Durability of mitral isthmus ablation with and without ethanol infusion in the vein of Marshall

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Abstract

Background: It is established that ethanol infusion in the vein of Marshall (EIVOM) effectively creates a linear ablation lesion in the mitral isthmus (MI). However, data on the long-term success rates of MI ablation remains limited. Methods and Results: Our cohort consisted of 560 patients with non-paroxysmal atrial fibrillation (AF) who underwent an initial MI ablation. Ablations were performed by only radiofrequency (RF) in 384 patients (RF group) or by RF and EIVOM in 176 patients (EIVOM/RF group). Ethanol of 5 mL was used to perform EIVOM in advance of RF. Following EIVOM, RF pulses were delivered to the lateral MI line. Bidirectional MI block was fully achieved in 353 (first 318, re-do 35) patients of the RF group and 171 (first 128, re-do 43) patients of the EIVOM/RF group (p = 0.09 in the first, 0.10 in the re-do ablation cases). In cases with complete MI line block, recurrent AF or atrial tachycardia (AT) was observed in 130 (37%) patients of the RF group and in 64 (37%) patients of the EIVOM/RF group (log-rank p = 0.12 in the first, 0.30 in the re-do ablation cases). Of the total 194 patients, 112 with drug refractory AF or AT proceeded to the subsequent ablation process. Reconnection of MI block line was observed in 39 (49%) patients in the RF group and 25 (58%) patients in the EIVOM/RF group (p = 0.32). Conclusion: EIVOM effectively ensures MI line block; however, the reconnection rate was similar between the two groups.

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Brief title: Durability of mitral isthmus ablation

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Structured abstract

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Keywords: atrial fibrillation; mitral isthmus; Marshall vein; ethanol infusion; chemical ablation

Introduction

The vein and ligament of Marshall (VOM and LOM) are associated with arrhythmogenic roles in atrial fibrillation (AF).[1-3]It is now well known that sympathetic and parasympathetic nerves promote a non-pulmonary vein trigger from the VOM and LOM, and that they contribute to AF maintenance.[4,5] The VOM and LOM are also associated with atrial tachyarrhythmia which develops in the context of AF ablation as an epicardial conduction pathway of the macro-reentry and localized reentry circuits.[6,7]Particularly, mitral annular flutter (MAF)—using the VOM and LOM—is often observed after AF ablation. It can be technically difficult to terminate MAF and create a complete block line in the mitral isthmus (MI) only by radiofrequency (RF) ablation at the endocardium and coronary sinus (CS).[8-10]

It is established that ethanol infusion in the VOM (EIVOM) is safe and effective for creating a linear ablation lesion in the MI and for ablating MAF using the VOM.[11,12] EIVOM is recognized as an adjunctive strategy of MI ablation which is refractory to RF. Moreover, previous studies have demonstrated that EIVOM provides good outcomes in patients with both paroxysmal AF and non-paroxysmal AF and MAF.[13-14] However, few studies have reported on the actual reconnection rate of MI block line in the distant period remains. This study was conducted to reveal the long-term outcomes of MI line block with and without EIVOM.

Methods

Study population

Our study consisted of 560 consecutive patients (419 males and 141 females, mean age ± standard deviation = 67.2 ± 9.1 years) with non-paroxysmal AF who underwent initial MI ablation in the Kimitsu Central Hospital. The study duration was from January 2012 to September 2019; however, EIVOM has been started in our institute since February 2015. EIVOM and RF ablation were performed in 176 patients (EIVOM/RF group) with the amenable VOM. In the remaining 384 patients, MI block line was created via only RF because the patients underwent catheter ablation before then, or they lacked the amenable VOM. All patients provided informed consent before the procedure. This study was conducted according to the protocol that was approved by the Ethic Committee at the Kimitsu Central Hospital.

Ablation procedure

Anti-arrhythmic drugs (AADs) were discontinued for at least five half-lives prior to ablation. Oral anticoagulant drugs were skipped just before the procedure. EnSite Navx^{TM} (Abbott, St Paul, MN, USA) was used to perform all ablation procedures. The ablation strategy consisted of liner ablations, including the roof, bottom, and MI, as well as pulmonary vein (PV) and superior vena cava (SVC) isolation under general anesthesia. The CS was cannulated using a guiding catheter (CPS Aim^{TM} SL; Abbott) via an approach from the internal jugular vein. Subsequently, a contrast agent was injected through Berman^{TM} angiographic catheter (Teleflex, Morrisville, NC, USA) while a balloon was being inflated (Figure 2A). If angiography adequately confirmed the VOM, then EIVOM was performed in advance of RF ablation.

