Advanced EP: ethanol ablation of the vein of Marshall

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Introduction

- Catheter ablation is an established treatment strategy for patients with drug-refractory atrial fibrillation (AF). However, success rates in patients with persistent AF remain modest (43%-69%).

- Current ablation strategies for treatment of persistent AF can be categorized into tailored approaches, aimed at eliminating sources of AF maintenance (bursting foci, rotors, etc.), and anatomical approaches where left atrium is electrically partitioned by predefined linear lesion sets (Cox-maze).

- Tailored approaches have been associated with high risk of subsequent organized atrial tachycardias (AT) and impairment of atrial function. For anatomical approaches, creating durable linear lesions remains challenging.

- Both approaches have failed to demonstrate superiority to pulmonary vein isolation (PVI) in prospective randomized trials.

Europace 2018;20:f366–f376, J Am Coll Cardiol. 2004;43:2044-2053
J Cardiovasc Electrophysiol. 2005;16:1125-1237
Semin Thorac Cardiovasc Surg. 2000;1:53-55
N Engl J Med 2015;372:1812–1822

Stepwise approach

- A combination of both approaches into the “stepwise approach” improved freedom from arrhythmic events, but at the cost of extensive ablation with impaired atrial physiology and recurrent AT needing redo procedures.

- High-density mapping of these arrhythmias has pointed out: first, a patchy lesion set is highly proarrhythmogenic, favoring macro-re-entry through conduction slowing and providing pivots for localized re-entries and second, discrete anatomical structures such as the vein of Marshall (VOM) and the coronary sinus (CS) have epicardial muscular bundles that are more frequently involved in re-entry than previously expected.

Circ Arrhythm Electrophysiol. 2015;8:18-24
Heart Rhythm. 2017;14:S452
Heart Rhythm. 2018;15:S82
Heart Rhythm. 2018;15:17-24

The vein of Marshall (VOM)

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Figure 1
A, Anatomy of the LOM (by Tung R, Card Electrophysiol Clin, 2020).

B, Pathophysiological mechanisms linking the LOM and MB with arrhythmia (Pacing Clin Electrophysiol. 2021;44:782–791)

- VOM is an embryological remnant of the left SVC and has been implicated in the pathogenesis of AF, as a source of AF triggers, and a tract for parasympathetic and sympathetic innervations that modulate EP properties of atrial tissue and contribute to AF maintenance.
- VOM ethanol infusion has gained growing interest for the treatment of persistent AF. This technique, pioneered by Valderrabano et al. in 2009 ensures efficient elimination of the VOM bundle, which is otherwise protected from standard radiofrequency by fat insulation.

Heart Rhythm 2021;18:529–537, J Am Coll Cardiol. 2000;36(4):1324-1327
J Physiol Heart Circ Physiol. 2007;293(3):H1629-H1635, J Cardiovasc Electrophysiol. 2006;17(8): 839-846
Circ Arrhythm Electrophysiol. 2009;2(1):50-56, J Cardiovasc Electrophysiol. 2012;23(6): 583-591

VENUS Trial and MARS-AF Trial

VENUS randomized trial (Catheter Ablation With VOM Ethanol Infusion vs Catheter Ablation Alone on Persistent AF):

- at 6 and 12 months, the proportion of patients with **freedom from AF/AT** after a single procedure was **49.2%** (91/185) vs **38%** (60/158), (P = 0.04).
- AF burden (zero burden in 78.3% vs 67.9%, P = 0.01), freedom from AF after multiple procedures (65.2% vs 53.8%, P = 0.04), and success achieving perimitral block (80.6% vs 51.3%, P < 0.001) were significantly improved in vein of Marshall–treated patients.

