



Atrial bipolar voltage analysis to assess vein of Marshall ethanol infusion acute effectiveness and its implication in predicting mitral isthmus block

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Abstract

Background The vein of Marshall (VoM) is a promising therapeutic target for persistent atrial fibrillation (PeAF) treatment. Ethanol infusion into the VoM (VoM-EI) has demonstrated high effectiveness in facilitating mitral isthmus (MI) block, a fundamental part of the anatomical ablation setup for the treatment of PeAF. However, reliable indexes for optimal ethanol delivery are still lacking, and the role of voltage analysis after VoM-EI in predicting MI block has been poorly explored.

Purpose To evaluate the role of voltage analysis after VoM-EI in predicting acute bidirectional MI block and the need of coronary sinus (CS) radiofrequency (RF) applications.

Methods Fifty-three PeAF patients who underwent catheter ablation were retrospectively enrolled. Left atrial (LA) high-density bipolar voltage mapping was performed before and after VoM-EI. Low voltage areas (LVA) were assessed for all LA maps using the area measurement tool, and the difference in area width between pre- and post-VoM-EI was defined as Δ LVA. An anatomical lesion set including VoM-EI, pulmonary vein isolation (PVI) and linear lesion for dome, lateral MI, and cavo-tricuspid isthmus (CTI) was performed. In case of residual conduction across MI, additional endocardial and/or epicardial ablations approaching the CS musculature were performed. The time required to achieve bidirectional MI block (AblTime-MI) was collected and the VoM length was measured.

Results Forty-eight out of 53 patients enrolled (90.5%) achieved acute bidirectional MI block. After VoM-EI, mean bipolar Δ LVA was 6.6 ± 4.4 cm², and mean AblTime-MI was 14.7 ± 10.4 min. RF applications targeting CS musculature were required in 22/53 patients (41.5%). Linear regression showed a strong inverse correlation between Δ LVA and AblTime-MI ($r = -0.70$, $\beta = -128.2$; 95% CI -165.3 , -91.2 ; $p < 0.001$). Patients with higher Δ LVA were less likely to need CS applications [OR = 0.70 (95% CI 0.56–0.88); $p = 0.002$]. Patients requiring CS applications had significantly longer AblTime-MI (21.0 ± 9.0 min vs 8.8 ± 8.2 min; $p < 0.001$), and larger left atrial volume index (LAVI) (37.0 ± 10.0 ml/m² vs 31.8 ± 6.6 ml/m²; $p = 0.03$). Δ LVA showed the best performance in predicting the need for CS applications (AUC 0.79) with a threshold of < 5.30 cm² associated with a higher risk of requiring additional RF applications.

Conclusions VoM-EI-induced LA lesions align with VoM trajectory and anatomy. Larger Δ LVA correlates with shorter ablation time for bidirectional MI block and predicts fewer residual epicardial MI gaps requiring RF application in CS musculature. Δ LVA represents a reliable indicator of VoM-EI effectiveness, predicting MI block failure due to epicardial gaps.

Keywords Persistent atrial fibrillation · Atrial fibrillation catheter ablation · Marshall vein · Mitral isthmus block predictors

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1 Introduction

The VoM is a promising therapeutic target for PeAF [1, 2] as it perfectly fits with Coumel's triangle of atrial fibrillation arrhythmogenesis. Triggers such as focal activities [3] or stable re-entries [4], which initiate PeAF, typically arise from tissue surrounding the VoM. Ethanol injection into the vein generates a local ablation through elimination of arrhythmia triggers [5]. The VENUS and the Marshall-PLAN case-series have demonstrated the impact of VoM-EI in increasing procedural success and preventing atrial arrhythmic recurrences in PeAF patients [6, 7]. Recent data from the PROMPT-AF randomized trial and MARSHALL-Plan showed that, in patients undergoing a first ablation procedure, adding VoM-EI to PVI and linear ablation significantly improved arrhythmia-free survival at 12 months compared to the PVI-alone strategy [7, 8].

Previous study in the literature showed that the completeness and validation of the full anatomical ablation scheme with the bidirectional block validation of the three main isthmuses (LA dome, lateral MI, and cavotricuspid isthmus) represented a crucial predictor of the long-term procedural outcome [9]. VoM-EI facilitates lateral MI ablation and its bidirectional block [6–8, 10].

