails. This article provides it.

A second important contribution is the validation of the VOM ethanol injection approach. Although the technical success reported was lower than that reported by other operators (70% vs 89%[18]), the overall effects confirm the previous reports and support the therapeutic utility of VOM ethanol for eliminating epicardial connections to the left PVs[10] and epicardial connections across the mitral isthmus.[13] In addition, the authors refrained from injecting ethanol in cases where the VOM appeared small or too richly collateralized. Our experience supports the safety of ethanol injections in such veins[19] since collaterals are obliterated by ethanol. Greater operator experience certainly increases technical success.

RF remains the electrophysiologist's workhorse. The use of chemical ethanol ablation via coronary veins is a niche approach limited to RF failures. Chugh et al[17] confirmed its clinical utility in the VOM. In addition, we have reported its value in other atrial veins[19] and in ventricular veins for refractory ventricular tachycardia.[20] As operators face increasingly complex arrhythmogenic substrates, familiarity with chemical ablation tools may become increasingly useful. Chugh et al's experience is a step toward greater adoption of this technique.

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