Characteristics and treatment of pericarditis after vein of Marshall Ethanol infusion for persistent atrial fibrillation

Yuyang Chen[1], Hao-bin Li[1], Dan-ying Guo[1], Yong Xie[1], rong lin[1], Yong-tong Chen[1], Bi-fang Mai[1], Jing Yang[1], Yuan Li[1], Jing-feng Wang[1], and Shuang-lun Xie[1]

[1]Sun Yat-Sen Memorial Hospital Department of Cardiology

January 14, 2023

Abstract

Background: The vein of Marshall ethanol infusion (VOM-EI) provides an opportunity to achieve bidirectional conduction block of mitral isthmus. However, this technique may induce traumatic pericarditis. There is a lack of research on which populations are prone to pericarditis after VOM-EI and how to treat it more effectively. Methods: This retrospective study included 77 consecutive patients who voluntarily underwent persistent atrial fibrillation radiofrequency ablation combined with VOM-EI. With the occurrence of postoperative pericarditis as the end point, the characteristics and risk factors of postoperative pericarditis were analyzed. The curative effect was evaluated by the symptom relief rate of pericarditis 48 hours after treatment. Results: 15 had postoperative pericarditis among the 77 patients, accounting for 19.5%. The hospital stay of the patients with pericarditis was longer than that without pericarditis (10.0 vs 8.0 days, $P = 0.045$). Of the 15 patients with postoperative pericarditis, 8 received colchicine. Among the patients treated with colchicine, the average treatment intensity was 1.04 mg/d, 7 patients were relieved within 48 hours, and the symptomatic remission rate was 87.5%. Among the remaining 7 patients who did not receive colchicine, only 2 patients had symptomatic remission. Compared with the group without colchicine, the duration of symptoms was significantly shorter (27.88 vs 51.93 hours, $P = 0.024$). In the multivariate logistic regression analysis, colchicine was the only effective method to relieve the 48 hours symptoms of postoperative pericarditis (OR =17.500, CI 1.223-250.4, $P = 0.035$). Conclusion: Postoperative pericarditis is one of the complications of VOM-EI, and colchicine may have a good short-term effect on it.

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in adults, and is also an important cause of stroke disability and cardiogenic mortality in recent years. In the European guidelines for the diagnosis and treatment of atrial fibrillation in 2020, catheter ablation has been elevated to class IIa indication for persistent atrial fibrillation with poor control of antiarrhythmic drugs (AADs)[1]. Perimitral flutter (PMF) around the mitral isthmus is one of the mechanisms of recurrence of atrial arrhythmias after atrial fibrillation ablation, accounting for 33%-60% of atrial arrhythmias[2-5]. However, the mitral isthmus usually has thick myocardium and is adjacent to the coronary artery circumflex branch. It is sometimes difficult to completely achieve transmural injury only by radiofrequency energy during endocardial ablation. In addition, for some PMFs connected with epicardium and endocardium, it sometimes seems powerless to rely on endocardial ablation alone.

The vein of Marshall (VOM) is located on the epicardial surface behind the mitral isthmus, between the coronary sinus and the left inferior pulmonary vein, which provides a golden anatomical opportunity for epicardial ablation of the mitral isthmus[6, 7]. It is a new technique to block mitral isthmus from epicardium by infusing ethanol into VOM. VENUS study showed that compared with catheter ablation alone, catheter ablation combined with VOM ethanol infusion (VOM-EI) significantly reduced the incidence of atrial fibrillation or atrial tachycardia at 6 and 12 months after AF radiofrequency ablation, while the incidence

of adverse events was not significantly different between the two groups [8]. This suggests that VOM-EI effectively improve the success rate of mitral isthmus block, and thus improve the success rate of catheter ablation for persistent atrial fibrillation.

