Durability of Left Atrial Lesions after Ethanol Infusion in the Vein of Marshall

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Abstract

Background Ethanol infusion in the vein of Marshall (EIVM) has shown to be effective for treating atrial fibrillation (AF) and perimitral left atrial (LA) flutter (PMLAF). Aims To assess the persistence of LA lesions created by EIVM by electro-anatomical mapping (EAM) at repeated procedure for recurrent atrial tachycardia (AT) or AF. Methods We included consecutive patients who underwent EIVM then repeated CA for recurrent AT or AF with high-definition EAM in a single center. Acute and long term EIVM effect was assessed at the index and redo procedures by comparing the area of bipolar voltage <0.05 mV in the vein of Marshall (VOM) region before, immediately after and late after EIVM. Results 24 consecutive patients (mean age 68.6±6.1 years, 58% men) underwent redo procedure after previous successful EIVM for persistent AF (n=21; 88%) or PMLAF (n=5; 21%). In each case, EIVM had an acute effect, with a post-EIVM scar in the VOM (median 12.4 cm2 [interquartile range (IQR) 7.6–15.7]). Mitral isthmus (MI) bidirectional block was obtained in 20/24 patients (83%). In each patient, the EIVM-related lesion persisted, with a chronic scar in the VOM region (median 13.1 cm2 [IQR 8.1–15.9]). One quarter of patients (5/20) had late MI reconnection, which was located at the mitral annulus edge or in the coronary sinus. Conclusions Atrial lesions created by EIVM are durable, which reinforces the efficacy profile of EIVM. Reconduction sites in the MI are located at the edge of the mitral annulus and in the coronary sinus.

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Ethanol infusion in the vein of Marshall (EIVM) has shown to be effective for treating atrial fibrillation (AF) and perimitral left atrial (LA) flutter (PMLAF).

Aims

To assess the persistence of LA lesions created by EIVM by electro-anatomical mapping (EAM) at repeated procedure for recurrent atrial tachycardia (AT) or AF.

Methods

We included consecutive patients who underwent EIVM then repeated CA for recurrent AT or AF with high-definition EAM in a single center. Acute and long term EIVM effect was assessed at the index and redo procedures by comparing the area of bipolar voltage <0.05 mV in the vein of Marshall (VOM) region before, immediately after and late after EIVM.

Results

24 consecutive patients (mean age 68.6±6.1 years, 58% men) underwent redo procedure after previous successful EIVM for persistent AF (n=21; 88%) or PMLAF (n=5; 21%). In each case, EIVM had an acute effect, with a post-EIVM scar in the VOM (median 12.4 cm^2[interquartile range (IQR) 7.6–15.7]). MI bidirectional block was obtained in 20/24 patients (83%). In each patient, the EIVM-related lesion persisted, with a chronic scar in the VOM region (median 13.1 cm^2 [IQR 8.1–15.9]). One quarter of patients (5/20) had late MI reconnection, which was located at the mitral annulus edge or in the coronary sinus.

Conclusions

Atrial lesions created by EIVM are durable, which reinforces the efficacy profile of EIVM. Reconduction sites in the MI are located at the edge of the mitral annulus and in the coronary sinus.

Abbreviations

AF: atrial fibrillation

AT: atrial tachyarrhythmia

CA: catheter ablation

CS: coronary sinus

EAM: electro-anatomical mapping

EIVM: ethanol infusion in the vein of Marshall

LA: left atrium

MI: mitral isthmus

PLMAF: perimitral left atrial flutter

PV: pulmonary vein

PVI: pulmonary vein isolation

RF: radiofrequency

SR: sinus rhythm

VOM: vein of Marshall

Introduction

The vein of Marshall (VOM), which runs in the epicardial posterolateral left atrium toward the coronary sinus (CS), is a target structure for AF ablation. It crosses the epicardial aspect of the mitral isthmus (MI) and contains cardiac autonomic nervous system structures, hosts atrial fibrillation (AF) drivers. Ablation of the VOM is required for treating perimitral left atrial (LA) flutter (PMLAF).[1–3] For these reasons, the VOM represents an interesting target for AF and PMLAF catheter ablation (CA). Ethanol infusion in the VOM (EIVM) is the most-used technique because it uses the VOM as a vascular access to myocardial tissue and provides direct damage to the atrial myocardium drained by the VOM.[2,4,5]

