Retrograde Ethanol Infusion in the Vein of Marshall
Regional Left Atrial Ablation, Vagal Denervation, and Feasibility in Humans

Miguel Valderrabano, MD; Harvey R. Chen, MD; Jasvinder Sidhu, MD; Liyun Rao, PhD; Yuesheng Ling, PhD; Dirar S. Khoury, PhD

Background—The vein of Marshall (VOM) is an attractive target during ablation of atrial fibrillation because of its autonomic innervation, its location anterior to the left pulmonary veins, and its drainage in the coronary sinus.

Methods and Results—We studied 17 dogs. A coronary sinus venogram showed a VOM in 13, which was successfully cannulated with an angioplasty wire and balloon. In 5 dogs, electroanatomical maps of the left atrium were performed at baseline and after ethanol infusion in the VOM, which demonstrated a new crescent-shaped scar, extending from the annular left atrium toward the posterior wall and left pulmonary veins. In 4 other dogs, effective refractory periods (ERP) were measured at 3 sites in the left atrium, before and after high-frequency bilateral vagal stimulation. The ERP decreased from 113.6±35.0 to 82.2±25.4 ms (P<0.05) after vagal stimulation. After VOM ethanol infusion, vagally-mediated ERP decrease was eliminated (from 108.6±24.1 to 96.4±16.9 ms, P=NS). The abolition of vagal effects was limited to sites near the VOM (ERP, 104±14 versus 98.6±12.2 ms postvagal stimulation; P=NS), as opposed to sites remote to VOM (ERP, 107.2±14.9 versus 78.6±14.7 ms postvagal stimulation; P<0.05). To test feasibility in humans, 6 patients undergoing pulmonary vein antral isolation had successful VOM cannulation and ethanol infusion; left atrial voltage maps demonstrated new scar involving the interoposterior left atrial wall extending toward the left pulmonary veins.

Conclusions—Ethanol infusion in the VOM achieves significant left atrial tissue ablation, abolishes local vagal responses, and is feasible in humans. (Circ Arrhythmia Electrophysiol. 2009;2:50-56.)

Key Words: ethanol □ ablation □ vein of Marshall □ atrial fibrillation □ vagal

Catheter ablation has become an integral part of the management of atrial fibrillation (AF) when a strategy to preserve normal sinus rhythm is required. However, critical details of the technique are still controversial, the procedure demands high technical dexterity, and it carries significant risk of complications. Isolation of the pulmonary veins (PVs) has been accepted as a requirement for procedural success. However, isolation of the left-sided veins can be difficult because of the presence of a thick pectinate muscle separating the veins from the left atrial appendage (“lateral ridge”). In addition, ablation of the left atrial posterior wall can lead to esophageal damage, which in turn can cause atrioesophageal fistula, a deadly complication.

Clinical Perspective see p 56

The ligament of Marshall is the embryological remnant of the left superior vena cava, which, as it becomes atretic during development, may remain open as the so-called vein of Marshall (VOM). This vein drains in the coronary sinus and runs posteriorly and superiorly in the epicardial surface of the left atrium, to join the anterior aspect of the left-sided PV, as part of the lateral ridge that separates the veins from the appendage.

The VOM and its neighboring tissue are attractive targets for ablation in AF. It contains autonomic parasympathetic and sympathetic innervations that have been implicated in the pathogenesis of AF. The atrial tissue surrounding the VOM, which connects the mitral annulus (coronary sinus) to the posterior left atrium, as well as the lateral ridge, are routinely targeted during ablation of AF.

The VOM is present in and can be cannulated in ≈70% of patients. We tested the hypothesis that infusion of ethanol via VOM could be used to ablate its nerve terminals and neighboring atrial tissues.

Animal Studies
Seventeen normal, adult Mongrel dogs (35 to 40 kg) were studied. The animal protocol was approved by the animal care and use...
Because the ligament of Marshall has been implicated as a parasym-
pathetic conduit, we evaluated the effects of ethanol injection in the
left atrium. In 5 dogs. In 3 dogs, a third voltage map of the left atrium
was performed 30 minutes after completion of the initial map to
assess the persistence of the lesions.