However, VOM-EI may cause transmural necrosis of the myocardium in the proximal end of the left lower pulmonary vein and part of the posterior wall of the left atrium, and induce pericarditis similar to Dressler syndrome. At the same time, ethanol may cause local leakage of VOM and induce traumatic pericarditis, resulting in postoperative fever, chest pain, dyspnea and other discomfort [9]. For the treatment of pericarditis after VOM-EI, it is basically based on the treatment principles of non-infectious pericarditis in the 2015 ESC guidelines for the diagnosis and treatment of pericardial diseases, and non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or glucocorticoids are recommended[10]. NSAIDs are the first-line drugs for the treatment of pericarditis. However, for patients with AF after radiofrequency ablation, NSAIDs may increase the risk of postoperative gastric mucosal irritation, gastroesophageal reflux and atrial esophageal fistula. Glucocorticoids have strong anti-inflammatory effects, but the potential side effects are large, and they have now retreated to second-line treatment. Colchicine, as an adjunct drug of NSAIDs in the treatment of pericarditis, combined with NSAIDs can improve the remission rate of 1 week and reduce the recurrence rate of pericarditis. However, there is no clinical evidence on whether colchicine is effective for pericarditis after VOM-EI. This study analyzed the characteristics and treatment methods of postoperative pericarditis after VOM-EI, explored its risk factors and the best treatment methods, and provided a basis for further randomized controlled clinical research in this field in the future.

Methods

Study population

This study is a retrospective study, including 81 consecutive patients who voluntarily underwent AF/AFL radiofrequency ablation combined with VOM-EI in Sun Yat-sen Memorial Hospital of Sun Yat-sen University from July 2020 to July 2022. The inclusion criteria included: 1) age [?] 18 years and [?] 80 years; 2) definite diagnosis of atrial fibrillation or atrial flutter by ECG or Holter and at least one AADs intolerance; 3) agreed to receive radiofrequency ablation of atrial fibrillation or atrial flutter combined with VOM-EI and signed the informed consent. Exclusion criteria included: 1) left atrial thrombus or left atrial myxoma; 2) the diameter of left atrium in parasternal long axis section [?] 65 mm; 3) failure of ethanol infusion due to lack of VOM or inability to access VOM; 4) medication history of glucocorticoids, NSAIDs or colchicine within 2 weeks; 5) history of myocardial infarction, PCI operation and stroke within 3 months; 6) history of CABG or valve replacement within 6 months; 7) Severe liver and kidney function damage before operation; 8) Left ventricular ejection fraction <40% or uncontrolled heart failure; 9) history of abnormal coagulation or bleeding, and anticoagulant contraindications; 10) presence of thrombus, tumor or other conditions in the vessel wall hindering catheter intervention; 11) ethanol allergy. The study was approved by the institutional review board (IRB) of Sun Yat-sen Memorial Hospital and the approval number of IRB was SYSKY-2023-029-01.

Research design

All data were collected by two independent researchers. The data include: clinical status (such as body mass index[BMI], duration of AF, previous hyperuricemia, hypertension, stroke, diabetes, history of coronary heart disease, history of PCI or CABG surgery, smoking and drinking history, CHA2DS2-VASC score, HAS-BLED score, vital signs at admission), ECG, Holter, echocardiography, transesophageal echocardiography (TEE), blood sampling test results at admission, radiofrequency ablation method, status of postoperative pericarditis, treatment and length of hospitalization. For patients with postoperative pericarditis, the symptom remission rate at 48 hours after medication was taken as the evaluation index of the treatment effect, and the starting time, degree and remission time of chest pain, the remission degree, and the treatment method of alleviating symptoms (including glucocorticoids, NSAIDs, colchicine, antibiotics, proton pump inhibitor [PPI]) were recorded.

Echocardiographic evaluation

All enrolled patients underwent transthoracic two-dimensional echocardiography (Vivid 7, GE ultrasonic, USA) in the left supine position, and the images were obtained by 2.5-3.5 MHz sensors. Left atrial diameter (LAD) and left ventricular end diastolic diameter (LVEDd) were measured on the lateral long axis view, and LVEF was calculated by Simpson method. The examination steps of TEE were as follows: 1) patient took oral lidocaine gel for local anesthesia of the larynx and lay on the left side; 2) doctor applied coupling gel on the surface of the probe, gently delivered it to the patient's oropharynx, made the patient swallow and sent the probe into the esophagus; 3) doctor adjusted the depth and angle of the probe to obtain images of various sections of the heart, judged whether there was thrombus in the left atrium. Meanwhile, the left atrial appendage blood flow velocity was measured.

