Int J Clin Exp Med 2018;11(10):11134-11140
www.ijcem.com /ISSN:1940-5901/IJCEM0073272

Original Article

Oral amiodarone in blank period affects MMP-9 and TIMP-1 level in post-ablation paroxymal atrial fibrillation patients

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Received May 23, 2017; Accepted May 24, 2018; Epub October 15, 2018; Published October 30, 2018

Abstract: Objective: This study is to investigate whether post-ablation oral amiodarone in blank period could affect levels of MMP-9/TIMP-1 and long-term recurrence in patients with paroxymal atrial fibrillation (PAF). Methods: A total of 100 patients with PAF undertaken pulmonary vein isolation (PVI) and were divided into two groups (50 in each group): group A received oral amiodarone therapy for three months after catheter ablation, and group B were not given amiodarone post-ablation. Atrial arrhythmic data including atrial premature, atrial tachycardia, atrial flutter, and atrial fibrillation (AF) were collected by routine electrocardiogram (ECG) and 24 h-Holter every month during 1-year post-operation follow-ups. MMP-9 and TIMP-1 levels were measured before ablation and at 1, 3, 6, 9, and 12 months post-ablation. Results: During the blank period, the recurrence rate of AF and atrial premature was statistically lower in group A than in group B (both $P < 0.05$), but no difference was found in the recurrence rate of atrial flutter and atrial tachycardia (both $P > 0.05$). One-year AF ablation success rate of group A and B were at the same level ($P > 0.05$). MMP-9 level significantly decreased in both successful ablation sub-groups, while TIMP-1 level increased simultaneously. PVI was prone to affect MMP-9 and TIMP-1 levels, however, there were no statistically differences between two groups. Conclusion: Oral amiodarone could reduce the recurrence rate of AF in blank period. MMP-9 in both successful ablation sub-groups was significantly lower than that of recurrence group during post-ablation follow-up, while TIMP-1 in successful ablation sub-groups was significantly higher than that in the recurrence group.

Keywords: Paroxymal atrial fibrillation, catheter ablation, amiodarone, MMP-9, TIMP-1

Introduction

Pulmonary vein isolation (PVI) has been widely accepted as a standard treatment for atrial fibrillation (AF), however, the recurrence rate is still nearly 30% in paroxysmal AF and 50% in persistent AF [1]. It is illustrated that left atrial reverse remodeling increases the rate of AF recurrence, and this effect is related to inflammation and collagen turnover [2]. Increasing evidence shows that left atrial reverse remodeling, as an independent predictor, might occur during the mid- and long-term follow-up periods after successful AF ablation [3].

Extracellular matrix (ECM), an important component of cardiac myocyte structure, consists of collagen fibers, proteoglycan, and bioactive signaling molecules. ECM transmits messages between cells, coordinates the dilatation and contraction, maintains the collocation of myocyte and cardiac myofiber, and restricts the overstretching of myocytes [4]. Recently, the progression of atrial remodeling has been demonstrated to be independently associated with ECM turnover [5]. Matrix metalloproteinase (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) are important enzymes that regulate ECM metabolism and play significant roles in atrial remodeling [4]. Matrix metallopeptidase 9 (MMP-9) is an enzyme that degrades the extracellular matrix and its activity is moderated by TIMP metallopeptidase inhibitor 1 (TIMP-1) [6]. Rachel R *et al.* found that elevated levels of MMP-9 are independently associated with increased risk of AF [7].