In both groups, an irrigation catheter (FlexiAbility^{TM}or TactiCath^{TM}; Abbott) was used to deliver RF pulses (30 W, 40 s) point-by-point at the endocardium of the lateral MI under left atrial appendage (LAA) pacing (Figure 2E). The ablation catheter was supported by steerable introducer (Agilis^{TM} NxT steerable introducer; Abbott) to gain adequate contact force and stability. If a bidirectional block line was not fully achieved, additional RF pulses (25 W, 30 s) via approaches from the femoral and internal jugular veins were delivered to the inside of the CS, which was opposite the endocardial MI line. (Figure 2F & G) Bidirectional block was confirmed by a differential pacing maneuver from the distal and proximal CS sites.

Ethanol infusion in the vein of Marshall

Following confirmation of the amenable VOM, a guidewire (Cruise; Asahi Intecc, Aichi, Japan) and an over-the-wire balloon catheter (1.5 or 2 mm) (Emerge^{TM}; Boston Scientific, Marlborough, MA, USA) were inserted into the VOM using double guiding catheters (Figure 2B). A VOM angiography was performed while locating the inflated balloon at most distal site of the VOM (Figure 2C). Subsequently, anhydrous ethanol of total 5 mL was infused into the VOM. EIVOM was divided into two parts, which were performed at the most distal and proximal sites in the VOM according to a previous study (Figures 2C & D).[11]

Evaluation of acute effect by high-density grid-mapping catheter

The acute effect of EIVOM was evaluated in the consecutive 20 patients of the EIVOM/RF group in advance of left pulmonary vein isolation (PVI). A high-density grid-mapping catheter (Advisor^{TM} HD grid-mapping catheter; Abbott) was used to create the voltage map before, just after, and one hour after EIVOM under 10 V of pacing from the proximal CS site following a cardioversion. Advisor^{TM} HD grid-mapping catheter was used to obtain a bipolar electrogram. A low-voltage area (LVA) of the left atrium was set at $<$0.50 mV. It was measured by two independent observers (excluding the authors).

Follow-up after the ablation

Patients were followed up periodically in an outpatient clinic. They were evaluated for episodes of AF recurrence or atrial tachycardia (AT) based on regular 12-lead electrocardiograms at 1, 4, 7, 10, and 13 months after the ablation. An event recording (Spiderflash-T^{TM}; Japan Lifeline, Tokyo, Japan) was performed at 3, 6, and 12 months after the ablation. Patients were also periodically followed up in our institute or clinics. AF lasting $>$30 s on these recordings after a 3-month blanking period was evaluated as a recurrence. AADs were resumed after the ablation and discontinued if recurrent AF or AT was not documented by an event recording obtained at 3 months after the ablation. Patients who originally had not taken AADs were followed up without taking AADs. AADs were commenced, or changed to amiodarone or bepridil, if recurrent AF or AT was documented on these recordings. The subsequent ablation process proceeded if AF or AT was refractory to medical therapies. In the next session, bidirectional MI block was confirmed by differential pacing maneuver as well as the first ablation session.

MI reconnections and repeat procedure

The reconnection sites were evaluated by electrogram sequences of the left atrial myocardium and CS musculature recorded inside the CS under LAA pacing.[15] If the electrograms showed an endocardium reconnection pattern, RF applications were delivered to the endocardium (Figure 3B). In the case of epicardial reconnection pattern, we first tried EIVOM, and subsequently ablated inside of the CS. In the case or AT, we

estimated MI endocardium reconnections using an activation map that was created using an Advisor^{TM} HD grid-mapping catheter.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median (25^{th}–75^{th} percentile). Chi-squared (χ^2) analysis or Fisher's exact test was used for categorical variables. Data were analyzed with one-way analysis of variance or Student's t-test. A P value <0.05 was considered statistically significant. Kaplan-Meier survival curve analysis with log-rank tests was applied to examine the survival-free from AF recurrence in the samples of this study. Multivariate logistic regression included variables with P <0.05 on univariate analysis. It was used to analyze the risk factors of MI reconnection with results expressed as odds ratios with 95% confidence intervals. JMP version 14.3 (SAS institute Inc, Cary, NC, USA) was used to perform these statistical analyses.

Results

Patient characteristics

Figure 1 shows the flowchart of the patient enrollment and disposition in this study. The RF and EIVOM/RF groups consisted of 384 (First 346, Re-do 38) and 176 (First 133, Re-do 43) patients, respectively. Out of the 384 patients in the RF group, 301 patients underwent MI ablation before February 2015, when we started EIVOM in our institute, as was previously mentioned. The amenable VOM was not confirmed by angiography in 54 patients. We had difficulty inserting a guidewire in the VOM in 13 patients. A posterior VOM was observed in 13 patients. We canceled angiography for 3 patients due to their previous history of contrast allergy.

Table 1 shows the baseline patient characteristics in this study. The rate of long-standing persistent AF patient in the RF group of the first ablation group was 53% (184/346), and it was higher than that (43%; 57/133) in the EIVOM/RF group; however, left atrial diameter of the two groups were 49 ± 6.1 in the RF group and 49 ± 5.0 mm in the EIVOM/RF group, and similar between the two groups. No significant difference was observed between the two groups regarding other parameters.

