RESEARCH ARTICLE

Mmp-9 and the catheter ablation tactics choice

Oleksiy V. Goriachyi, Anatoliy I. Gozhenko

Goriachyi OV, Gozhenko AI. Mmp-9 and the catheter ablation tactics choice. Clin Cardiol J 2019;3(1):9-15

OBJECTIVES: The purpose of this study was to determine the relationship between matrix metalloproteinase 9 and atrial fibrillation recurrence after catheter ablation.

BACKGROUND: Matrix metalloproteinase – 9 (MMP-9) is involved in extracellular matrix remodeling which is a marker of extracellular collagen degradation.

METHODS: An enzyme-linked immunosorbent assay prior to a radiofrequency catheter ablation (RFA) procedure was used for measuring the serum level of MMP-9 in 210 patients: 80 patients without history of atrial fibrillation (AF) and 80 patients with idiopathic AF (paroxysmal AF – 30, persistent AF – 32, long-standing AF – 35 and permanent AF – 33). Their relationship with intraoperative efficacy and recurrence of AF was evaluated throughout the entire observation period.

RESULTS: The observation period was 22.2 ± 7.9 months. MMP-9 level was higher in the groups of patients with AF than in the control group: 170.5 ± 24.2, 202.7±28.4, 230.8 ± 21.1 and 252.6 ± 24.5 ng/ml for paroxysmal, persistent, long-standing and permanent forms of AF. In the control group, MMP-9 level was 75.9 ± 14.6 ng/ml. MMP-9 level increased with the progression of AF ($p < 0.05$).

A multifactor analysis showed that MMP-9 level, history of atrial fibrillation and left atrial volume were independent predictors of sinus rhythm recovery and recurrence of AF.

CONCLUSION: An increase in MMP-9 level in patients with AF has been shown. An increase in MMP-9 levels was observed as AF progressed. MMP-9 is an independent predictor of arrhythmia recurrence after RFA.

Key words: *Metalloproteinase-9; Recurrence; Fibrillation; Ablation; Matrix.*

Acronyms and Abbreviations: AF: Atrial Fibrillation; AFL: Atrial Flutter; AT: Atrial Tachycardia; ESC: European Society of Cardiology; LA: Left Atrium; Mmps: Matrix Metalloproteinases; RFA: Radiofrequency Catheter Ablation; Timps: Tissue Inhibitors of Metalloproteinases.

INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia in clinical practice. Recent prevalence estimates suggest that at least 33.5 million persons are affected by atrial fibrillation (AF) (1). Its prevalence increases with age, from 0.1% in people younger than 55 years to more than 9% by 80 years of age (2). Catheter ablation is the most promising treatment for AF.

The multiple procedure success rate of pulmonary vein isolation for paroxysmal AF is approximately 70% - 80% after long-term follow-up (3,4). However, the success rates of pulmonary vein isolation for non-paroxysmal forms are ranging from 55%-70% for persistent and 50-60% for long standing AF.

Recurrences are common after an initial procedure for non-paroxysmal forms of AF ablation and repeat ablation is often required to maintain freedom from AF (5). Thus, new non-invasive preoperative predictors for assessment atrial structure remodeling are necessary to select the optimal ablation strategy for patients with AF.

Experimental and clinical researches have shown that, whatever the initial cause or trigger, there is a relationship between AF and alterations in atrial electrical properties (6). The longer the duration of AF, the more persistent it becomes because of atrial remodeling.

Remodeling of cellular ultra-structures, such as myolysis occurring in the atrial myocardium, is known to develop progressively during AF (7). An increase in the expression of the gap junctions (connexin 40) has been reported to induce changes in the biophysical properties of the atrial tissue during AF (8,9). Enhanced disintegrin and metalloproteinase activity was also reported to be an important mechanism of AF (10,11) that could lead to atrium diameter expansion, atrial wall thinning and, thus, atrium structure reconstruction. (12).

Endogenous proteolytic enzymes involved in extracellular matrix remodeling include the matrix metalloproteinases (MMPs) and the tissue inhibitors of metalloproteinases (TIMPs), consequently, the serum level of MMP-9, TIMP-1 and their relationship are a marker of extracellular collagen degradation (13).

In particular, many reports have demonstrated that MMP-9 may be implicated in the development of myocardial fibrosis. For example, the MMP-9 level is an important index for myocardial fibrosis, (14,15) and has a close relationship with other cardiovascular diseases (16,17).

The purpose of this study was to investigate the relationship between the serum MMP-9 and arrhythmia recurrence after catheter ablation in patients with AF at different stages of disease progression.

MATERIALS

This study included 208 consecutive patients with various forms of AF. The main group consisted of 128 patients with AF resistant to drug therapy. The control group consisted of 80 patients without heart rhythm disorders and practically healthy patients (Table 1).

The mean age of patients in the main group was 53.5 ± 7.6 years, of them: 54 (41%) women and 77 (59%) men. The mean age of patients in the control group was 52.7 ± 5.6 years, of them: 31 (38.8%) women and 49 (61.3%) men. Both groups are comparable in age (U-test, $p = 0.17$) and gender (Fisher test, $p = 0.55$).

AF was diagnosed according to a manual (ESC Clinical Practice Guidelines 2016). Exclusion criteria were structural heart diseases; hematologic, renal, or hepatic disorders; inflammations; neoplastic diseases; recent (<3 months) myocardial infarction or stroke; thyrotoxicosis-associated AF; or any acute infections. The study was approved by the Ethical Committee of the Odessa Regional Clinical Hospital, Odessa National Medical University. All patients signed an informed consent.

