Vein of Marshall Ethanol Infusion: Feasibility, Pitfalls, and Complications in over 700 Patients

Running title: *Kamakura et al.; Ethanol infusion in the VOM*

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Abstract:

Background - Vein of Marshall (VOM) ethanol infusion is a relatively new therapeutic option for atrial tachyarrhythmias. We aimed to evaluate the feasibility, pitfalls, and complications associated with this procedure in a large cohort of patients.

Methods - Successful ethanol infusion, VOM-related lesion extent, and serious complications were evaluated in 713 consecutive patients treated with VOM ethanol infusion.

Results - While feasible in 88.9% of cases, VOM ethanol infusion failure mainly resulted from non-identification (6.2%), non-cannulation (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. Multivariable analysis identified previous coronary sinus ablation as the only predictor for non-identification. The mean area of VOM-related endocardial scarring was 10.2 ± 5.3 cm². VOM dissection (10.7%), iodine leakage (3.0%), and VOM morphology without visible branches (3.0%) were associated with smaller VOM-related scarring (5.0 ± 3.9 cm², 6.6 ± 3.5 cm² and 4.7 ± 2.3 cm², with a $p < 0.0001$, $p < 0.044$, and $p < 0.0001$, respectively). Ethanol infusion in a wrong vein was associated with less mitral line block (72.7% vs. 95.8%, p=0.012). A total of 14 serious complications (2.0%) occurred: 7 tamponades, of which were 6 delayed and treated with pericardiocentesis (2 of these patients had per-procedural VOM perforation), 4 strokes, 1 anaphylactic shock, 1 atrioventricular block, and 1 left appendage isolation. Only 4 of these complications occurred during the procedure.

Conclusions - Although limited by previous coronary sinus ablation, VOM ethanol infusion is a highly feasible treatment for atrial tachyarrhythmia, with a low rate of serious complications.

Key words: atrial fibrillation; atrial tachycardia; complication; Vein of Marshall, ethanol infusion

Nonstandard Abbreviations and Acronyms
AF: atrial fibrillation
AT: atrial tachycardia
CS: coronary sinus
LA: left atrium
LAA: left atrial appendage
PV: pulmonary vein
VOM: vein of Marshall
VV: valve of Vieussens

Introduction

Experimental and clinical studies have demonstrated that the vein of Marshall (VOM) bundle can support random reentries priming atrial fibrillation (AF), or stable reentries that are either perimitral or localized.[1, 2] Since it is insulated by fat, physical ablation of the VOM bundle by radiofrequency has been highly challenging since long. Chemical ablation by retrograde ethanol infusion has provided a critical step forward for its efficient elimination.[3] This technique, pioneered by Valderrabano, has proved determinant for mitral isthmus block, both in terms of acute success and lesion durability.[4] As a strategy beyond pulmonary vein (PV) isolation, a prospective multicenter trial has recently shown that VOM ethanol infusion decreased the likelihood of atrial tachyarrhythmias in patients with persistent AF.[5] VOM ethanol infusion has thus gained growing attention as a new therapeutic option for AF. However, there are no detailed reports in a large cohort of patients on the events that occur during the procedure and their outcomes.

This study aimed to investigate the feasibility of VOM ethanol infusion, as well as its associated pitfalls and complications.

Methods

Study population

The data that support the findings of this study are available from the corresponding author upon reasonable request. In this retrospective study, we included all cases in which VOM ethanol infusion was attempted for the treatment of AF or atrial tachycardia (AT), from July 2017 to August 2020 in the Haut Leveque Hospital (Bordeaux, France). Informed consent was obtained from all patients. The ablation protocol was approved by our institutional ethics committee on human research.

Ablation protocol

General principles

Technical details of the procedure have been previously reported.[6] The procedure was carried out under conscious sedation, with the CARTO 3 (Biosense Webster, Diamond Bar, CA) or the Rhythmia (Boston Scientific, Cambridge, MA) mapping systems. First ablation procedures were performed in persistent AF patients, and followed three steps as previously described: [1] VOM ethanol infusion; [2] PV isolation; and [3] linear lesions created at the mitral, roof, and cavotricuspid isthmuses to achieve a conduction block.[6] Redo ablation procedures included VOM ethanol infusion for one of these 3 reasons: [1] treating the clinical tachycardia, if the VOM bundle was potentially involved (bursting focus or localized reentry at the ridge, perimitral flutter with epicardial bypass); [2] blocking the mitral line, if not yet achieved; or [3] as an adjunct therapy for AF, beyond the initial lesion set created during the first procedure. Of note, in the present work, the terms "proximal" or "distal" will not be defined by the natural blood flow, but rather by the location toward the ostium or the tributaries of the vein considered, respectively.

VOM ethanol infusion

The coronary sinus (CS) was cannulated with a steerable long sheath (Agilis NxT; Abbott, St Paul, MN) inserted from the right femoral vein. An angiography catheter (5-Fr left internal mammary artery [LIMA]; Medtronic, Minneapolis, MN) was proximally positioned inside the CS lumen, and contrast (iodine) was injected to localize the VOM ostium. When not identified, a CS venogram was performed by dedicated balloon occlusion. Subsequently, an angioplasty wire (Whisper 0.014, Abbott or Sion Blue 0.014, Asahi) was advanced inside the VOM lumen and used to position a preloaded over-the-wire balloon (MINI TREK, 1.5–3 mm diameter and 6–15 mm length, Abbott) within the first 15 mm of its proximal portion. After inflation at 2–6 atm (until some resistance was felt) and wire removal, a selective angiography was performed through the wire port to confirm balloon occlusion and visualize VOM arborization. Absolute ethanol (96%) was collected in a metal bowel. Three successive injections (1–3 ml) were slowly administered over 1 minute, with selective VOM angiogram repeated each time to confirm balloon stability (Figure 1A).[7]

