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Vein of Marshall Ethanol Infusion in Setting of Atrial Fibrillation Ablation

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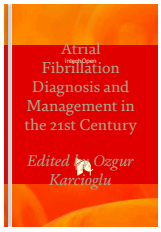

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Abstract

Catheter ablation especially in persistent atrial fibrillation has limited success. Strategies beyond pulmonary veins isolation failed to demonstrate improvement of long-term rhythm maintenance. The vein of Marshall (VOM) is a promising therapeutic target as it fit perfectly with “Coumel’s triangle”: triggers in form of focal activities or stable reentries priming atrial fibrillation comes typically from tissue surrounding the VOM, it colocalize with mitral line especially in the epicardial part difficult to approach by endocardial ablations, it contains autonomic parasympathetic and sympathetic innervation implicated in arrhythmogenesis. Epicardial chemical ablation by ethanol delivery directly inside the vein of Marshall represents an attractive therapeutic approach eliminating arrhythmic triggers and autonomic modulators and, as it colocalize with the trajectory of the mitral isthmus, completing the integrity of that linear lesion. Based on advantages provided from VOM alcoholization, this technique has been progressively introduced in addiction to standard ablation strategies in atrial fibrillation treatment. This chapter aims to describe the electrophysiological characteristics of vein of Marshall, the technical aspects of ethanol delivery and the evidences from the literature supporting the emerging role of VOM alcoholization in atrial fibrillation treatment.

Keywords

vein of Marshall | alcoholization | VOM-ETHO | atrial fibrillation | ablation

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Chapter sections

1. Introduction

Experimental and clinical studies have demonstrated that atrial myocardial tissue surrounding the vein of Marshall (VOM) can support electrical focal activities [ ] or stable reentries [ ] priming atrial fibrillation or synchronized atrial arrhythmias. Moreover, the epicardial region along the path of VOM contains autonomic parasympathetic [,] and sympathetic [ ] innervation that have been implicated in triggering AF [ ] unveiling important technical issues in the treatment of this arrhythmia and in the maintenance of sinus rhythm after ablation procedures. Thus, VOM is a promising therapeutic target because it fits perfectly with Coumel’s triangle components (trigger, substrate and autonomic tone).

Since it is insulated by epicardial fat, physical ablation of the VOM bundle by radiofrequency has been highly challenging and potentially harmful. Chemical ablation by retrograde ethanol infusion in the Marshall vein (VOM-ETHO) has provided a new attractive approach for an efficient elimination of triggered activity originating from this region. As the atrial tissue surrounding the VOM connects the mitral annulus (coronary sinus) to the posterior left atrium (as well as the lateral ridge), this technique has proved to be highly effective in determining a complete mitral isthmus block both in terms of acute success and lesion durability [ ].

2. Anatomical considerations

Embryologically, the VOM is a remnant of the left superior vena cava, which, as it becomes atretic during fetal growth, may remain open in form of small vein diramation draining into the coronary sinus [ ]. In 1850 Marshall first described this venous structure draining into the coronary sinus with trajectory directed toward the lateral and posterior wall of left atrium and directed up to the left pulmonary veins [ ]. The VOM descends obliquely, posterior to the left atrial (appendage (LAA) on the epicardial aspect of the LA lateral ridge, running along the postero-lateral LA toward the CS. A comprehensive study of the atrial venous anatomy is provided by Valderrabano and colleagues based on analysis of a series of VOM-ETHO procedures performed on a large population of 218 patients scheduled for atrial fibrillation ablation interventions [ ]. In this research, beyond the VOM, that was the most commonly cannulated vein, other atrial veins were variably opacified by dye infusion through collateral flow. A consistent pattern of atrial branches arising from coronary ostium were observed (as depicted in): septal vein, a second inferior vein, the VOM, LAA veins, anterior roof veins. Other veins not connected to the CS were detected such as roof veins commonly connected with posterior veins and extracardiac collaterals.