METHODS

The day before the RFA, the serum MMP-9 level was determined, and a transesophageal echocardiography was performed. The method for determining the serum MMP-9 level is described in the literature (11). In brief, blood samples were obtained by puncture of the peripheral vein and centrifuged at 3200xg for 10 minutes at a temperature of 4°C within one hour after collection. The serum was separated and stored at a temperature of -80 ° C until the patient-blinded personnel performed the analysis. The serum MMP-9 level was determined using a standard commercial enzyme-linked immunosorbent assay *in vivo* according to the manufacturer's guidelines (Ray Biotech INC, Atlanta, Georgia, USA). The coefficient of variation within and between assays was <10 and <12%, respectively.

Ukrainian Research Institute of Transport Medicine, Odessa Regional Clinical Hospital, Ukraine

Correspondence: Oleksii Goriachyi, Ukrainian Research Institute of Transport Medicine, Odessa Regional Clinical Hospital, Odessa, Bocharova str.40 fl.31, 65111, Ukraine, Tel: +380505733030, e-mail: avgoryachyi@gmail.com

Received: January 15, 2019, Accepted: February 27, 2019, Published: March 05, 2019

TABLE 1
Baseline characteristics of the patients

	Paroxysmal AF (n = 30)	Persistent AF (n = 32)	Long-standing AF (n = 35)	Permanent AF (n = 33)	Control (n=80)	p
	30	32	35	33		
Age (years)	52.6 ± 6.8	53.4 ± 7.2	54.1 ± 8.1	53.9 ± 8.2	51.8 ± 7.9	0.41
Gender (male), n (%)	19 (63.3)	18 (56.3)	21 (60)	20 (60.6)	39 (48.8)	0.3
Gender (female), n (%)	11 (36.7)	14 (43.8)	14 (40)	13 (39.4)	41 (51.3)	0.28
Body mass index (kg/m^2)	25.9 ± 4.9	26.4 ± 5.3	27.1 ± 4.4	26.6 ± 4.8	26.7 ± 4.5	0.34
AF history (years)	5.3 ± 0.7	6.1 ± 0.6	5.7 ± 1.1	6.4 ± 1.3	-	0.31
AH, n (%)	19 (63.3)	20 (62.5)	23 (65.7)	21 (63.6)	11 (13.8)	0.2
IHD, n (%)	4 (13.3)	4 (12.5)	5 (14.3)	4 (12.1)	-	0.24
AH+IHD, n (%)	2 (6.7)	2 (6.3)	3 (8.6)	4 (12.1)	-	0.29
Idiopathic AF, n (%)	5 (16.7)	6 (18.8)	4 (11.4)	4 (12.1)	-	0.28
EHRA I, n (%)	5 (16.7)	5 (15.6)	10 (28.6)	15 (45.5)	-	
EHRA II, n (%)	19 (63.3)	18 (56.3)	4 (11.4)	10 (30.3)	-	
EHRA III, n (%)	6 (20)	9 (28.1)	21 (60)	8 (24.2)	-	
Ventricular arrhythmias, n(%)	11 (36.7)	11 (34.4)	12 (34.3)	11 (33.3)	-	*0.38
Supraventricular arrhythmias, n(%)	13 (43.3)	12 (37.5)	14 (40)	14 (42.4)	32 (40)	*0.06
NYHA I class, n (%)	18 (60)	6 (18.8)	6 (17.1)	6 (18.2)	27 (33.8)	
NYHA II class, n (%)	12 (40)	25 (78.1)	28 (80)	26 (78.8)	-	
absent	0 (0)	1 (3.1)	1 (2.9)	1 (3.0)	53 (66.3)	0.45
MMP-9, (ng/ml)	170.5 ± 24.2	202.7 ± 28.4	230.8 ± 21.1	252.6 ± 24.5	75.9 ± 14.6	0.05
LA diameter, mm	35.7 ± 2.1	41.4 ± 3.2	44.3 ± 3.4	47.5 ± 4.4	34.3 ± 2.0	0.05
Right lower pulmonary vein, mm	15.6 ± 0.7	15.1 ± 0.5	15.1 ± 0.8	15.7 ± 0.9	14.8 ± 0.7	0.05
Right upper pulmonary vein, mm	15.6 ± 1.1	15.9 ± 0.9	15.7 ± 1.2	16.0 ± 1.3	15.1 ± 1.1	0.05
Left lower pulmonary vein, mm	14.5 ± 1.2	14.4 ± 1.1	14.1 ± 1.3	14.7 ± 1.4	14.3 ± 1.2	0.05
Left upper pulmonary vein, mm	16.0 ± 1.1	16.1 ± 0.8	15.8 ± 1.2	16.2 ± 1.3	15.3 ± 1.1	0.05

*p = Mann-Whitney test, p * = Fisher criterion, AF = atrial fibrillation, AH = artery hypertension, IHD = Ischemic heart disease, EHRA = European heart rate association, NYHA = New York Heart Association, CHF =chronic heart failure, MMP-9 = matrix metalloproteinase–9.*

The anatomical study of the left atrium (LA) and pulmonary veins was carried out on a spiral computed tomography (computed tomography) scanner "HiSpeed computed tomography/i" manufactured by "General Electric" (USA), with a gantry rotation speed at spiral scanning of 1 rotation per second. The study was conducted against the background of the administration of non-ionic contrast agents using an automatic injector "SimtRac DH" manufactured by Siemens (Germany). The procedure was performed on an empty stomach, under conventional therapy.

As a rule, the left cubital vein was punctured to perform a computed tomography scan with angiography of the LA and LV. A 20G venous catheter was inserted into the vein and an automatic injector was connected. The volume of the contrast agent and the rate of its injection were set up in the injector. The volume of the contrast agent depended on the patient's weight and height (usually 70-100 ml). Contrast agents "Iohexol (GE Healthcare AC, Ireland/Norway)" and "Iopromid (Bayer Pharma AG, Germany)" were used.