VoM-EI induces a typical 'collar-shaped' lesion in the LA [9], which represents a qualitative description of its anatomical distribution and is known to facilitate the achievement of bidirectional MI block. However, no clear quantitative indicators are currently available to assess the effectiveness of alcoholization. Limited data exist on the systematic use of LA bipolar voltage mapping to evaluate the acute effectiveness of VoM-EI.

2 Objective of the study

This study aims to evaluate the role of bipolar voltage mapping in assessing the acute effectiveness of VoM-EI during catheter ablation for PeAF. Specifically, we investigated whether the extension of endocardial newly formed lesions correlates with the achievement of bidirectional MI block.

3 Methods

We retrospectively enrolled a cohort of patients scheduled for their first catheter ablation procedure for PeAF. Patients aged 18 years or older who provided informed consent were included. This study was performed in accordance with the Declaration of Helsinki.

PeAF was defined as atrial fibrillation episodes lasting longer than 7 days and not self-terminating [11]. All patients

were treated using a predefined standardized anatomical ablation approach (VoM-EI, antral PVI, linear lesions for dome, lateral MI, and CTI). All procedures were performed under general anesthesia using CARTO3® (Biosense Webster, Irvine, CA, USA) mapping system, and high-density voltage maps of the LA were acquired before and immediately after VoM-EI with multipolar mapping catheters (Pentaray, Biosense Webster Irvine, CA, USA; Octaray, Biosense Webster Irvine, CA, USA). All electroanatomical maps were acquired in sinus rhythm, after electrical cardioversion when required, using 0.05–0.50 mV cutoffs. VoM identification and ethanol delivery were performed as previously described [4, 6, 12] and VoM length was measured in centimeters over X-ray images along the main branch of the vein (Fig. 1).

During the VoM-EI procedure, we administered three doses of 3–4 mL each of ethanol, resulting in a total minimum volume of 10 mL [6]. Additional doses were administered as needed to address alcohol drainage caused by collaterals or retrograde leakage. Following each dose, an angiogram was performed using an over-the-wire balloon catheter. One milliliter of contrast medium was injected with each ethanol dose to assess for leakage, myocardial staining, and potential VoM dissection or perforation.

Low-voltage areas (LVA) during baseline LA mapping were measured using dedicated area measurement tools, identifying regions of abnormal voltage while excluding the pulmonary vein ostia. After VoM-EI, the newly formed LVA was measured and the basal LVA was subtracted to obtain the Δ LVA (Fig. 2). VoM length was measured on fluoroscopic images acquired during selective angiography, using the longest branch of the vein in cases of arborization.

After VoM-EI and subsequent LA map obtained in sinus rhythm, RF-ablation setup including antral PVI isolation and LA linear ablations were performed (ThermoCool® SmartTouch® or QDOT MICRO®, Biosense Webster Inc., Irvine, CA, USA; ablation settings: 40–50 W based on ablation-index values or high-power-short-duration application for antral PVI and 40–50 W based on ablation-index values for linear lesions). Bidirectional blocks of lateral MI line and LA dome were validated during continuous LA appendage pacing at 600 ms drivetrain. The ablation time required to achieve bidirectional MI block (AblTime-MI) was systematically recorded from the first application until the MI block was achieved, defined as CS electrogram sequence inversion (septal-to-lateral) during LAA pacing [13]. If bidirectional MI block was not obtained after endocardial applications, systematic epicardial gaps via CS were mapped at great cardiac vein (GCV) location, either at anchor-GCV or free-wall-GCV musculature. All patients were maintained on antiarrhythmic drug therapy during the 3-month blanking period, and therapy was suspended based on medical decision in the absence of arrhythmia recurrence.