VOM-EI procedure

After obtaining the vascular access, the coronary sinus electrode was placed. After successful puncture of the atrial septum, under the guidance of the three-dimensional mapping system (Carto, BioSense Webster), a star-shaped magnetoelectric double positioning mapping catheter (Pentaray, BioSense Webster, Irvine, CA) was inserted to perform anatomical modeling and three-dimensional voltage mapping of the left atrium and pulmonary vein. The definition of scar was preset as local bipolar voltage <0.1 mV, and the color code of 0.1-0.5 mV was used to display the borderline low voltage. Pentaray were placed in the left atrial appendage, followed by VOM-EI. The 8.5F SL1 long sheath is used to enter the inferior vena cava through the femoral vein, and the JR3.5 or 4.0 coronary artery guiding catheter and PTCA wire were sent from the SL1 long sheath. The guiding catheter was guided into the coronary sinus under the support of the PTCA wire. Coronary sinus angiography showed the presence of VOM in RAO 30° . The VOM was a coronary sinus branch, located at the proximal end of the Vieussens valve, pointing backward and upward to the left atrium and pulmonary vein. Putting the guiding catheter directly to the VOM opening, and preassembled the OTW balloon (diameter: 2.0 ˜ 2.5 mm × 8˜20mm,Boston Scientific, Marlborough, MA) with PTCA wire in the central cavity into the guide catheter. The PTCA wire was pushed to the distal end of the VOM, followed by the OTW balloon, which completely crossed the guiding tube and entered the VOM opening. The balloon was inflated to 6 standard atmospheres, and contrast agent was injected at the tail end of the OTW balloon to clearly show the VOM at the distal end of the balloon, while there was no obvious contrast agent reflux, which confirmed that the balloon blocked the VOM well. Inject 3-4 ml of 95% ethanol within 2 minutes, wait for 5 minutes, and then inject another 3-4 ml of ethanol again. Then, the distal end of the OTW balloon was imaged, and the myocardial contrast agent in the VOM distribution area could be seen. The balloon was deflated, the VOM ethanol ablation system was withdrawn, and the three-dimensional voltage mapping of the left atrium was performed in a repeated manner to measure the scar after ethanol infusion (the area with bipolar voltage less than 0.1 mV). Then, the catheter radiofrequency ablation procedure was described below.

Catheter radiofrequency ablation procedure

Ablation was performed using a cold saline perfusion pressure ablation catheter (Smart-touch, BioSense Webster, Irvine, CA) under the guidance of a three-dimensional mapping system (Carto BioSense Webster). The basic strategy was circumpulmonary vein vestibular isolation, and the block line was at least 1cm away from the pulmonary vein orifice. The ablation catheter was electrically isolated from the peripheral pulmonary vein along the block line, and the Pentaray was placed in the ipsilateral pulmonary vein. When the circumferential pulmonary vein was electrically isolated, the pulmonary vein potential on the Pentaray on this side disappeared. After pulmonary vein isolation, whether to add more ablation sites according to the judgment of the operator. These necessary measures include isolation of the left atrium roof wall and mitral isthmus. If AF changes to atrial flutter before or during ablation of the mitral isthmus, activation mapping or entrainment mapping was required to determine the reentry loop. If there was atrial flutter in the tricuspid isthmus, ablation of the tricuspid isthmus was required. If the atrial fibrillation rhythm still existed after the ablation of the left atrial roof wall and mitral isthmus, the posterior wall isolation (Box isolation) and the anterior wall complex fragmentation potential ablation should be performed. If endocardial and VOM-EI still could not completely block the mitral isthmus, epicardial ablation of the corresponding mitral isthmus

in the coronary sinus should be performed. Finally, bidirectional conduction block in the mitral isthmus was examined.