Acute success rate of MI ablation

Table 2 summarizes the ablation data. Bidirectional MI block line in the first ablation cases was fully achieved in 318 (92%) and 128 (96%) patients in the RF group and EIVOM/RF group, respectively ($p = 0.09$). Complete MI line block was also achieved in 35 (92%) and 43 (100%) in each group in re-do ablation cases ($p = 0.10$). The application time of MI ablation in the EIVOM/RF group was significantly shorter than that in the RF group (First 802 ± 407 s, Re-do 738 ± 428 s in the RF group vs. First 502 ± 220 s, Re-do 538 ± 205 s in the EIVOM/RF group, $p < 0.01$ in both). However, total radiation exposure was greater in the EIVOM/RF group compared to the RF group (First 315 ± 252 mGy, Re-do 305 ± 223 mGy in the RF group vs. First 495 ± 336 mGy, Re-do 418 ± 446 mGy in the EIVOM/RF group, $p < 0.01$ in the first, $p = 0.17$ in the re-do ablation). This is because fluoroscopy was required more frequently for insertion of a guidewire or infusion of ethanol into the VOM during angiography. The rate of ablation from the inside of the CS was similar between groups. Bottom line ablation was less performed in the EIVOM/RF group than in the RF group. Pericardial effusion was observed in four patients in the RF group. Two of these patients experienced cardiac tamponade caused by a steam pop while ablating the MI, in which immediate pericardiocentesis was required.

Effect of ethanol infusion

Figure 4 and Supplementary data 1 demonstrate the variation in the left atrial LVA (<0.5 mV) of the consecutive 20 patients in the EIVOM/RF group. This was evaluated by two independent observers—excluding the authors—before, just after, and one hour after EIVOM. LVA was originally observed in eight patients before EIVOM. Extravasation of contrast medium into the epicardium occurred in three patients during the procedure, which did not cause cardiac tamponade. LVA measured just after EIVOM significantly increased

to 11.7 ± 8.1 cm^2 (measured by the observer 1) or 11.2 ± 7.9 cm^2 (measured by the observer 2) compared to that before EIVOM ($p < 0.05$ in both). At one hour after EIVOM, the LVA of the left atrium was 11.9 ± 10.5 cm^2 (observer 1) or 12.3 ± 9.9 cm^2 (observer 2). The effect of EIVOM appeared immediately and sustained during the procedure.

Outcome of AF ablation

Figure 5 demonstrated a Kaplan-Meier survival analysis. In the first ablation cases, AF recurrence or AT was observed in 117/299 (39%) patients in the RF group (AF = 87, AT = 30), and observed in 47/124 (38 %) patients (AF = 33, AT = 15, both = 1) in the EIVOM/RF group. In the re-do ablation cases, AF recurrence or AT was observed in 13/35 (37%) patients in the RF group (AF = 10, AT = 3), and in 17/43 (40 %) patients in the EIVOM/RF group (AF = 13, AT = 4). There was no statistically significant difference in AF- or AT-free survival rate between the two groups in both cases (log-rank p = 0.12 in the first, 0.30 in the re-do ablation cases). Of the total 194 patients who experienced recurrent AF or AT, 122 (79 in the RF group and 43 in the EIVOM/RF group) proceeded to the subsequent ablation process as shown in Figure 1. A patient in the RF group who newly developed paroxysmal supraventricular tachycardia without AF recurrence or AT also underwent the subsequent ablation procedure. The remaining 72 patients did not receive additional ablation because either medical therapy restored with maintained sinus rhythm, or the patients received rhythm control therapy.

Long-term success rate of MI ablation

The intervals between the initial and next ablation process were 418 ± 336 days in the RF group and 335 ± 239 days in the EIVOM/RF group. Table 3 demonstrates the reconnection rate of each ablation site in the subsequent ablation session. Reconnections of MI line were observed in 39/80 (49 %) (endocardium = 10, epicardium = 9, both = 20) in the RF group and 25/43 (58%) (endocardium = 10, epicardium = 2, both = 13) in the EIVOM/RF group (p = 0.32). In the subsequent ablation session, MI line blocks were recreated only for EIVOM in five patients who did not undergo EIVOM in the previous ablation session. The second ablation fully recreated an MI line block in 36/39 patients of the RF group (RF and 9 EIVOMs) and in 22/25 patients of the EIVOM/RF group (only RF), respectively.

PV reconnections were 44/80 (55%) (left PV = 13, right PV = 10, both =21) in the RF group and 30/43 (70%) (left PV = 4, right PV = 11, both = 15) in the EIVOM/RF group (p = 0.11). Bottom line reconnections were 23/59 (39%) in the RF group and 14/22 (64%) in the EIVOM/RF group (p = 0.05).

