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Features of The Dynamics of Profibrotic Markers and Regression of Left Ventricular Hypertrophy After Renal Denervation in Patients With Resistant Hypertension and Stenosing Atherosclerosis of the Coronary Arteries

Aim — To compare the changes in serum concentrations of matrix metalloproteinases (MMPs) and their tissue inhibitor (TIMP) to the dynamics of blood pressure (BP) and parameters of left ventricular hypertrophy (LVH) 6 months after renal denervation (RD) in patients with resistant arterial hypertension (RAH) and complicated coronary atherosclerosis.

Material and methods — In 22 RAH patients with complicated coronary atherosclerosis (revascularization and/or history of myocardial infarction - MI), 24-hour BP monitoring, echocardiography, and measurement of blood MMPs and TIMP were performed at baseline and six months after RD. The comparison group consisted of 48 RAH patients without a history of coronary revascularization or MI.

Results — In 6 months after RD, BP was decreased comparably in both groups. In the group of complicated atherosclerosis, there were no significant changes in profibrotic markers or LVH parameters. Thus, at baseline and after 6 months, the values of the studied indicators were the following: left ventricular myocardial mass (LVMM) 233.1±48.1 and 243.0±52.0 g, LVMM index 60.6±14.5 and 62.8±10.9 g/m^2.7, proMMP-14.9 [2.1; 7.7] and 3.6 [2.0; 9.4] ng/ml, MMP-2290.4 [233.1; 352.5] and 352.2 [277.4; 402.9] ng/ml, MMP-9220.6 [126.9; 476.7] and 263.5 [82.9; 726.2] ng/ml, TIMP-1395.7 [124.7; 591.4] and 424.2 [118.2; 572.0] ng/ml, respectively. In the comparison group, on the contrary, there was a significant decrease in LVMM from 273.6±83.3 g to 254.1±70.4 g, LVMM index from 67.1±12.3 to 64.0±14.4 g/m^2.7, proMMP-1 from 7.2 [3.6; 11.7] to 5.9 [3.5; 10.9] ng/ml, MMP-2 from 328.9 [257.1; 378.1] to 272.8 [230.2; 343.2] ng/ml, MMP-9 from 277.9 [137.0; 524.0] to 85.5 [34.2; 225.9] ng/ml, and the MMP-9/TIMP-1 ratio from 0.80 [0.31; 1.30] to 0.24 [0.07; 0.76]. The BP dynamics in this group was inversely correlated with MMP-2 at 6 months (r=–0.38), and the MMP-9/TIMP-1 ratio was correlated with LVMM and the LVMM index at baseline (r=0.39 and r=0.39) and at 6 months (r=0.37 and r=0.32). The change in TIMP-1 from 543.9 [277.5; 674.1] to 469.8 [289.7; 643.6] ng/ml was not significant (p=0.060).

Conclusion — In RAH patients with complicated coronary atherosclerosis, the dynamics of profibrotic biomarkers and LVH parameters after RD was absent despite the pronounced antihypertensive effect, probably due to the low reversibility of cardiovascular remodeling processes or more complex regulatory mechanisms of the MMP system.

Keywords — Resistant arterial hypertension; renal denervation; matrix metalloproteinases