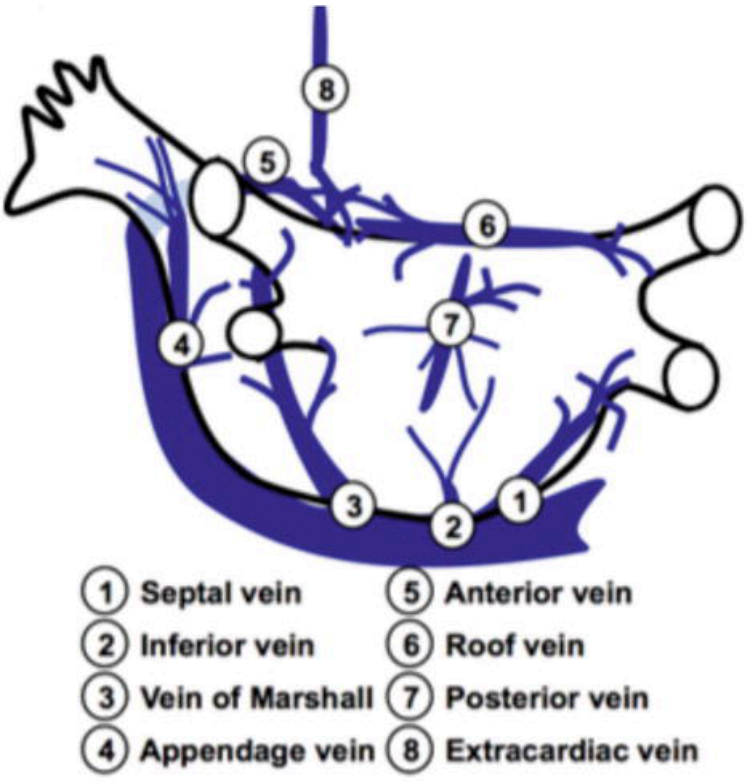

Figure 1.

Diagrammatic representation of atrial venous circulation from the posterior aspect of the left atrium. From: Valderrabano et al. [9].

VOM is typically localized at the ostial aspect of the valve of Vieussens. The incidence of VOM identification is about 75–92% according to data in the literature [,]. Distance between CS ostium and VOM is 4.25 ± 2.57 cm, with substantial variability. VOM length before branching was 2.99 ± 1.82 cm. VOM is typically a true atrial vein, with branches and visible venules draining the neighboring atrial tissue. Variable branching was present in 78.2% of cases. According to relation to the left inferior pulmonary vein, VOM presents variable trajectory: smaller VOM which terminates before reaching the left inferior PV (17.6%), VOM visible up to the left inferior pulmonary vein (72.8%), VOM can reach the left superior pulmonary vein (9.6%). Communication between VOM and left pulmonary veins was demonstrated by contrast drainage in the left PVs during the VOM venogram, appearing to connect through the left pulmonary vein carina (it happens in 37.7% of cases).

3. VOM-ETHO procedure

The technique was pioneered by Valderrabano and coworkers in 2009 [ ]. The protocol was studied in 17 dogs. VOM was visualized in 13. The electroanatomical map of left atrium repeated after ethanol infusion demonstrated a new crescent-shaped scar extending from mitral annulus in the posterior wall toward left pulmonary veins. To test the feasibility of VOM-ETHO in humans, 6 patients undergoing pulmonary veins antral isolation, had successful VOM cannulation and ethanol infusion with the confirmation of a new scar formation involving the infero-posterior left atrial wall extending toward the left pulmonary veins.

A right jugular approach [, , ,] and femoral vein approach [ ] have been described for VOM cannulation and alcohol delivery. There are reports of success rate of 74% (23 out 31 patients) for VOM venogram using the right jugular approach and 89% (17 out 19 patients) using the femoral approach. Valderrabano et al. reported that 86% (188 of 218) of the VOM was accessible using a right jugular approach with a LIMA angiographic catheter [ ].

The technique for VOM cannulation and ethanol infusion was subsequently well reported by the Bordeaux group [ ] demonstrating a high success rate of VOM cannulation of 92.6% (50 of 54) with a femoral approach using the LIMA (left internal mammary artery) catheter ( ).

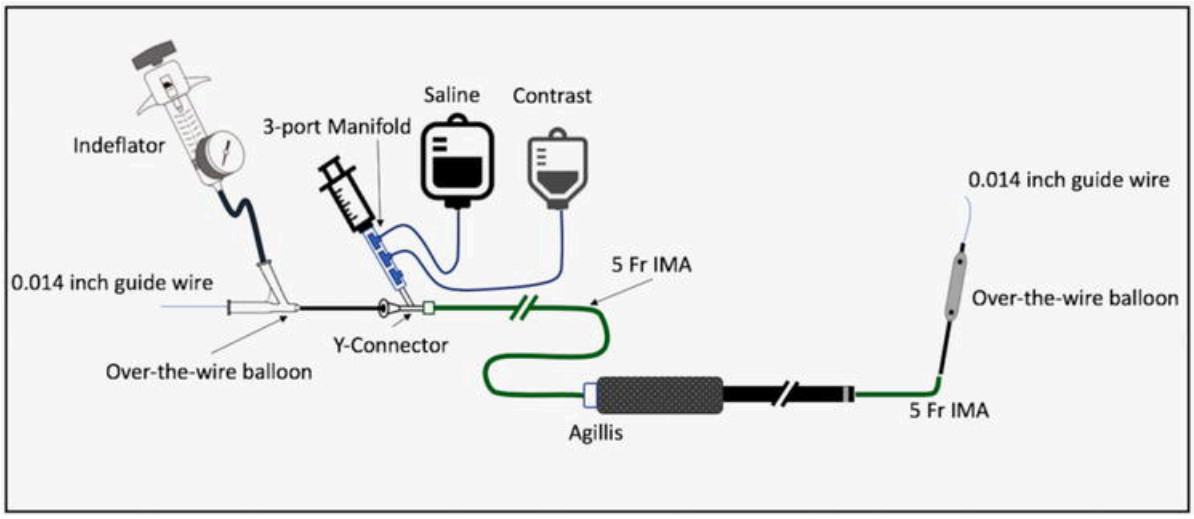

Figure 2.

