

## Original Article

# Impact of amiodarone on cardiac structural function and MMP-2 and TIMP-2 levels in atrial fibrillation radiofrequency ablation

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**Abstract:** Objective: The aim of this study was to determine the mechanisms of action of amiodarone on cardiac structure and function and on levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-2 (TIMP-2) after radiofrequency ablation of atrial fibrillation (AF). Methods: Eighty-six patients with AF, treated by radiofrequency ablation, were randomized into the experimental group (n=43) and control group (n=43). The experimental group received amiodarone hydrochloride tablets after the operation, while the control group did not receive any antiarrhythmic drugs. Electrocardiograms and echocardiography were used to determine the number of AF, duration of AF, left atrial end-diastolic diameter, left atrial end-systolic diameter, as well as left ventricular ejection fraction (LVEF), before the operation and 6 months after the operation. Serum levels of MMP-2 and TIMP-2 were measured by ELISA and qRT-PCR, respectively, before and 6 months after the operation. Relevant data were analyzed by statistics. Results: Six months after the operation, the number and duration of AF, left atrial end-diastolic diameter, and left atrial end-systolic diameter decreased significantly. LVEF increased significantly, compared to pre-operation values in both control and experimental groups (all  $P < 0.05$ ). Furthermore, the number and duration of AF, left atrial end-diastolic diameter, and left atrial end-systolic diameter were significantly lower. LVEF was significantly higher in the experimental group 6 months after the operation, compared to those in the control group, with statistical significance (all  $P < 0.05$ ). Relevant data were analyzed by statistics. MMP-2 messenger ribonucleic acid and protein levels in serum decreased significantly, while TIMP-2 mRNA and protein levels increased significantly 6 months after the operation, in both groups, compared to pre-operation levels (all  $P < 0.05$ ). The experimental group had significantly lower MMP-2 mRNA and protein levels in serum and significantly higher TIMP-2 mRNA and protein levels, compared to the control group (all  $P < 0.05$ ), 6 months after the operation. Conclusion: After AF radiofrequency ablation, amiodarone can protect cardiac structure and function, reduce MMP-2 levels, and increase TIMP-2 levels.

**Keywords:** Atrial fibrillation radiofrequency ablation, amiodarone, the heart, matrix metalloproteinase-2, tissue inhibitor of metalloproteinase-2

## Introduction

Atrial fibrillation (AF) is a kind of arrhythmia characterized by fainting, fatigue, palpitations, and chest pain. Some patients, however, may have no specific symptoms [1, 2]. In recent years, epidemiological surveys have shown that the total prevalence rate of AF, worldwide, was 0.73%, while the clinical incidence rate in China was slightly higher (0.77%) [3]. Radiofrequency ablation of AF can improve symptoms and repair the structure of the left atrium [4]. However, it is still associated with a high recurrence rate after the operation. About one third of the AF patients that receive

radiofrequency ablation suffer from recurrence [5, 6]. Amiodarone can prevent recurrence of AF, to some extent, and has certain ameliorative effects on AF [7]. The heart consists of a variety of cells and extracellular matrix (ECM). Collagen is the most important ECM protein and more than three quarters of the myocardial interstitial is composed of type I and III collagens. Interaction between matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-2 (TIMP-2) determines the remodeling process in myocardia, playing a part in the occurrence of AF [8, 9]. MMP-2 is an important hydrolase of ECM in myocardia. Its catabolism is disrupted during myocardial fibrosis. Levels

of MMP-2 in patients with paroxysmal AF are significantly upregulated [10]. TIMP-2 is an endogenous specific inhibitor of MMPs. Interactions among MMPs, TIMPs, and their regulatory factors determine the process of myocardial interstitial remodeling [11]. The effects of amiodarone on recurrence of AF after radiofrequency ablation have been studied, but effects on cardiac structure and function, as well as levels of MMP-2 and TIMP-2, in patients with AF after radiofrequency ablation have not been studied.

In this study, 86 patients with AF, treated with radiofrequency ablation, were divided into the amiodarone group (experimental group) and non-amiodarone treated group (control group). Effects of amiodarone on cardiac function and MMP-2 and TIMP-2 levels were observed in both groups.