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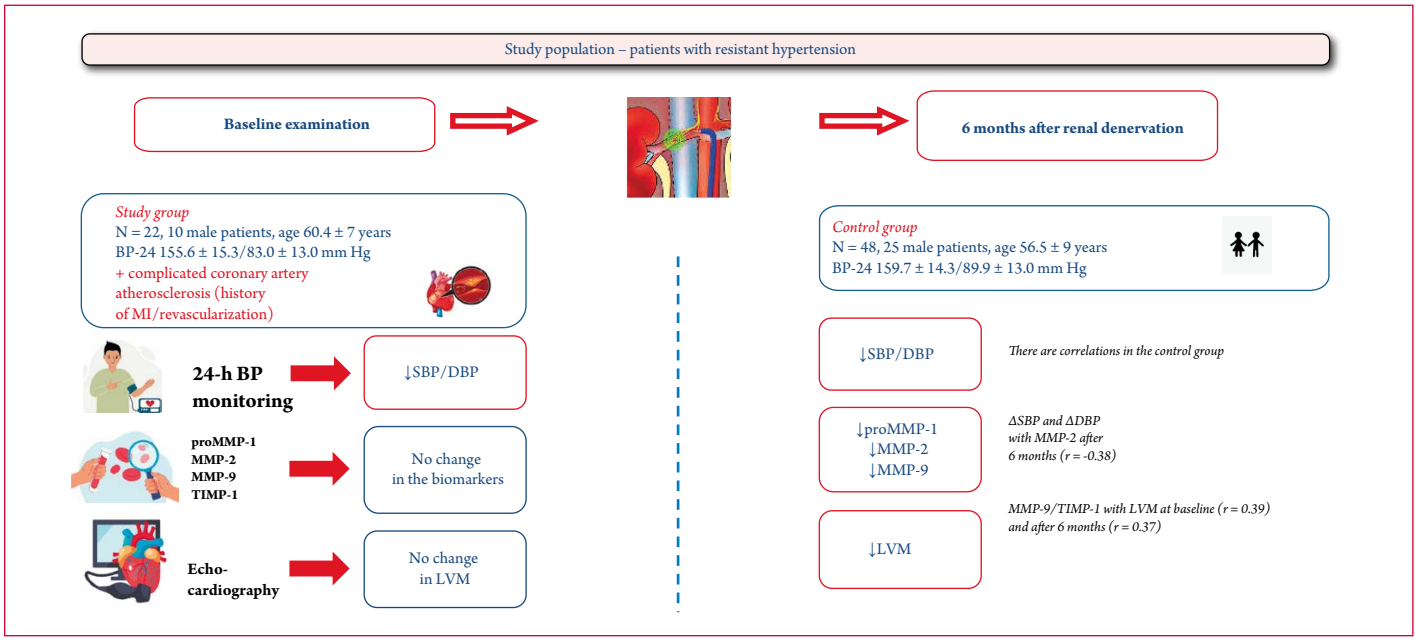
Introduction

Matrix metalloproteinases (MMPs) constitute a family of zinc-dependent endopeptidases that are capable of degrading all types of extracellular matrix proteins. MMPs play an important role in tissue remodeling, angiogenesis, cell proliferation, migration, differentiation, apoptosis, the inhibition of tumor growth, and other processes [1]. The prognostic and therapeutic potential of the MMP family and their inhibitors in patients with cardiovascular disease is currently the subject of extensive investigation [2–4]. A considerable amount of contradictory data is available in the literature regarding the variations in the concentrations

Central illustration. Features of The Dynamics of Profibrotic Markers and Regression of Left Ventricular Hypertrophy After Renal Denervation in Patients With Resistant Hypertension and Stenosing Atherosclerosis of the Coronary Arteries



BP, blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; LVM, left ventricular mass; Δ, delta.

of these biomarkers in relation to the different nosological classes and drug therapies [5].

MMP-1 regulates stage 1 of collagen degradation, forming two peptides: a small C-terminal telopeptide (CITP) and a larger telopeptide. The latter is subsequently broken down by other MMPs, including MMP-2 and MMP-9 [6]. Tissue inhibitor of metalloproteinase 1 (TIMP-1) forms a complex with the majority of MMPs, including MMP-1 and MMP-2, as well as with the precursor of MMP-9, thereby inhibiting its activation by stromelysins. A balance between MMPs and their inhibitors is of great importance, as a violation of this balance can lead to the development of a number of diseases [7].

With regard to cardiovascular pathology, it is hypothesized that the MMP family, particularly MMP-2 and MMP-9, plays a role in postinfarction remodeling of the left ventricle, which is accompanied by dilatation of the ventricle cavity and the development of heart failure. Experiments showed that a reduction in the concentrations of these enzymes in mice following myocardial infarction (MI) is associated with a significant decrease in the intensity of these processes [8].

A reduction in the CITP/MMP-1 ratio is associated with an increased risk of hospitalization for decompensated heart failure (HF) [9], while elevated levels of MMP-2, MMP-9 and TIMP-1 are associated with an elevated risk of all-cause mortality in patients with chronic heart failure (CHF) [10].

There is a great deal of inconsistency in the literature data on MMP concentrations in patients with hypertension. Previous studies have demonstrated a reduction in MMP-1, MMP-2, and MMP-9 concentrations and an increase in TIMP-1 levels in patients with hypertensive heart disease (HHD) and left ventricular hypertrophy (LVH), and the association of elevated TIMP-1 levels with the development of diastolic dysfunction in such patients [9]. In our previous work, we demonstrated that elevated MMP-9 levels and a reduced TIMP-1/MMP-9 ratio in patients with resistant hypertension (RH) and type 2 diabetes mellitus (DM) were associated with enhanced intrarenal blood flow and renal filtration function [11]. At the same time, Stakos et al. [12] demonstrated higher proMMP-1/TIMP-1 ratios in hypertensive patients, with this ratio also correlating with carotid-femoral pulse wave velocity, indicating that vascular stiffness is increased in patients with hypertension and dysregulated collagen metabolism.