A comprehensive schematic representation of the technical setting for ethanol infusion in the VOM. From Kitamura et al. [17].

3.1 A step-by-step list actions

from the right femoral vein, a steerable long sheat (Agilis NxT; Abbott) or long fixed curve sheath was inserted into the CS, guided by ablation catheter or steerable catheter. Once the long sheath was in place, a CS venogram was acquired (, panel 1).

A selective venogram of the VOM was performed using a 5-Fr angiography catheter (left internal mammary artery [LIMA] via the long sheat). To acquire a clearer venogram of the VOM and avoid the overlapping CS, a right anterior oblique (RAO) view was preferred (, panel 2). The LIMA catheter was inserted into the CS point both posteriorly and superiorly in the RAO view. In addition, the contrast indentation indicating the location of the valve of Vieussens was carefully explored to find the ostium of VOM. At each location, a small amount of the contrast was injected through the LIMA catheter to confirm engaging the VOM. When the VOM was not identified, a balloon occlusion venogram of CS was performed to explore the VOM.

After engaging VOM by LIMA catheter, an angioplasty wire 0.014 inch supported by an over-the-wire balloon catheter was advanced into the VOM. An appropriate size of balloon (1.5–2.5 mm diameter and 6–15 mm length) was used depending on the size of the VOM (, panel 3–4)

The balloon was started to be inflated at low pressure (1–2 atm) until the operator feel some resistance on the inflator with a maximum of 6–8 atm in the VOM. After the balloon was inflated completely, the wire was removed.

A selective venogram of the VOM was obtained by injecting 1 mL of contrast medium through the wire port of the balloon (, panel 5)

After confirming balloon occlusion and VOM distribution, 0.5–3 mL of ethanol (96% ethanol 10 mL) was slowly injected over 1 minute and selective venography of the VOM was repeated (, panel 6–8). A total of 6 to 12 mL of ethanol was used as a maximum dose.

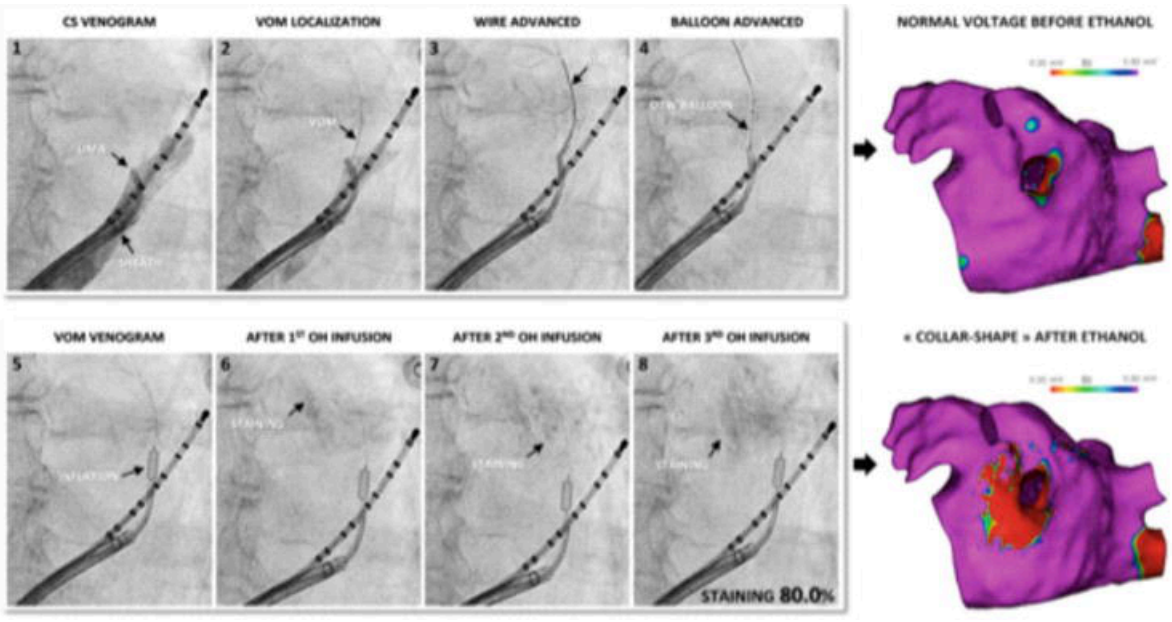

Figure 3.
Step-by-step actions for VOM cannulation and ethanol delivery (right panels). Left panels: Pre and post-VOM-ETHO bipolar maps indicating typical location and shaping of scarring formation. From: Kitamura et al. [17].