Protocol 2: VOM Ethanol Infusion and Parasympathetic
Control in the Left Atrium

To evaluate the effects of ethanol injection in the parasympathetic modulation of the left atrium in 4 dogs. Similar to
protocol 1, after securing the cannulation of the VOM, we performed
a trans-septal puncture form the right femoral vein. A sheath was
advanced into the left atrium, through which a multielectrode basket
catheter (Constellation, EP Technologies) was inserted and ex-
panded. Bilateral cervical dissections were performed to expose the
vagus trunk. Cuff electrodes were positioned in each vagus nerve and
were connected to a Grass stimulator. High-frequency vagal stimu-
lization was titrated to achieve 30% to 50% decrease in heart rate. Left
atrial effective refractory periods (ERP) were measured at 3 left atrial
sites with and without vagal stimulation, and both before and after
VOM ethanol infusion. The basket catheter was pushed toward the
lateral atrial wall so that contact close to the VOM region was
obtained. One pacing site was chosen from each region, and the other
2 from equidistant splines, as determined by tissue contact and
capture.

Induction of AF during vagal stimulation was performed by burst
pacing before and after ethanol infusion. Pacing from 3 different
atrial sites was performed, starting at a cycle length of 300 ms and
decreasing approximately every 5 seconds by 10 ms until loss of 1:1
capture or AF induction. Five induction attempts were performed
from each site. If AF persisted more than 1 minute, it was considered
sustained, and vagal stimulation was discontinued to allow return of
normal sinus rhythm. Mean AF cycle length was quantified by
averaging beat-to-beat intervals from selected atrial sites.

Human Feasibility Studies

The human protocol was approved by the Institutional Review Board
at the Methodist Hospital and all subjects signed an informed consent
form describing the experimental nature of the study. Patients
subjected to ablation of AF were included in the study. After
obtaining routine intravenous access, an 8-F sheath was advanced
into the coronary sinus under fluoroscopy. A balloon occlusion
venogram was performed to delineate the coronary sinus anatomy.
The presence of the VOM was established when a posteriorly
directed vein branch was visible in the right anterior oblique
projection. An angiographic LIMA catheter was then inserted in the
coronary sinus aiming its tip toward the VOM, and an angioplasty
wire was advanced over the VOM. An angioplasty balloon was then
advanced over the wire and placed in the proximal VOM.

We then proceeded with obtaining double trans-septal access
under intracardiac echocardiographic guidance. A baseline
3-dimensional map of the left atrial geometry and bipolar voltage
amplitudes was constructed using either the CARTO (Biosense-
Webster) or the NavX-EnSite (St Jude Medical) systems.

Subsequently, we inflated the angioplasty balloon in the proximal
VOM as defined by radiographic contrast injection. To ascertain
flow in the VOM, 1 mL of echocardiographic contrast agent
(Definity) was delivered via the lumen of the angioplasty balloon.
Afterward, we performed 2 infusions of 1 cc each of 100% ethanol,
2 minutes apart. We then repeated a 3-dimensional bipolar voltage
map of the left atrium to define the tissue areas ablated by ethanol.
Finally, conventional radiofrequency ablation of the pulmonary vein
antra was performed. Pacing in the coronary sinus was performed to
assess for peri-mitral conduction block after ethanol infusion.

Data Analysis

Data are presented as mean ±SD. To compare ERP before and after
vagal stimulation, we used the paired t test. To compare ERP before
and after vagal stimulation, before and after VOM ethanol infusion, we used
repeated-measures ANOVA with the Bonferroni test for multiple
comparisons. A probability value <0.05 was considered significant.
The authors had full access to and take full responsibility for the
integrity of the data. All authors have read and agree to the
manuscript as written.

Results

Animal Studies

VOM Characteristics and Cannulation

A visible VOM was present in 13 of 17 dogs, identified as a
posteriorly directed branch of the coronary sinus in the right

anterior oblique fluoroscopic view. Figure 1 shows representative appearances of the VOM.

In 4 dogs, there was no discernable VOM. In the remainder, the length of the VOM was variable (29.7±10.7 mm) and so was its caliber. In all dogs, the vein communicated with the left atrial lumen, as shown by the presence of contrast in the left atrium via venous collaterals in the left atrial appendage. In 1 dog, a large VOM communicated with the innominate vein as a persistent left superior vena cava (Figure 1D).

Successful cannulation of the vein with an angioplasty wire was performed in 11 dogs. After several tools and strategies were attempted, the most reliable technique to cannulate the VOM involved advancing an angiographic left internal mammary (LIMA) catheter in the coronary sinus, so that its tip faced upwards, in contact with the roof of the coronary sinus. Two angioplasty wires were used: 1 was advanced in the lumen of the coronary sinus for fluoroscopic reference and 1 into the VOM through the LIMA catheter, with a preloaded angioplasty balloon (8 mm long, 2-mm diameter). The angioplasty wire (most commonly a Cross-It 0.014-inch wire) was then advanced through the LIMA catheter at different points of the roof of the coronary sinus, probing it at different locations until it could be advanced in the VOM. The wire was advanced in the VOM for a length of 25.4±11.7 mm from the vein ostium.