The participation of the MMP family in collagen degradation contributes to the development and progression of atherosclerosis, including in coronary arteries [13]. These enzymes have been demonstrated to cause atherogenesis by inducing a reduction in the elasticity of the vascular wall, through elastin degradation and arterial wall calcification [14]. In addition to the degradation of extracellular matrix components and remodeling of the vascular wall, MMP-2 and MMP-9 are believed to be responsible for the inflammation and rupture of atherosclerotic plaques [15]. The levels of MMP-9 and TIMP-1 are linked to a risk of cardiovascular complications and mortality [16].

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Radiofrequency ablation of renal arteries, or renal denervation (RD), is an effective and safe method for the treatment of hypertension [17–21]. In addition to its antihypertensive effect, this method has a number of pleiotropic effects [22, 23], the mechanisms of which are currently under active investigation. The hypothesis of this study was that the sympatholytic effect of RD modulates the renin-angiotensin-aldosterone system (RAAS) activity, resulting in alterations in a number of biochemical parameters, including markers of fibrosis and collagen formation. These changes may be associated with the antihypertensive and organoprotective effects of the procedure. The data on changes in the concentrations of MMPs and their inhibitors after RD remain scarce and extremely contradictory [24, 25]. Furthermore, there has been no previous comparison of the changes in fibrosis markers with the changes in blood pressure (BP) and LVH after RD in patients with complicated coronary atherosclerosis.

Objective

Examine the peculiarities of changes in serum concentrations of MMPs and TIMPs in comparison with BP changes and parameters of LVH six months after RD in patients with RH and a complicated course of coronary artery atherosclerosis.

Material and methods

The simple comparative prospective study included 70 patients who were followed up at the Research Institute of Cardiology of the Tomsk National Research Medical Center within the framework of the scientific program «Development and Implementation of New Methods of Diagnosis and Treatment of Patients with Hypertension and High Risk of Complications» (state registration number: AAAA-A17-117052310076-7 dated 23/05/2017), who had been followed up for six months and had documented serum concentrations of MMPs and TIMPs. The study was conducted in accordance with good clinical practice and the tenets of the Declaration of Helsinki. It was registered on ClinicalTrials.gov under NCT02667912 and NCT01499810 and approved by the local ethics committee. All patients signed the informed consent prior to the inclusion in the study.

Inclusion criteria:

- Male and female subjects under the age of 80 with essential hypertension.
- Resistant nature of hypertension (according to national guidelines) [26].
- Anatomy of the renal artery that is suitable for intervention.

Exclusion criteria:

- Estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2.
- History of anaphylactic reactions to X-ray contrast agents.
- Severe comorbidities or conditions that are associated with a high risk of intervention.

The primary group (Group 1) comprised 22 patients with a complex history of coronary atherosclerosis, including prior revascularization and/or myocardial infarction (MI). The control group (Group 2) consisted of 48 patients without documented coronary events.

Each patient received an individualized antihypertensive regimen, which included three or more drugs at the maximum tolerated doses. In all cases, a diuretic was included in the regimen. Adherence to treatment was evaluated based on the oral information provided by the patients.

The main clinical characteristics of patients are presented in Table 1.

RD was conducted in the X-ray surgery room at the Research Institute for Cardiology. Three types of catheters were employed: an endocardial catheter, the MarinR 5F (n=6), and two different systems, the Symplicity Flex 4F (n=42) or Spyral (n=22).

A clinical and laboratory examination was conducted at baseline and six months after the surgery. A 24-hour BP monitoring procedure was conducted using an automatic measurement system, AVRM-04 (Meditech, Hungary), and the oscillometric method to determine the daily means of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP). An echocardiographic examination was conducted using an expert-class ultrasound system in accordance with the established protocol, via the parasternal and apical views. Left ventricular changes were diagnosed according to the recommendations for patients with hypertension and using the relevant echocardiographic criteria [26]. The left ventricular mass index (LVMI) was calculated using the formula for overweight and obese patients: LV mass/height $(m)^{2,7}$; left ventricular (LV) cavity sized was determined using the formula: LV end-diastolic dimension (cm)/height (m).

Blood samples were collected in the morning, prior to any food intake, to determine biochemical markers. Pro-MMP-1 and MMP-2 levels were quantified using R&D Systems immunoassay kits (USA), while MMP-9 and TIMP-1 levels were determined by Bender MedSystems (Austria).