Evaluation criteria

Feasibility

Procedural success was defined as ethanol delivered inside the VOM lumen, but not in other veins. VOM identification required the three following features: [1] an ostium location before the valve of Vieussens (VV), as reported in anatomical series; [2] a superior course toward the left atrial (LA) ridge[8]; and [3] a typical lesion with a "collar-shape" electrical silence recorded after ethanol infusion just below, posterior to, and in front of the left inferior PV ostium (Figure 1). VV identification was based on at least one of the two following features: [1] clear iodine pooling reproducibly observed at the same level of the vessel; and [2] direct visualization of a

translucent structure (Figure 2A). VOM arborization has been extensively described by

Valderrabano et al.[9] To view this varying anatomy in the perspective of the procedural impact,

we distinguished three key morphologies: [1] "multiple branches" if the VOM exhibited ≥2

branches with the trunk not exceeding the diameter of the LIMA; [2] "large trunk" if the VOM

exhibited ≥2 branches but with the trunk exceeding the diameter of the LIMA; and [3] "no

branches" if the VOM was straight without visible branches (Figure 2B).[6] Veins misidentified as

the VOM included: [1] the inferior LA vein, which originates before the VV and runs toward the

posterior, or even septal wall of the LA; and [2] the left atrial appendage (LAA) vein, which

originates after the VV and exhibits an anterior course (Figure 2C). In case of unusual anatomy,

veins that did not fit the above-mentioned definitions were labeled "undefined."

Pitfalls

Procedural "pitfall" was defined as any event that is likely to mitigate the impact of VOM

ethanol infusion, either in terms of tissue lesion or electrophysiological criteria. Voltage was

measured immediately after VOM ethanol infusion and before any endocardial radiofrequency

application at the mitral isthmus by electroanatomic mapping using peak-to-peak electrogram

amplitude, with a threshold set at 0.5 mV in sinus rhythm and 0.2 mV in AF (Figure 1). Mitral

line block was validated during LAA pacing by the combination of a proximal-to-distal

activation of the CS catheter with a septal-to-lateral activation of the LA posterior wall, and

differential pacing maneuvers. Critical events were thoroughly identified, as follows: [1] VOM

staining corresponded to progressive iodine diffusion due to distal extravasation inside the tissue

favored by ethanol-induced fragilization of the vessel, without loss of distal vascular arborization

(Figure 1); [2] VOM dissection corresponded to an abrupt iodine densification with loss of distal

vascular arborization occurring before any ethanol infusion, mostly during the first selective

venogram (Figure 3A); [3] mechanical leakage corresponded to a loss of iodine into the CS due to incomplete occlusion during all VOM selective angiograms (Figure 3B); and [4] anatomical drainage corresponded to a loss of iodine into the atria, the great cardiac vein, the CS, or the superior vena cava via natural vascular anastomoses with the VOM (Figure 3C).

Complications

All patients underwent transthoracic echocardiography within 48 hours after the procedure. A procedural "complication" was defined as any adverse event considered to be life-threatening or likely to impair the functional status of the patient.

Statistical analysis

Data were analyzed using JMP12 software (SAS Institute Inc., Cary, NC). Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR: 25th-75th percentile) and analyzed using an independent Student's t-test or a Mann-Whitney U test, as appropriate. Categorical variables are expressed as numbers and percentages and were analyzed using Fisher's exact test or the chi-square test. Univariable and multivariable logistic regression was used to identify predictors of VOM identifiability. For the multivariable analysis, variables with a p-value <0.05 in the univariable analysis were selected. A p-value <0.05 was considered statistically significant.

Results

General characteristics

The study population comprised a total of 713 patients. Of these, VOM ethanol infusion was performed without any previous ablation procedure in 378 patients (53.0%). Among the 335 patients (47.0%) with previous AF ablation, 100 patients (14.0%) had undergone CS

endovascular radiofrequency application. Ablation was indicated for AF in 555 patients (77.8%), and for AT in 158 patients (22.2%). Clinical characteristics are detailed in Table 1. The temporal evolution of the main outcomes of this technique is summarized in Figure 4.

VOM ethanol infusion

Feasibility

VOM ethanol infusion was achieved in 634 patients (88.9%) after the first attempt (Figure 2). CS venogram with dedicated balloon occlusion was performed in 51 patients (7.2%) and helped identify the VOM in 20 patients (2.8%). VOM morphology was "multiple branches" in 583 patients (92.0%), "large trunk" in 32 patients (5.0%), and "no branches" in 19 patients (3.0%). The VV was visible in 401 patients (63.2%), either indirectly by contrast pooling in 354 patients (55.8%) or directly in 47 patients (7.4%). All the visible VV were located after the VOM ostium.

The reasons for procedure failure in the remaining 79 patients (11.1%) were: [1] non-identification of the VOM in 44 patients (6.2%); [2] non-cannulation of the VOM in 11 patients (1.5%); [3] ethanol infusion inside a wrong vein (inferior LA vein: 0, LAA vein: 10, undefined vein: 2) in 12 patients (1.7%); [4] CS dissection in 6 patients (0.8%); [5] persistent left superior vena cava in 4 patients (0.6%); and [6] VOM perforation in 2 patients (0.3%).

