Spectrum of atrial arrhythmias using the ligament of Marshall in patients with atrial fibrillation

Aman Chugh, MD, FHRS, Hitinder S. Gurm, MD, Kavita Krishnasamy, MD, Mohammed Saeed, MD, Watchara Lohawijarn, MD, Kyle Hornsby, MD, Ryan Cunnane, MD, Hamid Ghanbari, MD, Rakesh Latchamsetty, MD, FHRS, Thomas Crawford, MD, FHRS, Krit Jongnarangsin, MD, Frank Bogun, MD, Hakan Oral, MD, FHRS, Fred Morady, MD

From the Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan.

BACKGROUND The role of the ligament of Marshall (LOM) in patients with atrial fibrillation (AF) has not been well defined.

OBJECTIVE The purpose of this study was to describe the role of the LOM in patients with AF and related arrhythmias.

METHODS Fifty-six patients (mean age 63 ± 11 years; persistent AF in 48 [86%]; ejection fraction 0.49 ± 0.13; left atrial diameter 4.7 ± 0.6 cm) with LOM-mediated arrhythmias were included.

RESULTS A LOM–pulmonary vein (PV) connection was present in 18 patients (32%) and was eliminated with radiofrequency (RF) ablation at the left lateral ridge or crux (n = 12), at the mitral annulus (n = 3), or with alcohol/ethanol (EtOH) ablation of the vein of Marshall (VOM; n = 3). A LOM-mediated atrial tachycardia (AT) was present in 13 patients (23%). Thirty-one patients with refractory mitral isthmus conduction were referred for potential EtOH ablation. In the 6 patients in whom VOM was injected during perimitral reentry, EtOH resulted in slowing in 3 patients and termination in 1 patient. In others, EtOH infusion resulted in complete isolation of the left-sided PVs and left atrial appendage. Repeat RF and adjunctive EtOH ablation of the VOM tended to be more effective in creating conduction block across the mitral isthmus than RF ablation alone (P = .057).

CONCLUSION The LOM is responsible for a variety of arrhythmia mechanisms in patients with AF and atrial tachycardia. It may be ablated at any point along its course, at the mitral annulus, at the lateral ridge/PV antrum, and epicardially in the coronary sinus and the VOM itself. EtOH ablation of the VOM may be an adjunctive strategy in patients with refractory perimitral reentry.

KEYWORDS Ligament of Marshall; Vein of Marshall; Atrial fibrillation; Atrial flutter; Catheter ablation; Coronary sinus

Introduction

The ligament of Marshall (LOM) has been implicated as an arrhythmogenic source in patients with atrial fibrillation (AF). Prior studies in humans have primarily described the connections of the LOM to the coronary sinus (CS) and left atrium (LA)/pulmonary veins (PVs) in patients with and without LOM-mediated atrial arrhythmias.1–4 More recently, the LOM has been targeted in patients with refractory isthmus conduction despite radiofrequency (RF) ablation of perimital atrial flutter.5 The goal of the present study was to describe the role of the LOM in a series of patients undergoing catheter ablation of AF or postablation atrial tachycardia (AT).

Methods

The study was approved by the institutional review board of the University of Michigan School of Medicine. Fifty-six consecutive patients who underwent an ablation procedure for AF and/or related arrhythmias from 2010 to 2016 and in whom there was evidence of LOM-mediated arrhythmias were included. Specifically, patients in whom a PV connection was shown to be mediated by the LOM (by pacing techniques described below) or was eliminated by ethanol (EtOH) injection into the vein of Marshall (VOM), AT from the LOM (diagnostic criteria are described below), and refractory perimital tachycardia requiring EtOH injection were included in this series. Patient characteristics are shown in Table 1. Most patients (48 [86%]) had persistent AF, and 53 (95%) had previously undergone at least 1 prior ablation procedure (mean 2.2 ± 1.0). Structural heart disease was present in 37 patients (66%): cardiomyopathy and/or heart failure in 19; valve repair, replacement, or mitral valvuloplasty in 7; pacemaker or defibrillator in 8; coronary artery disease in 7; and hypertrophic cardiomyopathy in 5 patients.