All patients were evaluated for atherosclerotic coronary artery disease via invasive coronary angiography or multislice computed tomography of the coronary arteries

prior to intervention. This evaluation was conducted to identify potential indications for revascularization. Additionally, a history of coronary events (MI, revascularization) was also considered. The examination of the patients using ultrasound methods of investigation (ultrasound of carotid, femoral, renal arteries) did not reveal any clinically significant peripheral atherosclerosis.

Table 1. Clinical characteristics of patients

Parameter	Group 1 (n=22)	Group 2 (n=48)	p
Male, n (%)	10 (45)	25 (52)	0.765
Age, years	60.4±7.0	56.5±9.1	0.067
Duration of hypertension, years	21.5±12.8	20.6±10.3	0.781
Number of antihypertensive drugs	4.0±1.0	4.3±1.0	0.260
Statins, n (%)	22 (100)	39 (81)	0.575
Body mass index, kg/m^2	34.2±4.9	34.3±5.3	0.934
Obesity, n (%)	20 (91)	42 (88)	0.919
LVH, n (%)	18 (82)	44 (92)	0.765
LV mass, g	233.1±48.1	273.6±83.3	0.006
LVMI, g/m$^{2.7}$	56.5 [46.3; 60.6] in male patients, 68.6 [53.0; 74.5] in female patients	68.6 [60.0; 77.6] in male patients, 63.3 [56.2; 72.0] in female patients	0.023 0.872
RWT	0.51±0.08	0.56±0.10	0.034
LV cavity size, cm/m	2.91±0.22	2.97±0.50	0.591
Diabetes mellitus type 2, n (%)	17 (77)	23 (48)	0.243
CAD, n (%)	22 (100)	22 (46)	0.047
PICS, n (%)	8 (36)	0	0.000
History of CVA, n (%)	3 (14)	5 (10)	0.727
Creatinine, μmol/L	96.0±28.3	90.0±25.2	0.366
eGFR, mL/min/1.73m^2	68.8±21.0	73.6±18.6	0.324
CKD stage III, n (%)	8 (36)	13 (27)	0.569
SBP-24, mm Hg	155.6±15.3	159.7±14.3	0.271
DBP-24, mm Hg	83.0±13.0	89.9±13.0	0.044
PP-24, mm Hg	72.6±14.6	69.8±14.2	0.454

The data are expressed as the mean and standard deviation (M ± SD), the median and interquartile range (Me [LQ; UQ]), and number of patients (n (%)); LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, relative wall thickness; LV, left ventricle; CAD, coronary artery disease; PICS, postinfarction cardiosclerosis; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate (CKD-EPI); CKD, chronic kidney disease; SBP-24 , mean 24-hour systolic blood pressure; DBP-24, , mean 24-hour diastolic blood pressure; PP-24, , mean 24-hour pulse pressure.

The statistical processing was conducted using STATISTICA 10.0. The hypothesis on normal distribution was verified using the Shapiro–Wilk test. If the distribution of the sample was normal, the data were expressed as the mean and standard deviation (M ± SD) and compared using the Student's t-test. In the absence of a normal distribution, the data were presented as the median and the interquartile range (Me [LQ; UQ]). The Mann-Whitney test was employed to ascertain the significance of intergroup differences, while the Wilcoxon test was utilized to assess the changes of indicators. The nonparametric Spearman's coefficient was employed to assess the correlations. A conjugacy table analysis (Pearson's chi-square) was employed to analyze the qualitative data. The differences between the values were significant at $p<0.05$. The data analysis was conducted in accordance with the established protocol. The delta (Δ) of a parameter was calculated as the difference between the baseline value and the value obtained over time.

The primary endpoint used to evaluate the efficacy of RD was a decrease in the mean 24-hour SBP. The secondary endpoints were a decrease in DBP and PP, regression of LVH, and changes in laboratory parameters.

Results

In the group of patients with complicated coronary artery atherosclerosis (Group 1), the baseline DBP was found to be lower (p=0.044). The groups were comparable with respect to sex, age, BMI, duration of HHD, prevalence of type 2 DM and stage 3 CKD, baseline SBP and PP, and number of antihypertensive medications continuously taken. Despite a comparable percentage of patients with LVH, LVM was higher in the control group (Group 2) (p=0.006). This was predominantly due to male patients. The left ventricular relative wall thickness (RWT) exceeded normal values in both groups, indicating a high incidence of concentric myocardial remodeling in patients with RH. It is evident that a more pronounced LVH in the control group was accompanied by a greater RWT (p=0.034). There was no evidence of LV dilation in the subjects.