Another procedure for atrial tachyarrhythmia recurrence was performed in 177 out of the 713 patients of the cohort: repeat VOM ethanol infusion was attempted in 59 patients. Of the 41 patients with previous VOM ethanol infusion success, the VOM could be identified in 7 patients (17.1%), and ethanol delivered in 6 patients (14.6%). Of the 18 patients with previous VOM ethanol infusion failure, ethanol could be delivered in 15 patients (83.3%). Thus, VOM could be identified in a total of 662 patients (92.8%) after multiple attempts and VOM ethanol infusion was achieved in 649 patients (91.0%). Multivariable analysis identified previous CS ablation as

the only predictor for VOM non-identification (odds ratio 4.08, 95% confidence interval 1.65-10.19, p=0.0024) (Supplemental Table I). Neither cardiac resynchronization therapy nor mitral valve surgery were predictors.

The yearly success rate significantly increased from 84.3% in the first year to 92.6% in the third year (p=0.0047) (Figure 4).

Pitfalls

Among the 634 patients where VOM ethanol infusion was successful, some procedural events were observed (Figures 1 and 3). In decreasing order of frequency, we found: [1] VOM staining in 507 patients (80.0%); [2] at least one anatomical drainage in 223 patients (35.2%); [3] VOM dissection in 68 patients (10.7%); [4] persistent mechanical leakage in 19 patients (3.0%).

Voltage in the VOM-related area could be assessed before any endocardial radiofrequency application at the mitral isthmus in 251 patients. The increase in the area of VOM-related endocardial scarring was 10.2 ± 5.3 cm². Patients with VOM dissection had significantly smaller endocardial scarring than those without (5.0 ± 3.9 cm² with vs. 10.8 ± 5.2 cm² without, p<0.0001). Among the latter, mechanical leakage significantly decreased endocardial scarring (6.6 ± 3.5 cm² with vs. 11.1 ± 5.1 cm² without, p=0.044), while anatomical drainage did not (11.2 ± 4.8 cm² with vs. 11.1 ± 5.3 cm² without, p= 0.84). Of note, the "large trunk" morphology was associated with a significantly higher incidence of mechanical leakage than other morphologies (34.4% vs. 1.3%, p<0.0001), but only the "no branches" morphology was associated with significantly decreased endocardial scarring (4.7 ± 2.3 cm² with vs. 11.1 ± 5.1 cm² without, p<0.0001).

The rate of mitral line block in the 477 patients with first mitral line attempt was 95.8% at the end of the procedure, without significant difference with regard to VOM dissection (96.1%

with *vs.* 95.8% without, p=1.0), mechanical leakage (88.9% with *vs.* 95.9% without, p=0.32) or VOM morphology (100% for "no branches" VOM vs. 95.7% for others VOM morphologies, p = 1.0). The area of VOM-related endocardial scarring was larger in patients with mitral line block than those without, but not statistically significant (10.4±5.4 vs. 7.3±3.7 cm^2, p=0.065). Ethanol infusion inside a wrong vein was the only event significantly associated with a lower rate of mitral line block (72.7% *vs.* 95.8%, p=0.012).

The yearly incidence of VOM dissection significantly decreased from 15.1% in the first year to 7.1% in the second year (p=0.013) (Figure 4).

Complications

After a mean follow-up of 9.5±8.3 months, the following adverse events were reported: [1] VOM perforation in 20 patients (2.8%), defined as iodine extravasation into the pericardial space; [2] pericarditis in 13 patients (1.8%), defined as chest pain and limited pericardial effusion; [3] cardiac tamponade in 7 patients (1.0%); [4] stroke in 4 patients (0.6%); [5] anaphylactic shock in 1 patient; [6] high-degree atrioventricular block (AVB) in 1 patient; and [7] LAA isolation in 1 patient (Figure 5). In total, serious complications occurred during the procedure in 4 patients (0.6%) and were delayed in 10 patients (1.4%).

Regarding cardiac tamponade, pericardiocentesis was performed during the procedure in 1 patient, after one week in 1 patient, and after at least 14 days (14-106 days) in 5 patients (0.7%). During pericardiocentesis, cardiac effusion was serous in 4 patients (0.6%). The rate of cardiac tamponade was significantly higher in patients with VOM perforation than in patients without VOM perforation (10% *vs* 0.7%, p=0.014). The rate of VOM perforation (28.6% *vs* 1.9%, p=0.0089) and the age at the time of the procedure (70.4 ± 4.6 years *vs* 63.3 ± 10.2 years, p=0.0059) were significantly higher in patients with than in those without cardiac tamponade

(Supplemental Table II).

The anaphylactic shock started with a coughing spell during the first ethanol injection, followed by a cutaneous rash and a complete electro-mechanical dissociation in less than 1 minute. Resuscitation maneuvers, including external cardiac massage, intravenous adrenaline, systemic corticosteroid, intubation with mechanical ventilation, and nebulization with a β2-agonist, resulted in rapid and complete recovery. The high-degree AVB (2:1) occurred during the first ethanol infusion and persisted for 3 days, finally leading to pacemaker implantation. The LAA isolation also occurred during the first ethanol injection. Stroke occurred in 4 patients (0.6%), within 24 hours in 3 patients, and several weeks later in another patient. None of the ethanol deliveries in the LAA vein resulted in complete scarring of the LAA, and no thrombus was observed during follow-up.

Over the three years, the yearly incidence of VOM perforation and serious complications did not statistically differ (Figure 4).