Electrophysiology study

The indication for the procedure was AF in 12 patients (21%), postablation AT in 37 (66%), and AF and AT in 7
patients (13%). The electrophysiology study was performed in the fasting state under conscious sedation. The procedure was performed from a femoral vein. In patients who were being considered for EtOH ablation of the VOM, internal jugular venous access was also obtained. Oral anticoagulation with warfarin was not interrupted. Novel oral anticoagulants were discontinued 36 hours before the procedure. After the transseptal puncture, systemic anticoagulation was achieved with intravenous heparin and the activated clotting time was maintained at ~350 seconds throughout the procedure.

In patients with persistent AF, the ablation protocol consisted of PV isolation (or reisolation in patients presenting for a repeat session), ablation of complex electrograms, linear ablation at the LA roof, and right atrial ablation if a right-to-left gradient in frequency or complexity was documented. In patients with paroxysmal AF, only PV isolation was performed using a 3-dimensional mapping system (CARTO 3, Biosense Webster, Inc., Diamond Bar, CA) and 3.5-mm irrigated-tip ablation (25-W) catheter (ThermoCool, Biosense Webster, Inc.). In patients presenting to the laboratory in AT, an activation map was performed using the 3-dimensional mapping system. Findings on activation mapping were verified with entrainment mapping. The end points of the AT procedure were tachycardia termination, PV reisolation as needed, linear block at all relevant isthmi, and non-inducibility with rapid atrial pacing to 160 ms, ensuring 1:1 capture and programmed atrial stimulation during isoproterenol infusion (10–20 μg/min).

**Mapping and ablation of the LOM**

If the left PVs could not be electrically isolated during antral ablation, the earliest breakthrough on the ring catheter was then targeted. This entailed RF energy delivery at the crux between ipsilateral veins and then at the ostia of the PVs, as required for complete isolation. If the PVs remained connected thereafter, differential pacing was performed from the distal CS and LA appendage. In the setting of a conventional LA-PV connection, pacing from the distal CS would be expected to accentuate the delay between LA and PV potentials (LA activation followed by PV activation). In the context of a LOM-PV connection, CS pacing would be expected to advance the LOM potential, resulting in a reversal of activation (ie, LOM activation followed by atrial activation). Such a connection can be considered a "bypass tract" by which the Marshall bundle connects directly to the PV myocardium without intervening LA myocardium. RF energy was delivered at appropriate sites along the course of the LOM, that is, the left lateral ridge, the myocardium outside the anterior aspect of the left-sided PVs, and the lateral or posterolateral mitral isthmus.

A diagnosis of a reentrant AT involving the LOM was considered after excluding the conventional macroreentrant LA ATs, as previously described. Briefly, a roof-dependent macroreentrant AT was excluded if the anterior and posterior walls of the LA were not involved as shown by entrainment mapping. Likewise, lack of participation of both septal and lateral aspects of the mitral annulus excluded the presence of perimetal flutter. Other criteria included either distal-to-proximal CS activation or mid-CS activation preceding proximal and distal CS activation. In addition, a difference between the postspacing interval and the tachycardia cycle length ≤20 ms at the left lateral ridge, posterior base of the LA appendage, inferolateral LA (overlying the CS), and/or the mid-to-distal CS region confirmed the participation of the LOM. These tachycardias were distinguished from clockwise mitral isthmus–dependent flutter by documenting long return cycles during entrainment mapping from the septal annulus. A focal AT or AF was considered to be originating from the Marshall bundle if the earliest activation (with respect to the p wave) was found along the endocardial course of the LOM or epicardially at the mid-to-distal CS, that is, at the origin of the VOM, as confirmed by venography.