### Methods and materials

#### *Subjects and groupings*

Eighty-six patients with AF, treated with radiofrequency ablation, in Baoji Hi-Tech People's Hospital, from July 2014 to May 2016, were enrolled in the study. Ages of patients ranged from 41-75 years old, with 44 males and 42 females. The duration of atrial fibrillation was 0.5-3.1 years.

**Inclusion criteria:** Patients diagnosed with paroxysmal atrial fibrillation, confirmed by clinical electrocardiogram (ECG); Patients without tumors; Patients without administration of antiarrhythmic drugs; Patients that underwent first annular pulmonary vein ablation that reached the end point of ablation.

**Exclusion criteria:** Patients with coronary heart disease and hyperthyroidism; Patients whose AF was due to other diseases; Patients with cardiac diseases other than AF; Patients with contraindications of amiodarone.

Enrolled patients were randomized into the control group (n=43; 21 males and 22 females) and experimental group (n=43; 23 males and 20 females). After the operation, experimental group patients were given amiodarone hydrochloride (0.2 g/tablet; 150267, Sanofi Pharmaceutical Co. Ltd., France) for 6 months. The dosage was 200 mg, three times a day, in

the first week. It was twice a day during the next two weeks and once a day thereafter. The control group did not receive any antiarrhythmic drugs after the operation. Informed consent was obtained from all patients and the experiment was approved by the Ethics Committee of Baoji Hi-Tech People's Hospital.

#### *ECG examinations*

ECG examinations were conducted for all patients before the operation and 6 months after the operation. Before the ECG, patients were laid supine for three minutes and an electrocardiograph (Kenz108, Suzuken, Japan) was used to trace the lead V<sub>1</sub> for 24 seconds. The calibration voltage was 20 mm/mV and the speed of recording paper was 50 mm/s. The amplitudes of wave in lead V<sub>1</sub>, which was not close to QRS synthesis wave, T wave, and U wave, were measured. A total of 20 waves were measured, consecutively, and the average value was calculated.

#### *Thoracic echocardiography*

Patients in the two groups were examined by echocardiography before the operation and 6 months after the operation. An ultrasound diagnostic instrument (GE Vivid E9, USA) was used. Probe frequency was 2.5-10 MHz. Left atrial end-diastolic diameter and left atrial end-systolic diameter were measured with M-mode ultrasound. Left ventricular ejection fraction (LVEF) was calculated using the Single-plane Simpson's method.

#### *ELISA detection of MMP-2 and TIMP-2 levels in the serum*

Venous blood (3 mL/patient) of the two groups was collected early in the morning before and 6 months after the operation. It was centrifuged at 4,000 rpm for 15 minutes at 4°C. Serum levels of MMP-2 and TIMP-2 were detected using ELISA kits (Product No. 70-EK1M021 and RK-KOA0314; MultiSciences Company, China), according to manufacturer instructions. The ELISA kit was equilibrated for 20 minutes at room temperature and the detergent was prepared. After the standard product was dissolved, 100 µL was taken and added to the reaction plate to make the standard curve. A total of 100 µL of standard preparation or sample was dispensed per well and incubated at

## Impact of amiodarone on cardiac structural function and MMP-2 and TIMP-2 levels

**Table 1.** Primer sequences of PCR

Name	Primer sequence
MMP-2	Forward: 5'-TGACTTTCTTGGATCGGGTCG-3'
	Reverse: 5'-AAGCACCACATCAGATGACTG-3'
TIMP-2	Forward: 5'-AAGCGGTCAGTGAGAAGGAAG-3'
	Reverse: 5'-GGGGCCGTGTAGATAAACTCTAT-3'
GAPDH	Forward: 5'-CGTCTTACCACCATGGAGA-3'
	Reverse: 5'-CGGCCATCACGCCACAGTTT-3'

Note: MMP-2, matrix metalloproteinase-2; TIMP-2, tissue inhibitor of metalloproteinase-2.