Discussion

The present study is the first to extensively characterize the VOM ethanol infusion procedure in a large cohort of patients. The main findings are: [1] its high feasibility with a success rate of 88.9% during the first attempt, while previous CS ablation is the only predictor identified for failure; [2] VOM dissection, mechanical leakage, "no branches" morphology, and ethanol infusion inside a wrong vein are the four pitfalls reducing its impact on tissue lesion extent or mitral line block; [3] serious acute complications during the procedure, although challenging to anticipate, are rare (0.6%); and [4] experience in performing the procedure ensures a progressive increase in success rate and decrease in VOM dissection.

Feasibility

Recent studies have shed light on the therapeutic benefits of VOM ethanol infusion during persistent AF ablation.[5, 6, 8] However, very few have focused on the technical details that guarantee its feasibility.[9, 10] With a total success rate of 91% in the largest series to date, the present work points out the importance of VOM identification. Its ostium is characterized by a variable absolute distance from the CS ostium (range of 5–50 mm), but a consistent relative position to the VV (within 1 cm proximal).[11, 12] The VV is therefore a key anatomical marker. Although frequently found in anatomical series (74% to 87%), the VV exhibits different morphologies that may not all be suitable for angiographic identification.[11, 13] However, with proximal iodine injection, the VV was visible in almost two-thirds of patients, making it very helpful to circumscribe the area of interest. VOM identification can be further facilitated by: [1] CS venogram with dedicated balloon occlusion, which ensured VOM identification in 2.8% of patients; [2] placing a catheter at the posterior LAA edge to help distinguish the VOM from the LAA vein in case of equivocal course; and [3] suspended endocardial scarring remote from the inferior ridge should caution of ethanol infusion inside a wrong vein, and prompt for a reappraisal of the initial venous angiography. Together, the increasing success rate over the years along with a good success rate (83.3%) of repeat VOM ethanol infusion after a previous failure suggest that this procedure improves with experience.

Of interest, previous CS ablation was the only predictor for procedure failure, probably due to lesion-induced VOM stenosis. This advocates the need for integrating VOM ethanol infusion at an early stage of the ablation strategy, if necessary, to increase the chances of success.

Pitfalls

Regarding lesion extent, a restriction of either the spatial distribution or the distributed amount of

ethanol was found to have the potential to limit its penetration into the tissue. VOM staining proved to be an innocuous event inherent to progressive tissue penetration. Anatomical drainage – due to anastomosis variants – did not hinder the large distribution of a sufficient amount of ethanol. By contrast, three pitfalls were significantly associated with smaller VOM-related endocardial scarring: [1] "no branches" morphology; [2] VOM dissection, and [3] mechanical leakage. The absence of branches was not a modifiable factor and was previously identified by Valderrabano et al. as a cause of limited scarring.[9] The remaining two pitfalls were significantly reduced with growing experience. VOM dissection was circumvented by not overinflating the balloon or pushing the wire too far inside the lumen. Mechanical leakage – especially in the "large trunk" morphology – could be corrected either by the distal repositioning of the balloon where the vessel diameter seemed more suitable, or by using a larger balloon (diameter, 2.5–3 mm) maintained at the proximal portion of the VOM. Of note, the poor success rate (14.6%) of repeat VOM ethanol infusion after previous success at the first attempt proves that it must be seen as a "single-shot" procedure. Therefore, even when VOM dissection occurs, it is preferable to carry on with the ethanol infusion.

Regarding electrophysiological effect, none of the above pitfalls significantly altered the rate of mitral line block; on the contrary, ethanol infusion inside a wrong vein did. This emphasizes that the location – beyond the amount or the extent – of ethanol into the tissue is a crucial determinant. This may reflect the preferential location of the VOM bundle at the ridge. Its epicardial course is both protected against endocardial radiofrequency by fat, and not directly accessible by conventional means. A suspended and upper endocardial scarring, as found in LAA vein ethanol infusion, will not help eliminate it, and will thus make mitral line block still difficult to achieve.

Complications

In total, serious complications occurred in 14 patients (2.0%), which is the usual range previously reported (Figure 5).[14] Cardiac tamponade, which had been previously described, occurred in 7 patients (1.0%).[15] Since the majority of patients had a delayed onset and a serous nature, an inflammatory reaction was considered the most frequent underlying mechanism. The higher rate of cardiac tamponade observed in patients with VOM perforation evokes a causal relationship between the inflammatory reaction and the inadvertent drainage of ethanol in the pericardial space. Thus, anti-inflammatory drugs and a close follow-up with repeated echocardiography should be proposed after ethanol infusion inside a perforated VOM.

Of importance, 3 patients (0.4%) experienced a serious complication, previously undescribed in the setting of VOM ethanol infusion. An anaphylactic shock occurred and could have been lethal if it had not been diagnosed and treated immediately. Therefore, anaphylaxis should in priority be evocated in case of hemodynamic collapse. High-degree AVB occurred in a patient with a very proximal VOM. We hypothesized that a septal branch (not visible) probably damaged the conduction system. A more distal balloon position might be advised in such proximal VOM, to limit the risk of impacting the septum. Of note, the patient had previously undergone an aortic valve replacement surgery that may have fragilized nodo-Hissian conduction. However, careful monitoring of atrioventricular conduction during ethanol infusion should be the rule in all cases. LAA isolation occurred in a patient with multiple procedures based on repeated electrical substrate ablation at the anteroseptal wall. If extensive scarring is suspected, careful LA mapping should be performed before VOM ethanol infusion, to confirm that conduction to the LAA is still effective via the Bachmann bundle.