3.2 Tissue Ablation by VOM-ETHO

Ethanol infusion in the VOM leads to generation of a new low-voltage area 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. The area of the scarring depends on the size of the VOM. Valderrabano et al. reported that the area of scar (bipolar voltage amplitude <0.5 mV) was 10.2 + −5.7 cm^2 (range, 3.3 to 15.3 cm^2) in the first human experience. On large population of over 700 patients, the Bordeaux group reported a scarring area of 10.2 + −5.3 cm^2 [,]. In this experience factors contributing to reduction of VOM-ETHO effectiveness in lesion formation were: VOM dissection (10.7%), iodine leakage (3.0%), and VOM morphology without visible branches (3.0%). Ethanol infusion in a wrong vein was associated with less mitral line block (72.7% versus 95.8%, P = 0.012).

3.3 Technical issues and considerations

VOM-ETHO is highly feasible with a success rate of 91% from latest data on a population of over 700 patients [ ]. Factors associated to procedural failure were: nonidentification of VOM (6.2%), noncannulation (1.5%) or ethanol infusion in the wrong vein (1.7%). The Vieussens valve was a helpful landmark and was visible in 63.2% of cases. Remarkably, previous ablation inside the coronary sinus was strictly associated to VOM nonidentification. The success rate of VOM-ETHO procedures increases with the experience of operators.

3.4 Complications

Complications related to VOM-ETHO procedures are reported in .

Event	Rate (%)	Time	Comment	Management
VOM perforation	2.8	Acute	Infusion still feasible but with higher risk of delayed tamponade	Anti-inflammatory drugs and repeated echocardiography
pericarditis	1.8	Delayed	Usually at day 2	anti-inflammatory drugs
Delayed tamponade	0.8–6	Delayed	serous nature of cardiac effusion in ⅔ of patients. Usually due to inflammatory reaction	pericardiocentesis
Stroke	0.6–1	Delayed	stroke rate in the reported range	medical management
Acute tamponade	0.1–0.2	Acute	related to cannulation manoeuvers and eventual per-procedural stem pops	Surgical drainage necessary
Anaphylaxis	<0.2	Acute	generally in case of hemodynamic collapse during infusion	adrenaline, corticosteroids
High Degree AVB	<0.2	Acute	must be favored by very proximal VOM ostium	monitoring AV conduction during ethanol infusion
LAA Isolation	0.2	Acute	risk increased in case of large anterior scarring	Bachmann conduction assessment prior to VOM-ETHO in case of history of previous extensive ablations

Table 1.

Complications rate during VOM-ETHO procedures.

Modified from: Kamakura et al. [ ]; and Valderrábano et al. [ ].

Acute and delayed pericardial effusion represented the most described complications. During the procedure, pericardial tamponade was generally due to inadvertent CS perforation during VOM cannulation maneuvers or steam pops occurred during ablation. After the procedure, subacute pericardial effusion requiring pericardiocentesis was related to inflammatory reaction after alcohol delivery. The higher rate of delayed cardiac effusion or tamponade observed in patients with VOM perforation advocates a causal relationship between the inflammatory reaction and the inadvertent drainage of ethanol in the pericardial space. LAA isolation occurring after VOM-ETHO procedures may be observed in patients with previous extensive ablation settings involving septal and anterior scarring.

4. Role of VOM Bundle in atrial tachycardias

Atrial tachycardias (ATs) are often seen in the context of atrial fibrillation ablation implicating macroreentrant or scar-related mechanisms [,]. Radiofrequency catheter ablation is an effective therapy for patients with AF but perimitral ATs and localized reentry circuits commonly appear after pulmonary vein isolation or additional linear lesion in the left atrium [ ]. Patients having connections between Marshall bundle and the myocardium of coronary sinus, left atrium or pulmonary veins, may develop the anatomical substrate to generate localized reentry circuits or macroreentrant ATs around the mitral isthmus, using the epicardial Marshall bundle [ ]. Vlachos et al. [ ], considering a population of 140 patients previously underwent a pulmonary vein isolation procedure, reported that the Marshall bundle is involved in a higher proportion of post-AF ablation ATs (30.2%), being 51.7% macroreentrant ATs and 48.3% localized reentry. Marshall bundle-dependent ATs can be terminated with RF ablation, either endocardial via Marshall-bundle-left atrium connection, or epicardially via Marshall bundle-CS connections, and with ethanol infusion inside the VOM being the Marshall bundle an electrically protected, isolated anatomical structure, difficult to target with RF ablation (and) [ ].