At six months following RD, comparable reductions in SBP, DBP, and PP were observed in both groups. The target blood pressure levels were achieved by 5 (22.7%) patients in Group 1 and by 12 (25%) patients in Group 2. The decrease in LVM was observed only in Group 2 (Table 2). The remaining echocardiographic parameters demonstrated no changes in either group.

Significant differences were observed in the changes of fibrosis markers between the groups (Table 3). In the group of patients with RH and complicated coronary atherosclerosis, there were no changes observed. In contrast, in the control group, there was a significant positive

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Table 2. Changes in BP and echocardiographic parameters 6 months after RD

Parameter	Group 1 (n=22)	Group 2 (n=48)	p*
SBP at baseline, mm Hg	155.6±15.3	159.7±14.3	0.271
SBP, 6 months, mm Hg	147.3±17.7	147.0±15.7	0.952
Δ SBP, 6 months, mm Hg	14 [-5; 21], p=0.042	11 [1; 23], p=0.000	0.574
DBP at baseline, mm Hg	83.0±13.0	89.9±13.0	0.044
DBP, 6 months, mm Hg	76.3±13.7	82.3±13.2	0.107
Δ DBP, 6 months, mm Hg	6 [-2; 11], p=0.068	6 [-1; 13], p=0.000	0.702
PP at baseline, mm Hg	72.6±14.6	69.8±14.2	0.454
PP, 6 months, mm Hg	70.8±15.2	64.7±14.6	0.132
Δ PP, 6 months, mm Hg	5 [-4; 14], p=0.131	5 [-1; 11], p=0.001	0.908
LVM, at baseline, g	233.1±48.1	273.6±83.3	0.006
LVM, 6 months, g	243.0±52.0, p=0.143	254.1±70.4, p=0.009	0.161
LVMI, at baseline, g/m$^{2.7}$	56.5 [46.3; 60.6] in male patients, 68.6 [53.0; 74.5] in female patients	68.6 [60.0; 77.6] in male patients, 63.3 [56.2; 72.0] in female patients	0.023 0.872
LVMI, 6 months, g/m$^{2.7}$	58.5 [48.9; 69.6] in male patients, p=0.053. 68.3 [57.6; 72.6] in female patients, p=1.0	64.0 [50.6; 80.6] in male patients, p=0.180. 60.1 [55.0; 69.8] in female patients, p=0.548	0.296 0.427
RWT at baseline	0.51±0.08	0.56±0.10	0.034
RWT 6 months	0.53±0.07. p=0.072	0.56±0.08. p=0.680	0.103
LV cavity size at baseline, cm/m	2.91±0.22	2.97±0.50	0.591
LV cavity size 6 months, cm/m	2.90±0.21. p=0.859	2.87±0.20. p=0.246	0.550

The data are expressed as the mean ± standard deviation (M ± SD), the median and interquartile range (Me [LQ; UQ]); SBP-24, mean 24-hour systolic blood pressure; DBP-24, mean 24-hour diastolic blood pressure; PP-24, mean 24-hour pulse pressure; LVM, left ventricular mass; LVMI, left ventricular mass index; RWT, relative wall thickness; LV, left ventricle; p, statistical significance level used to assess changes in an indicator; p*, statistical significance level for intergroup comparison.

trend, with a decrease in proMMP-1, MMP-2, and MMP-9, as well as in the MMP-9/TIMP-1 ratio. The serum concentration of TIMP-1 and the proMMP-1/TIMP-1 ratio remained unchanged in both groups.