Limitations

The present work was an observational single-center study, conducted in a high-volume institution that performs over 200 VOM ethanol infusions per year. The rate of success and complication can be affected by the time invested in the procedure, the number of venograms attempted, and the operator's experience. Although the reported results improved over time, VOM ethanol infusion rapidly proves effective.

Conclusions

VOM ethanol infusion is highly feasible, with an excellent success rate after the first attempt. VOM dissection, mechanical drainage, and the "no branches" morphology are the only pitfalls limiting the expected effect. Serious complications are rare, and the majority were due to delayed cardiac tamponade related to an inflammatory reaction. The rate of success and dissection progressively improves with experience.

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Supplemental Material
Supplemental Tables I–II

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Table 1. Patient characteristics

	Total (n=713)
Clinical characteristics	
Age, years	63.5 ± 10.0
Male, n (%)	537 (75.3)
Body mass index, kg/m²	28.2 ± 4.7
Heart failure, n (%)	106 (14.9)
Hypertension, n (%)	343 (48.1)
Diabetes mellitus, n (%)	89 (12.5)
Stroke, n (%)	67 (9.4)
Structural heart disease, n (%)	280 (39.3)
$CHA_2DS_2\text{-}VASc_2$ score, n (range)	2 (1-3)
Cardiac resynchronization therapy, n (%)	16 (2.2)
History of open chest surgery, n (%)	62 (8.7)
History of mitral valve surgery, n (%)	31 (4.3)
Targeted arrhythmia	
Atrial fibrillation, n (%)	555 (77.8)
Atrial tachycardia, n (%)	158 (22.2)
Echocardiographic parameters	
Left atrium volume index, ml/m^2	42.4 ± 16.3
Left ventricular ejection fraction, %	56.3 ± 10.9
Previous procedure	
Median number, n (range)	1 (1-3)
Multiple procedure, n (%)	335 (47.0)
Pulmonary vein isolation only, n (%)	109 (32.5)
CS ablation, n (%)	100 (29.9)
MI ablation, n (%)	142 (46.4)

CS: Coronary sinus
MI: mitral isthmus

Figure Legends:

Figure 1 - Procedural steps

Venous angiographies: Successive 8 steps of VOM ethanol infusion. Note the progressive staining that increases with each ethanol infusion, but with a preserved arborization.

Electroanatomical maps: LA voltage before and after ethanol infusion. A "collar-shape" endocardial scarring appears in the vicinity of the left inferior pulmonary vein. *Stepwise diagram*: key procedural details related to each step.

CS: Coronary sinus; LA: Left atrium; LIMA: An angiography catheter (5-Fr left internal mammary artery); OH: ethanol; OTW: Over the wire; VOM: Vein of Marshall.

Figure 2 – Feasibility. **A**: Tips and tricks for VOM localization. VOM ostium always sites slightly proximal from the VV, which is distinguished either indirectly by iodine pooling or directly as a translucent structure. A large balloon occluding the CS was sometimes helpful to visualize the VOM. **B**: Different types of VOM. A representative example of "multiple branches", "large trunk", and "no branches" morphologies. **C**: Representative example of inadvertent LAA vein infusion. Note that none of the 3 key criteria for VOM identification were fulfilled: the VV is visible but proximal to the targeted vein, the targeted vein points toward the catheter tip placed at the LAA apex, and the endocardial scarring impacts the lateral portion of the LAA.

LAA: Left atrial appendage; VOM: Vein of Marshall; VV: Valve of Vieussens; LIMA: An angiography catheter (5-Fr left internal mammary artery).

Figure 3 – Pitfalls. **A**: Angiogram of a patient with VOM dissection (*blue arrows*) during the first selective VOM angiogram. Note that distal VOM arborization is never visible. **B**: Angiogram of a patient with a "large trunk" morphology and a mechanical leakage (*blue arrows*) that is proximal from the balloon, with iodine loss into the CS. **C**: Representative examples of the 4 types of anatomical drainage (*blue arrows*) via natural anastomosis between the VOM and the GCV, LA, CS, or the SVC.

CS: Coronary sinus; GCV: Great cardiac vein; LA: Left atrium; SVC: Superior vena cava; VOM: Vein of Marshall.

Figure 4 - Learning curve. Evolution of key procedural events over the years: successful VOM ethanol infusion (*black line*), VOM dissection (*pale blue*), wrong vein ethanol infusion (*dark blue*), VOM perforation (*yellow*), and serious complications (*orange*). Statistical comparison with a p-value is shown between each year (*black-framed rectangle*) and for each item (*following identical color code*).

LAA: Left atrial appendage; VOM: Vein of Marshall.

Figure 5 – Complications. *Column 1*: type and number of minor (*no frame*) and serious (*black framed*) events. *Column 2*: event rate. *Column 3*: event timing, considered acute if it occurs during the procedure, or delayed if it occurs after the procedure. *Column 4*: comment related to VOM ethanol infusion. *Column 5*: specific management related to VOM ethanol infusion.

LAA: Left atrial appendage; VOM: Vein of Marshall.

What is Known?