**Table 2.** Comparison of general data between the two groups ( $\bar{x} \pm sd$ )

Item	Experimental group (n=43)	Control group (n=43)	$\chi^2/t$	P
Male (case)	23	21	0.186	0.666
Female (case)	20	22		
Age (year)	65.3±9.6	67.5±8.4	1.131	0.261
Medical history (years)	2.6±0.5	2.7±0.3	1.125	0.264

37°C for 90 minutes. After washing the wells with detergent, 100  $\mu$ L of the biotinylated antibody was added and incubated at 37°C for 60 minutes. Following another wash, 100  $\mu$ L of the enzyme-conjugated reactant solution was added and incubated at 37°C for 30 minutes, protected from light. The plates were washed 3 times and 100  $\mu$ L of substrate was added and incubated at 37°C for 15 minutes. The stop solution was quickly added to terminate the reaction and the OD of each well was measured at 450 nm with a universal enzyme standard instrument (BioTek Synergy 2, USA), within 3 minutes. Based on OD values, a standard curve was drawn to calculate levels of MMP-2 and TIMP-2. The experiment was repeated three times.

### Quantitative RT-PCR of MMP-2, TIMP-2 mRNA levels

Fasting venous blood was collected from patients and centrifuged at 4,000 rpm for 15 minutes at 4°C. Total RNA was extracted from the serum supernatant using TRIzol Reagent (Invitrogen, Cal, SUA). Reverse transcription was performed using the Primescript TM RT-reagent Kit reverse transcription kit (Product No. RR037A, TaKaRa, Dalian, China). To amplify target genes and the reference gene (GAPDH), PCR reactions were carried out as follows: 25

$\mu$ L 10 $\times$  PCR Buffer, 2.5  $\mu$ L 25 mm/L  $MgCl_2$ , 1.5  $\mu$ L 10 mmol/L dNTP, 0.5  $\mu$ L 10 mmol/L Primer, 1  $\mu$ L 1 nmol/L Probe, 0.25  $\mu$ L Taq, 2.5  $\mu$ L cDNA, and 15  $\mu$ L of sterile distilled water. PCR was conducted in a fluorescence quantitative PCR instrument (ABI 7500, Applied Biosystems, USA) with the following reaction conditions: denaturation at 94°C for 5 minutes, 94°C for 30 seconds, 58°C for 45 seconds, and 72°C for 30 seconds, the denaturation cycled 40 times. After the denaturation cycles, a final elongation was at 72°C for 10 minutes. Every reaction set three wells. The mRNA expression levels were calculated using the  $2^{-\Delta\Delta Ct}$  formula. The experiment was repeated three times. Primer sequences are shown in **Table 1**.

### Observation index

ECG and thoracic echocardiography were performed before and 6 months after surgery in all patients. The number and duration of AF, left atrial end-diastolic diameter, left atrial end-systolic diameter, and LVEF were recorded. Serum MMP-2 and TIMP-2 levels in the two groups of patients, before and 6 months after the operation, were measured by ELISA. Their mRNA levels were measured by qRT-PCR before and 6 months after surgery. Changes in cardiac function, before and after treatment with amiodarone (left atrium end-diastolic diameter, left atrial end-systolic diameter, LVEF), and serum levels of MMP-2 and TIMP-2 were the main indicators.

### Statistical analysis

Statistical analyses were performed using SPSS21.0 software (SPSS, Inc, Chicago, IL, USA). All experiments were repeated 3 times. Measurement data are expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ) and were in accordance with normal distribution and homogeneity of variance. An independent sample t-test was used for comparisons within groups, while a paired t-test was used for comparisons of multiple time points within a group. Quantitative data were compared using Chi-squared test.