**CS venography and EtOH ablation**

Patients who had failed a prior procedure for either mitral isthmus–dependent flutter or suspected LOM-mediated tachycardia were offered a repeat procedure using EtOH ablation of the VOM as described by Valderrabano and colleagues. A selective balloon occlusion venogram was obtained from the right internal jugular vein. The VOM was defined as a branch originating near junction of the CS and great cardiac vein, which coursed superiorly and posteriorly (toward a catheter placed in the left inferior PV in the anteroposterior/right anterior oblique view).

An angioplasty wire (Asahi Soft, Abbott Vascular) supported by an over-the-wire balloon catheter was advanced as distally as possible into the VOM and also used to record unipolar electrograms. An appropriately sized balloon (1.5–2.5 mm diameter and 12–15 mm length) was used depending on...
on the size of the VOM identified on the venogram. The balloon was inflated at low pressure (1–2 atm) in the distal part of the vein, and the guidewire was removed. A selective venogram of the VOM was obtained by injecting 0.5–1 mL of contrast medium through the wire port of the balloon. After confirming balloon occlusion, 0.5–1 mL of alcohol was slowly injected over 1 minute and selective venography of the VOM was repeated.

Follow-up
Patients were observed for overnight after the ablation procedure. Patients were discharged on an oral anticoagulant and rate-controlling medications. They were instructed to call a clinical care coordinator in case of recurrence or change in clinical status. The patients were seen in the office at 3, 6, and 12 months, and as needed thereafter. In patients without an obvious recurrence, a 30-day autotrigger (Lifestar AF Express, Life Watch Inc., Buffalo Grove, IL) was prescribed at 12 months after the ablation procedure. Recurrence was defined as sustained (>1 minute), symptomatic, or asymptomatic AF or AT after the 3-month blanking period.

Statistical analysis
Continuous variables, expressed as mean ± SD, were compared using the Student t test or paired t test, as appropriate. Categorical variables were compared using the Fisher exact test. P < .05 indicated statistical significance.

Results
PV-LOM connections
A PV connection mediated by the LOM was observed in 18 of the 56 study patients (32%) (Figure 1). Fifteen of the 18 patients (83%) had previously undergone complete antral PV isolation in a conventional fashion, with no evidence of a LOM-mediated PV connection during the prior procedure. In 2 of the 3 remaining patients, a LOM connection was responsible for acute reconnection during the index ablation procedure. The LOM connection was eliminated during RF energy delivery outside the anterior aspect of the left-sided PVs (left lateral ridge, myocardium outside the PV ostia, or crux) in 12 of the 18 patients (67%) (Figure 1). In 3 patients (16%), the LOM-PV connection was eliminated during RF energy application at the ventricular aspect of the lateral or posterolateral mitral annulus (Figure 2). In the remaining 3 patients (17%), the left inferior PV was completely isolated after EtOH injection into the VOM without any RF energy delivery (see below).

AT and AF
A LOM-mediated tachycardia was present in 13 patients (23%). In 9 patients, the mechanism was reentry, and in the other 4, the mechanism was focal activity. In the latter 4 patients, AT was also found to be triggering episodes of AF. In the 13 patients with reentry, the AT terminated during RF application at the ridge in 5, distal CS in 1, and the lateral mitral annulus in 1 patient (Figure 3). After restoration of

![Figure 1](https://example.com/figure1.png)  
An example of a ligament of Marshall (LOM)–pulmonary vein (PV) connection. During sinus rhythm, the ring catheter placed in the left superior PV (LSPV) records 2 potentials, a far-field left atrial (LA) potential followed by the LOM. Pacing from the distal coronary sinus (CS) advances the second potential and results in reversal of activation, confirming the presence of a LOM-PV connection. The LOM is activated immediately after CS activation. Pacing from the LA appendage (LAA) further accentuates the delay between the LA and the LOM. After elimination of the LOM connection with radiofrequency ablation, delay is longer (130–160 ms), confirming the presence of a LOM connection. (Mitral isthmus block could not be achieved in this patient owing to the presence of a large pouch at the lateral isthmus.)
sinus rhythm during RF energy application in the latter patient, that tachycardia persisted at the anterolateral mitral annulus despite sinus rhythm, that is, complete exit block to the remaining atrial mass (Figure 3). In 2 others, RF ablation was unsuccessful in terminating the reentrant AT. One of these patients presented for a repeat procedure for possible EtOH ablation but venography revealed no VOM. In the 4 patients with focal AT/AF, RF ablation eliminated