- The growing interest in VOM ethanol infusion calls for a better understanding of the events that can occur during this procedure.
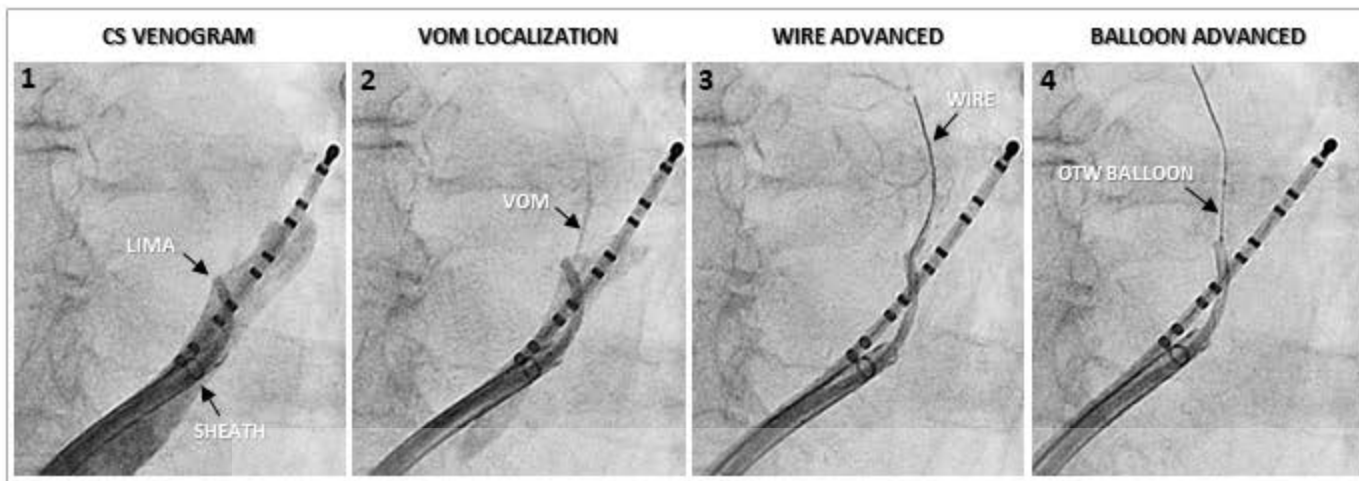
What the Study Adds?

- By including the largest number of patients to date, the present work clarifies the associated feasibility, pitfalls, and complications. These data can help optimize the effect VOM ethanol infusion.

- Although highly feasible with a low complication rate, further research is required to identify patients who benefit most from VOM ethanol infusion.

| CS VENOGRAM | VOM LOCALIZATION | WIRE ADVANCED | BALLOON ADVANCED | NORMAL VOLTAGE BEFORE ETHANOL |

1 — LIMA, SHEATH
2 — VOM
3 — WIRE
4 — OTW BALLOON

| VOM VENOGRAM | AFTER 1ST OH INFUSION | AFTER 2ND OH INFUSION | AFTER 3RD OH INFUSION | « COLLAR-SHAPE » AFTER ETHANOL |

5 — INFLATION
6 — STAINING
7 — STAINING
8 — STAINING   STAINING 80.0%

STEP 1 — The steerable sheath positioned at the CS ostium. Iodine is injected via the LIMA catheter.

STEP 2 — VOM is usually identified when the LIMA catheter is pointing slightly posteriorly.

STEP 3 — The angioplasty wire is advanced inside the first centimeters of the VOM lumen.

STEP 4 — An over-the-wire (OTW) balloon is placed within the proximal portion of the VOM.
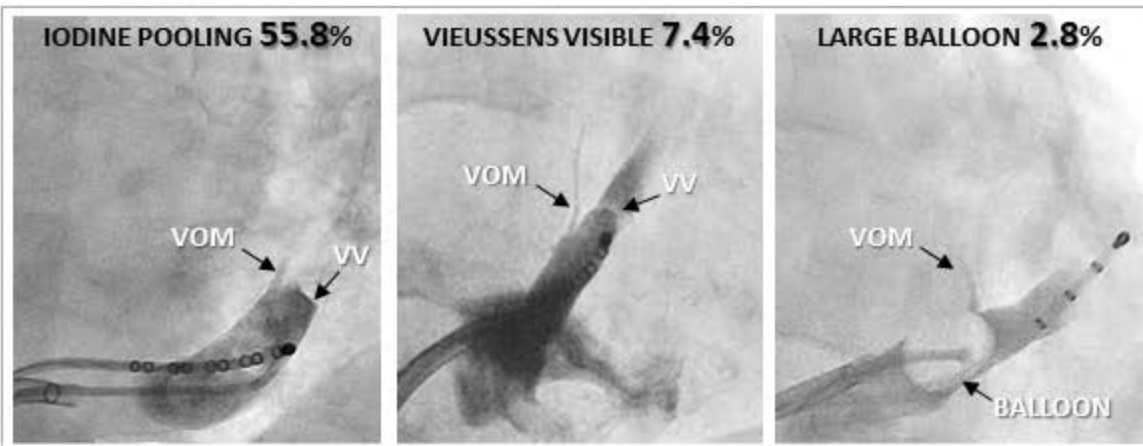
STEP 5 — The wire is removed after balloon inflation (*2-6 atm*), and iodine is injected to see VOM arborization
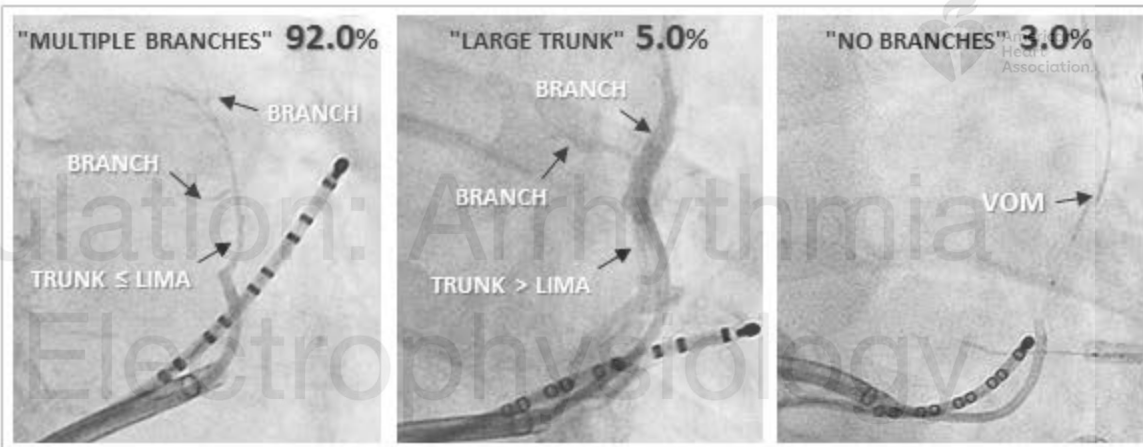
STEPS 6-8 — Each OH injection (*1-3 mL over 1 min*) is followed by iodine injection to confirm balloon stability.