Once enough wire was advanced in the VOM, the angioplasty balloon was advanced over the wire into the proximal VOM. Contrast was injected through the balloon lumen to confirm VOM cannulation. The balloon was then inflated to maintain it in place while we proceeded with the experimental protocol. Direct contrast injection via the angioplasty balloon lumen demonstrated the full extent of the VOM and consistently some degree of myocardial staining. In 2 dogs, the length and caliber of the VOM significantly enlarged after selective contrast injection via the balloon (Figure 2A). Despite balloon inflation to achieve 2-mm diameters, complete occlusion of the VOM was never achieved, and contrast leakage into the coronary sinus lumen was consistently present.

Extent of Endocardial Tissue Ablated

At baseline, 3-dimensional maps demonstrated that bipolar voltage signals in the left atrium exceeded 2 mV in all dogs, consistent with normal healthy tissue. Infusion of 5 cc of 100% ethanol in the VOM was performed over 2 minutes and was not associated with hemodynamic or heart rate changes (in 1 dog that did not have a discernable VOM, rapid ethanol bolus infusion in the main coronary sinus was associated with ST-segment elevation and cardiac arrest). Immediately after ethanol infusion, a repeat bipolar voltage map was performed. This consistently demonstrated a new area of low voltage in the region corresponding to the VOM, extending from the mitral annulus, posteriorly and superiorly toward the left PV. The low-voltage area measured 0.5±0.3 cm² using a threshold of <0.1 mV, and 2.7±1.7 cm² using a threshold of <0.5 mV. Figure 2 shows a typical example. In Figure 2A, the angiographic appearance of the VOM is shown, with significant enlargement of the vein after cannulation and angioplasty balloon inflation. Figure 2B shows 3-dimensional voltage maps pre- and postinfusion of ethanol, with a clearly demarcated area of low voltage that extends from the mitral annulus (Figure 2B, top) toward the posterior wall of the left atrium, encompassing the area adjacent and anterior to the left PV.

The low-voltage surface areas were variable in extent and distribution, depending on the course, size, and length of the VOM. Figures 2 through 4 show different examples. In Figure 3, the lesion extends mostly toward the posterior wall of the left atrium in between the left and right PV. In some cases, the extension of the ablation lesions was small. In Figure 4, 2 examples are shown where small lesions were created: Figure 4A shows an example of a very small VOM in which cannulation with an angioplasty balloon was only possible in its very proximal portion; and Figure 4B...
shows a case where a communication between VOM and the innominate vein was present (persistent left superior vena cava), and the lesion size was also small because of ethanol shunting to the central venous circulation.

Lesions were persistent over time. In 3 dogs, repeat voltage maps were performed 30 minutes after completion of the initial map and no significant differences were found. Figure 5 shows the endocardial and epicardial appearance of the lesions after extraction of the heart.

Figure 3. Posterior left atrial ablation after VOM ethanol infusion. A, Course of the VOM on the coronary sinus venogram (left panel), wire cannulation (mid panel: top wire is in the VOM advanced via a left internal mammary artery angiographic catheter; bottom wire is in the main coronary sinus lumen), and selective VOM venogram via an inflated angioplasty balloon. B, Bipolar voltage 3-dimensional maps of the left atrial geometry before (left) and after (right) VOM ethanol infusion, in the posterior-anterior view (top) and in an inferior view (bottom). The low-voltage area created by VOM ethanol infusion is posteriorly directed between left and right pulmonary veins.

Figure 4. Anatomic factors leading to reduced ablation area. A, Small VOM. On coronary sinus venogram (left panel, left anterior oblique projection), the VOM is a small twig arising from the roof of the coronary sinus. Cannulation was successful, but the angioplasty balloon could only be advanced in the very proximal VOM (mid panel). A small annular area of ablation was created (right panel). B, Communication between VOM and left innominate vein superiorly. Despite a large VOM on the coronary sinus venogram (left panel, right anterior oblique projection) and successful VOM cannulation with an angioplasty balloon (mid-left panel, left anterior oblique projection), multiple ethanol infusions only created small ablation lesions on voltage maps (right panel). A communication between the VOM and the superior vena cava was obvious when the VOM was cannulated from above (mid-right panel).

Vagal Denervation by VOM Ethanol Infusion: Effects on AF Induction

ERP were measured at 3 atrial sites via basket electrodes before and after vagal stimulation. A decrease in ERP was demonstrable after vagal stimulation. After ethanol infusion, a significant blunting of vagally-mediated decrease in ERP was found (Figure 6). However, this effect was not uniform across the 3 left atrial sites tested; only sites in the neighborhood of the ablated tissue exhibited blunting of the vagal effect (Figure 6B).