Supplementary data 2 shows the univariate and multivariate analyses regarding MI reconnections in this study. They demonstrated no predictive value.

Discussion

Major findings

First, our study demonstrated that adjunctive EIVOM did not statistically increased the acute success rate of MI ablation. EIVOM significantly reduced the RF application time to complete MI block line; however, the total fluoroscopy tended to be more in the EIVOM group than in the RF group. Second, EIVOM did not reduce AF recurrence or AT compared to the ablation performed by only RF. Third, MI durability was similar between the RF and EIVOM/RF groups.

Ethanol infusion in patients with non-paroxysmal atrial fibrillation

Catheter ablation for patients with non-paroxysmal AF remains challenging. The Star AF II trial demonstrated that the rate of freedom from AF was 60% in patients underwent PVI alone at 12 months after the procedure.[16] The trial did not show any differences among the three ablation strategies: PVI alone, PVI plus electrograms, and PVI plus lines. However, complete conduction block across both lines was achieved in 74% of the group assigned to PVI plus lines. This means that full achievement of MI block line is crucial for precisely estimating the efficacy of linear ablation in the left atrium. Our present study demonstrated a higher rate of 96% (128/133) in the EIVOM/ RF group and 92% (318/346) in the RF group regarding

creating a complete MI block line during the procedure. AF- and AT-free survival rate at 12 months after the procedure was 70% in both groups.

A recent, prospective, multicenter, randomized clinical trial (VENUS-AF trial) comparing these two procedures was published.[17,18] The VENUS-AF trial demonstrated that EIVOM/RF reduced recurrence of AF or AT. In this trial, bidirectional MI block line was obtained in 51.3% of the group in which ablation was performed by only RF. Meanwhile, our study did not show a superiority of the EIVOM/RF group compared to the RF group regarding clinical outcome. We anticipated that the result was caused by a high success rate of MI complete block in the RF group. However, AF recurrences were naturally caused by PV reconnections. PV reconnections were observed in 55% of the RF group, and 70% of the EIVOM/RF group. The concern that these findings would have an effect on AF recurrence remains.

Mitral isthmus reconnections in the distant period

Nakashima et al. recently demonstrated that the proportion of patients with MI reconnection was lower in the EIVOM/RF than that of the RF group (37% [13/35] vs. 67% [31/46]).[19] Given the fact that all patients received ablation inside the CS before EIVOM in this study, the durability of the MI block in the EIVOM/RF group might be improved. However, the acute and long-term success rate of the RF group was significantly lower (acute 63.6%, long-term 32.6%) compared to that of our study. In our cases, all patients underwent RF ablation under general anesthesia to gain a stable contact force. It was possible to achieve high success rate in the RF group during the procedure.

Reconnections in only the VOM were observed in five patients of the RF group; one of them was MAF using the VOM. EIVOM terminated the MAF and recreated a simultaneous MI line block. Meanwhile, there were no reconnections of the VOM in the EIVOM/RF group, which may offer an advantage in that EIVOM prevented subsequent MAF after AF ablations, as the previous study reported.[14]

We used Advisor^{TM} HD grid-mapping catheter to evaluate the left atrial LVA and the effect of EIVOM. The potential is maximized when used in conjunction with the Best Duplicate algorithm of EnSite Prescision^{TM}. Accurate evaluation of the left atrial LVA is feasible.[20] It showed that the effect of EIVOM appeared immediately and was maintained throughout the procedure. Despite of its efficacy, endocardium reconnections were observed in 21/43 (48%) patients of the EIVOM/RF group, which was higher than 29/80 (36%) of the patients in the RF group. This finding suggests that the effect of EIVOM is reversible. Stunned myocardium of the MI area tend to regain conductivity as time progressed.

EIVOM as an adjunctive therapy was observed to have a high clinical success rate during the procedure without excess RF application, which leads to steam pop and cardiac tamponade. There was no parameter that could predict the reconnection of the MI in this study.

Limitations

We encountered several limitations in this study. First, this is a retrospective, single-center study. Therefore, it was not randomized. EIVOM was performed in all cases with the amenable VOM as often as possible. Second, the ablation strategy was changed during the research period. During a certain period, linear ablation for the left atrial bottom line was performed less than for the roof line. Therefore, a significant difference was observed between the two groups regarding the bottom line ablation. Third, a total of 23 patients were not followed because of personal reasons. It might have had an effect on the result of the AF/AT- free survival rate. Fourth, the right PV and bottom line reconnections were significantly higher in the EIVOM/RF group than in the RF group. It was possible that these differences had a distinct impact on the AF/AT- free survival rate. Fifth, as was previously mentioned, we determined the first re-ablation site according to the information on the electrogram sequences recorded inside the CS. If we achieved an MI line block through EIVOM or RF ablations in the CS, we would determine that reconnection existed only in the epicardium. However, both EIVOM and RF ablations were possible in the development of a transmural lesion. Sixth, it was impossible to evaluate the pure effect of EIVOM in the subsequent ablation session, because the MI area was already ablated by RF in the first session. Finally, the reconnection rates shown in Table 3 occurred

only in AF recurrence or AT cases, which went into a subsequent ablation session. The true reconnection rate was limited due to MI durability when the success cases were unidentified.