Fig. 1 **A, B** Non-selective and selective VoM angiograms performed using a LIMA catheter. Following guidewire advancement and over-the-wire balloon inflation. **C** A selective VoM angiogram. **D** myocardial staining after VoM ethanol infusion

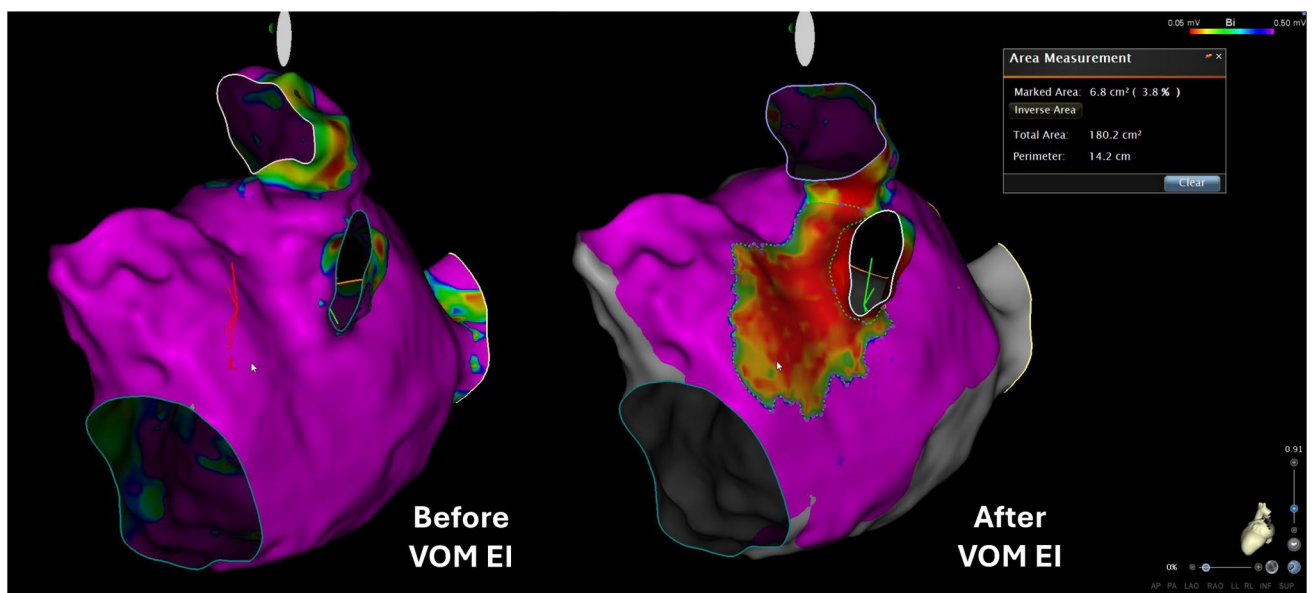
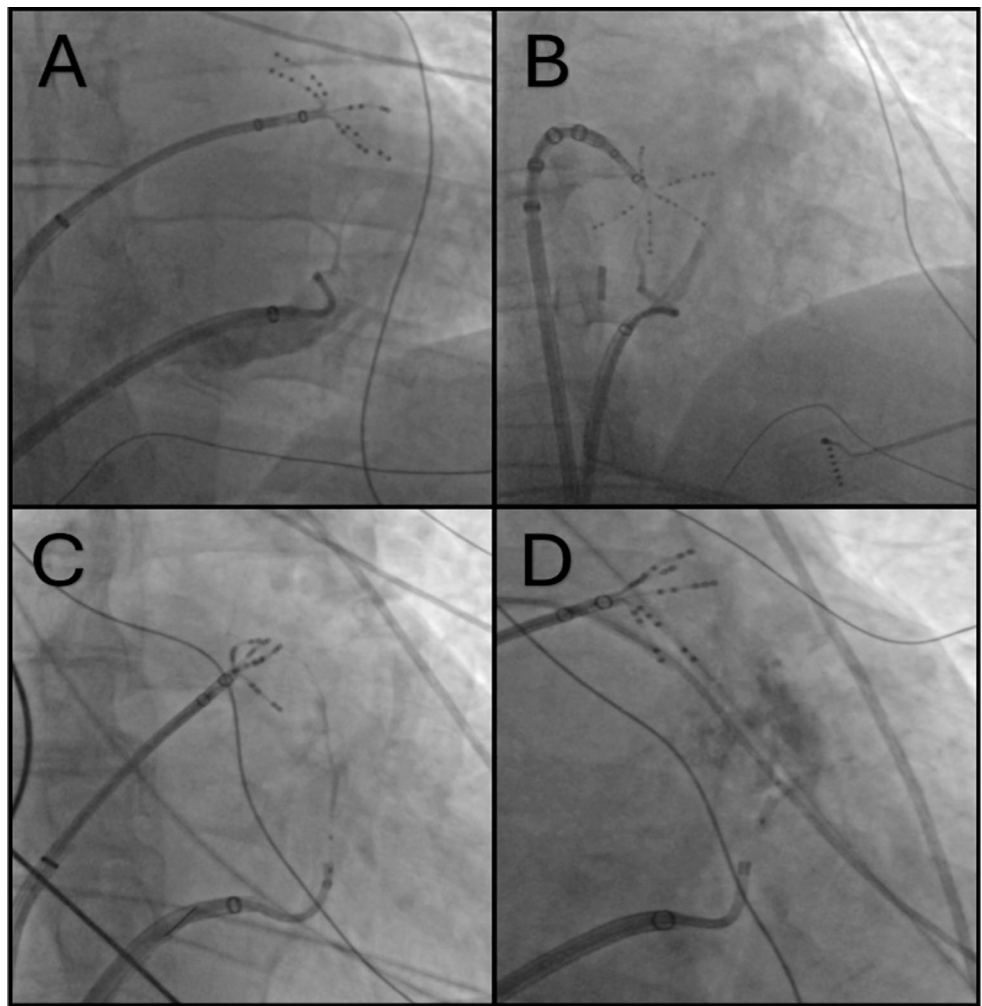