MARS-AF randomized trial (Catheter Ablation With VOM Ethanol Infusion vs Catheter Ablation Alone in Repeat Ablation of Persistent AF):

- no significant benefit of VOM Ethanol Infusion in an unselected population of previously failed AF ablation with multiple mechanisms. At 12 months, the proportion of patients with freedom from AF/AT after a single procedure was 41.5% (17/41) in the VOM-CA group compared with 50.0% (18/36) in the CA alone group (P = 0.45).

JAMA. 2020;324:1620–162

Heart Rhythm 2021; 18 (8 supplement): S398

Marshall PLAN

- Novel ablation strategy that systematically targets anatomical atrial structures: Marshall bundle elimination (CS and VOM musculature), PVI, and Line completion for ANatomical ablation of persistent AF (mitral, roof, and cavotricuspid isthmus [CTI]).

- Prospective single center study.
- VOM ethanol infusion was completed in 69 patients (92%).
- The full Marshall-PLAN lesion set (VOM, PVI, mitral, roof, and CTI with block) was successfully completed in 68 patients (**91%**).
- At 12 months, 54 of 75 patients (**72%**) were free from AF/AT after a single procedure (no antiarrhythmic drugs) and in the subset of patients with a complete Marshall-PLAN lesion set (n= 68), the single procedure success rate was **79%**.
- After 1 or 2 procedures, 67 of 75 patients (**89%**) remained free from AF/AT (no antiarrhythmic drugs).
- After 1 or 2 procedures, VOM ethanol infusion was complete in 72 of 75 patients (**96%**).
- 13% patients undergoing VOM ethanol infusion had evidence of venous dissection during infusion.

Heart Rhythm 2021;18:529–537

Procedural steps for VoM-Et

Pre-interventional considerations and preparation

- Additional procedural time for VoM-Et is about 20–30 min when the operator is learning the procedure and decreases to 10–15 min when the operator has greater familiarity.
- Additional fluoroscopy time usually is 5–10 min in the beginning and can decrease to 2 min with experience.
- Contrast agent usually is 40–70 mL.
- When an operator is to learn the procedure and in difficult cases, there should be a low threshold for seeking assistance from a second operator. It also may be useful to consult with interventional cardiologists in the beginning.

Heart Rhythm. 2021 Jul;18(7):1083-1087

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Materials necessary for ethanol injection:

- Long deflectable steerable sheath
- Left internal mammary catheter, 5F
- Coronary angioplasty guidewire, 0.014 inch, 190 cm
- Coronary dilation balloon catheter, 1.5–2.5 x 6–8 mm
- Inflation device
- 100-mL contrast agent, contrast agent injection kit, and 10-mL
- screw syringe
- Y-connector
- 2 x 3-mL screw syringes for ethanol and contrast injection via balloon catheter
- 10-mL ethanol 96%

Heart Rhythm. 2021 Jul;18(7):1083-1087
J Cardiovasc Electrophysiol. 2019;1-9

Access to CS

- We introduce a long deflectable steerable sheath via a right femoral approach to reach the CS.
- First, we cannulate the CS with a 3.5-mm-tip ablation catheter through the sheath.
- Second, we push the sheath over the ablation catheter into the CS, thereby minimizing the risk of CS dissection.
- In addition, we routinely place a decapolar diagnostic catheter in the CS, which helps with orientation on fluoroscopy.

Heart Rhythm. 2021 Jul;18(7):1083-1087

Angiographic VoM visualization

Figure 2

Figure 3A

Figure 3B

- The ablation catheter is exchanged for a 5F left internal mammary artery (IMA) guiding catheter with a Y-connector for contrast injection and wire placement.
- During introduction of the IMA catheter, careful attention should be paid to avoid CS dissection. The IMA catheter is pointing posteriorly toward the assumed VoM. During slow, manual contrast injection, the IMA catheter is moved gently up and downward. It is important to start the injection slowly, as the IMA catheter already might have directly intubated the VoM trunk, and injection too quickly might severely damage the vein.