**Table 3.** Comparison of the number and duration of AF, left atrial end-diastolic diameter, left atrial end-systolic diameter, and LVEF in two groups of patients before and 6 months after surgery ( $\bar{x} \pm sd$ )

Item	Number of AF (time/half year)	Duration of AF (hour)	Left atrial end-diastolic diameter (mm)	Left atrial end-systolic diameter (mm)	LVEF (%)
Control group (n=43)					
Before surgery	10.51±4.62	10.63±3.43	44.96±4.53	32.86±4.05	53.15±6.02
Six months after surgery	3.31±1.31 <sup>t1</sup>	6.91±1.92 <sup>t1</sup>	41.62±3.86 <sup>t1</sup>	29.73±4.26 <sup>t1</sup>	60.03±7.04 <sup>t1</sup>
Experiment group (n=43)					
Before surgery	10.61±3.62	10.70±3.32	45.01±4.49	32.72±3.98	54.41±6.31
Six months after administration	1.63±0.41 <sup>t2,t3</sup>	4.31±1.22 <sup>t2,t3</sup>	39.73±3.72 <sup>t2,t3</sup>	25.46±4.01 <sup>t2,t3</sup>	66.32±7.21 <sup>t2,t3</sup>
t <sub>1</sub>	9.832	6.206	3.680	3.492	4.871
P <sub>1</sub>	<0.0001	<0.0001	0.0004	0.0008	<0.0001
t <sub>2</sub>	16.160	11.850	5.938	8.426	8.151
P <sub>2</sub>	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
t <sub>3</sub>	8.026	7.495	2.312	4.786	4.093
P <sub>3</sub>	<0.0001	<0.0001	0.0232	<0.0001	<0.0001

Note: Compared with the control group before the operation, <sup>t1</sup>P<0.05; compared with the experimental group before the operation, <sup>t2</sup>P<0.05; compared with the control group after the operation, <sup>t3</sup>P<0.05. AF, atrial fibrillation; LVEF, left ventricular ejection fraction.

P<0.05 (bilateral) indicates statistical significance.

**Results**

*Comparison of general data between the two groups*

General clinical data of all patients are shown in **Table 2**. There were no significant differences between the two groups in terms of age, gender, and medical history (all P>0.05).

*Effects of amiodarone on the reduction of AF after radiofrequency ablation*

In control and experimental groups, the number and duration of AF, left atrial end-diastolic diameter, and left atrial end-systolic diameter were significantly decreased at 6 months after surgery, compared to those before surgery. LVEF increased significantly, compared to pre-surgery values (all P<0.05). There were no significant differences in pre-surgery cardiac function parameters between control and experimental groups (all P>0.05). At six months after surgery, however, left atrial end-systolic diameter, the number and duration of AF, and left atrial end-diastolic diameter values were significantly lower. LVEF was significantly higher in the experimental group, compared to that in the control group (all P<0.05). See **Table 3**. Taken together, amiodarone reduced AF and

improved cardiac structure and function after radiofrequency ablation of AF.

*Effects of amiodarone on reductions of MMP-2 mRNA and protein levels and increases of TIMP-2 mRNA and protein levels in serum after radiofrequency ablation of AF*

Results of ELISA and qRT-PCR are shown in **Table 4** and **Figure 1**. In control and experimental groups, serum MMP-2 mRNA and protein levels were significantly lower and TIMP-2 mRNA and protein levels were significantly higher at 6 months after surgery than those before surgery (all P<0.05). Although no significant differences were seen between control and experimental groups for pre-surgery serum MMP-2 and TIMP-2 mRNA and protein levels (all P>0.05), MMP-2 mRNA and protein levels were significantly lower and TIMP-2 mRNA and protein levels were significantly higher in the experimental group than those in the control group at 6 months after surgery (all P<0.05).

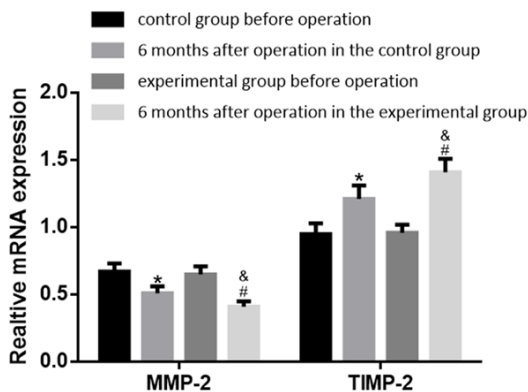
**Discussion**

Studies have shown that MMP-2 plays a very important role in atrial structural reconstruction in patients with mitral stenosis and AF [12]. MMP-2 in cardiomyocytes can degrade type IV collagen [13, 14]. Compared to patients with sinus rhythm, MMP-2 expression in the right