Postoperative follow-up and endpoints

All patients underwent ECG and blood pressure monitoring after operation, and recorded temperature, respiration, heart rate and blood pressure. The onset time and degree of chest pain and shortness of breath were recorded. The degree of pain was determined by (Visual Analog Scale [VAS]). The basic method was to use a scale with a length of about 10cm. One side was marked with 10 scales, and the two ends were "0" and "10" respectively. "0" indicated no pain, and "10" indicated the most severe pain that was unbearable. The diagnosis of postoperative pericarditis was defined by at least two criteria as follows: 1) typical chest pain (severe and pleurisy, improved by sitting up and leaning forward); 2) pericardial friction or pericardial friction sound; 3) ECG suggested changes (extensive ST segment elevation or PR depression), and 4) new or worsening pericardial effusion. For patients with postoperative pericarditis, we took the 48 hours symptom remission rate after medication as the evaluation index of treatment effect, recorded the onset time, degree and remission time of symptoms, the remission degree, recorded the treatment method (including glucocorticoids, NSAIDs, colchicine, antibiotics, PPI, etc.) of remission symptoms, and the examination results of blood samples after medication.

Statistical analysis

Continuous data of normal distribution were expressed as mean +- standard deviation, continuous data of non-normal distribution were expressed as median (IQR), and dichotomous data were expressed as numbers and percentages. Independent sample t-test was used to compare the continuous data of normal distribution between the postoperative pericarditis group and the non-pericarditis group. Mann Whitney U test was used to compare the continuous data of non-normal distribution between the postoperative pericarditis group and the non-pericarditis group. Chi square was used for dichotomous variables (χ^2) Test or Fisher's exact test. In order to explore the predictive factors of within 48 hours symptom remission rate, a multivariate logistic regression model was constructed by positive stepwise method. The predictors ($P < 0.05$) that were significantly related to the 48 hours symptom remission rate in univariate analysis were included in the logistic model. All analyses were performed using PASW statistics for Windows version 22.0 (SPSS Inc, Illinois, Chicago). Statistics showed that there was a significant difference between the two sides ($P < 0.05$).

Results

Comparison of baseline characteristics between patients with and without pericarditis after VOM-EI

Among the 81 consecutive patients included, 4 patients met the exclusion criteria and were excluded from the cohort. Among them, 2 patients had thrombus in the left atrial appendage, 1 patient did not undergo VOM-EI because VOM was not found by angiography, and 1 patient took colchicine one week before operation. Finally, a total of 77 patients were included in the study (Figure 1). Among them, there were 15 cases of pericarditis after VOM-EI, accounting for 19.5% of the total included. Table 1 showed the comparison of baseline characteristics between patients with pericarditis after VOM-EI (n = 15) and those without pericarditis (n = 62). It can be seen that the hospital stay was longer than that of patients with pericarditis (10.0 days vs 8.0 days, $P = 0.045$). Multivariate logistic regression analysis did not show the risk factors of pericarditis after VOM-EI.

Baseline characteristics of patients with pericarditis after VOM-EI treated with or without colchicine.

Table 2 showed the baseline characteristics of patients with pericarditis after VOM-EI with or without colchicine. Of the 15 patients with pericarditis, 8 were treated with colchicine and the other 7 were not treated. Among the 8 patients treated with colchicine, the longest treatment time of colchicine was 10 days, the highest total treatment dose was 15mg, the shortest treatment time was 2 days, and the lowest total treatment dose was 1mg. The average treatment time of colchicine per person was 4.2 days, the average treatment dose was 4.4 mg, and the average treatment intensity was 1.04mg per day. 7 cases with colchicine group relieved within 48 hours, and the 48 hours remission rate was 87.5%. Among the 7 cases without

colchicine group, 2 patients had symptomatic remission within 48 hours, and the 48 hours remission rate was only 28.6%. As for the 72 hours remission rate, there was no statistical difference between the colchicine group and non-colchicine group (100% vs 85.7%, $P = 0.467$). The above showed that symptomatic treatment of pericarditis could generally relieve the symptoms of most cases within 72 hours, and application of colchicine could shorten the symptom relief time to 48 hours.

Compared with the non-colchicine group, the initial pain score (VAS scale) of the colchicine group was significantly higher (6.5 vs 5.0,$P = 0.044$), the duration of symptoms was significantly shorter (27.88 hours vs 51.93 hours, $P = 0.024$), and the change value of the decreased pain score $(^{V}AS score) after treatment was also significantly higher (5.0 vs 3.0, P = 0.030)$.