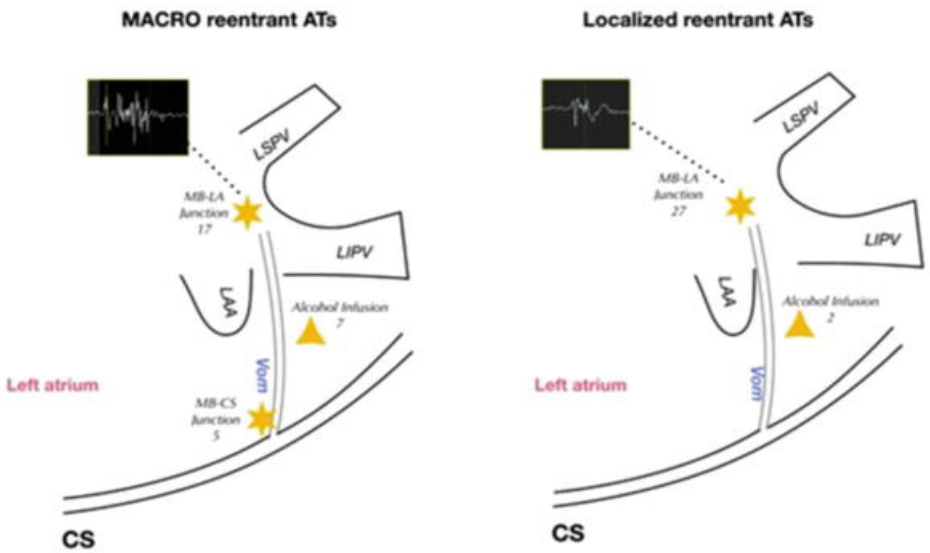

Figure 4.

The bipolar EGMs recorded in MB-LA connections and MB-CS connections have a characteristic electrophysiological pattern: high-frequency long-duration amplitude multicomponent (multiphasic) EGMs. From Vlachos et al. [2].

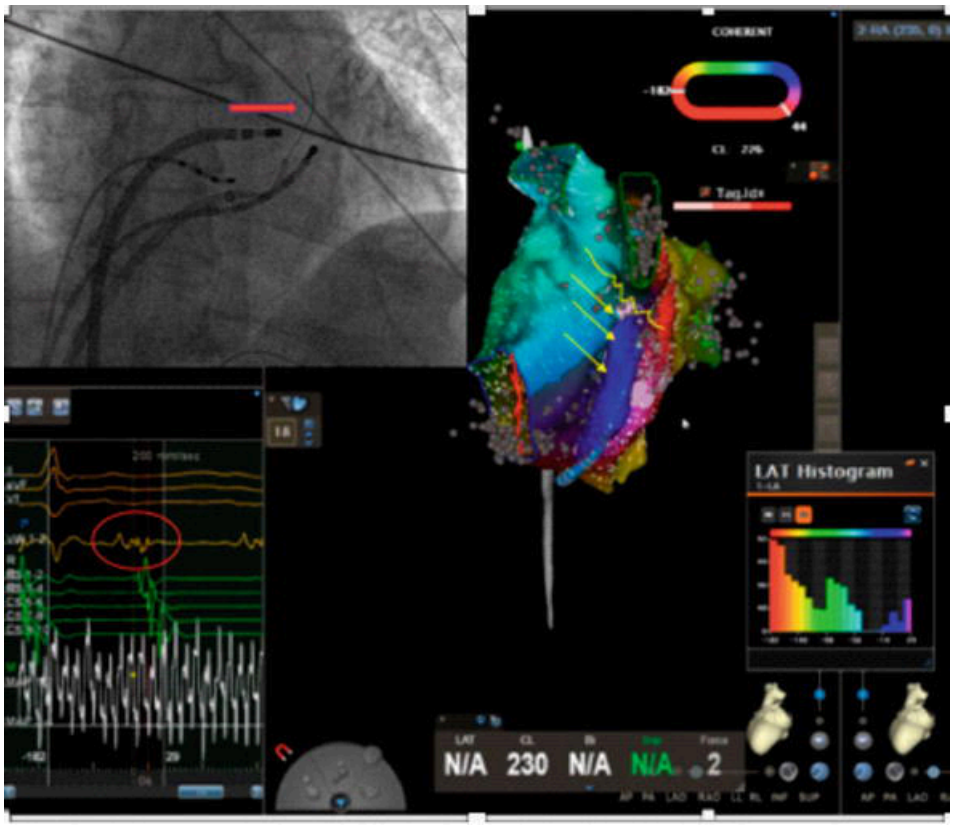

Figure 5.

Example of Marshall Bundle-related perimitral circuit in a patient with previous pulmonary vein isolation and linear lesions in the left atrium (mitral line and roofline). Note that part of the circuit is lacking during endocardial mapping on the LAT Histogram (CARTO7 module). Circuit mapping is completed by annotating signals recorded on Vision-Wire (red arrow) in the VOM. Diastolic signal recorded on the mapping wire placed in the VOM appears fragmented and of long duration.

Endocardial ablation from within the left atrium may not successfully ablate the Marshall bundle, owing to the distance from endocardium to the critical site. As RF ablation induces a tissue heating by mostly resistive mechanism, the difficult to reach the epicardial Marshall bundle may explain the high failure rate of mitral isthmus block in published studies [,]. For these reasons ethanol infusion inside the VOM may represent an adjunctive standalone strategy in patients with refractory Marshall bundle-related perimitral ATs or localized reentry circuits [, ,]. The additional use of VOM-ETHO strategy seems to improve ablation rates when compared with RF ablation alone [,].