Table 1. Basic characteristics in patients

		Group A	Group B	*P* value
Patients	Age	58.3 ± 10.8	54.8 ± 10.9	0.108
	Female/Male	27/23	29/21	0.687
	BMI (kg/m^2)	29.0 ± 3.0	27.6 ± 3.1	0.087
	Duration (month)	5.7 ± 3.1	5.4 ± 3.2	0.612
	Diabetes	7 (14%)	8 (16%)	0.779
	HTN	15 (30%)	13 (26%)	0.656
	Hyperlipidemia	18 (36%)	20 (40%)	0.680
	Smoking	14 (28%)	16 (32%)	0.663
	Alcohol	13 (26%)	10 (20%)	0.476
Echo Measure	EF (%)	63.0 ± 10.2	65.3 ± 9.8	0.245
	LA (mm)	41.3 ± 5.3	39.6 ± 4.3	0.073
	LAV (ml/m^2)	38.8 ± 9.0	38.3 ± 9.5	0.799

BMI, body mass index, kg/m^2; HTN, hypertension; EF, ejection fraction, %; LA, left atrial, mm; LAV, LA volume, ml/m^2.

Table 2. Atrial Arrythmias record in blank period

	Group A	Group B	*P* value
Atrial fibrillation	6 (12%)	14 (28%)	0.046*
Atrial flutter	5 (10%)	8 (16%)	0.372
Atrial tachycardia	2 (4%)	3 (6%)	1.000
Atrial premature	12 (24%)	22 (44%)	0.035*

Note: *P < 0.05.

Clinically, patients who receive PVI are suggested to take amiodarone for three months (blank period), which has became a standard regime to reduce short-term atrial arrhythmias after PVI. However, whether oral amiodarone in blank period could reduce long-term AF recurrence and whether this regime could affect atrial remodeling as well as levels of MMP-9/TIMP-1, remain unknown so far. By measuring blood level of MMP-9 and TIMP-1 in paroxysmal AF patients receiving PVI, we aimed to reveal whether oral amiodarone in blank period could affect MMP-9/TIMP-1 level, which might affect atrial remodeling in AF.

Materials and methods

Study patients

A total of 100 consecutive patients (44 men and 56 women, mean age 57.2 ± 18.3 years) with paroxysmal AF treated at The First Affiliated Hospital, College of Medicine, Zhejiang University from January 2012 to May 2014 were enrolled in this retrospective study. All cases were divided into two groups (50 in each group). Patients in group A received oral amiodarone therapy for three months after catheter ablation while patients in group B were not given amiodarone post-ablation. All patients received PVI smoothly.

The inclusion criteria of subjects were patients aged between 18 and 70 years and received symptomatic paroxysmal AF refractory to anti-arrhythmic drugs. Paroxysmal AF is defined as AF lasting less than 7 days. The exclusion criteria were as follows: thrombocytopenia (platelet < 80 × 10^9/L); contraindication to anti-coagulation drugs (warfarin/heparin); the diameter of left atria ≥ 55 mm; severe heart diseases (moderate to severe mitral regurgitation/severe valvular heart diseases/dilated cardiomyopathy/hypertrophic cardiomyopathy); abnormal thyroid function; severe liver or renal dysfunction (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3 times of upper limits of normal, serum creatinine (SCr) > 3.5 mg/dl or creatinine clearance (CCr)- < 30 ml/min); a history of surgery in the last 3 months before ablation, and previous ablation procedures; pregnant women; and expectation of life less than 12 months.

The study protocol was approved by the local ethics committee of The First Affiliated Hospital, College of Medicine, Zhejiang University and all patients had signed the informed consents.

Blood sampling and echocardiography

Baseline blood samples were collected from the femoral vein and transesophageal echocardiography (TEE) was performed to exclude left appendage thrombosis before the ablation. All cases underwent echocardiographic examination before the ablation and 12-month post-ablation with ACUSON Sequoia C256 echocardiography system (Siemens Medical Solutions USA, Inc., Malvern, PA). Echocardiographic data included ejection fraction (EF) and left atrial diameter (LAD). Left atrial volume (LAV) was evaluated by biplane Simpson's method, and

Table 3. One-year atrial fibrillation ablation success rate

Group	Num	Recurrence num	Success rate (%)	P
Group A	50	7	86.0	0.779
Group B	50	8	84.0	