In terms of adverse reactions, one patient in the combined colchicine group stopped taking colchicine prematurely because he did not tolerate the side effects of diarrhea colchicine. The days of administration of colchicine in this case were 2 days, the total dose was 1mg, and the incidence of adverse events was 12.5%. There was one drug-related adverse reaction in the non-colchicine group. There was no significant difference in the incidence of adverse reactions between the two groups (12.5% vs 14.1%, $P = 1.000$).

Combined with colchicine was an important measure to relieve pericarditis after VOM-EI

Among the 15 cases of pericarditis, 9 cases were relieved within 48 hours, and 6 cases were not significantly relieved. Among them, the number of 48 hours symptomatic remission cases in the combined colchicine group was 7, and the remission rate was 87.5%. The number of 48 hours symptomatic remission cases in the non-combined colchicine group was 2, and the remission rate was 28.6%. The results of univariate and multivariate logistic regression analysis are shown in Table 3. Among them, Model 1 only contains the type of medication, and Model 2 contains the type of medication and age. In the multivariate logistic regression analysis, colchicine was the only effective method to relieve the 48 hours symptoms of pericarditis (OR =17.500,CI 1.223-250.4, $P = 0.035$).

Discussion

The emergence of VOM-EI has effectively reduced the incidence of atrial arrhythmia after radiofrequency ablation of persistent atrial fibrillation, and the safety indicators of VOM-EI have also received more and more attention. Pericardial effusion and pericarditis are common complications. However, there are few studies on pericarditis after VOM-EI. The results of this study showed that although there was no clear risk factor for pericarditis after VOM-EI, the proportion of pericarditis after VOM-EI was not low. Colchicine was an effective method to treat pericarditis after VOM-EI in persistent atrial fibrillation. The main side effect of colchicine was gastrointestinal reaction, but the incidence was relatively low, and most patients could tolerate it.

Anna Lam reported that 16% of patients had pericardial effusion and 5% had mild pericarditis after VOM-EI[11]. Takamitsu Takagi also reported that the proportion of pericardial effusion on the first day after VOM-EI was 3.4% [12]. However, it was not clear whether pericardial effusion was related to pericarditis in both studies. This study was a retrospective study, and the proportion of pericarditis observed was 19.5%, which was higher than the two studies. The reason might be that the total of ethanol was more used in our study. The average amount of ethanol in our center was 6.8ml, which was more than the total amount of median 4ml ethanol in two above studies and VENUS study. It was not hard to image that the more ethanol was used, the wider the destruction range of mitral isthmus, and the more likely postoperative pericarditis will occur. Until now, no systemic effects were detected at the doses of ethanol used tested. Therefore, the proportion of pericarditis after VOM-EI was uncertain in different studies.

The principle of ethanol infusion is that ethanol damages the capillary network distributed at the distal end of the VOM through hypertonic action, and permeates and diffuses to the nerve, fiber bundle and atrial muscle around the VOM, so as to damage the epicardial electrical connection of the mitral isthmus. The mechanism of pericarditis after VOM-EI is the injury effect. Ethanol permeates the epicardium and pericardium, causing aseptic necrosis of epicardium and inflammation of visceral pericardium, thus inducing

pericarditis. The diagnosis of pericarditis induced by VOM-EI is still based on the diagnostic criteria of the 2015 ESC guidelines for the diagnosis and treatment of pericardial diseases, including chest pain, pericardial friction, ECG changes and pericardial effusion. At least two of the above four criteria are met[10]. In addition, some postoperative indicators can reflect the severity of pericarditis after VOM-EI, such as the duration of postoperative fever and chest pain, leukocyte and hsCRP levels, myocardial damage markers, left atrial systolic function and pericardial effusion change[13]. Some characteristics of clinical manifestations, such as body temperature > 38 ° C, subacute course of disease, massive effusion or tamponade, failure of NSAIDs treatment, etc., which indicates poor prognosis and be easy to become recurrent pericarditis.