Fig. 2 A post alcoholization high-density map of the LA shows a collar shape lesion. The area measurement tool was used to quantify the lesion's extent. In this case, the baseline voltage analysis revealed normal atrial voltages

3.1 Statistical analysis

Kolmogorov–Smirnov test was performed to evaluate the distribution of continuous variables. Continuous variables with a normal distribution were reported as mean±standard deviation, while those with a non-normal distribution were reported as median and interquartile range. Discrete variables are reported as absolute number and relative percentage.

Univariate linear regression was performed to assess the correlation between AblTime-ML and Δ LVA, with statistical power expressed using the Pearson coefficient. Univariate logistic regression was conducted to evaluate the relationship between the need for CS applications and Δ LVA. To compare population characteristics, Student's *t*-test was performed for normally distributed continuous variables, while the Wilcoxon test was applied for non-normally distributed variables.

A receiver operating characteristic (ROC) analysis was performed to assess the ability of Δ LVA to predict the need for CS applications. All *P* values<0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics.

Table 1 Data are provided as mean±standard deviation or mean and percentage (%). LA left atrium, LV left ventricle, AF atrial fibrillation

	Mean	% or±SD
Baseline characteristics		
Patients (<i>n</i>)	53	100%
Age (years)	64.9	±7.6
Males (<i>n</i>)	34	64.2%
Valvular heart disease (<i>n</i>)	4	7.5%
Ischemic cardiomyopathy (<i>n</i>)	7	13.2%
Hypertrophic cardiomyopathy (<i>n</i>)	1	1.9%
Dilated cardiomyopathy (<i>n</i>)	3	5.7%
AF-induced cardiomyopathy (<i>n</i>)	6	11.3%
Arterial hypertension (<i>n</i>)	33	62.3%
Years from first episode (years)	6.1	±4.8
Echocardiographic data		
LA volume index (ml/mq)	33.9	±8.4
LA enlargement (<i>n</i>)	46	87.8%
LV end diastolic volume (ml)	51.3	±5.8
Left ventricular ejection fraction (%)	59.2	±9.2
Antiarrhythmic drugs		
Class Ic (<i>n</i>)	24	45.3%
Amiodarone (<i>n</i>)	8	15.1%
Beta blockers (<i>n</i>)	46	86.8%
Sotalol (<i>n</i>)	3	5.7%
AF type		
Early persistent (<3 months, <i>n</i>)	12	22.6%
Persistent (<i>n</i>)	21	39.6%
Long standing (>12 months, <i>n</i>)	20	37.7%

4 Results

Fifty-three consecutive patients (mean age 64.9 ± 7.6 years, 64.2% male) were included in this study. Baseline characteristics are reported in Table 1. Procedural data are summarized in Table 2.