Table 4. MMP-9 and TIMP-1 levels in group A and group B during 3 months' blank period

		Group A	Group B	*P* value
MMP-9 (ng/ml)	Pre	309.2 ± 29.8	299.3 ± 27.1	0.896[@]
	1 month	300.6 ± 21.4	307.0 ± 28.9	0.731[&]
	3 month	299.1 ± 23.3	305.7 ± 28.7	0.051[%]
TIMP-1 (ng/ml)	Pre	108.4 ± 13.5	107.7 ± 11.0	0.114[@]
	1 month	112.0 ± 12.2	107.5 ± 13.0	0.883[&]
	3 month	109.7 ± 17.3	114.3 ± 12.7	0.056[%]

MMP-9, Matrix metallopeptidase 9, ng/ml; TIMP-1, metallopeptidase inhibitor 1, ng/ml. [@]*P* value is calculated upon time main effect; [&]*P* value is calculated upon grouping main effect; [%]*P* value is calculated upon interaction effect.

the left ventricular EF was assessed by means of M-mode echocardiography. Measurements from three consecutive beats were averaged.

Blood samples were obtained by a peripheral venipuncture and were centrifuged at 3,200 g for 10 min at approximately 4°C within an hour of collection. The serum was separated into aliquots and stored at -80°C until personnel blinded to the patients' clinical information performed the analysis. Serum MMP-9 and TIMP-9 levels were determined using commercial standardized *in vitro* enzyme-linked immunosorbent assay (ELISA) methods according to the manufacturer's instructions (RayBiotech INC, Atlanta, Georgia, USA). Blood samples for MMP-9 and TIMP-1 measurements were obtained before the ablation and at 1-month, 3-month, 6-month, 9-month, 12-month post-ablation, respectively.

Ablation procedure

PVI was performed according to the following standard criteria: A 6F decapolar catheter (Diag, St. Jude Medical, USA) was inserted into the coronary sinus (CS) via the left subclavian vein; A 6 Fr quadripolar catheter (Diag, St. Jude Medical, USA) was positioned in the right ventricle via the right femoral vein; Two 8 Fr 65vm-long sheaths (SL1, St. Jude Medical, USA) were advanced to the left atrium through standard transseptal punctures; After the transseptal punctures, intravenous heparin was administered to maintain an activated clotting time of 250-300 seconds; Angiogram of PV and LA were then performed in the left anterior projection 45° and the right anterior projection 30°; A deflectable quadripolar open irrigated catheter (Thermo-cool, Biosense Webster, St. Jude Medical, USA) was inserted into the LA for mapping and ablation; Intra-cardiac electrograms were recorded using a digital electrophysiological recording system (Prucka CariodLab, General Electric Health Care System Inc., USA); After catheter placement, 3D anatomical shell of the LA and PV were constructed using the circular mapping system (Ensite-NavX, St. Jude Medical); PV ostia were added on the map as guided by the angiography; Irrigated radiofrequency energy with a flow rate of 17-30 mL/min was delivered at the targeting ablation sites; The maximum temperature was set to 45°C and the maximum power was 35 W.

The circular mapping catheter was positioned sequentially within each of the PV antra as guided by the 3D electro-anatomical map and angiogram to record PV potential. Circumferential radiofrequency applications were then delivered outside the PV ostia to electrically isolate PV from the LA. The endpoint of PVAI isolation was the complete disappearance of PV potentials or dissociated PV potentials with LA electrograms.

Post-ablation follow-up

After ablation procedure, all patients received subcutaneous injection of low-molecular weight heparin for 3 days and continued anticoagulation with warfarin for at least 3 months. Blank period was defined as the first three months after AF ablation.