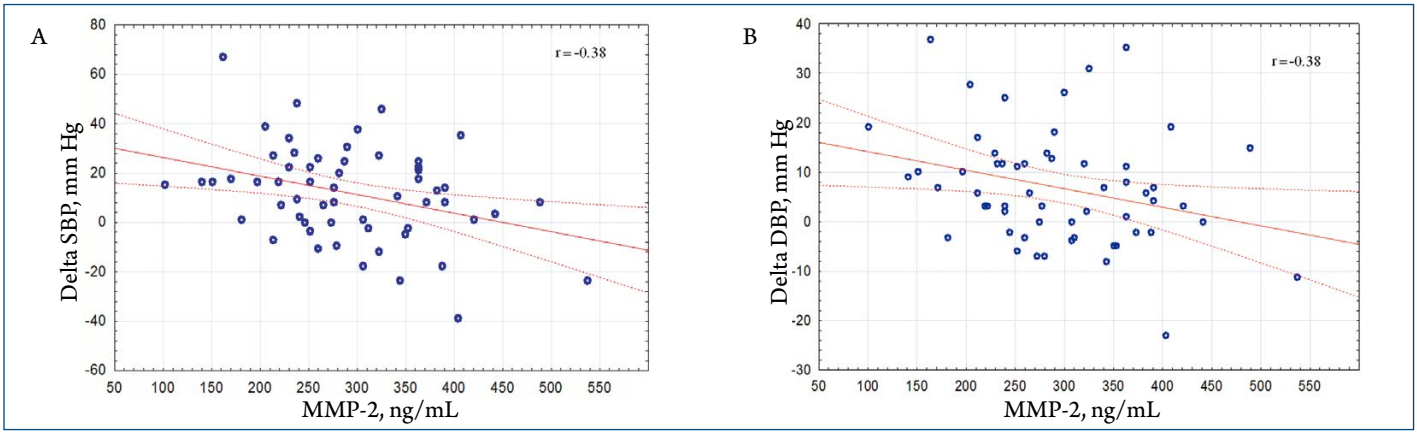
The control group also demonstrated a correlation between changes in SBP and DBP and MMP-2 levels after six months. (r= – 0.38, p<0.05) (Figure 1).

Table 3. Changes in profibrotic markers 6 months after RD

Indicator, ng/mL	Group 1 (n=22)	Group 2 (n=48)	p*
proMMP-1 at baseline	4.9 [2.1; 7.7]	7.2 [3.6; 11.7]	0.067
proMMP-1 6 months	3.6 [2.0; 9.4]	5.9 [3.5; 10.9]	0.127
Δ proMMP-1	2.2 [-0.2; 5.7] p=0.831	0.5 [-0.5; 5.2] p=0.006	0.756
MMP-2 baseline	290.4 [233.1; 352.5]	328.9 [257.1; 378.1]	0.571
MMP-2 6 months	352.2 [277.4; 402.9]	272.8 [230.2; 343.2]	0.024
Δ MMP-2 6 months	-18.8 [-87.5; 20.2] p=0.112	38.7 [-12.6; 107.3] p=0.017	0.007
MMP-9 baseline	220.6 [126.9; 476.7]	277.9 [137.0; 524.0]	0.693
MMP-9 6 months	263.5 [82.9; 726.2]	85.5 [34.2; 225.9]	0.024
Δ MMP-9 6 months	80.3 [-509.5; 242.3] p=0.983	85.5 [34.2; 225.9] p=0.002	0.293
TIMP-1 at baseline	395.7 [124.7; 591.4]	543.9 [277.5; 674.1]	0.508
TIMP-1 6 months	424.2 [118.2; 572.0]	469.8 [289.7; 634.6]	0.817
Δ TIMP-1 6 months	2.1 [-132.8; 69.3] p=0.758	19.3 [-31.1; 232.9] p=0.060	0.193
proMMP-1/ TIMP-1 at baseline	0.011 [0.003; 0.015]	0.016 [0.008; 0.021]	0.105
proMMP-1/ TIMP-1 6 months	0.010 [0.007; 0.017]	0.014 [0.008; 0.023]	0.405
Δ proMMP-1/ TIMP-1 6 months	-0.001 [-0.005; 0.001] p=0.374	0.001 [-0.003; 0.002] p=0.664	0.382
MMP-9/TIMP-1 at baseline	0.64 [0.32; 1.75]	0.80 [0.31; 1.30]	0.619
MMP-9/TIMP-1 6 months	1.01 [0.19; 1.44]	0.24 [0.07; 0.76]	0.022
Δ MMP-9/TIMP-1 6 months	0.035 [-0.542; 0.683] p=0.733	0.328 [0.062; 0.798] p=0.002	0.586

The data are expressed as the median and interquartile range (Me [LQ; UQ]); MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinases, p, statistical significance level used to assess changes in an indicator; p*, statistical significance level for intergroup comparison.

Figure 1. Dot plots of the correlations between Δ SBP (A) and Δ DBP (B) and MMP-2 levels after 6 months. (r=-0.38)



Furthermore, in this group, the MMP-9/TIMP-1 ratio was found to be correlated with LVM, with baseline r=0.39 and after six months r=0.37 (Figure 2), and with LVMI, with r=0.39 and r=0.32, respectively ($p<0.05$). In contrast, no such relationships were observed in patients with complicated atherosclerosis.