Forty-eight patients (90.6%) achieved acute bidirectional MI block. After VoM-EI, mean bipolar LVA was 7.9 ± 4.4 cm². Mean procedural AblTime-MI was 14.7 ± 10.4 min. Patients who did not obtain MI block showed smaller Δ LVA with respect to those with MI block (3.7 ± 1.2 cm² vs 6.9 ± 3.4 cm²; *p*=0.03).

RF applications targeting CS musculature were required in 41.5% of the patients. Among patients without bidirectional MI block completed after endocardial ablations, 50.0% had MI block validated after ablating anchoring-GCV, while 50.0% needed GCV-free wall musculature RF applications.

Linear regression showed a good correlation between Δ LVA and AblTime-MI [*r*=−0.70; β =−128.2 (95% CI −165.3, −91.2); *p*<0.001] (Fig. 3), while no correlation was found between Δ LVA and LAVI (*p*=0.12).

Table 2 Data are provided as mean±standard deviation or mean and percentage (%). RF radiofrequency, VOM-EI vein of Marshall ethanol infusion

	Mean	% or±SD
Procedural data		
Ablation time (min', sec'')	13'53''	±10'26''
RF applications (<i>n</i>)	17.6	±10.5
Mitral block obtained (<i>n</i>)	48	90.6%
Low voltage areas		
Mean bipolar low voltage areas pre-VoM-EI (cm ²)	1.3	±2.7
Mean bipolar low voltage area post-VoM-EI (cm ²)	7.9	±4.4
Delta low voltage areas (cm ²)	6.6	±3.4
Catheter ablation		
Endocardial only RF (<i>n</i>)	31	58.5%
Coronary sinus applications (<i>n</i>)	22	41.5%
└ Anchoring applications (<i>n</i>)	└ 22	└ 100%
└ Free wall applications (<i>n</i>)	└ 11	└ 50%
Periprocedural complications		
Pericardial effusion (<i>n</i>)	3	5.7%
Cardiac tamponade (<i>n</i>)	0	0%
VOM dissection (<i>n</i>)	7	13.2%
VOM perforation (<i>n</i>)	2	3.3%
CS dissection (<i>n</i>)	2	3.3%
Clinical follow-up		
Mean follow-up (months)	18.5	±7.4
Clinical recurrences (<i>n</i>)	10	18.9%