Data post-processing included the reconstruction of axial slices, the construction of two- and three-dimensional images. A soft-tissue filter was always used to reduce noise and increase contrast resolution.

The results of the study were evaluated first by axial slices. Subsequently, reconstructed axial slices were used for a multiplanar reconstruction (multiplanar reconstruction). The construction of two- and three-dimensional reconstructions was performed on the GE workstation "Advantage Windows 2.0". The dimensions of the mouth of the pulmonary veins were measured in the axial plane and in the oblique plane of the multiplanar reconstruction. The three-dimensional reconstruction was performed in SSD mode, the anatomical structure of the left atrium and pulmonary veins was assessed (the number of veins flowing into the LA by their own mouth, the convergence of the pulmonary veins mouths, the common pulmonary veins collector).

Catheter AF ablation

All patients had a catheter AF ablation under general anesthesia. Patients were heparinized to maintain an activated clotting time for more than 300 s. A three-dimensional electroanatomical model was constructed using a NavX electroanatomical mapping system (St. Jude Medical, St. Paul, MN). The ablation procedure included following steps: 1) isolation of pulmonary veins, 2) linear ablation of the mitral isthmus, in the absence of an effect – ablation of the left atrial roof. In the absence of efficiency of the stages 1 and 2, linear ablations were additionally performed, which included a line along the posterior wall of the LV, a line along the cavotricuspid isthmus and isolation of the superior vena cava. The endpoint of the procedure was considered the termination of AF. In the absence of an effect, the sinus rhythm (sinus rhythm) was restored using electrical cardioversion.

According to the 2015 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF, any atrial tachycardia (AT), atrial flutter (AFL) or an episode of AF lasting more than 30 seconds three months after ablation should be defined as a recurrence.

Observation period

All patients were monitored every month at the Polyclinic Department of the Odessa Regional Clinical Hospital. If patients complained of heart palpitations, fatigue, or other symptoms related to arrhythmias, the patients underwent 24-hour ECG monitoring. Patients were also advised to visit the attending doctor at any time when they develop symptoms for a 12-lead ECG or 24-hour ECG monitoring. Asymptomatic patients underwent 24-hour or situational ECG monitoring every 3 months after the procedure. The endpoint of the observation period was recording of an AT/AFL/AF recurrence with duration of more than 30 s.

RESULTS

In the postoperative period (12.3 ± 6.4 months), 35 (27.3%) patients developed recurrent AT/AFL/AF. The baseline characteristics of the patients in both groups are shown in Table 1. The data in the table showed no significant differences in age, gender, body mass index (body mass index), hypertension, left ventricle ejection fraction, or medication between the two groups. However, the group of patients with recurrent arrhythmias had a longer history of arrhythmias, greater LA diameter and a higher MMP-9 level compared to the group without recurrence (Table 2).

Ablation procedure and electric cardioversion

We retrospectively analyzed data from patients in both groups. The level of the recovery of sinus rhythm at stages 1, 2 and 3 in the two groups did not differ significantly. The only difference between the two groups was the linear ablation of the LA roof. At this stage, rhythm recovery was observed in

9 patients in group 1 and 7 patients in group 2 (9.7% and 20%, respectively, p = 0.04) (Table 2).

STATISTICAL ANALYSIS

Statistical data processing was carried out with the aid of the statistical package Statistica 6.1.

Testing of the parameters for normality was carried out using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive data for quantitative features with normal distribution were presented as mean and standard deviation (M ± o), those with non-normal distribution were presented in the form of median and interquartile interval (Me). Correlation analysis was performed using the Spearman's R-test for quantitative values. The relationship between values was evaluated as significant at R> | 0.7 |, moderate at R from | 0.3 | to | 0.7 |, weak at R <| 0,.3 | (Tables 3, 4, 5).

Correlation analysis

Calculations according to formula:

|r|={exp[2t/(n-1,5)0,5-1}/{exp[2t/(n-1,5)0,5+1} gives following threshold values of correlation coefficient modules for a sample of n = 130 persons. Graphic image of correlation between MMP-9 and LA volume is shown on Figure 1.

If the effectiveness in the absence of recurrence after 2 years is estimated according to the Harrington scale using integers, we obtain a non-linear relationship graph. If non-integers are used to quantify the severity of arrhythmias, we obtain a practically straight-line dependence of the effect of the operation on the severity of arrhythmia Figure 2.

Cluster analysis

Using Cluster analysis, the preoperative level of MMP-9 was determined in patients with various effects of the operation (Table 6).

In the group of patients without relapse, MMP-9 level was higher in the groups of patients with relapses of AF than in the group without relapses: 251.8 ± 8.4, 253.5 ± 8.3 and 203.6 ± 3.8 ng/ml for the groups with relapse through 2 years and 7 days and in a group without relapse, respectively. In the group without effect, the MMP-9 level was 238.4 ± 6.6 ng/ml, which indicates the completion of structural myocardial remodeling. In the control group, MMP-9 level was 75.9 ± 14.6 ng/ml. MMP-9 level increases with the progression of AF until complete structural myocardial remodeling (Figure 3).

It should be noted that the clinical features of the patients played an important role on the consequences of the operation (Table 7).

The main contribution to the recurrence of atrial fibrillation made hypertonic disease and heaviness of the arrhythmia (Figure 4).