Discussion

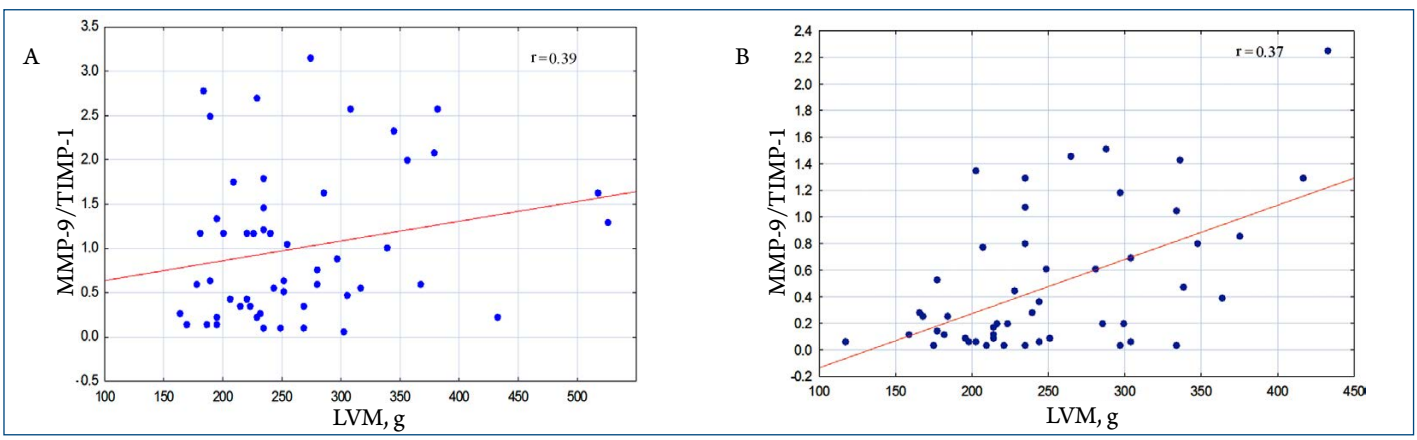
MMPs are enzymes that facilitate the breakdown of collagen and elastin, the primary components of connective tissue in the human body. Consequently, the levels of these enzymes exhibit considerable variability. Their blood levels can be influenced by a number of factors. Recent studies have suggested that MMPs may be involved in intracellular processes in cardiomyocytes. Additionally, these enzymes have been observed in vascular endothelial and smooth muscle cells, as well as in fibroblasts [27].

MMPs play an important role in the processes of atherogenesis, as they are responsible for the degradation of extracellular matrix (ECM) proteins. This is because collagen and elastin not only provide elasticity to the vascular wall but also serve as a subendothelial barrier that impedes the migration and subsequent infiltration of leukocytes and smooth muscle cells [28].

Regarding the effect of RD on the progression of atherosclerosis, the available literature contains few conflicting data. Wang H. et al. demonstrated that the process of atherogenesis was slowed after RD in a mouse model with apolipoprotein E deficiency, regardless of the reduction in blood pressure [29]. In contrast, Wang Y. et al. observed an increase in atheroma in apolipoprotein E-deficient mice following subcutaneous infusion of angiotensin II. This increase correlated with a decrease in norepinephrine. The authors of this paper postulated that the mechanism underlying this effect is due to the increased expression of MMP-2, which they also observed in the RD group in comparison to sham controls. Nevertheless, the authors acknowledge the potential impact of external, unaccounted-for factors [30].

In our study, patients with and without complicated atherosclerosis demonstrated no baseline differences in MMP and TIMP concentrations. However, following the intervention, there was a significant decrease in MMP-2 and MMP-9 and in the MMP-9/TIMP-1 ratio in the control group, which led to differences in these parameters at the six-month follow-up. It was not feasible to evaluate the effect of the intervention on the progression of

Figure 2. Dot plots of the correlations between MMP-9/TIMP-1 with LVM at baseline (r=0.39) (A) and after 6 months (r=0.37) (B)



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atherosclerosis and was not within the purview of this particular study section.

The alterations in MMP concentrations subsequent to RD are likely to be influenced by intricate mechanisms that involve the RAAS. RAAS activation results in elevated MMP expression and a dysregulation of MMPs and their inhibitors through a variety of mechanisms [31]. By reducing the effects of angiotensin II, RD prevents remodeling of the vascular wall, which is achieved by decreasing smooth muscle contractility, reducing smooth muscle cell migration, as well as the synthesis and release of ECM proteins. As a result, the intensity of fibrosis is also reduced. Furthermore, the rise in MMP activity during vascular remodeling associated with hypertension may serve an adaptive function, aiming to enhance microvascular circulation. Consequently, a reduction in hemodynamic load subsequent to RD no longer necessitates the elevated activity of proteolytic enzymes to enhance tissue perfusion. This concept is corroborated by a more pronounced reduction in MMP-2 levels in patients exhibiting lower post-intervention blood pressure values. The lack of substantial MMP alterations subsequent to RD in patients with RH and complicated atherosclerosis can be attributed to the limited reversibility of fibrotic processes in such patients.