Conclusions

EIVOM in addition to RF effectively ensured a high success rate of MI ablation during the procedure. However, the durability of MI block line was similar between the EIVOM/RF and RF groups.

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Figure legends

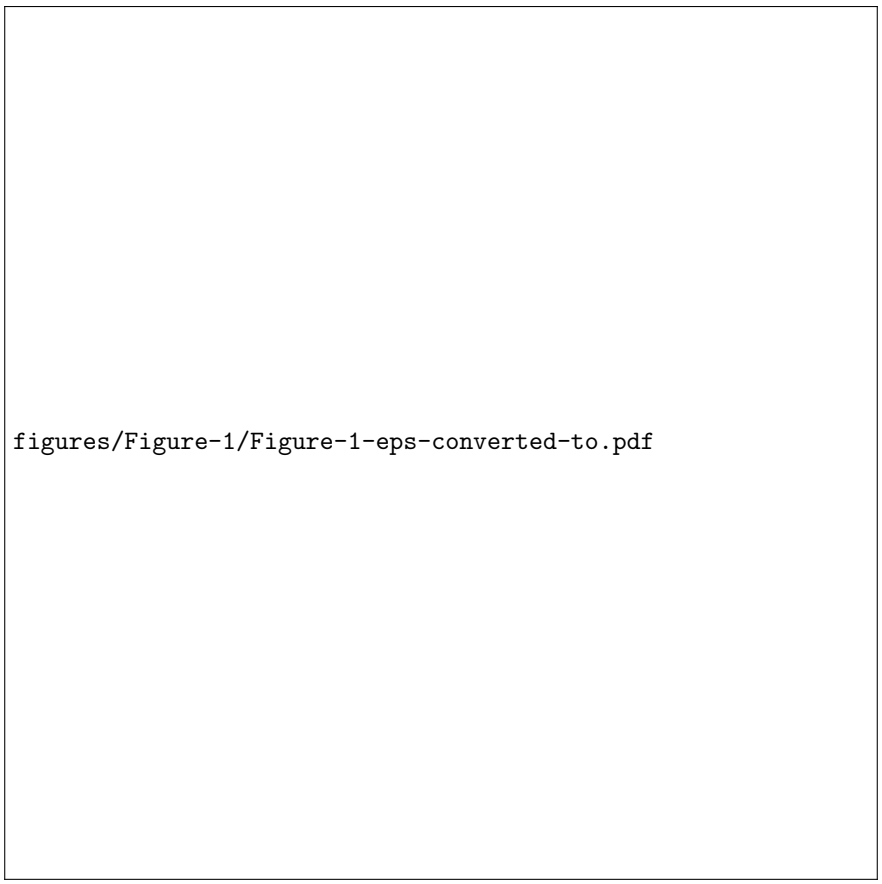
Figure 1. Flowchart of patient enrollment and disposition in this study. AF = atrial fibrillation, AT = atrial tachycardia, EIVOM = ethanol infusion in the vein of Marshall, MI = mitral isthmus, PSVT = paroxysmal supraventricular tachycardia, RF = radiofrequency, VOM = vein of Marshall