Adjunct EIVM has been shown to provide good long-term freedom from atrial tacchyarrhythmia (AT) after non-paroxysmal AF ablation and improves acute and mid-term success of PMLAF ablation by addressing epicardial connections at the MI.[6–13] As opposed to radiofrequency (RF) ablation, which provides direct thermal injury to tissue, EIVM-created atrial scarring relies on a different mechanism.[2] Acute EIVM-induced atrial scarring in the VOM region has been demonstrated [5,9,14,15], but little is known about the long-term EIVM effect and the persistence of acute EIVM-created lesions.

In this study, we assessed the durability of EIVM by comparing acute and late scar induced by EIVM in patients who underwent redo LA procedure.

Methods

Screening and study population

Overall, 256 consecutive patients who underwent EIVM in a single center and had at least 6-months' post-ablation follow-up were screened for repeated CA procedures. We included consecutive patients who underwent repeated CA for recurrent AT after EIVM. At the index procedure (EIVM), patients were referred for EIVM for persistent AF (initial or redo procedure) or post-AF LA flutter. EIVM was not performed if a bidirectional block at the MI was documented during LA mapping.

Index procedure: EIVM

After written consent was obtained, procedures were performed under general anesthesia and uninterrupted anticoagulation (uninterrupted direct oral anticoagulants and vitamin-K antagonists with an international normalized ratio target of 2–3, 120 U/kg of intravenous heparin given after femoral puncture for activated clotting time target > 300). EIVM was performed as described.[9]Briefly, after transseptal access and high-density LA bipolar voltage mapping performed during sinus rhythm (SR), AF or LA flutter, the CS was cannulated with a standard SL0 or a steerable Agilis sheeth. To visualize the VOM ostium, non-selective CS angiography (anteroposterior) was performed with a multipurpose coronary angiography 5F LIMA catheter. When the VOM ostium could not be seen, selective CS angiography with a Swan-Ganz balloon catheter was performed at the median and proximal CS with 30° left and right anterior oblique views. The VOM was cannulated with the LIMA catheter and a straight Whisper guidewire (Boston Scientific, Marlborough, MA) was inserted in the Marshall venous network over a 2.00- to 6.00-mm MiniTrek balloon angioplasty catheter (Abbott, Chicago, IL). After VOM balloon occlusion, injections of 3 mL of 96% ethanol were administered sequentially, separated by injections of 3 mL contrast agent, until an aspect of the LA myography was seen, indicating ethanol penetration into the LA myocardial tissue.

Index procedure: electro-anatomical mapping (EAM) and associated RF ablation lesions

After EIVM and visualization of LA myography, the acute effect of EIVM was assessed by repeated LA voltage mapping (see below). PVI was completed in case of PV reconnection on both sides. A roof line was performed or completed and the MI line was completed endocardially (mitral annulus side) and epicardially by RF applications within the CS. Electrical cardioversion was then performed in the absence of organization to an LA flutter or regularization to SR. Bidirectional blocks of PV, MI and roof lines were then assessed by activation mapping and differential pacing.[16] Cavotricuspid isthmus ablation was then performed (or bidirectional block assessed). All lines were re-assessed 30 min later. All ablations involved the 3.5-mm, bidirectional, open-irrigated, contact force-sensing SmartTouch SurroundFlow catheter (Johnson & Johnson, Irvine, CA). Involved RF powers included 50 W at the endocardial MI (target ablation index 450–500), 25 W in the CS (target ablation index 300), 30 to 40 W in the LA (target ablation index 430 anterior and 380 posterior) and 40 W at the cavotricuspid isthmus (target ablation index 450).