DISCUSSION

In the present study, we have prospectively studied the MMP-9 level as predictors of the recurrence of arrhythmia after a procedure of RFA of AF. We found that MMP-9 levels in patients with AF were significantly higher those in the healthy control population, indicating that MMP-9 may play a role in the occurrence and maintenance of AF. The mechanism behind AF is complicated and AF is often caused by several factors (18). Including myocytes of the atrium and fibrous changes in the connective extracellular matrix (EM), which contribute to the development of AF. In turn, fibrosis is caused by an imbalance between degradation and deposition of cardiac

TABLE 2

Patients characteristics depending on the effectiveness of the ablation

	Without reccurence (n = 93)	With reccurence (n = 35)	*p*
Age (years)	51.3 ± 7.6	54.6 ± 7.9	0.057
Gender (male), n (%)	50 (53.8)	18 (51.4)	0.83
Body mass index (kg/m^2)	26.1 ± 4.9	27.4 ± 6.1	0.33
AF history (months)	43.2 ± 15.9	52.7 ± 17.7	0.03
Hypertension n, (%)	12 (12.9)	4 (11.4)	0.82
Left atrial diameter (mm)	39.4 ± 7.6	44.8 ± 9.2	0.01
Left ventricle diameter (mm)	51.3 ± 8.1	53.4 ± 7.3	0.49
LVEF (%)	56.8 ± 7.3	57.5 ± 9.2	0.74
ACE inhibitor n, (%)	19 (20.4)	4 (11.4)	0.36
Amiodarone n, (%)	47 (50.5)	20 (57.1)	0.74
B-blockers n, (%)	87 (93.5)	33 (94.3)	0.99
MMP-9 (ng/ml)	234.41 ± 93.36	297.73 ± 81.28	0.01
	Catheter ablation results		
Step 1: Pulmonary vein isolation n, (%)	19 (20.4)	4 (11.4)	0.33
Step 2: linear ablation of left atrium n, (%)	40 (43)	20 (57.1)	0.29
Mitral Isthmus ablation n, (%)	31 (33.3)	13 (37.1)	0.55
Left atrial roof n, (%)	9 (9.7)	7 (20)	0.04
Step 1 + 2 n, (%)	59 (63.4)	241 (68.6)	0.61
Step 3: additional lines n, (%)	34 (36.6)	11 (31.4)	0.33
Step 1 +2 + 3 n, (%)	76 (81.7)	26 (74.3)	0.08
Electrical cardioversion n, (%)	15 (16.1)	9 (25)	0.15

p = Mann-Whitney Test, AF = Atrial Fibrillation, LVEF = Left Ventricle Ejection Fraction, ACE = Angiotensin-Converting-Enzyme, MMP-9 = Matrix Metalloproteinase – 9.

TABLE 3

Matrix of correlation relationships between enzymes/cytokines and clinical indices

	HD	IHD	Arhythm-1	Arhythm-2	EHRA	NYHA	Sex	Age
MMP-9	,35	,28	**,44**	**,71**	**,40**	,30	-,09	,17

MMP-9 = Matrix Metalloproteinase-9, HD = Hypertension Disease, IHD = Ischemic Heart Disease, EHRA = European Heart Rate Association, NYHA = New York Heart Association, Arhythm-1 = Supraventricular Arrhythmia, Arhythm-2 = Ventricular Arrhythmia.

TABLE 4

Matrix of correlation relationships between enzymes/cytokines and left atrium volume/pulmonary vein diameter

	LAVZ	LAV	RIPV	RSPV	LIPV	LSPV
MMP-9	,71	**,98**	,52	**,64**	,57	,56

LAV = Left Atrial Volume, RIPV = Right Inferior Pulmonary Vein, RSPV = Right Superior Pulmonary Vein, LIPV = Left Inferior Pulmonary Vein, LSPV = Left Superior Pulmonary Vein, MMP-9 = Matrix Metalloproteinase-9.

TABLE 5

Four-fold matrix of the relationship between the form of atrial fibrillation and operation efficacy

		Effect after procedure					
		Without reccurence	**Reccurence after 2 years**	**Reccurence after 7 days**	**Without effect**	**Total**	$(\Sigma n^2/Nx)/N$
Paroxysmal AF	n	23	0	2	1	26	
	n^2/Nx	20,346	0	0,154	0,038	20,538	0,790
Persistent AF	n	22	2	3	4	31	
	n^2/Nx	15,613	0,516	0,290	0,516	16,548	0,534
Long-standing AF	n	25	4	4	3	36	
	n^2/Nx	17,361	0,444	0,444	0,250	18,499	0,514
Permanent AF	n	23	4	5	3	35	
	n^2/Nx	15,114	0,457	0,714	0,257	16,543	0,473
Total	Ny	93	10	14	11	128	2,311

AF – Atrial Fibrillation, $\Xi^2 = [(\Sigma n^2/Nx)/N] - 1 = 1,311$, $\Phi^2 = \Xi^2 - (X-1)(Y-1)/N = 1,311 - (4-1)(4-1)/128 = 1,241$, $R = \{\Phi^2/(1+\Phi^2)[Xy/(X-1)(Y-1)]^{0,5}\}^{0,5} = [1,241/2,241 \cdot (16/9)^{0,5}]^{0,5} = 0,860$, $M_r = (1-R^2)/(N-2)^{0,5} = 0,023$ $R = 0,860 \pm 0,023$.

TABLE 6

Peculiarities of the MMP-9 level of patients with various consequences of the operation.

	Cluster	NR	R2y	R7d	NE	Norm
MMP-9	µg/L	203.6 ± 3.8	251.8 ± 8,4	253.5 ± 8.3	238.4 ± 6.6	61.0 ± 3.0

MMP-9 = Matrix Metalloproteinase-9, NR = No Relapse, R2y = Relapse In 2 Days, R7d = Relapse In 7 Days, NE = No Effect.