Figure 2  A: An example of a ligament of Marshall (LOM)–pulmonary vein connection that was eliminated during radiofrequency ablation at the lateral mitral annulus (MA). B: Fluoroscopic image showing the position of the ablation catheter and the ring catheter in the left superior pulmonary vein (LSPV). CS = coronary sinus; LA = left atrium.

Figure 3  A: Termination of a reentrant atrial tachycardia involving the ligament of Marshall (LOM) during radiofrequency (RF) ablation at the lateral mitral annulus in a patient who had previously undergone excision of the left atrial (LA) appendage as part of a surgical maze procedure. B: Further mapping actually revealed that tachycardia persisted at the anterior mitral annulus during sinus rhythm, suggesting that the LOM and the subjacent atrial myocardium responsible for maintaining the tachycardia were insulated from the endocardium, which was activated by the sinus rhythm wavefront. C: Schema showing the likely mechanism of the tachycardia (red arrows) and proposed route of activation of the atrial mass. Conduction block across the Bachmann bundle (BB) was caused by RF ablation of another tachycardia that was ablated at the anterior LA (not shown). D: Schema showing ongoing tachycardia with conduction block to the coronary sinus (CS) and the atria during sinus rhythm. GCV = great cardiac vein; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RA = right atrium; SA = sinoatrial node; VOM = vein of Marshall.
the arrhythmia during RF energy delivery in the distal CS in 3 patients and the lateral mitral annulus in 1 patient.

**VOM venography for perimital reentry or AT**

In the remaining 31 patients of the 56 study patients, the Marshall bundle was targeted in patients with perimital reentry (n = 29) or in whom a suspected epicardial AT from the LOM could not be eliminated with RF ablation in the CS during a prior procedure (n = 2). In the former 29 patients, either perimital reentry (or mitral isthmus conduction) could not be eliminated during a prior procedure or AT recurred during follow-up despite successful mitral isthmus ablation during a prior procedure. Balloon occlusion venography revealed a VOM branch in 23 of the 31 patients (74%) (Figures 4A and 4B). Unipolar atrial electrograms from the VOM were recorded before and after EtOH infusion (Figure 5). EtOH was infused into the VOM in 16 of the 23 patients (70%). EtOH was not infused in 7 patients because of the small caliber of the VOM (n = 4), complete lack of atrial electrograms in the VOM (n = 2), or extensive collateralization (n = 1) (Figure 4C). In the last patient, there was already evidence of severe LA scarring, and it was felt that EtOH infusion may exacerbate atrial uncoupling, which would be widespread owing to the extensive venous communication with the VOM.

**Acute effects of EtOH ablation**

EtOH ablation of the VOM resulted in linear block across the mitral isthmus (n = 2) (Figure 6A), complete isolation of the left inferior PV (n = 3) (Figure 6B), and complete isolation of the lateral LA and LA appendage (n = 1) (Figure 6C), without any RF energy delivery. In the 6 patients who underwent alcohol ablation of the VOM during mitral isthmus-dependent flutter, EtOH resulted in termination (Figure 7) of the tachycardia in 1 patient and slowing (10–30 ms) in 3 patients; in 2 others, there was no change in the cycle length.