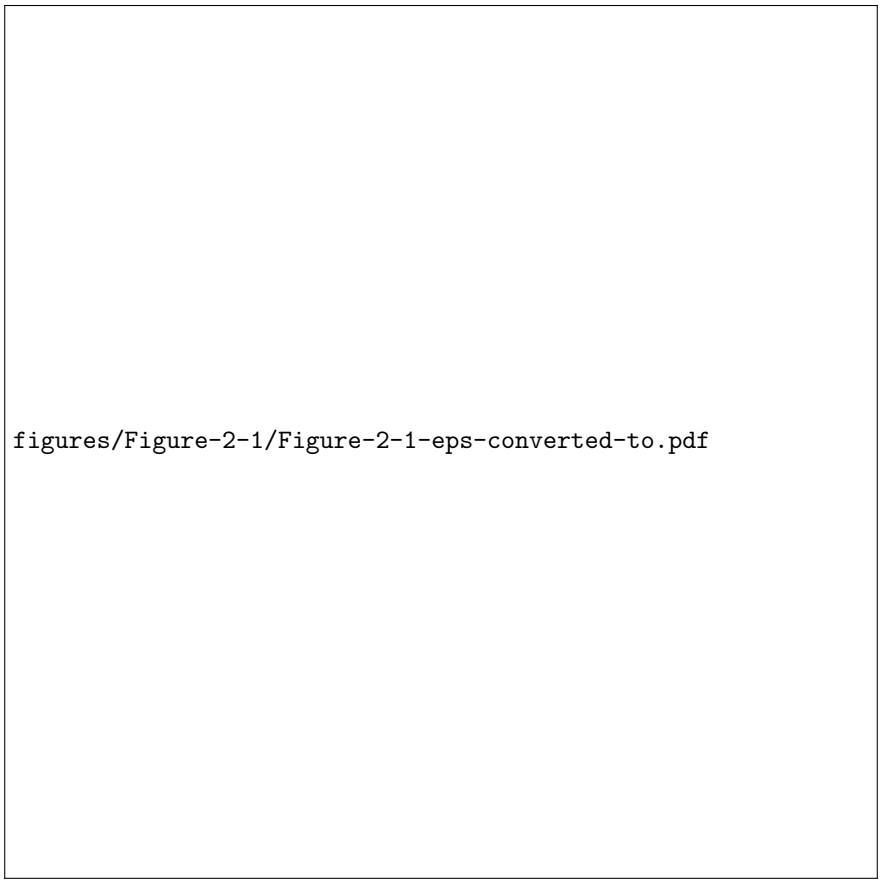
Figure 2. (A) A thermometer was in the esophagus, guiding catheter, and balloon catheter placed in the great cardiac vein. The cineangiography while inflating a balloon catheter revealed the existence of the Marshall vein (black arrows). CS = coronary sinus, GCV = great cardiac vein, RAO = right anterior oblique, VOM = vein of Marshall (B) A guidewire is inserted into the VOM through an over-the-wire balloon. An ablation catheter and Advisor HD grid^{TM} mapping catheter are in the left atrium. (C) An over-the-wire balloon is placed in the most distal site of the VOM. Cineangiography is performed to confirm that the over-the-wire balloon is correctly inserted in the VOM. The balloon inflation pressure is set at 4 atm to avoid leakage of the contrast medium. Following angiography, anhydrous ethanol of 2 mL was infused in the VOM over 2 min. (D) Immediately after the first infusion, the over-the-wire balloon was pulled back to the most proximal site of the VOM, 3 mL more ethanol was infused in the VOM over 2 min while inflating the balloon at 4 atm. (E) RF applications (30 W, 40 s) were first delivered in the endocardium of the MI line using a steerable introducer under LAA pacing. RF = radiofrequency, LAA = left atrial appendage, MI = mitral isthmus (F) If the MI line block was not fully achieved, additional RF applications (25 W, 30 s) were delivered in the CS. (G) If those extra applications failed to make a complete MI line, we approached the CS from the jugular vein to gain enough contact force.

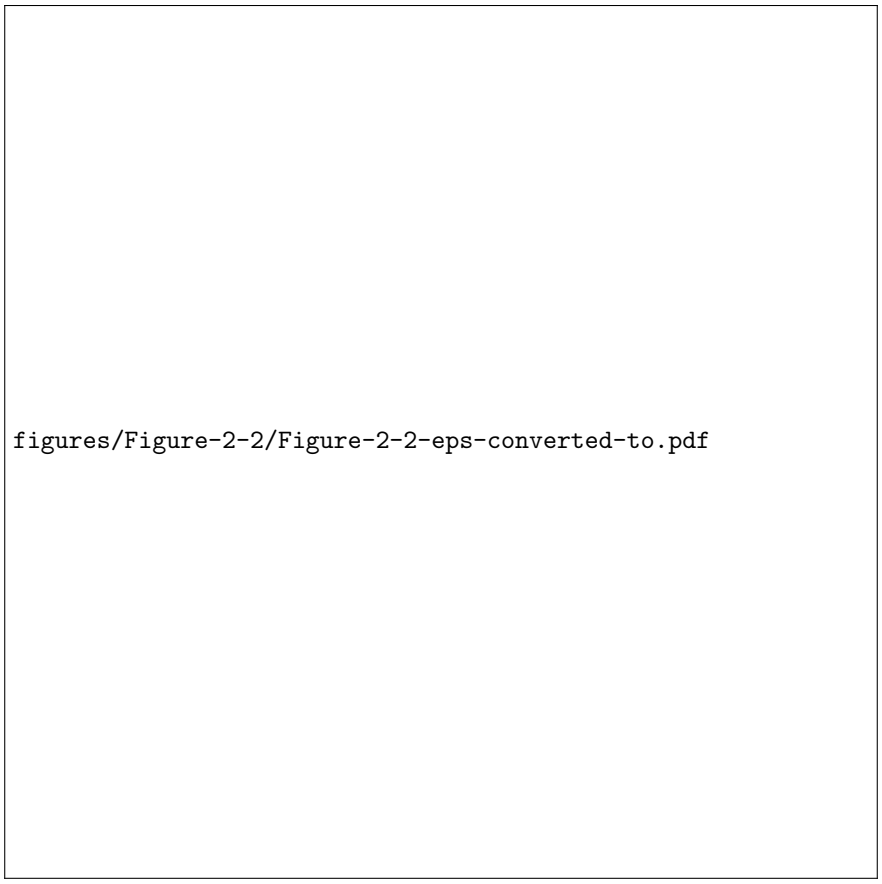
Figure 3. (A) The schema shows reconnection of both endocardium (red arrow) and epicardium (blue arrow). The electrogram reveals double and parallel potentials, which consist of endocardium (dull) and epicardium (spiky) potential, which were conducteda from the distal to the proximal site of the CS under LAA pacing. (B) The schema represents an endocardium-only reconnection. The dull potentials conducted from the distal to the proximal site were observed. Meanwhile, the spiky potentials were recognized in the proximal-to-distal sequence. Note that these two potentials were not discreated enough. (C) The schema represents an epicardium-only reconnection. The spiky potentials are recognized as the proximal-to-distal sequence. The dull potentials were recognized as the proximal-to-distal sequence, which are blocked at the site of CS 3-4.