TABLE 7

Peculiarities of the clinical status of patients with different consequences of the operation

Clusters of Consequences (n)	**Hypertonic Disease (No=0; Yes=1)**	**Ischemic Heart Disease (No=0;Yes=1)**	**NYHA (0; 1; 2)**	**EHRA (1; 2; 3)**	**Arhythmia-1 (No=0; Supra-ventricular=1; Ventricular=2)**	**Arhythmia-2 Fibrillation Heaviness, points**
No Relapse (93)	0.72 ± 0.05	0.08 ± 0.03	1.31 ± 0.08	1.76 ± 0.07	0.83 ± 0.07	2.15 ± 0.07
Relapse after 2 years (10)	1.00 ± 0.00	0.50 ± 0.17	1.50 ± 0.27	2.80 ± 0.20	1.90 ± 0.10	2.57 ± 0.08
Relapse after 7 days (14)	0.86 ± 0.10	0.57 ± 0.14	1.57 ± 0.23	2.93 ± 0.07	1.93 ± 0.07	2.35 ± 0.16
No Effect (11)	0.91 ± 0.09	0.36 ± 0.15	1.16 ± 0.29	2.41 ± 0.32	1.41 ± 0.28	2.37 ± 0.15

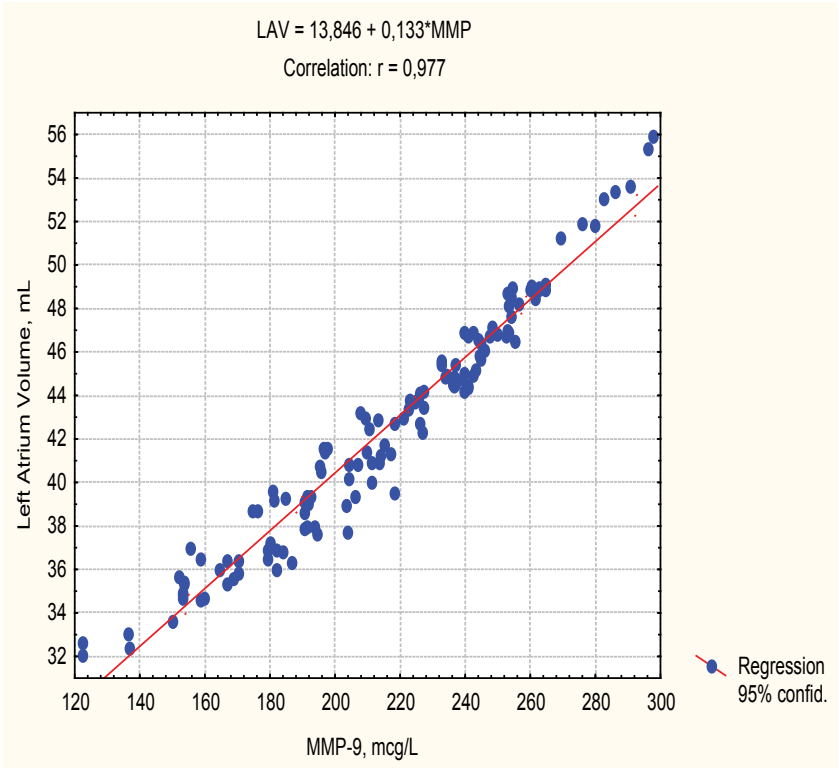
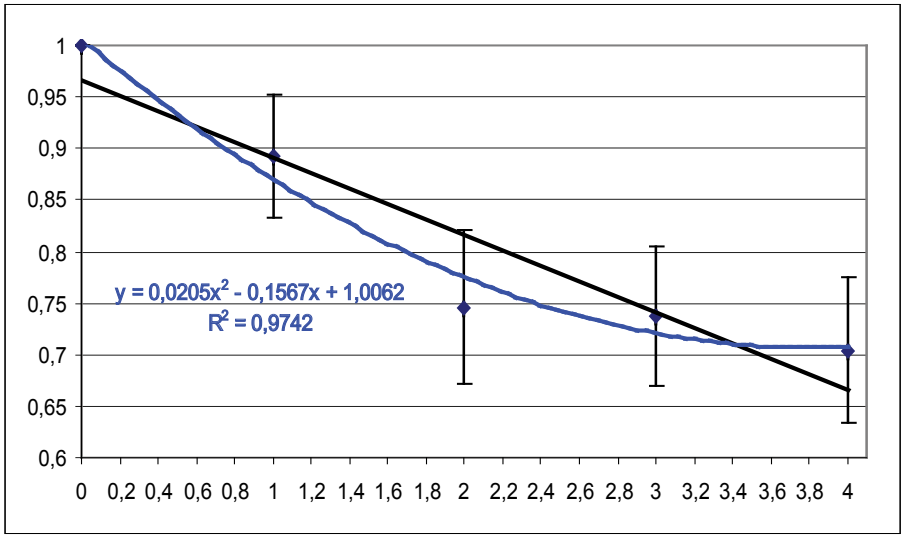
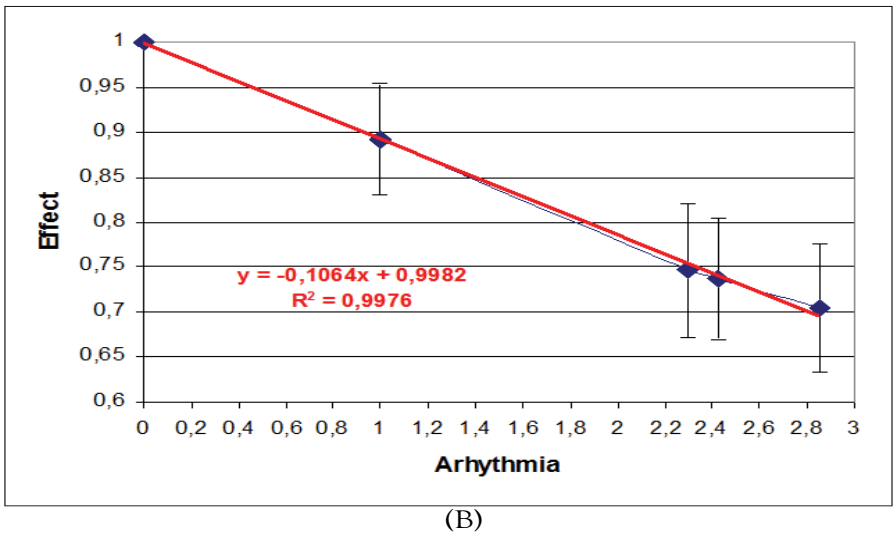