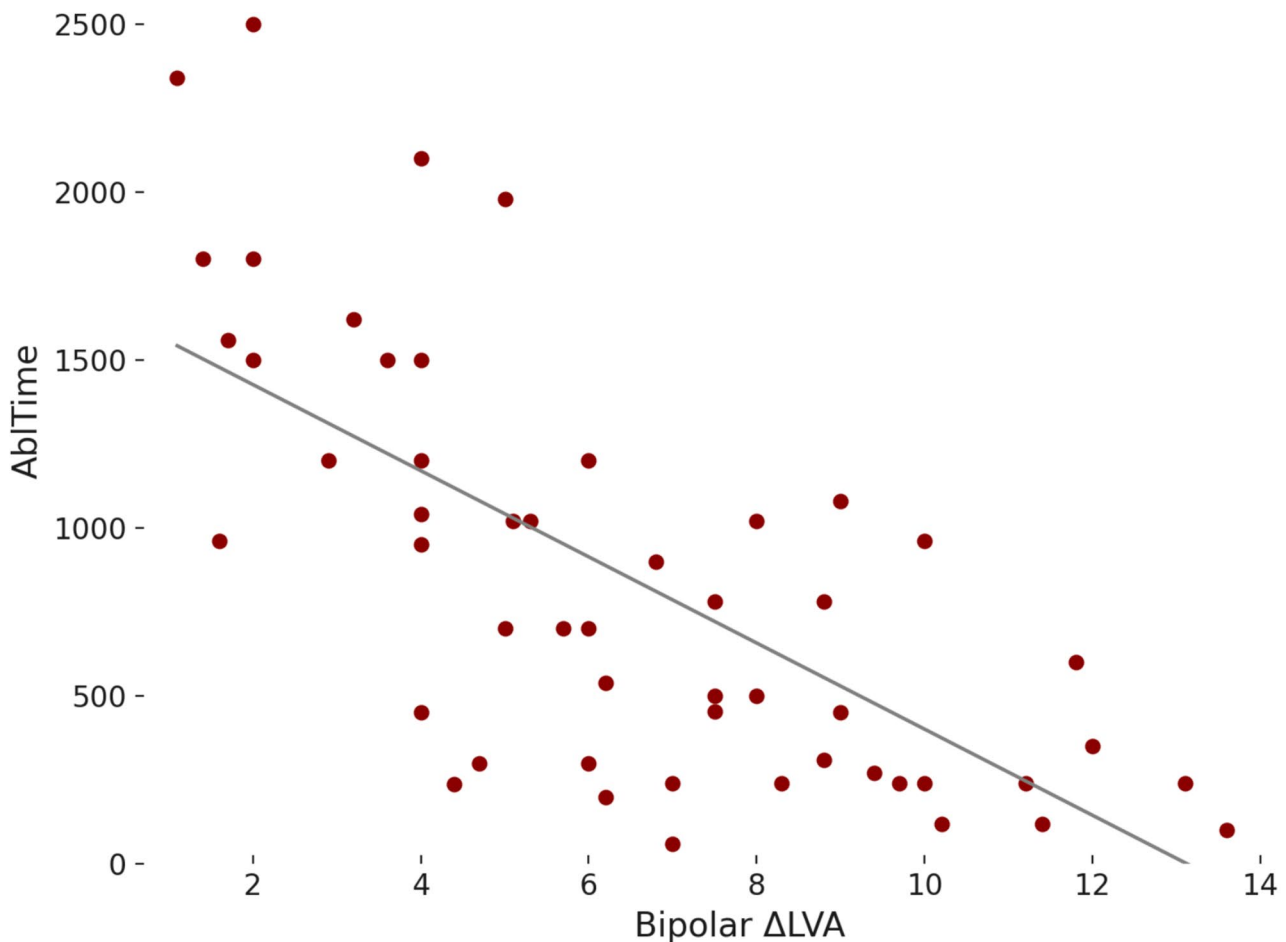


Fig. 3 Linear regression shows a good correlation between AblTime-MI and Δ LVA [$r=-0.70$; $\beta=-128.2$ (95% CI $-165.3, -91.2$); $p<0.001$]

In addition, patients having higher Δ LVAs were less likely to show epicardial gaps with subsequent CS musculature RF applications at the binary logistic regression [OR=0.70 (95% CI 0.56–0.88); $p=0.003$]. Patients who required CS applications did not present significant variations in VoM length ($p=0.18$) but showed wider LAVI (37.0 ± 10.0 ml/m² vs 31.8 ± 6.6 ml/m²; $p=0.03$) and longer AblTime-MI (21.0 ± 9.0 min vs 8.8 ± 8.2 min; $p<0.001$). To assess the predictive value of Δ LVA in identifying patients requiring CS ablation, a ROC curve analysis was performed (Fig. 4). VoM-EI newly formed LVA and VoM length showed moderate and poor discriminatory ability (AUC: 0.69 and 0.36). When applied on Δ LVA, the model showed the best performance (AUC, 0.79) and the best cut off according to the Youden index was 5.3 cm² (sensitivity 73.0%, specificity 81.0%).