The 2015 ESC guidelines for the diagnosis and treatment of pericardial diseases recommended the use of aspirin or NSAIDs as first-line treatment for acute pericarditis. However, it was mainly empirical evidence that supports this therapy[10]. In fact, as of 2014, there were no randomized controlled studies evaluating the suitability of NSAIDs for acute pericarditis. Langee insisted that observational studies believe that the effective rate of NSAIDs in the treatment of acute pericarditis was 85%-90%, and different NSAIDs (aspirin, ibuprofen and indomethacin) had similar curative effects[14]. Evidence of NSAIDs could be seen in the systematic review of clinical trials of drug treatment of acute pericarditis by Lotrionte et al[15]. In this review, although included trials evaluated the benefits of colchicine, corticosteroids, and statins, all trials used NSAIDs as their background therapy. The review concluded that NSAIDs appeared to be effective and consistent with accepted pathophysiology. Although there was a lack of scientific literature supporting the use of NSAIDs in acute pericarditis, they were widely used.

In addition, there was considerable evidence to support the use of colchicine as an adjunct to NSAIDs, which could improve the remission rate by 1 week compared with NSAIDs alone, and reduce the recurrence rate of acute pericarditis[16]. The symptom relief rate after 72 hours in the combined colchicine group was also better than that in the non-combined group (36.7 vs 11.7%; $P = 0.003$)[16]. Snyder believed that colchicine plus NSAIDs could reduce symptoms, reduce recurrence rate, and was well tolerated[17]. This seemed to be supported by a randomized, double-blind, controlled trial comparing the effects of colchicine combined with NSAIDs and NSAIDs combined with placebo. The study found that the incidence of recurrent pericarditis was 16.7% in the colchicine group and 37.5% in the placebo group[18].

This study indeed observed that the patients with pericarditis after VOM-EI in the colchicine group had the best effect of relieving chest pain within 48 hours after operation, and the duration of pericarditis symptoms was the shortest. Colchicine was an important measure to relieve acute pericarditis after VOM-EI. This was consistent with the results of Snyder's study[17]. This suggested that colchicine had a very good effect on pericarditis after VOM-EI. Pericarditis after VOM-EI was the same as pericarditis caused by inflammation. Colchicine and NSAIDs had a synergistic anti-inflammatory mechanism. Some studies found that colchicine could inhibit the adhesion, migration and aggregation of neutrophils, and played a vital role in reducing the inflammatory response[19]. Colchicine mainly interfered with leukocyte migration and phagocytosis by inhibiting tubulin polymerization. At low concentrations, colchicine could change the distribution of E-selectin on the surface of endothelial cells, thus clearing the adhesion between neutrophils. At higher concentrations, colchicine induced the shedding of L-selectin, an adhesion molecule of neutrophils, and further inhibited the aggregation of neutrophils in inflammatory tissue[20].

Limitations

Although this study took the lead in finding that colchicine has an effective effect on alleviating pericarditis after VOM-EI, there were still shortcomings in this study: 1) this study was a single center retrospective study with a small number of cases and a low level of evidence; 2) Most patients with postoperative pericarditis did not collect all objective indicators of inflammation, such as white blood cell count, hsCRP, troponin I or T, CK-MB level, left atrial systolic function and pericardial effusion changes. It was not comprehensive and accurate to evaluate the therapeutic effect of pericarditis only by the degree of chest pain relief. Prospective multicenter randomized controlled studies can be designed in the future to further expand the sample size and increase objective evaluation indicators to make the conclusions more convincing.

Conclusion

Postoperative pericarditis is one of the complications of VOM-EI for persistent atrial fibrillation. Colchicine can quickly relieve the symptoms of pericarditis caused by VOM-EI, shorten the length of hospital stay without increase adverse reaction.

Acknowledgments

This study was supported by the National Natural Science Foundation Project to Shuang-lun Xie (No. 82070412) and the City-school Joint Funding Project of Guangzhou to Yu-yang Chen (No. 202102010219), respectively.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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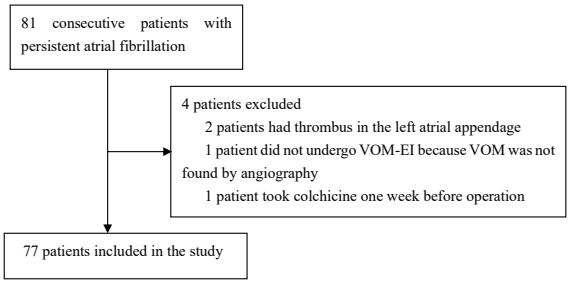

Figure 1 Flow chart of patients selection.

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