All patients received surface ECG monthly post-operation. Twenty four-hour Holter recording was performed every 3-month for the presence of arrhythmias related symptoms. Atrial arrhythmic data including atrial premature, atrial tachycardia, atrial flutter, and AF were recorded. Ablation recurrence was defined as any atrial arrhythmic events (atrial tachycardia,

Table 5. Comparison of MMP-9 levels in the group during post-ablation follow-up

	Group A			Group B		
	Success (n = 43)	Recurrence (n = 7)	P	Success (n = 42)	Recurrence (n = 8)	P
Pre	305.4 ± 29.4	332.4 ± 21.8	0.024	295.7 ± 27.5	318.7 ± 14.0	0.026
1 month	298.0 ± 20.5	316.4 ± 21.1	0.034	302.8 ± 28.9	328.8 ± 17.8	0.018
3 month	296.0 ± 23.1	318.7 ± 13.8	0.015	301.7 ± 28.3	327.0 ± 21.5	0.021
6 month	299.0 ± 24.3	320.7 ± 12.0	0.025	301.8 ± 20.6	318.6 ± 8.9	0.029
9 month	304.6 ± 23.3	327.5 ± 20.4	0.018	294.0 ± 25.2	319.5 ± 24.6	0.011
12 month	302.0 ± 18.2	325.0 ± 10.3	0.002	299.5 ± 21.5	321.5 ± 27.3	0.014

Table 6. Comparison of TIMP-1 levels in the group during post-ablation follow-up

	Group A			Group B		
	Success (n = 43)	Recurrence (n = 7)	P	Success (n = 42)	Recurrence (n = 8)	P
Pre	110.3 ± 13.1	97.1 ± 10.8	0.015	109.1 ± 10.2	100.2 ± 12.5	0.032
1 month	113.5 ± 12.2	102.7 ± 7.4	0.028	109.1 ± 12.7	99.1 ± 11.7	0.046
3 month	111.9 ± 17.3	96.3 ± 9.7	0.025	115.9 ± 12.5	105.7 ± 10.5	0.035
6 month	114.1 ± 16.2	98.0 ± 16.7	0.019	110.1 ± 14.9	97.4 ± 11.5	0.015
9 month	110.3 ± 14.6	95.3 ± 18.4	0.019	114.5 ± 10.6	106.0 ± 8.0	0.036
12 month	113.1 ± 16.1	97.7 ± 15.0	0.022	114.3 ± 13.7	102.4 ± 8.3	0.023

atrial flutter, AF) persisting for more than 30 seconds.

Statistical analysis

Parametric data were expressed as the means ± standard deviation (SD). Student's unpaired test and the chi-square test were used to compare differences across the groups. The repeated measurement data were compared using repeated measurement ANOVA. The relationship among the parameters was investigated by Pearson's correlation coefficient test. $P < 0.05$ was taken as statistically significant difference.

Results

Patient characteristics and ablation outcomes

A total of 100 consecutive patients with paroxysmal AF were enrolled in our study (Supplementary Data). The patients' clinical characteristics and echocardiography variables are shown in **Table 1**. No statistical difference was found in basic characteristics. Pre-ablation echocardiography measurements in two groups were comparable (EF 63.0 ± 10.5% vs 65.3 ± 9.4%, $P > 0.05$, LA 41.3 ± 5.6 mm vs 39.3 ± 6.1 mm, $P > 0.05$, LAV 38.9 ± 10.0 ml/m^2 vs 38.3 ± 12.7 ml/m^2, $P > 0.05$). The results showed that the grouping was reasonable.

Arrythmias record in blank period and 1-year ablation success rate

To analyze the influence of oral amiodarone on the atrial fibrillation during blank period, the incidence of AF, atrial premature, atrial flutter, and atrial tachycardia were evaluated; and 1-year AF ablation success rates were compared in two groups. As shown in **Table 2**, the incidence of AF and atrial premature in blank period was statistically lower in group A than that of group B (AF 14% vs 26%, $P < 0.05$; atrial premature 28% vs 44%, $P < 0.05$). No difference was found in the incidence of atrial flutter and atrial tachycardia (atrial flutter 10% vs 16%, $P > 0.05$; atrial tachycardia 4% vs 6%, $P > 0.05$; **Table 2**). Moreover, 1-year AF ablation success rates were similar (86.0% vs 84.0%, $P > 0.05$; **Table 3**). The results argued that oral amiodarone during blank period could reduce the recurrence rate of AF and atrial premature in blank period.