Figure 1) *Correlation between matrix metalloproteinase-9 (MMP-9) and left atrial volume (LAV)*



(A)



(B)

Figure 2) *Correlation between the severity of paroxysmal arrhythmia, (A) estimated by integers and (B) non-integer numbers (X axis), and the efficiency of the operation (axis Y).*

EM, which is a nonspecific response to cardiomyocyte necrosis or apoptosis. MMPs, which represent a multifaceted family of structurally and functionally homogeneous proteolytic enzymes, regulate the turnover of EM and can play a determining role in the structural remodeling of atriums involved in the development and maintenance of AF (19). Previous experimental studies showed that MMP-9 plays a key role in heart remodeling and promotes chamber dilatation and excessive collagen accumulation in both senile hearts and in post-infarction hearts (20,21). It has recently been established that MMP-9 levels are closely related to the initiation and maintenance of AF. According to various researchers, elevated MMP-9 levels were shown to be independently associated with an increased risk of AF development (22). It is noteworthy that the MMP-9 level correlated with AF development. With progression of idiopathic AF, the MMP-9 level gradually increased from paroxysmal to persistent and constant form of AF (23). In addition, previous studies also showed that the MMP-9 level was associated with atrial remodeling in patients with AF. For the first time, a close relationship between MMP-9 and AF (24) was demonstrated. It has been shown that increased expression of MMP-9 may contribute to the structural remodeling of atriums and to atrial dilatation during AF. MMP-9 also participates in atrial remodeling after catheter ablation. In addition, a significant increase in MMP-9 regulation is associated with a large decrease in the size of the left atrium (25). Patients who developed recurrence had a higher serum MMP-9 level, indicating a more serious atrial remodeling and form of AF. These assumptions were confirmed by a long history of AF and large sizes of the LA in this group. To date, the efficacy of RFA in patients with persistent, long-standing and permanent forms of AF remains unsatisfactory. Despite the adoption of new techniques, recent studies have shown that up to 40% of patients had a recurrence of tachycardia after the primary procedure (26). What patient characteristics can be used to evaluate their prognosis remains unclear. Various candidates were reported to predict the recurrence of AF after catheter ablation, including age, gender, body mass index, ECG, echocardiographic data, observations made using cardiovascular magnetic resonance imaging (magnetic resonance imaging) and some serum or plasma factors (27). Some of these studies contradict one another, while the most accurate predictors of recurrences after ablation of AF remain uncertain. AF progresses with worsening fibrosis and inflammation. Various inflammatory factors cause focal myocardial necrosis, modulate the functionality of the ion channel, and then initiate structural and electrical atrial remodeling. MMP-9 is one of the markers of fibrosis and inflammation, which is associated with atrial remodeling in patients with AF. Elevated levels of MMP-9 are associated with the occurrence and maintenance of AF (28). In this article, we investigated the factors that may have prognostic significance for the results of catheter ablation of AF in the early and late postoperative period. We observed that traditionally reported factors, such as a history of AF and left atrium diameter, were also significantly associated with AF recurrence. In addition, the serum MMP-9 level was found to be an independent predictor of recurrence. Thus, to eliminate this bias, the presence of AF without structural heart disease was confirmed in all patients registered in our study. Our data showed that serum MMP-9 level was effective in predicting the recurrence of AF in this cohort. There are many members in the superfamily of MMPs. In addition to MMP-9, some other members (MMP-2, MMP-3 and MMP-7) and tissue MMP inhibitors, such as TIMP 1-3, also have a strong

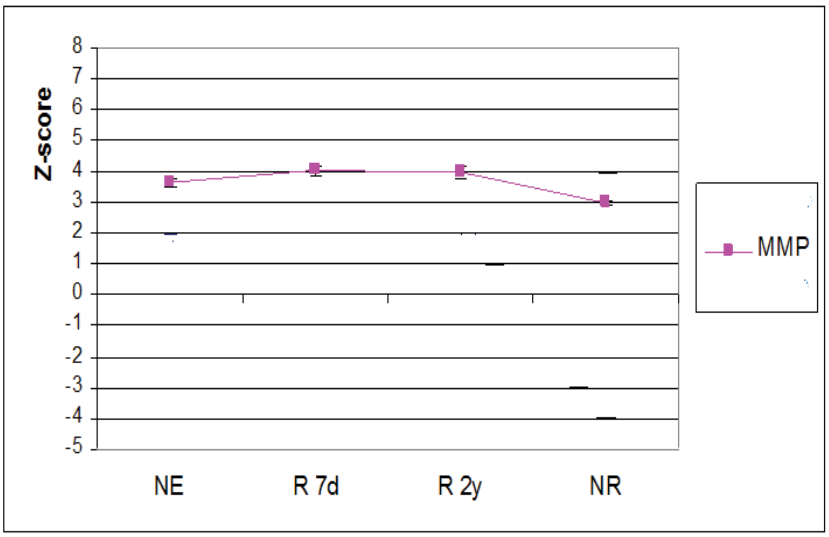


Figure 3) *The MMP-9 activity features of patients with the various consequences of the operation, MMP = Matrix Metalloproteinase-9, NR = No Relapse, R2y = relapse in 2 days, R7d = Relapse in 7 days, NE = No Effect.*