Assessment of acute EIVM effect by EAM

LA bipolar voltage mapping was performed before and immediately after EIVM by using the duodecapolar PentaRay catheter and the CARTO3 v6 or v7 EAM system (Johnson & Johnson, Irvine, CA) with the Tissue Index Proximity tool activated to ensure tissue contact for each recorded electrogram. The rhythms during which voltage mapping was performed was SR, AF or PLMAF before EIVM and SR, AF or PLMAF after EIVM. For patients in whom EIVM acutely changed the atrial rhythm (n=8 [29%], including AF to PMLAF, n=4; PMLAF to sinus rhythm, n=3; PMLAF to roof-dependent flutter, n=1), we performed no specific correction to take into account the correlation of electrogram amplitude to the type of atrial rhythm. The scar area in the VOM region was defined as the area with bipolar voltage <0.05 mV. The PV was excluded from scar area analyses because PV volume acquisition may vary substantially between procedures. The scar area was delineated by using the "Area Measurement" tool of the CARTO3 software. Scar areas in the VOM region before and immediately after EIVM were compared to assess the acute EIVM effect (Figure 1).

Follow-up after index procedure

All patients were followed by 2 electrophysiologists (AZ, BC) at the center where the index ablation was performed. Follow-up consisted of an in-patient visit every 3 months, which included at least 12-lead ECG. A 7-day Holter ECG monitoring was systematically performed at 3 months and 1 year after the index procedure. No patient was lost to follow-up.

Repeated CA and assessment of EIVM durability

All patients underwent repeated CA for persistent recurrent AT or AF after EIVM. Durability of EIVM-created atrial lesions was assessed by comparing the scar area in the VOM region at redo versus that at the index procedure, similar to assessing acute EIVM lesions.

Statistical analysis

Continuous data are reported as mean ± standard deviation or median (interquartile range [IQR]) depending on their distribution. Categorical data are presented as frequencies (percentages). Comparative analyses involved the Wilcoxon matched-pairs signed rank test. Complete data were available for all patients. Statistical analyses were performed with JMP v9 (SAS Institute Inc., Cary, NC) and PRISM v7 (GraphPad, San Diego, CA).

Results

Patient characteristics at EIVM

Among 256 patients who underwent EIVM for persistent AF or PMLAF in a single center with [?] 6 months available follow-up data, we included 24 (14 [58%] men, mean age at EIVM 68.6+-6.1 years) who underwent repeat CA for symptomatic, sustained, recurrent AT between February 2019 and May 2020. Patient characteristics at the time of the index procedure (including EIVM) are summarized in Table 1. Amiodarone was included in the daily drug regimen of 14 (58%) patients.

EIVM, acute EIVM-induced lesion and associated RF lesions at the index procedure

Arrhythmias prior to EIVM and procedural characteristics are detailed in Table 2. VOM was identified and EIVM was achieved in every patient. After sequential ethanol and contrast-agent injection, an aspect of LA myography was reached in every patient. In one patient, EIVM initially failed to reach LA myography, and post-EIVM bipolar voltage mapping showed no lesion created. After further injections at a more proximal site, LA myography was reached and a scar was created. In 8 (29%) patients, EIVM acutely changed the atrial rhythm (AF to PMLAF, n=4; PMLAF to SR, n=3; PMLAF to roof-dependent flutter, n=1). Each patient showed an acute EIVM-created lesion. The median area of bipolar voltage < 0.05 mV in the VOM region was 12.5 cm^2(IQR 7.6–15.7) immediately after EIVM as compared with 0 cm^2 (0–1.65) before EIVM ($p<0.0001$) (Figure 1). At the end of the procedure, 14 (58%) patients showed a return to SR or organization to AT. Bidirectional MI block was obtained in 24 (83%) patients. Two patients had a procedural complication: 1 femoral pseudo-aneurysm requiring stenting and 1 transient sinus node dysfunction requiring isoprenaline infusion.