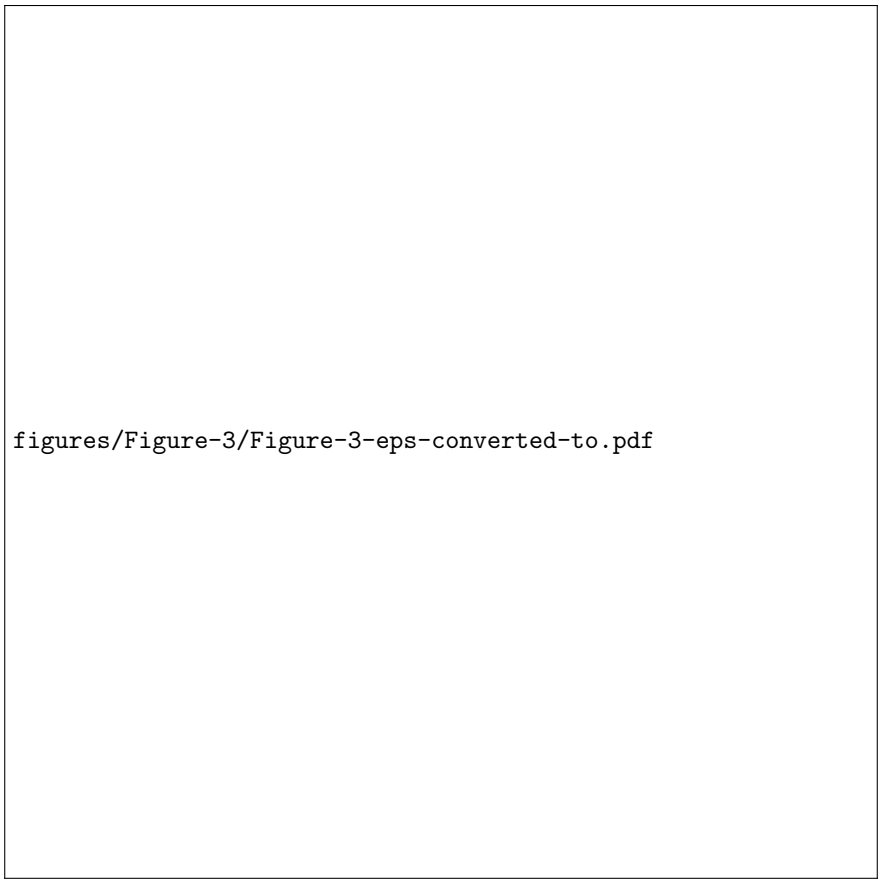
Figure 4. (A) A representative case (Patient 16 in the Supplementary data 1) of low-voltage area caused by EIVOM. Low-voltage and scarred area are set at <0.5 and <0.05 mV, respectively. EIVOM = ethanol infusion in the vein of Marshall, LIPV = left inferior pulmonary vein, LSPV = left superior pulmonary vein, MA = mitral annulus, RIPV = right inferior pulmonary vein, RSPV = right superior pulmonary vein (B) Point and box-whisker plots represent individual low-voltage areas of initial, just after EIVOM, and one hour after EIVOM in the 19 patients of the EIVOM/RF group. These were measured by two independent observers, excluding the authors. The height of the boxes corresponds to the interquartile range, and the horizontal lines on boxes represent median value.