5. VOM-ETHO in setting of atrial fibrillation. Randomized clinical trials

The VENUS-AF Trial (Vein of Marshall EthaNol in Untreated perSistent) completed in 2018 and published in 2020 [ ], was a multicenter, randomized clinical trial comparing the rhythm-control effectiveness of 2 ablation strategies: catheter ablation alone or combined with vein of Marshall ethanol infusion in de novo ablation of AF in a 1:1.15 fashion (including 15% more patients in the VOM group predicting a 15% failure to complete the VOM procedure thus being able to compare VOM-completed patients with controls in a 1:1 ratio). Patients were recruited from 12 referral centers in the United States and were eligible if they were between 18 and 85 years of age and had symptomatic persistent AF (sustained AF lasting >7 days) refractory to at least 1 antiarrhythmic agent. Exclusion criteria included previous AF ablation attempts and left atrial diameter or volume exceeding 65 mm or 200 mL, respectively. The primary endpoint was freedom from AF or AT 30-second duration over 1-year follow-

up, with 1-months continuous monitoring at 6 and 12 months, after a single procedure. A total of 343 patients were enrolled (185 randomized to VOM and 158 to PVI). VOM-ETHO was successfully completed in 155 of 185 patients. After a single procedure, 49.2% (91/185) in the VOM group resulted free from AT/AF compared to 38% (60/185) in the PVI group (p = 0.04). Considering patients with VOM-ETHO procedure successfully completed (as-treated analysis), the primary outcome was reached in 80/115 patients in the VOM group (51.6%, p = 0.02). Notably, AF burden, freedom from AF after multiple procedures and mitral line block achievement were significantly improved in VOM-treated patients. Kaplan–Meier plots showed significant reduction in AF or AT recurrence in the VOM group, in both the as-randomized analysis (hazard ratio 0.73; 95% CI 0.53–1.00; P 5 0.05) and the as-treated analysis (hazard ratio 0.67; 95% CI 0.47–0.93; P 5 0.02) ( ). Interestingly, considering subjects with mitral line bidirectional block achievement, patients randomized to VOM-ETHO group (75 of 138) showed a better outcome respect to patients randomized to "ablation only" group (30 of 81) in terms of freedom from AT/AF in 1 year follow-up (54.3% vs. 37%, OR 0.49; 95% CI 0.28–0.87; P 5 0.01) [ ].

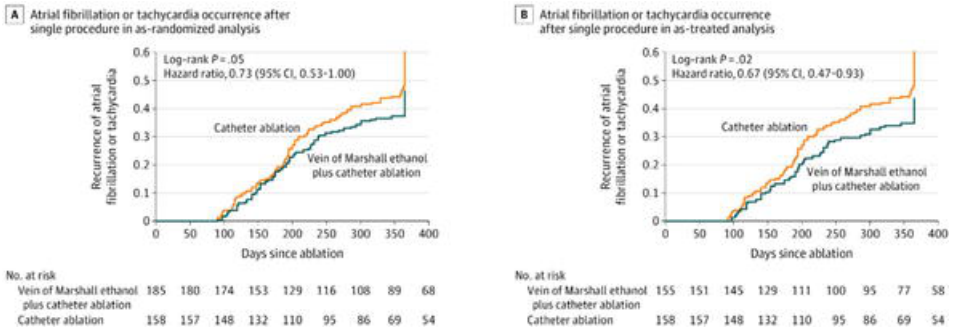

Figure 6.

Outcomes of the VENUS trial. A: time-to-recurrence of atrial fibrillation/atrial tachycardia "as randomized". B: time to recurrence excluding patients "as-treated", excluding patients in whom VOM-ETHO procedure was not completed. From: Valderrábano et al. [18].

Marshall-PLAN trial from the Bordeaux group adopted VOM-ETHO added to routine workflow in AF catheter ablation. Marshall-PLAN (Marshall bundle elimination, Pulmonary vein isolation, and Line completion for ANatomical ablation) trial [ ] prospectively enrolled 75 consecutive patients with persistent AF for a de novo ablation procedure. All patients underwent VOM-ETHO and coronary sinus musculature ablation, PVI and anatomical isthmuses linear ablation (mitral, roof and cavotricuspid isthmus) ( ). The primary endpoint was 12-months freedom from AF/atrial tachycardia. VOM-ETHO was completed in 69 patients (92%). The full lesion set was successfully completed in 68 patients (91%). At 12 months, 54 of 75 patients (72%) were free from AF/AT after a single procedure (without antiarrhythmic drugs) in the overall cohort. In the subset of patients with a complete lesion set (VOM-ETHO and anatomical lines), the single procedure success rate was 79%. After 1 or 2 procedures, 67 of 75 patients (89%) remained free from AF/AT without antiarrhythmic drugs ( ).