Durability of EIVM-induced lesions and persistence of MI block

Each of the 24 patients were referred for redo CA of symptomatic recurrent AF or AT (Table 3). At least one PV was reconnected in 7 (29%) patients and the roof line was reconnected in 6 (25%). The MI was reconnected in 5 of the 20 (25%) patients with complete MI block at the index procedure. The site of reconnection was endocardial at the lower (mitral annulus) extremity in 2 patients and was epicardial in the CS in 3. The 4 patients with failure to obtain MI block at the index procedure showed residual conduction at the left PV ridge aspect of the MI. The EIVM-created lesion was maintained in every patient. The median area of bipolar voltage < 0.05 mV in the VOM region (13.1 cm^2 [IQR 8.1–15.9]) was comparable to the area present immediately after EIVM (median 12.4 cm^2 [IQR 7.6–15.7], $p=0.27$) (Figure 2). At the end of the redo procedure, bidirectional block of all lines including MI was achieved.

Discussion

This is the first study evaluating the long-term durability of EIVM-induced atrial lesions. Our main results are that 1) EIVM created durable lesions that persisted through time; 2) despite 83% immediate success in achieving MI block, one quarter of these patients underwent late MI reconnection after EIVM. MI gaps are located at the mitral annulus edges and in the coronary sinus, but not within the EIVM created scar.

Durability of EIVM-created atrial lesions

This study investigated the long-term effect of EIVM by comparative EAM before, immediately after and at the time of repeated CA for recurrent AT. The nature of the myocardial lesions created by EIVM are distinct from those created by RF owing to their intrinsically different mechanisms. RF lesions, created by external thermal energy, have a variable degree of sustainability, which depends on energy delivery parameters, contact force and atrial tissue characteristics.[17] In contrast, retrograde ethanol delivery creates a chemical lesion related to ethanol penetration in the myocardium, with venous drainage depending on the VOM, including a variable extent of the LA posterior wall and MI.[2] In dogs, EIVM creates an acute and dense pale patch, visible from the endocardium, which suggests transmural damage and transmyocardial ethanol flow.[2] In humans, several studies have consistently shown EIVM creating a low-voltage lesion in the VOM region, although to a variable extent.[4–6,18,9,14,15,12]However, no study has evaluated the sustainability of EIVM over time.

Here, by demonstrating EIVM-created lesion durability in all consecutive patients referred for repeated CA after EIVM, we closed a knowledge gap regarding EIVM lesion characteristics.

MI reconnection after EIVM and considerations for associated RF lesions

The success rate of RF alone to achieve acute MI block ranged from 32% to 91% in several studies.[19–22, 25] Also, MI reconnection rate late after endo-epicardial RF has been reported as high as 73%.[23] These variable and overall low acute and late outcomes are due to the heterogeneous and complex structure of the MI,

consisting of a thick myocardium, vascular and nervous structures, epicardial muscular fibers sometimes requiring extensive ablation within the CS and difficulty to achieve catheter-tissue contact and stability.[22] Added to RF, EIVM significantly increases MI block success, PMLAF termination rate and long-term freedom from PMLAF relapse.[7,8,11,12, 16] In a recent study of 84 patients undergoing EIVM added to RF for MI ablation, MI block was successful in 93% of patients.[18] In our study, EIVM added to RF achieved successful MI block in 83% of cases. One case of intra-EIVM scar reentrant AT has been reported,[24] but EIVM has consistently been found to create homogenous lesions — in terms of endocardial voltage — and additional RF mostly needed at the mitral annulus edge of the MI.[12] Our results are in line with Nakashima's et al study[25], showing same rate of MI reconnection and sites of reconnection. In our study of 24 consecutive patients referred for CA of recurrent AF or AT after EIVM, the MI was reconnected in 25%. The site of MI reconnection was not within the EIVM-related scar but rather at its mitral annulus border in 40% of patients and within the CS in 60%. Additionally, in patients with acute MI ablation failure, residual MI conduction was found at the ridge aspect of the MI at procedure redo.