Follow-up blood sampling and echocardiographic study

In order to analyze the level of MMP-9 and TIMP-1, blood samples were obtained and echocardiographic was studied before the ablation and at 1-month, 3-month, 6-month, 9-month, and 12-month post-ablation, respectively. The results indicated that patients in

Table 7. Comparison of MMP-9 and TIMP-1 levels at different follow-up times

		Pre	1 month	3 month	6 month	9 month	12 month	P
Group A	MMP-9	305.4 ± 29.4	298.0 ± 20.5	296.0 ± 23.1	299.0 ± 24.3	304.6 ± 23.3	302.0 ± 18.2	0.345
	TIMP-1	110.3 ± 13.1	113.5 ± 12.2	111.9 ± 17.3	114.1 ± 16.2	110.3 ± 14.6	113.1 ± 16.1	0.766
Group B	MMP-9	295.7 ± 27.5	302.8 ± 28.9	301.7 ± 28.3	301.8 ± 20.6	294.0 ± 25.2	299.5 ± 21.5	0.543
	TIMP-1	109.1 ± 10.2	109.1 ± 12.7	115.9 ± 12.5	110.1 ± 14.9	114.5 ± 10.6	114.3 ± 13.7	0.051

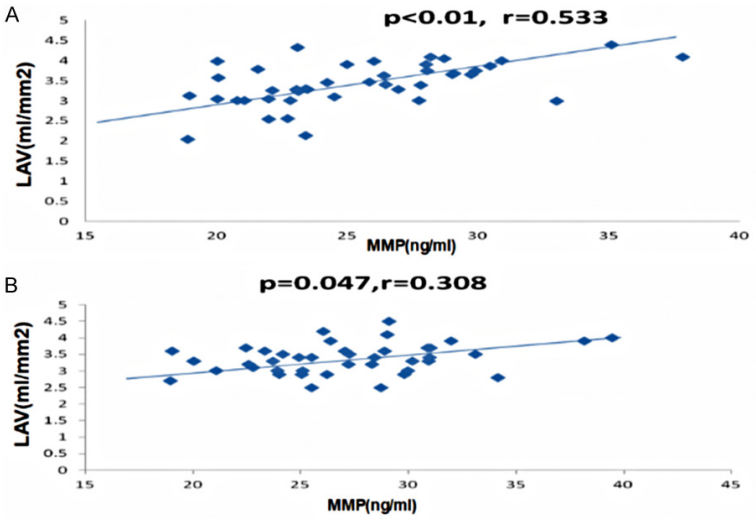

Figure 1. The correlation analysis between MMP-9 and LAV at 12-month after PVI by Pearson's test. Pearson's test of subgroup analysis in group (A); P < 0.01, r = 0.533, and P = 0.047, r = 0.308 in group (B).

group A and B had similar levels of MMP-9 and TIMP-1 before ablation (P > 0.05), and no difference was found in MMP-9 and TIMP-1 levels in three months' blank period between two groups (**Table 4**). The level of MMP-9 in both successful ablation sub-groups was significantly lower than that of recurrence group during post-ablation follow-up (**Table 5**), while TIMP-1 level in successful ablation sub-groups was significantly higher than that in the recurrence group (**Table 6**). In each successful subgroup, the monthly changes of MMP-9 and TIMP-1 were not statistically significant (**Table 7**). Correlation analyses about the MMP-9 level and LAV at 12-month after PVI showed that MMP-9 had a positive correlation with LAV in both ablation sub-groups (group A: *P* < 0.01, r = 0.533, group B: *P* = 0.047, r = 0.308; **Figure 1**).