Sustained AF during vagal stimulation was uniformly inducible (n=4 dogs) after burst pacing in 3 atrial sites (37 of 45 attempts). In 1 dog, AF organized into atrial flutter before spontaneous return of sinus rhythm. After VOM ethanol infusion, AF was induced in 19 of 45 attempts (P<0.001). Mean cycle length of AF after VOM ethanol infusion was slightly longer after VOM ethanol infusion (118.8±22.3 versus 111.3±19.2 ms at baseline, P<0.05). Organization into atrial flutter was present in 2 of 4 dogs after VOM ethanol infusion.

Left Atrial Propagation Patterns and Perimital Conduction After VOM Ethanol Infusion

It has been suggested that the ligament of Marshall participates in the electric communication between the right and left atria, as the terminal component of the interatrial communication via the coronary sinus.9 We evaluated left atrial activation maps before and after VOM ethanol infusion and were unable to show appreciable differences in left atrial activation patterns. Similarly, there were no changes in perimital conduction patterns after VOM ethanol infusion.

Human Feasibility Studies

Nine patients were consented for the study. In 2 patients there was no visible VOM in the coronary sinus venogram. In 1 patient, a small coronary sinus dissection was created during
attempts to cannulate the VOM with an angioplasty wire, and the procedure was aborted without clinical complications. In the remaining 6 patients, successful cannulation of the VOM was performed. Injection of echocardiographic contrast in the VOM demonstrated earliest contrast appearance in the left atrial lumen, adjacent to the left-sided PV (Figure 7 and Movie 1 [available online only]). There were no acute hemodynamic or clinical changes during or after ethanol infusion.

**Tissue Ablation by VOM Ethanol Infusion**

Ethanol infusion in the VOM lead to the generation of a new, low-voltage region that appeared posterior and superior to the coronary sinus, encompassing variable extents of the posterior left atrial wall and the anterior aspect of the left inferior pulmonary vein. Figure 7 shows a typical example. The area of scar (bipolar voltage amplitude, <0.5 mV) measured 10.2±5.7 cm² (range, 3.3 to 15.3 cm²), depending on the size of the VOM as shown in the selective venogram.

**Procedural Impact**

The total added procedure time (including coronary sinus cannulation and venogram, VOM cannulation, balloon occlusion and ethanol infusion, and repeat 3-dimensional voltage map) was 52.6±12.8 minutes (range, 31 to 66 minutes), and the added fluoroscopy time was 8.2±2.8 minutes (range, 4.1 to 10 minutes). There was no evidence of mitral annular conduction block after VOM ethanol infusion. In all 6 patients, ethanol levels measured at the end of the procedure in venous blood from the femoral vein were undetectable. In
4 of 6 patients, the left inferior PV became electrically disconnected solely with ethanol infusion (in 1 of 6 patients, the left superior PV as well). The total radiofrequency ablation times required to achieve left inferior PV isolation in the 2 patients that required it were 0.8 and 4.6 minutes. On follow-up, 1 patient was taken back for atrial flutter caused by macro-reentry in the right PV antrum, remote to areas affected by VOM ethanol infusion and likely unrelated to the VOM procedure. This was successfully ablated by radiofrequency application in the septal aspect of the right superior PV, and remains in normal sinus rhythm. All other patients remain in normal rhythm as well.

Discussion
The major findings of our study are as follows: (1) the VOM is a viable route to deliver therapeutic agents into left atrial tissues; (2) retrograde VOM ethanol infusion leads to tissue ablation in areas of the left atrium routinely targeted during catheter ablation of AF; (3) regional parasympathetic ablation is achieved by retrograde VOM ethanol infusion; and (4) retrograde VOM ethanol infusion is feasible in humans.

VOM as a Therapeutic Target in AF
The ligament of Marshall has been solidly implicated in arrhythmogenesis. Scherlag et al demonstrated an inducible ectopic rhythm arising from the ligament area on left cardiac sympathetic nerve stimulation. Doshi et al went on to specifically demonstrate the role of the ligament of Marshall in such adrenergic atrial tachycardia. A wealth of clinical data supports the VOM as a source of ectopic foci driving the genesis and maintenance of AF. Mechanistically, there are electric connections between left superior pulmonary vein, left atrium, and ligament of Marshall. In addition, focal ectopy arising in the VOM triggering AF has been demonstrated clinically and in experimental models of AF. The ligament of Marshall contains parasympathetic and sympathetic innervation that mediate autonomic modulation of the left atrial tissue and have been implicated in the pathogenesis of AF. Ulphani et al have shown that ablation of the ligament of Marshall blunts the vagally mediated decreases in left atrial ERP. We show that similar effects are achieved via retrograde VOM ethanol infusion.