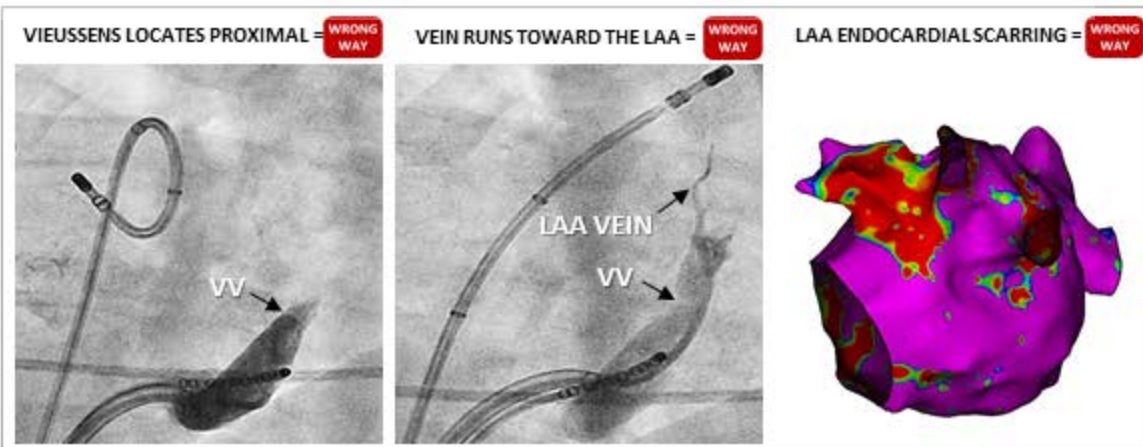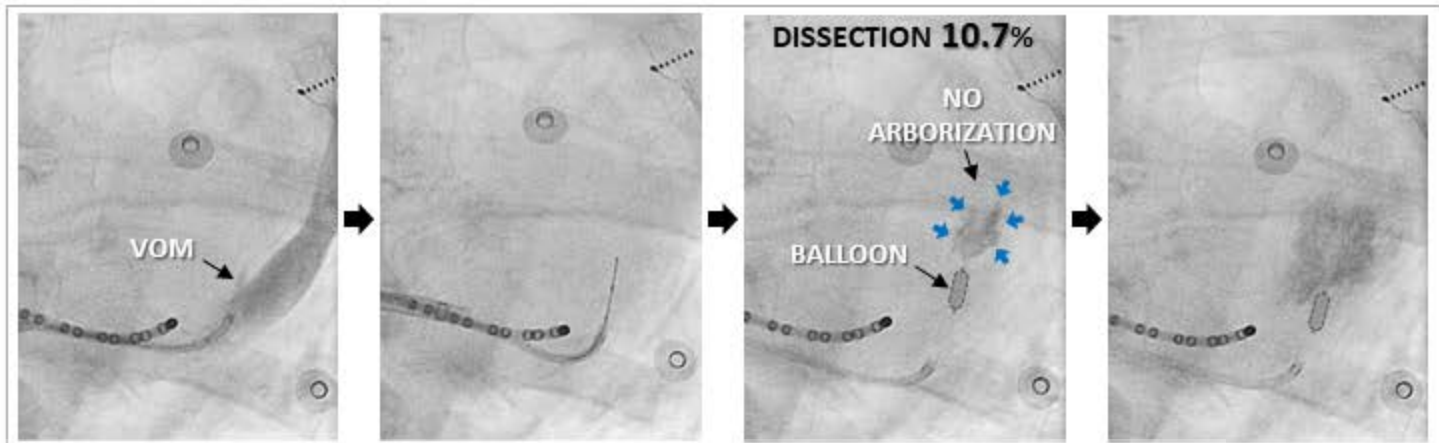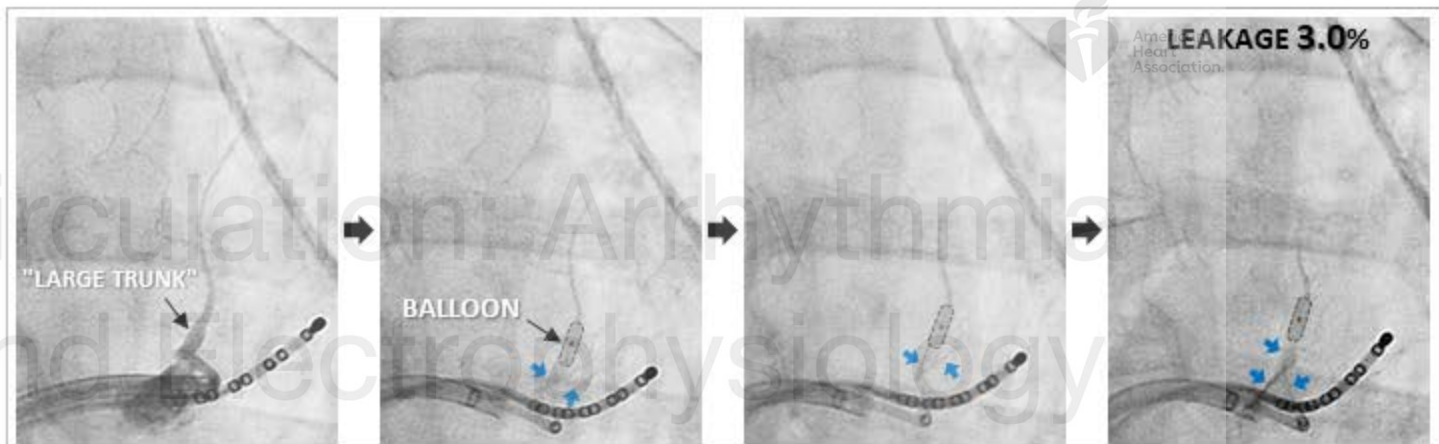**A — LOCALIZATION**