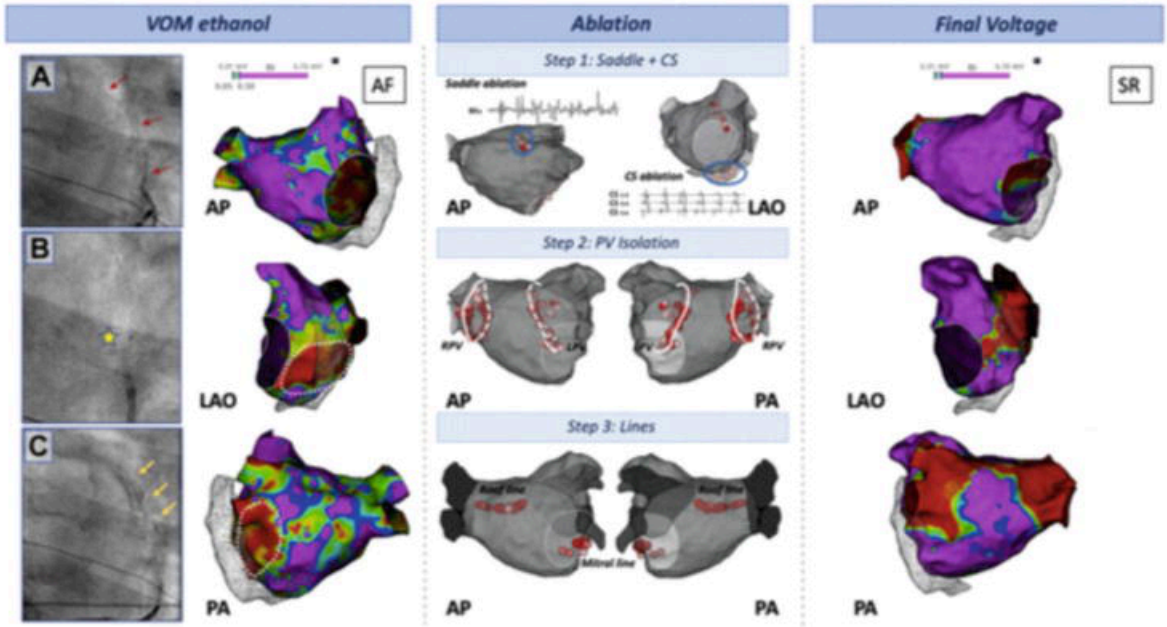

Figure 7.

Marshall-PLAN lesion set. Left: steps for ethanol infusion into vein of Marshall (VOM); A: contrast injection into the VOM with evidence of vein arborization (red arrows). B: (insertion of the angioplasty balloon inflated in the proximal portion of the VOM (yellow star: radiopaque marker of balloon). C: contrast injection in the VOM after alcoholization shows contrast staining. Middle: ablation set in the LA: targeting of CS musculature and "saddle" confirmed by fractionated local electrograms, pulmonary veins isolation and anatomical lines for roof and mitral isthmuses. Right: LA voltage map in sinus rhythm showing final lesion set. From: Derval et al. [30].

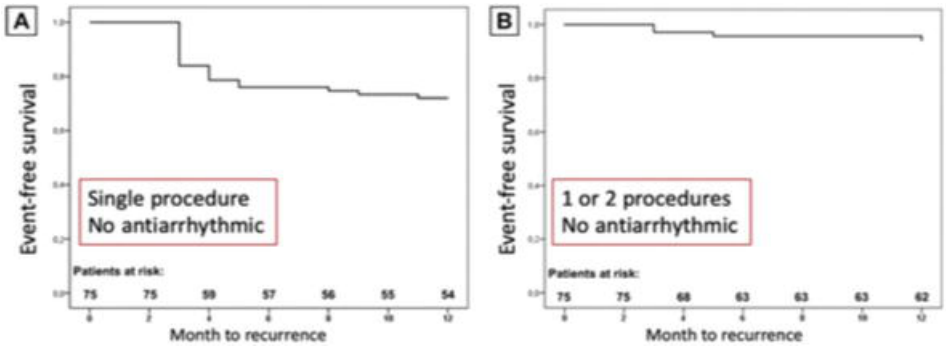

Figure 8.

Freedom from atrial fibrillation (AF)/Atrial tachycardia (AT)-Kaplan–Meier event-free survival curves after a single ablation procedure, without antiarrhythmic drugs (A), and after 1 or 2 procedures, without antiarrhythmic drugs (B). From Derval et al. [30].

In the Marshall-PLAN trial anatomical structures considered critical to the fibrillatory process were targeted (PVs, CS and Marshall bundle network). VOM ethanol infusion was central to the Marshall-PLAN as it enhances the success of subsequent PVI and linear ablation. Patients experiencing AF/AT recurrences after the first procedure demonstrated gaps in the original lesion set. Interestingly, anatomical sites of gaps were clustered in the right posterior carina/roofline and mitral line. Reconnections was not related to conduction recovery through the VOM but rather due to reconnections at the CS/LA interface. These findings suggest that other epicardial structures could play important roles in achieving durable transmural lesions, such as the septopulmonary bundle (for right PVs and roof line), the CS (for the mitral line), and the CTI. It is important to note that patients with incomplete lesion set at the index procedures had arrhythmic recurrences. In the Marshall-PLAN trial two patients experienced a transient ischaemic attack with no neurologic sequelae and four patients had post-ablation pericarditis. Three patients experienced minor groin hematoma.