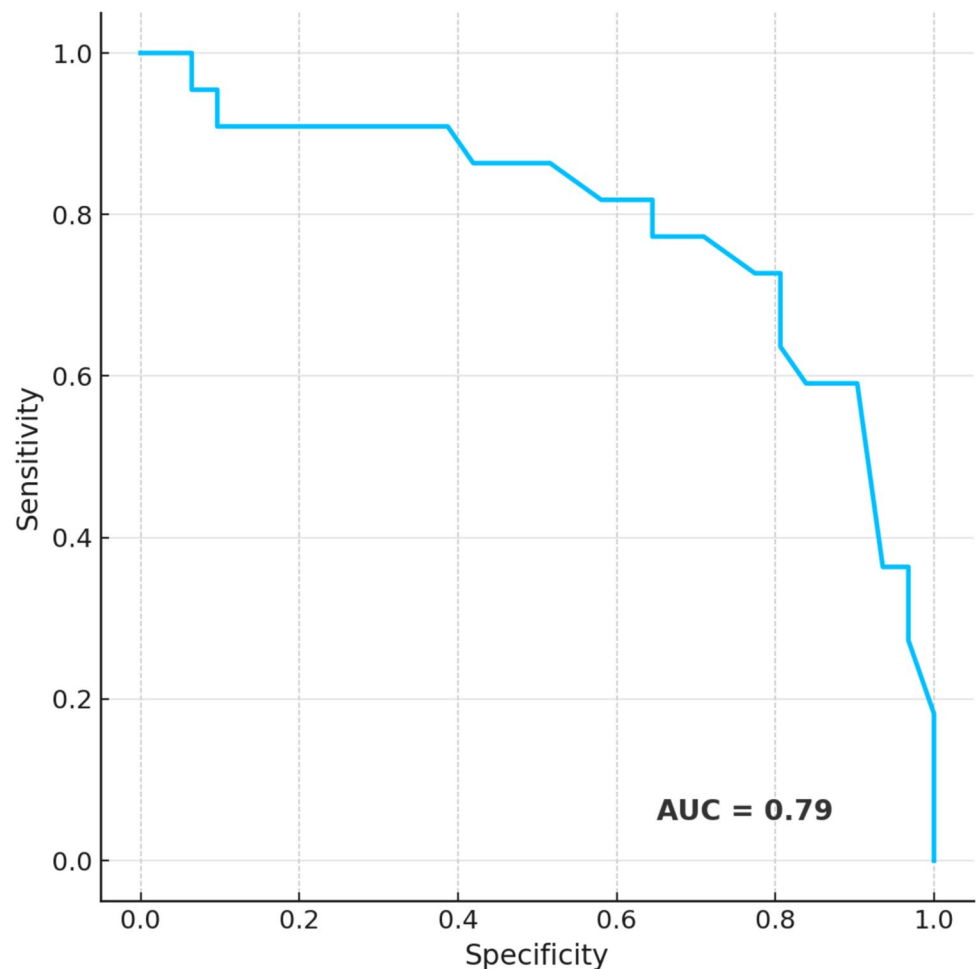
Mean clinical follow up was 18.5 ± 7.4 months. During follow-up, 18.9% of the patients experienced clinical recurrence.

4.1 Procedural complications

No patient experienced cardiac tamponade, hemodynamically significant pericardial effusion or hemodynamic instability. We reported two cases of VoM perforation resulting in mild pericardial effusion without the need to stop the procedure. In these cases, VoM-EI procedure was discontinued to avoid subsequent pericarditis due to alcohol drainage in the pericardial space.

Seven patients (13.2%) experienced dissection of the VoM not resulting in cardiac tamponade and without the need to suspend the procedure. Procedural VoM dissection did not cause longer AblTime-MI ($p=0.08$) despite a significant reduction in the LA newly formed lesion creation ($p=0.05$). All these seven cases achieved mitral block despite VoM dissection. We reported two cases of coronary sinus dissection without any significant hemodynamic consequences or impact on procedure continuation.

Fig. 4 ROC curve analysis showing the predictive performance of Δ LVA in identifying patients requiring CS ablation. The model demonstrated the best discrimination with an AUC of 0.79



5 Discussion

This study investigated the acute impact of VoM-EI on the newly formed LA lesions and its implication in MI bidirectional block achievement. The main findings of this study are the following: (a) VoM-EI led to newly formed LA lesion consistent with the trajectory of the VoM; (b) a greater LVA predicts a shorter AblTime-MI time with reduced need for epicardial gaps elimination into the CS for bidirectional MI block achievement; and (c) Δ LVA showed the highest predictive power for the presence of residual epicardial gaps leading to CS musculature RF applications.

In our cohort, acute bidirectional MI block was achieved in 90.6% of patients, a rate comparable to previous studies evaluating VoM-EI. Nakashima et al. reported a similar block rate (98.7%) in a larger population [10]. As reported by Gillis et al., higher success rates are achievable only with VoM-EI, whereas RF alone results in lower success rates, with only 43% of patients achieving MI block [14]. These findings support the procedural value of VoM-EI in facilitating MI block, although the need for epicardial ablation remains frequent.