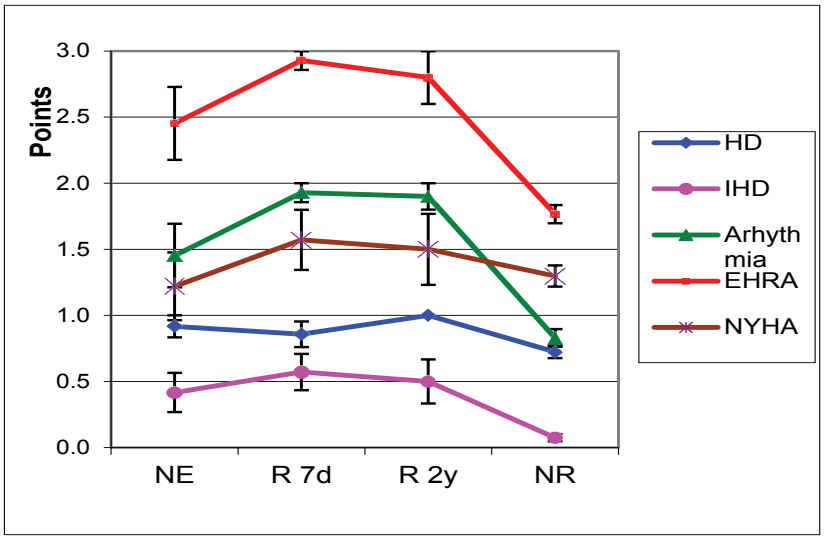


Figure 4) *Peculiarities of the Clinical Status of Patients with Different Consequences of the Operation, HD = Hypertension Disease, IHD = Ischemic Heart Disease, EHRA = European Heart Rate Association, NYHA = New York Heart Association, Arrhythmia = Atrial Fibrillation, NR = No Relapse, R2y = Relapse In 2 Days, R7d = Relapse In 7 Days, NE = No Effect.*

association with the frequency of AF (29). In this study, we focused on MMP-9, so other MMP/TIMP are candidates for further studies. Whether any of these MMPs/TIMPs (or their combinations) are also indicators of the risk of AF recurrence after catheter ablation remains a mystery. Our results can be useful for selecting the optimal candidate for catheter ablation of AF. Since the MMP-9 level correlates with atrial fibrosis and predicts AF recurrence, it can also be a therapeutic target. MMP inhibition and regulation of the extracellular collagen matrix can be therapeutically useful in patients with AF. Gene removal or pharmacological inhibition of MMP activity weakens atrial remodeling and reduces vulnerability to AF (30). In the TIPTOP study, the MMP tissue inhibitor doxycycline was used briefly in patients with acute myocardial infarction and left ventricular dysfunction. The results of the study showed that doxycycline therapy inversely correlated with the size and severity of infarction for six months and left ventricle dilatation (31). No clinical trials have been reported on the use of MMP platelet inhibitors for the treatment of AF. A prospective randomized study to determine the MMP-9 level in predicting AF recurrence and to evaluate the effect of a tissue MMP inhibitor on AF may be justified. The patients included in this study were a special group of AF. The MMP-9 level correlates with the intraoperative efficacy of rhythm recovery and relapse in the early and late postoperative period and increases as AF progresses. Patients with constant AF had more extensive fibrosis than patients with persistent AF (32). Constant AF usually coexists with structural heart disease, which can aggravate fibrosis and inflammation. In recent recommendations, catheter ablation is not recommended for patients with constant AF.

CONCLUSION

This study evaluated only patients with idiopathic AF without apparent structural concomitant pathology which could limit its generalizability. Serum MMP-9 levels were higher in patients with recurrence and were identified as an independent predictor of arrhythmia recurrence after catheter ablation. In conclusion, we explained that the expression of MMP-9 increases with the progression of AF and may contribute to structural atrial remodeling and increase the risk of relapse in the postoperative period. This requires the use of more complex integrated approach for the treatment.

LIMITATIONS

Limitations of the present study are its sample size a larger sample is needed for further research. Given that AF is a multifactorial disease with unclear etiology, that in the MMPs superfamily many members and tissue MMP inhibitors also have a strong connection with the progression of AF (29) further research should also be directed to study them. Whether any of these MMPs/TIMPs (or their combinations) are also indicators of the risk

of AF recurrence after catheter ablation remains a mystery. In conclusion, our study found that MMP-9 levels are higher in patients with AF than in healthy controls, and that MMP- 9 may therefore be associated with the development of AF. In addition, our findings provide indications of a relationship between the increase in the MMP-9 level and the progression of AF. Our results can be useful for choosing the optimal tactics of catheter and drug treatment. This study evaluated only patients with idiopathic AF without apparent structural concomitant pathology which could limit its generalizability. Further research is necessary.