Heart Rhythm. 2021 Jul;18(7):1083-1087
Heart Rhythm. 2021 Apr;18(4):529-537
J Cardiovasc Electrophysiol. 2019;1-9

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Figure 4

- When searching for the VOM, we focus immediately beneath the Vieussens valve, where the ostium of the VOM is almost always located.
- AP view demonstrating the VOM running relatively **parallel** to the great cardiac vein.
- RAO view the VOM is branching **toward** left atrium.

J Cardiovasc Electrophysiol. 2019;1-9
J Cardiovasc Electrophysiol. 2003;14(11):1254-1254
JACC Clin Electrophysiol. 2017;3(9):1020-1032

VoM cannulation

Figure 5

- After angiographic visualization of the VoM, an ¨over the wire¨ angioplasty balloon is introduced via the Y-connector of the IMA catheter and advanced on an angioplasty guidewire (0.014 inch, 190 cm).
- The size of the balloon is chosen based on visual estimation and size comparison to the 6F decapolar CS catheter or the 5F IMA catheter. It usually is 1.5–2.5 mm in diameter and 6–8 mm in length.
- The guidewire is gently introduced into the VoM with rotational movements, far enough to provide enough support to allow sliding of the balloon over the wire, but not too far to avoid distal vessel perforation.
- The balloon is then introduced over the wire to a proximal position and inflated to 2–4 atm until a slight resistance is felt, and the wire is taken out. Inflation pressure that is too high might lead to dissection of the VoM.

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Ethanol injection

Figure 5

- After balloon inflation, the VoM is visualized by direct contrast injection into the balloon catheter to check for leakage or collaterals back to the CS. In case of relevant leakage, the balloon is repositioned. In case of collaterals, the balloon is positioned more distally if possible, and ethanol is injected slowly. We then inject a total of 10 mL of 96% ethanol divided over 3 applications using a 3-mL syringe via the balloon catheter.
- Each injection takes about 60 sec and is followed by a repeat contrast injection to check for vessel integrity and LA wall staining. It is important to inject ethanol slowly for an optimal ablation effect and to minimize the risk of an anaphylactic reaction to ethanol. Staining represents capillary disruption, likely improves the effect of ethanol, and should increase after each injection. If high resistance is encountered during injection, the alignment of the IMA and the balloon catheter should be checked.
- After the last contrast injection, the balloon is deflated and the entire system is evacuated. We usually (re-)map the LA wall to evaluate the effect of VoM-Et infusion and adjust our ablation strategy for the left PV. If a scar is created that covers the lower, posterior part of the left lower PV, we do not additionally ablate with radiofrequency energy in this area to obtain PVI.

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Lateral mitral isthmus block

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Figure 6
Coronary sinus (CS) activation during left atrial appendage (LAA) pacing for evaluation of lateral mitral isthmus block.
A: Distal-to-proximal CS activation indicating no block (delay 94 ms).
B: After endocardial ablation, V-shaped CS activation indicates endocardial block but persistent epicardial conduction (delay 182 ms).
C: Proximal-to-distal CS activation indicating complete endocardial and epicardial block (delay 260 ms).
Arrows indicate CS activation.

- After VoM-Et, we usually aim for lateral mitral isthmus block by additional radiofrequency ablation. Only in very few instances does VoM-Et alone lead to complete mitral isthmus block.
- Using an irrigated, 3.5-mm-tip ablation catheter, we perform a linear ablation from the inferior left PV to the mitral annulus using point-by-point radiofrequency applications at power of 40–45 W. The ablation line is placed superior to the VoM–CS junction to avoid the high-density muscular fibers in this area.
- During ablation, we usually pace from the LAA and observe the activation pattern of the decapolar catheter placed in the CS, which in the vast majority of cases is distal to proximal in the beginning. When the activation changes to a proximal-to-distal pattern, we usually assume mitral isthmus block.