It is noteworthy that the MMP-9/TIMP-1 ratio has been found to correlate with LVM and LVMI. Myocardial hypertrophy is a multifactorial process that occurs not only in the presence of increased pressure load. The process is accompanied by both cardiomyocyte enlargement and changes in the components of the extracellular space [32]. As it is observed in other organs, the processes of collagen formation and degradation in the myocardium are typically in equilibrium. The impact of hemodynamic and humoral factors (hormones, growth factors, cytokines, etc.) in hypertension results in the disruption of this balance and the development of fibrosis [33].

MMPs have been demonstrated to be involved in the processes of ECM degradation during myocardial hypertrophy and remodeling. However, as is the case with all literature pertaining to MMPs and their inhibitors, the data is of a highly variable nature. For example, a team of researchers led by Euler G. concluded that cardiomyocyte MMPs can prevent myocardial hypertrophy, given that MMP inhibition promotes hypertrophic growth [4]. It is noteworthy that an earlier study documented a direct correlation between LVM and TIMP-1 levels, as well as the TIMP-1/MMP-2 ratio, in patients with RH and type 2 DM [34]. It is probable that the suppression of MMP activity and the accumulation of extracellular matrix in hypertensive patients are intended to reinforce the cardiac muscle framework in the context of increased hemodynamic load. Conversely, elevated MMP-2 activity was observed concurrently with hypertension, myocardial hypertrophy and fibrosis in mice subjected to angiotensin II infusion and prolonged volume overload, as reported by Odenbach et al. [35] and Matsusaka et al. [36], respectively. It can be concluded that the observed regression of LVH and the decrease in MMP levels in Group 2 are interrelated processes. This is evidenced by the correlations between LVM and LVMI and the MMP-9/TIMP-1 ratio, as well as by the absence of changes in the former and the latter in Group 1. It is possible that the presence of coronary atherosclerotic stenosis, as a reflection of the systemic atherosclerotic process, alters the pathophysiology of LVM increase in RH patients, limiting the possibility of LVH regression and MMP production reduction even with decreasing hemodynamic load. In our own studies, we have previously observed humoral mechanisms of the regression of LVH following RD [37]. In light of the newly discovered correlations, it is possible to hypothesize that the MMP family may also be involved in these processes. Further research is clearly required to gain a more detailed understanding of these mechanisms. The lack of observed changes in LV architecture over time (reduction in LV RWT and LV cavity size) is primarily attributable to the limited follow-up period. Despite the pronounced antihypertensive effect of the intervention, the majority of patients failed to attain target BP levels, which is unlikely to facilitate the reversal of concentric LV remodeling. It is important to note that there is a tendency for this indicator to decrease in the control group. Concurrently, the absence of alterations in LV cavity size appears to be a natural phenomenon, given that its initial values were within the normal range.

In consideration of the data indicating a correlation between elevated MMP levels and cardiovascular complications, it can be postulated that prognosis may be improved in patients without coronary atherosclerosis following RD, and that this treatment method may be employed more effectively in the future.

Conclusion

Thus, the alterations in the concentrations of matrix metalloproteinases and their inhibitors, as well as in the regression of left ventricular hypertrophy, are not observed in patients with resistant hypertension and complicated atherosclerosis of coronary arteries following renal denervation. This may indicate low reversibility of cardiovascular remodeling processes in these patients in the short-term follow-up period, or more complex mechanisms of matrix metalloproteinase system regulation. At the same time, patients exhibiting less pronounced baseline alterations in the vascular wall (i.e., no complicated atherosclerosis) following renal denervation demonstrate favorable changes,

including a reduction in profibrotic marker concentrations, a decline in blood pressure, and regression of left ventricular hypertrophy. Concurrently, the antihypertensive effect of renal denervation is not contingent upon the presence or severity of coronary atherosclerosis.

The study is limited by the small number of patients in the study group, the relatively short follow-up period, and the assessment of adherence to treatment based on survey data. The study of longer-term changes in the matrix metalloproteinase concentrations may be the subject of further research, as well as a comparison of the changes in matrix metalloproteinase levels after standard and distal renal denervation in light of the more pronounced cardioprotective effect of the latter [38].

No conflict of interest is reported.

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