5.1 Δ LVA

The impact of VoM-EI on atrial scarring exhibits wide variability, aligning with previous reports [6, 15]. Interpatient variability in Δ LVA depends on several factors, including VoM anatomy (length, presence of collaterals) and procedural-technical issues (VoM perforation/dissection, alcohol leakage). Moreover, the VoM-EI procedures demand a combination of interventional cardiology and electrophysiology skills, and the operator's familiarity with this specific workflow may influence the success of VoM ethanol ablation. As previously reported by our group, a localized myocardial staining formation could represent a possible indicator of the acute effectiveness of VoM-EI as it significantly relates to LA newly formed lesion extension, but its practical application in routine settings is challenging [16].

On the other hand, the voltage analysis following VoM-EI procedures represents an easy and reproducible indicator to evaluate the impact of alcohol delivery into the VoM on the newly formed lesion into the LA. In our cohort, MI block was completed after endocardial-only RF applications in 58.5% of the patients, whereas 41.5% required targeting

epicardial connections CS musculature. These findings are in line with previous experiences [14].

Notably, we observed a good correlation between Δ LVA and MI block achievement. Moreover, greater LVA values following VoM-EI demonstrated a reduced likelihood of requiring additional RF applications into the CS.

Δ LVA showed an optimal discriminatory capability to determine the need for CS application targeting residual epicardial connection for MI conduction when compared to other variables. According to our model, a Δ LVA smaller than 5.3 cm² may predict the need of more complex ablation, requiring CS applications (sensitivity 73.0%, specificity 81.0%). The ability to quantify the VoM-EI effectiveness through Δ LVA may help to identify patients at risk of suboptimal lesion formation and incomplete MI conduction block. A reduced Δ LVA may be driven by a lack of impact of ethanol delivery into the VoM due to technical issues, alcohol drainage, or variable anatomy of the VoM itself. In such cases, early recognition of limited VoM impact through Δ LVA evaluation could prompt a tailored ablation strategy, including CS mapping, reinforcement of the mitral line, or in selected cases a reassessment of the alcoholization itself or a change in the ablation strategy.

In conclusion, the predictive capacity of Δ LVA for identifying patients at risk of requiring epicardial ablation reinforces the potential utility of voltage mapping as a real-time feedback tool. While these results support the role of Δ LVA as a procedural marker, further prospective studies with a controlled design are needed to confirm its predictive value and assess the clinical benefit of VoM-EI in broader populations.

5.2 VoM dissection and suboptimal VoM-EI

VoM dissection represents a complication frequently reported in previous studies. In our experience, VOM dissection did not imply serious adverse outcomes, but it can be associated with suboptimal alcohol delivery, exhibiting smaller bipolar Δ LVAs and a reduced rate of MI block achievement. Two patients experienced VoM perforation, resulting in mild pericardial effusion in one, without need of drainage.

5.3 Limitations and perspectives

This study has some noteworthy limitations: first, the durability of the lesions cannot be explored with a single procedure and long-term reliability of the block cannot be assessed. Acute effectiveness was explored in this analysis, but long-term efficacy of acute Δ LVA cannot be predicted. Redo procedures may be considered in future studies to assess the correlation between optimal VoM-EI delivery and

mitral isthmus block durability. Additionally, the relatively small number of patients who did not achieve bidirectional block showed lower Δ LVA at the time of mapping; however, no clinical implications can be made, and larger cohorts should be investigated.

6 Conclusions

This study presents a comprehensive analysis of the impact of VoM-EI on newly formed LA bipolar lesions. VoM-EI-induced LA lesions are consistent with the VoM trajectory and anatomy. A larger Δ LVA correlates with a shorter ablation time required to achieve bidirectional MI block; furthermore, a larger Δ LVA predicts a reduced probability of residual epicardial MI gaps requiring RF application in the CS musculature. Ultimately, Δ LVA represents a reliable index of VoM-EI effectiveness, serving as a robust predictor of MI block failure attributable to the presence of epicardial gaps.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee.

Patient consent Informed consent was obtained from all participating patients prior to their involvement in this study.

Conflict of interest The authors declare no competing interests.

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