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- In case of endocardial mitral isthmus block with persistent epicardial connection, we usually see a V-pattern on the CS catheter electrodes. This is caused by proximal-to-distal endocardial CS activation but still remaining distal-to-proximal epicardial activation.

- To eliminate the remaining epicardial connection, we place the ablation catheter in the CS at the level of the endocardial ablation line pointing toward the LA. Using 25 W with a flow rate of 20 mL/min for up to 30 sec per ablation point, we ablate from slightly superior to inferior in relation to the endocardial ablation line.

- If block is not achieved, we perform a circular ablation in the CS to also target any lateral CS fibers that may be present. With the elimination of remaining epicardial CS connections, the CS activation pattern should clearly show proximal-to-distal activation during LAA pacing, and the delay usually further prolongs.

- Epicardial ablation inside the CS is necessary in about **1/2** of patients to obtain lateral mitral isthmus block after VoM-Et and endocardial ablation.

- To verify complete mitral isthmus block, pace sequentially from distal to proximal electrodes on the CS catheter. In case of complete mitral isthmus block, the CS–LAA delay should prolong by about 10 ms with sequential proximal-to-distal pacing.

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Complications

❖ VoM dissection:

might be caused by mechanical manipulation of the IMA catheter, injection of contrast too quickly with the IMA catheter intubating the VoM, manipulation of the guidewire, or application of balloon inflation pressure that is too high. Dissection usually has no impact on patient safety; however, it might preclude further access for VoM-Et.

❖ VoM perforation:

might be due to aggressive manipulation of the guidewire too distally into the vein or by bursting of the vessel with contrast injection that is too fast. If a small perforation is present, we usually try to finish VoM-Et with very slow ethanol injections. A small pericardial effusion might develop and should be watched for. In rare cases, pericardial puncture may be necessary.

❖ CS dissection:

due to mechanical manipulation of the IMA catheter or deflectable sheath. The highest risk of CS dissection is during entrance into the CS. Thus, we propose entering the CS with the ablation catheter via the deflectable sheath first, pushing the sheath over the catheter into the CS, and then exchanging the ablation catheter for the IMA catheter.

❖ Anaphylaxis due to ethanol:

potentially life-threatening complication of VoM-Et, minimize the risk of anaphylactic reaction, ethanol should always be injected as slowly as possible.

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Heart Rhythm. 2021 Apr;18(4):529-537
Circ Arrhythm Electrophysiol. 2021;14:e010001

Challenging cases

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Figure 7
A: Presence of left atrial appendage (LAA) vein originating distal to valve of Vieussens with anterior course.
B: Presence of posterolateral vein with proximal origin and posterior course.
C: Presence of VoM and LAA vein.
D: Improvement of sheath stability with sheath guidewire in the coronary sinus (CS) and posterior (clockwise) orientation.
E, F: Direct (E) and indirect (F) leak back into CS.

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Left atrial appendage vein ethanol infusion

Figure 8
Upper left: contrast injection in the LAA vein (red arrow).
Upper right: Contrast injection into the LAA vein showing staining of atrial tissue after 6 mL of ethanol administered (red arrows).
Lower panel: Voltage map of the left atria performed after ethanol infusion. Note the low voltage area located at the left appendage (dashed line).

Heart Rhythm. 2021 Apr;18(4):529-537

Conclusion

- VoM-Et is a promising strategy as part of an anatomic, primary ablation approach for persistent AF, treatment of AT using the ligament of Marshall, and AF redo procedures.

- The VOM is highly accessible using a femoral approach with an angiographic catheter and a steerable sheath (accessible in 93% of patients, only in 7% of patients VOM non identified or guidewire insertion impossible due to small VOM).

- The technique can be easily learned by electrophysiologists and can be applied broadly.

Circ Arrhythm Electrophysiol. 2021;14:e010001
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Thank you very much

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Venus Trial

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JAMA. 2020;324(16):1620-1628. doi:10.1001/jama.2020.16195

Venus Trial