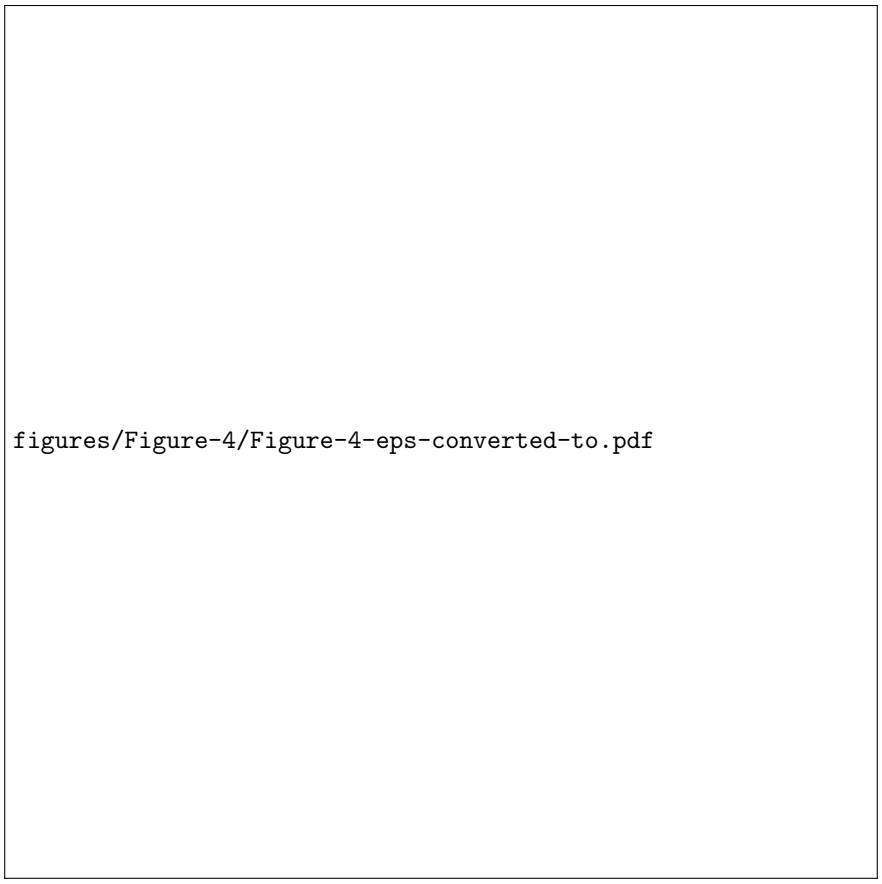
Figure 5. Cumulative AF- or AT-free survivals of the first and re-do ablation cases are shown. Dotted line represents a three-month blanking period after the procedure. AF = atrial fibrillation, AT = atrial tachycardia, EIVOM = ethanol infusion in the vein of Marshall, HR = hazard ratio, RF = radiofrequency

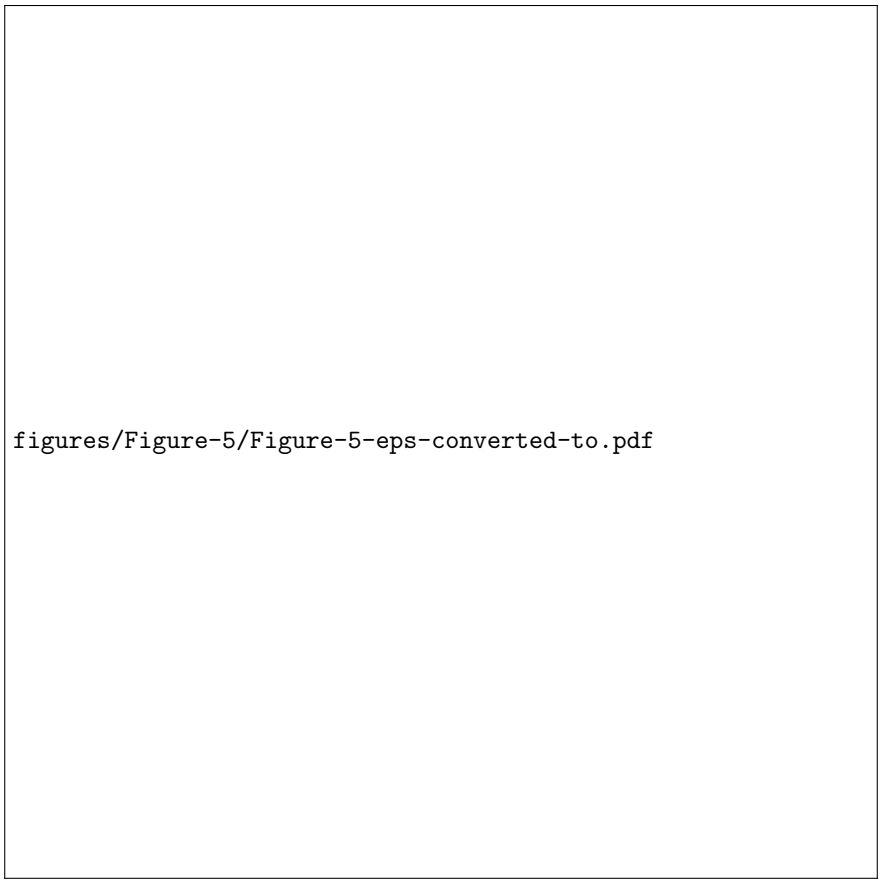












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