**Table 4.** Comparison of serum MMP-2 and TIMP-2 protein levels in the two groups of patients before and 6 months after surgery ( $\bar{x} \pm sd$ )

Item	MMP-2 (ng/mL)	TIMP-2 (ng/mL)
Control group		
Before surgery	386.74±36.84	64.53±6.06
Six months after surgery	320.62±32.63 <sup>t1</sup>	90.86±8.62 <sup>t1</sup>
Experimental group		
Before surgery	382.96±37.46	63.96±6.38
Six months after administration	280.72±29.32 <sup>t2,t3</sup>	108.62±9.68 <sup>t2,t3</sup>
t <sub>1</sub>	8.810	16.390
P <sub>1</sub>	<0.0001	<0.0001
t <sub>2</sub>	14.090	25.260
P <sub>2</sub>	<0.0001	<0.0001
t <sub>3</sub>	5.964	8.985
P <sub>3</sub>	<0.0001	<0.0001

Note: Compared with the control group before the operation, <sup>t1</sup>P<0.05; compared with the experimental group before the operation, <sup>t2</sup>P<0.05; compared with the control group after the operation, <sup>t3</sup>P<0.05. MMP-2, matrix metalloproteinase-2; TIMP-2, tissue inhibitor of metalloproteinase-2.



**Figure 1.** Comparison of serum MMP-2 mRNA and TIMP-2 mRNA levels in the experimental and control groups before and after surgery. Compared with the control group before surgery, \*P<0.05; compared with the experimental group before surgery, #P<0.05; compared with the control group after the surgery, &P<0.05. MMP-2, matrix metalloproteinase-2; TIMP-2, tissue inhibitor of metalloproteinase-2.

atrial appendage and free wall is significantly higher in patients with AF [15]. Related studies have shown that expression of TIMP-2 in patients with AF decreases significantly [16, 17]. Related studies have shown that MMP-2 expression was elevated and that TIMP-2 expression was decreased in patients with AF [18]. Other factors associated with AF include oxidative stress in the autonomic nervous system, ischemia, endocardial dysfunction, inflammation, and abnormal activity. Greenstein et al.

showed that the main cause of AF recurrence after radiofrequency ablation in patients was abnormal electro-cardiac conduction matrix recanalization [19]. Amiodarone is a commonly used antiarrhythmic drug which can inhibit abnormal electrical triggered activity [20]. In view of the above findings, the current study examined the effects of amiodarone on cardiac structure and function and MMP-2 and TIMP-2 levels after radiofrequency ablation.

The current study found that 6 months after surgery, the number and duration of AF, left atrial end-diastolic diameter, and left atrium end-systolic diameter were significantly lower. LVEF was significantly higher in the experimental group, which received amiodarone, compared to those in the control group.

Present findings clearly show that amiodarone can reduce AF and improve cardiac structure and function after radiofrequency ablation. Tsanaxidis et al. showed that ablation restored the AF rhythm to sinus rhythm, reversed atrial remodeling, and improved cardiac structure and function [21]. Amiodarone administration for 6 months after surgery in the experimental group significantly decreased serum MMP-2 levels and increased TIMP-2 levels. It affects cardiac electrophysiology and inhibits abnormal electrocardiographic trigger activity via the ion channels of myocardial cells, thus affecting MMP-2 and TIMP-2 levels in cardiomyocytes. Gai et al. reported MMP-2 upregulation and TIMP-2 downregulation in the atrial tissues of AF patients, consistent with present results. Taken together, amiodarone can improve the cardiac structure and function of patients after radiofrequency ablation of AF [22].

However, the current study had some limitations. First, the cohort size was small, which narrowed the data source. Second, this study did not examine the underlying mechanisms of amelioration on cardiac structure and function after radiofrequency ablation, only analyzing

related indicators. Therefore, more studies are necessary to clarify this aspect.

In summary, the application of amiodarone in patients with AF after radiofrequency ablation can significantly reduce MMP-2 levels and increase TIMP-2 levels, showing protective effects on the cardiac structure and function of patients.

### Disclosure of conflict of interest

None.

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