VOM Ethanol Infusion for Left Atrial Ablation
The aforementioned data support the VOM as a target of ablation in its own right from the mechanistic standpoint. Two additional facts support targeting the VOM: (1) the thick pectinate muscle between the left atrial appendage and left-sided PV can be difficult to ablate using current techniques, and it is precisely the course of the VOM on the epicardial side; and (2) the posterior wall of the left atrium in the vicinity of the VOM can also be close to the esophagus, and current ablation techniques entail risk of esophageal damage and atrioesophageal fistula, which can be deadly.

Cannulating the VOM allows delivery of therapeutic agents in left atrial tissue. The anatomic distribution of tissues reached includes not only the vein and associated innervation, but also areas routinely targeted during catheter ablation of AF. Ethanol infusion leads to effective tissue ablation in these areas, as limited by the size and extent of the VOM. Ethanol is routinely used to ablate tissue in hypertrophic cardiomyopathy, and occasionally ventricular tachycardias that do not respond to conventional RF ablation. In these instances, ethanol is delivered arterially. Besides direct toxic effects, ethanol-induced arterial sclerosis is thought to mediate tissue damage through ischemia, a mechanism absent when retrogradely delivered. Nevertheless, we found adequate tissue ablation from the electric standpoint by retrograde venous infusion. Transmyocardial cardiac communication between the epicardial VOM and the left atrial endocardium must have occurred for the toxic effects of ethanol to take place. Contrast leakage into the left atrial lumen was consistently demonstrable during selective VOM venograms. This was confirmed by the human data showing echocardiographic contrast in the left atrium when selectively injected in the VOM. Therefore, transmyocardial transit occurs. It should be emphasized that electroanatomic voltage maps showing tissue ablation by voltage criteria were obtained endocardially, whereas the VOM is an epicardial structure.

Ethanol infusion in the VOM is attractive in ablation of AF because local toxicity of ethanol would be limited to tissues in direct contact with it and would spare neighboring structures such as the esophagus, potentially increasing safety of the procedure. Second, VOM ethanol infusion would directly address mechanistic sources of AF located in the VOM such as autonomic nerves and ectopic foci triggering AF. Third, it could help in achieving adequate ablation of the lateral ridge from the epicardial side. Fourth, a large area of tissue could be ablated at once with a simple infusion, potentially saving procedural time. Furthermore, if performed in isolation, it would be a purely right-sided procedure, obviating the need for a trans-septal puncture and anticoagulation, which are significant sources of procedural complications. Although several surgical reports have reported some efficacy of similarly limited left atrial interventions, most included pulmonary vein isolation as well, and we do not anticipate isolated ethanol VOM infusion as a stand alone procedure, even if it achieved significant vagal denervation.

Conclusions
Retrograde ethanol infusion in the VOM leads to left atrial tissue and vagal ablation and is feasible in humans. Further studies are needed to evaluate its potential role in ablation of AF.

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Disclosures
None.
References


CLINICAL PERSPECTIVE

The vein of Marshall is an atrial branch of the coronary sinus that runs posteriorly and superiorly in the left atrium, anterior to the left pulmonary veins, and posterior to the left atrial appendage. It contains sympathetic and parasympathetic innervation implicated in the pathogenesis of atrial fibrillation. Its location and innervation make it an attractive target in catheter ablation of atrial fibrillation. We hypothesized that we could cannulate the vein of Marshall via the coronary sinus and that retrograde ethanol delivery in such a vein could achieve regional tissue ablation and vagal denervation. We developed a technique for such a purpose and demonstrated in dogs its effectiveness at achieving left atrial tissue ablation. Furthermore, regional vagal denervation in the left atrium was also achieved. We go on to demonstrate that the technique is feasible in humans and show in patients undergoing conventional catheter ablation of atrial fibrillation that retrograde ethanol infusion is well tolerated and leads to left atrial tissue ablation in areas commonly targeted in the ablation procedure. Further studies are required to delineate the role, if any, of retrograde ethanol infusion in the vein of Marshall in the catheter-based treatment of atrial fibrillation.
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SUPPLEMENTAL MATERIAL

**Movie Online.** Echocardiographic contrast injection (Definity ®) in the VOM. An intracardiac echocardiographic view of the left atrium with the left-sided pulmonary veins is shown. Upon contrast injection, the earliest site of contrast appearance is between the left superior and inferior pulmonary vein, to then reach the left atrial lumen. This supports transmyocardial flow between the epicardial VOM and the left atrial lumen.