IODINE POOLING **55.8%** · VIEUSSENS VISIBLE **7.4%** · LARGE BALLOON **2.8%**

VOM · VV · BALLOON

B — MORPHOLOGY

"MULTIPLE BRANCHES" **92.0%** · "LARGE TRUNK" **5.0%** · "NO BRANCHES" **3.0%**

BRANCH · BRANCH · TRUNK ≤ LIMA · BRANCH · BRANCH · TRUNK > LIMA · VOM

C — LAA VEIN

VIEUSSENS LOCATES PROXIMAL = WRONG WAY · VEIN RUNS TOWARD THE LAA = WRONG WAY · LAA ENDOCARDIAL SCARRING = WRONG WAY

VV · LAA VEIN · VV

A DISSECTION

VOM

DISSECTION **10.7**%

NO ARBORIZATION

BALLOON

B LEAKAGE

"LARGE TRUNK"

BALLOON

LEAKAGE **3.0**%

C DRAINAGE

GCV **22.9**%

VOM

LA **8.8**%

VOM

CS **4.9**%

VOM

SVC **2.2**%

VOM

EVENT	RATE	TIME	COMMENT	MANAGEMENT
VOM PERFORATION: 20	2.8%	ACUTE	Infusion still feasible, but with a higher risk of delayed tamponade (10% vs 0,7% p=0.014).	Anti-inflammatory drugs and repeated echography should be considered in this category of patients.
PERICARDITIS: 13	1.8%	DELAYED	Usually at day-2.	Anti-inflammatory drugs.
DELAYED TAMPONADE: 6	0.8%	DELAYED	Serous nature of cardiac effusion in 2/3 of patients: inflammatory reaction may play a key role.	Pericardiocentesis (surgical access not necessary)
STROKE: 4	0.6%	DELAYED	Stroke rate in the reported range.	Medical management.
ACUTE TAMPONADE: 1	< 0.2%	ACUTE	Related to per-procedural steam pop.	Surgical drainage necessary.
ANAPHYLAXIS: 1	< 0.2%	ACUTE	Must be evocated first, in case of hemodynamic collapse during infusion.	Adrenaline, corticosteroids.
HIGH-DEGREE AVB: 1	< 0.2%	ACUTE	Might be favored by very proximal VOM ostium.	Monitoring of atrioventricular conduction during ethanol infusion.
LAA ISOLATION: 1	< 0.2%	ACUTE	Risk increased in case of large anterior wall scarring.	Bachmann conduction assessment prior to VOM ethanol infusion, if history of extensive ablation.

Graphic Abstract

1ST VOM ATTEMPT:
713 PATIENTS

VOM SUCCESS:
634 PATIENTS (88.9%)

VOM FAILURE:
79 PATIENTS (11.1%)
- **2** VOM PERFORATIONS
- **4** LEFT SUP. VENA CAVA
- **6** VOM DISSECTIONS
- **11** NON-CANNULATIONS
- **12** WRONG VEINS
- **44** NON-IDENTIFICATIONS

CS ablation during previous procedure is the only predictor for VOM non-identification.

2ND VOM ATTEMPT:
18 PATIENTS

VOM SUCCESS:
15 PATIENTS (83.3%)

FEASIBILITY
EVENTS TYPICALLY OBSERVED DURING VOM OH INFUSION

VIEUSSENS **63.2**%
VIEUSSENS
VOM

MULTIPLE BRANCHES **92**%
BRANCHES

STAINING **80**%

SCARRING: 10.2 ± 5.3 CM²

PITFALLS
EVENTS THAT CAN ALTER SCARRING OR MITRAL BLOCK

DISSECTION **10.7**%

LEAKAGE **3.0**%
LEAKAGE

NO BRANCHES **3.0**%

WRONG VEIN **1.7**%
LAA VEIN
ABNORMAL SCARRING

COMPLICATIONS
EVENTS WITH DELETERIOUS SIDE EFFECTS

6 DELAYED TAMPONADES
0.8%

4 STROKES
0.6%

1 ACUTE TAMPONADE
< **0.2**%

1 ANAPHYLACTIC SHOCK
< **0.2**%

1 HIGH-DEGREE AVB
< **0.2**%

1 LAA ISOLATION
< **0.2**%

American Heart Association.