Discussion

In this study, oral amiodarone in blank period could reduce some atrial arrythmias (AF and atrial premature), but this regime did not affect long-term AF recurrence or MMP-9 and TIMP-1 levels during 1-year follow up in subjected PAF patients. Further correlation analysis showed that MMP-9 level was positively linked to LAV. The main purpose of the study was to characterize the first-year changes in the biomarkers after ablation and first-year ablation success rate.

The recurrence rate of atrial arrhythmias is higher in three months after PVI, which is named "blank period". Routinely oral anti-arrythmia drugs (AAD) are used in this period to prevent and reduce atrial arrhythmias. Amiodarone is one of AADs which could prevent arrhythmias. Shinakawa *et al.* [8]. found that amiodarone could decrease AF recurrence post-PVI. Takashi *et al.* reported that amiodarone could prevent the recurrence of AF [9]. However, the Antiarrhythmics After Ablation of Atrial Fibrillation study (5A study) has shown that oral AAD for 6 weeks could not reduce AF late recurrence although this could affect AF early re-happen rate [10]. Recently Kazuaki *et al.* reported that short-term application of AAD (including amiodarone) for 90 days following AF ablation just reduced the incidence of recurrent atrial tachyarrhythmias during the treatment period, which did not lead to improved clinical outcomes at the later phase [11]. In this study, our results showed that amiodarone in blank period could not reduce long-term AF recurrence.

Previous research found that elevated levels of MMP-9 are independently associated with an increased risk of AF [7]. It is revealed that during the progression of idiopathic AF, MMP-9 levels gradually increased from paroxysmal AF through persistent AF to permanent AF [12]. Further study demonstrated that increased

expression of MMP-9 might contribute to atrial structural remodeling and atrial dilatation during AF [13]. Additionally, a significant down-regulation of MMP-9 was associated with a greater reduction in the left atrial size [14]. The relationship between MMP-9 and LA volume was confirmed through correlation analysis in this study. However, different TIMP-1 level's change was observed in different studies. Several studies found TIMP levels did not significantly change between patients with AF and SR [13, 15-17], while in another study, lower TIMP-1 levels were observed in permanent AF subjects than those with paroxysmal AF or SR in Kalogeropoulos' study [18]. No further study observed that TIMP-1 level changed after PVI. In this study, compared with recurrence group, MMP-9 decreased in successful subgroup and had a definite positive correlation with LAV, while TIMP-1 increased statistically in these PVI successful cases.

Some previous studies reported that amiodarone could reduce LA diameter/atrial pressure extension of atrial wall [19, 20]. Further research in Shinakawa's study [8] found that amiodarone could reduce LA diameter and LAA. They also found that amiodarone was effective not only in preventing the development of atrial remodeling but also in reversing atrial remodeling established by rapid atrial pacing [8]. While in this study, short-term use of amiodarone for 90 days post PVI could not affect the MMP-9 and TIMP-1 level during 1-year follow up, which gave a clue that amiodarone could not affect left atrial remodeling (especially construct remodeling). However, MMP-9 and TIMP-1 level were tested in blood samples but not myocardial tissue. Further study should be focused on MMP-9 and TIMP-1 changes in myocardial tissue of animal model or human heart.

In summary, the data suggested that oral amiodarone could reduce the recurrence rate of AF in blank period, while it could not affect long-term recurrence rate of PVI and MMP-9/TIMP-1 levels. The level of MMP-9 in both successful ablation sub-groups was significantly lower than that of recurrence group during post-ablation follow-up, whereas TIMP-1 level in successful ablation sub-groups was significantly higher than that in the recurrence group.

Acknowledgements

This study was supported by The Nature Science Foundation of Zhejiang Province (grant nos. LY17H020006).

Disclosure of conflict of interest

None.

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