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 Study. Circulation. 2014;129:837-847.
2. Staerk L, Sherer JA, Darae K, et al. Helm atrial fibrillation epidemiology, pathophysiology, and clinical outcomes. Circulation. 2017; 120:1501-1517.
3. Pappone C, Vicedomini G, Augello G, et al. Radiofrequency catheter ablation and antiarrhythmic drug therapy: A prospective, randomized, 4-year follow-up trial: the APAF study. Circ Arrhythm Electrophysiol. 2011;4(6):808-814.
4. Elayi CS, Verma A, Di Biase L, et al. Ablation for longstanding permanent atrial fibrillation: Results from a randomized study comparing three different strategies. Heart Rhythm. 2008;5(12):1658-1664.
5. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012;14(4):528-606.
6. Kabra R, Heist EK, Barrett CD, et al. Incidence and electrophysiologic properties of dissociated pulmonary vein activity following pulmonary vein isolation during catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2010;21:1338-1343.
7. Noureldin M., Chen H, Bai D. Functional characterization of novel atrial fibrillation-linked GJA5 (C × 40) mutants. Int J Mol Sci. 2018; 19:977
8. Paramdeep S, Dhillon A, Rasheda A, et al. Relationship between connexin expression and gap–junction resistivity in human atrial myocardium. Circulation: Arrhythmia and electrophysiology. 2014;7:321-329.
9. Ueda N, Yamamoto M, Honjo H, et al. The role of gap junctions in stretch-induced atrial fibrillation. Cardiovascular Research. 2014; 104; 364-370.
10. Takahashi N, Kume O, Wakisaka O, et al. Novel strategy to prevent atrial fibrosis and fibrillation. Circ J. 2012; 76: 2318–2326.
11. Liu C, Fu H, Li J, et al. Hyperglycemia aggravates atrial interstitial fibrosis, ionic remodeling and vulnerability to atrial fibrillation in diabetic rabbits. Anadolu Kardiyol Derg. 2012; 12: 543-550.
12. Kostin S, Klein G, Szalay Z, et al. Structural correlate of atrial fibrillation in human patients. Cardiovasc Res 2002; 54: 361–379.
13. Veidal SS, Nielsen MJ, Leeming DJ, et al. Phosphodiesterase inhibition mediates matrix metalloproteinase activity and the level of collagen degradation fragments in a liver fibrosis *ex vivo* rat model. BMC Res Notes. 2012;5:686.
14. Fan D, Takawale A, Lee J, et al. Cardiac fibroblasts, fibrosis and extracellular matrix remodeling in heart disease. Fibrogenesis Tissue Repair. 2012;5:15.
15. Georgescu SP, Aronovitz MJ, Iovanna JL, et al. Decreased metalloprotease 9 induction, cardiac fibrosis, and higher autophagy after pressure overload in mice lacking the transcriptional regulator p8. Am J Physiol Cell Physiol. 2011;301:1046-1056.
16. Spinale FG, Coker ML, Heung LJ, et al. A matrix metalloproteinase induction/activation system exists in the human left ventricular myocardium and is upregulated in heart failure. Circulation. 2000;102:1944-1949.
17. Renko J, Kalela A, Jaakkola O, et al. Serum matrix metalloproteinase-9 is elevated in men with a history of myocardial infarction. Scand J Clin Lab Invest. 2004; 64:255-261.
18. Qiu XB, Xu YJ, Li RG, et al. PITX2C loss-of-function mutations responsible for idiopathic atrial fibrillation. Clinics. 2014;69(1):15-22.
19. Gramley F, Lorenzen J, Plisiene J, et al. Decreased plasminogen activator inhibitor and tissue metalloproteinase inhibitor expression may promote increased metalloproteinase activity with increasing duration of human atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18(10):1076-1082.
20. Yabluchanskiy A, Ma Y, Chiao YA, et al. Cardiac aging is initiated by matrix metalloproteinase-9-mediated endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2014;306(10): H1398-407.
21. Khalili H, Talasaz AH, Salarifar M. Serum vitamin D concentration status and its correlation with early biomarkers of remodeling following acute myocardial infarction. Clin Res Cardiol. 2012;101(5):321-327.
22. Huxley RR, Lopez FL, MacLehose RF, et al. Novel association between plasma matrix metalloproteinase-9 and risk of incident atrial fibrillation in a case-cohort study: The Atherosclerosis Risk in Communities study. PLoS One. 2013; 8(3):59052.
23. Li M, Yang G, Xie B, et al. Changes in matrix metalloproteinase-9 levels during progression of atrial fibrillation. J Int Med Res. 2014;42(1):224-230.
24. Nakano Y, Niida S, Dote K, et al. Matrix metalloproteinase-9 contributes to human atrial remodeling during atrial fibrillation. J Am Coll Cardiol. 2004;43(5):818-825.
25. Richter B, Gwechenberger M, Socas A, et al. Time course of markers of tissue repair after ablation of atrial fibrillation and their relation to left atrial structural changes and clinical ablation outcome. Int J Cardiol. 2011;152(2):231-236.
26. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). Eur Heart J. 2014;35(8):501-507.
27. Wynn GJ, Das M, Bonnett LJ, et al. Efficacy of catheter ablation for persistent atrial fibrillation: A systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. Circ Arrhythm Electrophysiol. 2014;7(5):841-852.
28. Combes S, Jacob S, Combes N, et al. Predicting favourable outcomes in the setting of radiofrequency catheter ablation of long-standing persistent atrial fibrillation: A pilot study assessing the value of left atrial appendage peak flow velocity. Arch Cardiovasc Dis. 2013;106(1):36-43.
29. Scaglione M, Gallo C, Battaglia A, et al. Long-term progression from paroxysmal to permanent atrial fibrillation following transcatheter ablation in a large single-center experience. Heart Rhythm. 2014;11(5):777-782.
30. Yuen HC, Roh SY, Lee DI, et al. Atrial fibrillation cycle length as a predictor for the extent of substrate ablation. Europace. 2015.
31. Sramko M, Peichl P, Wichterle D, et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. Int J Cardiol. 2015;179:351-357.
32. Lewkowicz J, Knapp M, Tankiewicz-Kwedlo A, et al. MMP-9 in atrial remodeling in patients with atrial fibrillation. Ann Cardiol Angeiol (Paris). 2015.