MI reconnection at its mitral annulus extremity after EIVM could be explained by 3 phenomena: 1) MI mitral annulus extremity being outside of VOM drainage territory, 2) incomplete VOM alcoolization related to balloon-occlusion of the most proximal branches and 3) progressive retraction of the EIVM-created lesion at its border. Scar measurement by using EAM systems may not be accurate enough to reliably assess the last hypothesis, and histopathological works in animals late after EIVM may shed light on this matter. Further works are also needed to optimize the EIVM technique. Ethanol infusion of the entire VOM network may be incomplete in some patients because of the great interindividual anatomical variability and the exclusion of most proximal VOM branches when using balloon occlusion. Development of a technique not involving balloon occlusion could be useful for that purpose. Finally, our results should encourage physicians to consolidate RF lesions at both extremities of the EIVM-created lesion.

Study limitations

For our main result — durability of the EIVM lesion — generalizability is limited by the small sample size, although the monocentric and consecutive enrollment and the follow-up data available for each patient limit the risk of biased selection. Second, assessment of scar area in the VOM region may have been limited by four main factors: 1) inaccuracy intrinsic to the area measurement tool of the CARTO system; 2) bipolar voltage measured in different atrial rhythms in some patients before, immediately after, and late after EIVM, although in a direction that may only result in underestimating the lesion size (AF to AT/SR or AT to SR); and 3) the impact of the associated RF lesions at the MI during the index procedure 4) absence of information of the epicardial scar related to EIVM.

Finally, due to the accuracy of the measure, we cannot confirm that the border of the EIVM created scar is always consistent.

Conclusions

The LA lesion created by EIVM was durable and did not significantly vary in size in patients who underwent repeated CA after EIVM. Despite this consistent scar, MI reconnection was observed in a substantial proportion of patients at repeated CA, which prompted the need for additional RF lesions at mitral annulus edges and in the coronary sinus, but not within the EIVM created scar.

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Tables

Table 1. Patient characteristics at the index procedure (EIVM) (n=24)

Age at procedure, years	68.6 ± 6.1
Male sex	14 (58)
$CHAD_2S_2VASc$ score	2 (1–3)
Hypertension	13 (54)
Diabetes	2 (8)
Stroke or TIA history	1 (5)
Structural heart disease	8 (33)
Ischemic	2 (8)
Valvular	6 (25)
LA size[a], cm^2	28.4 ± 4.6
LVEF[b], %	62 (55–75)
No. of previously failed lines of AAR drugs	2 (1–2)
Previously failed AAR drugs	
Amiodarone	23 (96)
Flecainide	5 (21)
Propafenone	1 (5)
Sotalol	1 (5)
None	1 (5)
Time since first sustained atrial arrhythmia, months	60 (22–108)
Time since persistent AF installation, months	7 (4–11)
Previous ablations	12 (50)
Previous CTI ablation	12 (50)
Previous AF ablation	10 (42)

Age at procedure, years	68.6 ± 6.1
[?] 2 previous AF ablations	4 (21)
Previous PVI	10 (42)
Previous roof line	7 (29)
Previous CFAE ablation	3 (13)
Previous mitral isthmus line	0 (0)
Previous anterior mitral line	1 (5)

Data are n (%), median (interquartile range [IQR]) or mean ± SD.

[a]: from multidetector CT. [b]: from Simpson method on transthoracic echocardiography.

Abbreviations. AF: atrial fibrillation; AAR: anti-arrhythmic; CFAE: continuous fractionated atrial electrograms; CTI: cavotricuspid isthmus; EIVM: ethanol infusion in the vein of Marshall; LA: left atrial; LVEF: left ventricular ejection fraction; PVI: pulmonary vein isolation; TIA: transient ischemic attack.

Table 2. Arrhythmia and procedural characteristics at the index procedure (EIVM) (n=24)