**Mitral isthmus conduction**

Among the 31 patients who were referred for potential alcohol ablation, venography revealed a suitable VOM in 23 and EtOH was infused into the vein in 16 patients (70%). Mitral isthmus block was achieved in 15 of the 16 patients (94%). The average conduction delay was 193 ± 32 ms during pacing. EtOH infusion alone yielded block in 3 of these patients (ie, without any RF energy), and RF energy was required endocardially and/or epicardially in the CS in the remaining 12 patients. In a patient with hypertrophic cardiomyopathy who received alcohol but in whom isthmus block could not be achieved, the maximal bipolar voltage at the lateral LA was 13 mV. In 12 patients in whom there was evidence of isthmus conduction who did not undergo EtOH infusion into the VOM (because of either its absence or its small caliber), conduction block was achieved in 7 (58%) with endocardial and/or epicardial ablation in the CS as compared with 15 of the 16 patients (94%) who were treated with EtOH infusion (P = .057). In 3 patients, further intervention at the mitral isthmus was not required owing to the presence of preexisting conduction block.

**Outcomes**

The end point of AT/AF termination and noninducibility was met in 48 patients (86%). Despite deep sedation, 2 patients (13%) experienced fleeting chest discomfort with EtOH infusion, without changes in the electrocardiogram. There were no other complications attributable to alcohol infusion or vascular complications related to internal jugular vein cannulation. Transient ischemic attack was noted in 1 patient. Fifty-two patients (93%) remained in sinus rhythm over a
follow-up of 23 ± 22 months, with 14 of these patients (25%) taking antiarrhythmic medications.

Discussion
Main findings
The LOM may be responsible for PV reconnection, focal tachycardias that can trigger AF, and reentrant ATs. The LOM also mediates epicardial conduction in patients with mitral isthmus–dependent atrial flutter. The LOM can be ablated anywhere along its course, from its insertion into the main body of the CS, endocardial aspect of the mitral annulus, the left lateral ridge/base of the LA appendage, or the crux between the left-sided PVs. The VOM itself is too small to be targeted by a conventional ablation catheter, but the atrial tissue drained by the vein may be ablated by EtOH infusion. In patients with recurrent perimitral flutter, EtOH ablation of the VOM along with supplemental RF energy seems to be more effective in eliminating isthmus conduction than RF ablation alone.

Figure 5  A: Unipolar electrograms recorded by a catheter inserted into the vein of Marshall (VOM). B: Instillation of 1 cm³ of ethanol (EtOH) into the VOM led to complete abolition of the atrial electrograms. (EtOH ablation of the VOM had no effect on atrial fibrillation; EtOH infusion in this case was performed for mitral isthmus conduction.) RAA = right atrial appendage.

Figure 6  Pleiotropic effects of ethanol (EtOH) ablation of the vein of Marshall (VOM). A: Without any radiofrequency (RF) energy delivery, infusion of 1 cm³ of EtOH yielded complete bidirectional block across the mitral isthmus in this patient with prior left atrial appendage (LAA) isolation. B: Complete isolation of the left inferior pulmonary vein (LIPV). C: Complete isolation of the LAA. A bipolar voltage map after EtOH infuision of the VOM showing absence of electrical conduction into the LAA. CS = coronary sinus; LLR = left lateral ridge; LSPV = left superior pulmonary vein; PV = pulmonary vein.
Anatomical considerations

The LOM, via the Marshall bundle, has variable connections to the adjacent myocardium. A majority of patients have ≥2 connections between the Marshall bundle and the myocardium of the CS, LA, or PVs. Han et al. conjectured that patients with 2 connections (ie, CS and PVs) may be able to generate macroreentry using the LOM. Macroreentry using the Marshall bundle was recently reported and is further confirmed in this study as shown in Figure 7. In another case of LOM-mediated reentrant AT (Figure 3), RF ablation at the mitral annulus eliminated a connection between the Marshall bundle and the LA, resulting in sinus rhythm despite ongoing tachycardia along the LOM. This observation is in keeping with the LOM serving as the “inferior interatrial pathway” as originally described by Scherlag et al.8

LOM and the PVs

In the context of a conventional LA-PV connection, CS pacing results first in atrial activation followed by PV activation, and also accentuates the delay between the two potentials. When there is a direct connection between the Marshall bundle and the left PVs, the latter may be activated directly without antecedent LA activation, in essence constituting a bypass tract between the CS and the PVs. In this setting, pacing from the CS would be expected to advance the LOM electrogram; that is, LOM activation precedes atrial activation. It is important to make a distinction between the disparate mechanisms of PV connections as the ablation strategy may be different. For PV connections attributable to the LOM, RF ablation may be required at sites not typically targeted during conventional antral ablation, for example, the left lateral ridge, mitral annulus, CS, or even the VOM itself.