In terms of LA function, the analysis of A-wave velocities suggested significant improvements in LA function at 12 months in patients without arrhythmic recurrences after the index procedure.

PROMPT-AF (Prospective Randomized Comparison between upgraded "2C3L" vs. PVI approach for the catheter ablation of persistent atrial fibrillation) [ ] aimed to compare VOM-ETHO added to PVI plus roofline, mitral line and CTI ablation to PVI alone with randomized design. Unlike the original project, the study published in 2021 [ ] does not have a randomized design and enrolled 191 patients who underwent their first catheter ablation of persistent atrial fibrillation (PeAF). The 2C3L technique is a fixed ablation approach consisting of bilateral circumferential PVI and three linear ablation lesion sets across the mitral isthmus, left atrial roof, and cavo-tricuspid isthmus. Patients were selected consecutively and compared for VOM-ETHO plus 2C3L approach (group 1) and 2C3L approach "RF only" (group 2). The follow-up duration was 12 months. The primary endpoint was the rate of documented atrial arrhythmias lasting >30 seconds without any antiarrhythmic drugs, in 12 months after index ablation procedures considering a blanking period of 3 months. The final population consisted of 191 patients (66 in the group 1 and 125 in the group 2). Successful VOM-ETHO was performed in 53 patients in group 1 (VOM not cannulated in 12, VOM dissection in one). At the index procedure, 100% of patients showed successful PVI, bidirectional roofline block and CTI block while mitral isthmus block was achieved in 95.5% of patients in group 1 and 80.8% in group 2 (p 0.006). At 12-months follow-up, 58 (87.9%) patients were free from AF/AT in group 1 compared with 81 (64.8%) in group 2 ($p < 0.001$) (2 in group 1 and 3 in group 2 patients were on AAD during the 12-months follow-up). Considering patients who received successful VOM-ETHO (53), freedom from AF/AT was achieved in 47 (88.7%). At the survival analysis, group 1 showed higher survival freedom from AT recurrence after adjustment for age, LA diameter, long-standing persistent atrial fibrillation, hypertension, and heart failure (HR 0.27, 95% CI 0.12–0.59) ( ). Two patient experienced mild complication in the "VOM-ETHO" group: one mild pericardial effusion with self-relief and one fluid overload during the procedure. Eight complications occurred in seven (5.6%) patients in "ablation only" group including four fluid overload, one mild pericardial effusion with self-relief, two arteriovenous fistulae, and one pleural effusion. No severe complications like death, stroke or atrial-esophageal fistula were observed.

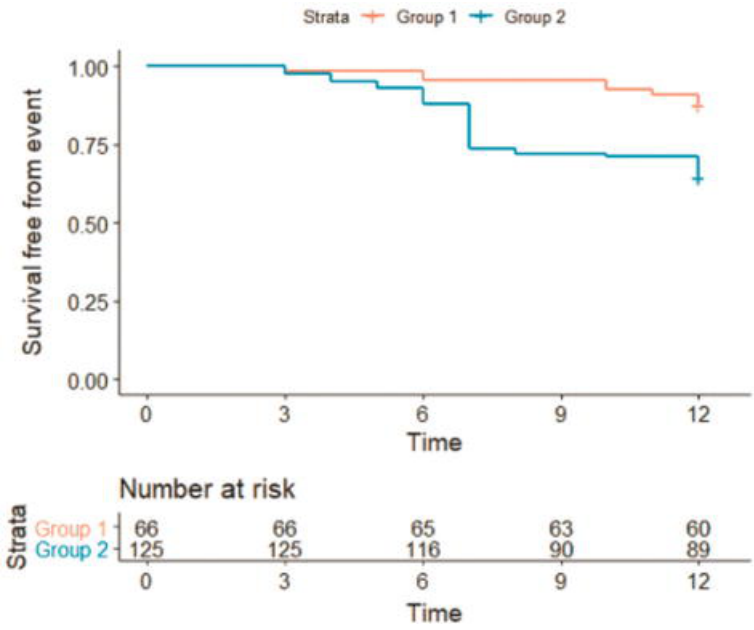

Figure 9.
K-M curve showing survival free from AT/AF recurrence with or without AAD in both groups. From Lai et al. [32].

6. Conclusions

Retrograde ethanol alcoholization of the vein of Marshall (VOM-ETHO) is a feasible, safe and effective strategy in treating atrial tachycardias depending on the mitral isthmus and improves long-term results if systematically added to conventional strategies in setting of persistent atrial fibrillation ablation. Results of randomized clinical trials adding VOM-ETHO to pulmonary vein ablation (VENUS AF) and PVI plus linear lesions (Marshall-PLAN) demonstrates beneficial impact of long-term sinus rhythm maintenance in patients with persistent atrial fibrillation.

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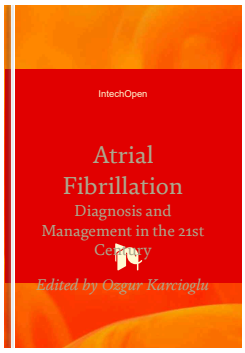

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