Atrial arrhythmia	
Persistent AF	21 (88)
Long-duration AF	5 (21)
Perimitral flutter	5 (21)
Native (no previous AF ablation)	1 (5)
Post-AF ablation	4 (17)
Associated with documented AF	3 (13)
Left septal macro-reentry	1 (5)
Ablation lesions at the index procedure	
PVI	20 (83)
Mitral isthmus line (endo)	24 (100)
Mitral isthmus line (epi, coronary sinus)	23 (96)
Roof line	21 (88)
Posterior wall isolation	9 (38)
Anterior mitral line	1 (5)
CFAE	6 (25)
CTI line	13 (54)
EIVM	
VOM identified by fluoroscopy	24 (100)
Absence of pre-alcoolization scar in the VOM region	18 (75)
Surface of post-alcoolization scar in the VOM region, cm^2	12.5 (7.6–15.7)
Success of PV, roof line and CTI bidirectional block	24 (100)
Success of mitral isthmus bidirectional block	20 (83)
Return to SR or organized AT by EIVM	10 (42)
Procedural characteristics	
Procedural time, min	180 (155–210)
Radiofrequency duration, min	68.6 ± 6.1
Fluoroscopy dose, $mGy.m^{-2}$	2.4 (1.7–4.3)

Data are n (%) or median (interquartile range [IQR]) or mean ± SD.

Abbreviations. AF: atrial fibrillation; AT: atrial tachycardia; CFAE: continuous fragmented atrial electrography; CTI: cavotricuspid isthmus; EIVM: ethanol infusion in the vein of Marshall; PV: pulmonary vein; PVI: pulmonary vein isolation; SR: sinus rhythm; VOM: vein of Marshall

Table 3. Arrhythmia and procedural characteristics at redo procedure (n=24)

Time after EIVM, months	7.1 ± 4.5
Patients with [?]2 atrial arrhythmias at redo procedure	9 (37)
Surface of post-EIVM scar in the VOM region, cm^2	13.1 (8.1–15.9)
Line reconnections at redo procedure	
PV reconnection	7 (29)
Mitral isthmus reconnection[a]	5 (25)
Roof line reconnection	6 (25)
CTI reconnection	3 (13)
Site of mitral isthmus reconnection, total n [a]	5
Within the scar	0 (0)
Mitral Annulus aspect alone	2(40)
Ridge of the left PV	0 (0)
Coronary sinus	3 (60)

Data are n (%) or median [interquartile range (IQR)] or mean ± SD.

[a]: for the 20 patients with successful MI block at index procedure

Abbreviations. AF: atrial fibrillation; AT: atrial tachycardia; CTI: cavotricuspid isthmus; EIVM: ethanol infusion in the vein of Marshall; PV: pulmonary vein; VOM: vein of Marshall

Figure Legends

Figure 1. Durability of atrial lesions created by EIVM

A. EIVM in a 53-year-old man referred for EIVM and catheter ablation of persistent AF. Contrast injection in the VOM through a LIMA angiographic catheter. **B.** After balloon expansion at the proximal VOM, the VOM network is seen with an aspect of LA myography.**C.** LA bipolar voltage map (PentaRay) during AF before EIVM shows absence of scar in the VOM region. **D.** Immediately after EIVM, repeated bipolar voltage map (still in AF) shows a scar (defined as bipolar voltage < 0.05 mV) of 6.2 cm^2 in the VOM region calculated by the area measurement tool of the CARTO system (outlined in green dots). The left PV area was excluded from EIVM scar area calculation because PV volume acquisition may vary significantly between procedures. Complementary RF at the mitral annulus edge of the MI was necessary to obtain the MI block. Additional RF lesions were created for PV isolation and roof-line block. **E.**Seven months after the index procedure, the patient was referred for repeat catheter ablation for recurrent AF. Bipolar voltage mapping (PentaRay) shows the persistence and durability of the EIVM-created scar (< 0.05 mV; 6.6 cm^2) in the VOM region. Scar region at the mitral annulus edge of the MI was not integrated in the area calculation because of complementary RF applications during the index procedure. Abbreviations: AF: atrial fibrillation; EIVM: ethanol infusion in the vein of Marshall; LA, left atrial; MI: mitral isthmus; PV: pulmonary vein; RF: radiofrequency; VOM: vein of Marshall.

Figure 2. Evolution of scar area in the VOM region, immediately and late after EIVM.

Comparative statistical analyses involved the Wilcoxon matched-pairs signed rank test.

*** P <0.0001.

Abbreviations. EIVM: ethanol infusion in the vein of Marshall; VOM: vein of Marshall.

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