LOM in latent PV conduction

In nearly all patients with a LOM-mediated PV connection in this series, the PVs had been isolated during conventional antral ablation, either during the initial or during the current procedure. However, recurrent PV conduction was not mediated by the typical connections between the LA myocardium and the PVs, but instead by the LOM. These observations suggest that there may be a hierarchy of PV connections, with those between LA and PV muscle sleeves superseding the LOM-PV connections. It is not clear why LOM connections do not manifest themselves acutely after the elimination of the conventional LA-PV connections in most cases.

It is likely that LOM-mediated PV connections are frequently ablated during the course of PV isolation, specifically at the crux, left lateral ridge (where the LOM is <3 mm from the endocardial surface), and the atrial myocardium inferolateral to the left inferior PV. In this series, RF ablation of conventional target sites failed to abolish PV conduction and pacing maneuvers elucidated the presence of LOM connections. Although a prior study found that the Marshall bundle was not found to be the major contributor to reconnection of the left PVs, latent LOM-mediated PV connections may be responsible for arrhythmia recurrence in some patients.11
Mitral isthmus conduction

Mitral isthmus–dependent tachycardia is among the most common macroreentrant tachycardias that occur in patients undergoing a substrate-based ablation procedure for AF. Anatomical factors such as endocardial pouches, presence of coronary arteries that exert a heat-sink effect, and myocardial thickness can make it difficult to achieve permanent conduction block in some patients. Also, isthmus block requires RF energy delivery in the CS in the majority of patients, which itself may be challenging owing to tortuosity, and is associated with a risk of injury to the coronary arteries.

In the present study, EtOH infusion per se resulted in slowing (n = 3) or termination (n = 1) in the 6 patients in whom alcohol ablation was performed during perimital flutter. The extent of response, of course, depends on the size and location (ie, endocardial vs epicardial) of the conduction gap. Even after extensive ablation during multiple procedures and infusion of alcohol into the VOM, perimital tachycardia may persist in some difficult cases. For example, the maximal bipolar voltage at the lateral LA in 1 patient in whom the tachycardia could not be eliminated was 13 mV. Myocardial thickness in this case probably helps explain why a combination of endocardial and epicardial ablation plus EtOH infusion into the VOM did not terminate perimital tachycardia.

Thus, EtOH ablation should not be considered a panacea for patients with recurrent arrhythmias after prior RF ablation attempts. Some anatomical limitations cannot be overcome despite multiple approaches. Furthermore, EtOH ablation targets only a specific and small portion of the lateral LA. The adjunctive role of EtOH ablation of the VOM in patients with AF is currently being evaluated in randomized studies (ClinicalTrials.gov Identifier NCT01898221).

LOM and the LA appendage

EtOH infusion of the VOM also resulted in complete electrical isolation of the LA appendage in one of the patients in this series. The LOM not only connects to the PV myocardium and the LA appendage, for example, owing to an epicardial source, despite extensive epicardial ablation, EtOH infusion of the VOM may be an option before attempting a formal epicardial ablation procedure.16–17

Conclusion

The LOM is responsible for both focal and reentrant arrhythmias in patients with AF. It also serves as a connection to the PVs, which may then serve as triggers and/or drivers of AF and related arrhythmias. The ligament may be ablated at any point along its course from the mid-to-distal CS to the LA appendage. If necessary, the VOM may be directly ablated using EtOH infusion to eliminate PV contribution, effect conduction block across the mitral isthmus, and others. EtOH ablation of the VOM supplemented with RF ablation may be more effective in yielding conduction block at the mitral isthmus than repeat RF ablation alone.

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