Online Journal of Biological Sciences

Original Research Paper

MMP-9 is a Potential Prognostic Marker of Left Ventricular Remodeling in Patients with Coronary Artery Disease

[1]Mikhail Aleksandrovich Popov, [2]Anastasia Vladimirovna Poznyak, [1]Dmitry Valerievich Shumakov, [1]Dmitry Igorevich Zybin, [3]Natalia Mikhailovna Kashirina, [3]Liudmila Nikolaevna Lipatova, [3]Mikhail Mikhailovich Peklo, [3]Pavel Nikolaevich Rutkevich, [3]Elena Vadimovna Yanushevskaya, [4]Elizaveta Mikhailovna Pleshko, [4]Victor Yurievich Glanz, [4]Vasily Nikolaevich Sukhorukov, [5]Dmitry Felixovich Beloyartsev and [4]Alexander Nikolaevich Orekhov

[1]Department of Cardiosurgery, Vladimirsky Moscow Regional Research Clinical Institute, Moscow, Russia
[2]Institute for Atherosclerosis Research, Moscow, Russia
[3]National Medical Research Center of Cardiology Named After Academician E. I. Chazov, Moscow, Russia
[4]Laboratory of Cellular and Molecular Pathology of Cardiovascular System, Petrovsky National Research Centre of Surgery, Moscow, Russia
[5]Vascular Surgery Department, A. V. Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

Article history
Received: 30-01-2024
Revised: 31-03-2024
Accepted: 17-04-2024

Corresponding Author:
Anastasia Vladimirovna Poznyak
Institute for Atherosclerosis Research, Osennyaya Moscow, Russia
Email: tehhy_85@mail.ru

Abstract: Matrix Metalloproteinase-9 (MMP-9) emerges as a promising prognostic marker for assessing left ventricular remodeling in patients with coronary artery disease, particularly in the context of Ischemic Heart Disease (IHD) complicated by left ventricular aneurysm. In this study, we conducted two parallel investigations to explore the prognostic significance of MMP-9 in patients with multivessel coronary artery disease undergoing left ventricular reconstruction via coronary artery bypass grafting. Two distinct cohorts were examined in this research. The first group underwent analysis of MMP-9 levels in biopsies of the left ventricular myocardium, focusing on paracollagen type 4-MMP-9. The second group had their blood plasma MMP-9 concentrations scrutinized. The study primarily aimed to assess the predictive value of MMP-9 in determining postoperative prognoses and treatment outcomes. Our initial findings from the biopsy analysis revealed a significant association ($p = 0.001$) between para-collagen type 4-MMP-9 levels and unfavorable prognoses in the early postoperative period. Furthermore, monitoring MMP-9 levels in blood plasma for 5 years indicated a correlation between elevated MMP-9 concentrations and ongoing ischemic changes post-myocardial revascularization, suggesting a progression toward congestive heart failure. Notably, a substantial decrease ($p = 0.002$) in MMP-9 concentration was observed in patients post-surgery, underscoring the positive impact of myocardial revascularization on MMP-9 levels. The research underscores the potential of MMP-9 as a valuable marker for predicting adverse outcomes post-myocardial revascularization and myocardial remodeling surgery. Elevated MMP-9 levels in plasma signify a risk of CHF progression, while decreased levels post-surgery point towards the benefits of revascularization interventions. This study offers critical insights into leveraging MMP-9 as a prognostic tool in guiding optimal treatment strategies for patients with coronary artery disease and left ventricular remodeling, emphasizing its relevance in enhancing patient care and clinical decision-making.

Keywords: Left Ventricular Aneurysm, Matrix Metalloproteinase 9, Chronic Heart Failure, Atherosclerosis

Introduction

The escalating rates of morbidity and mortality stemming from cardiovascular diseases present a significant global concern, causing substantial human losses and economic repercussions. Projections by experts indicate a looming increase in cardiovascular disease-related deaths, partly due to the gradual extension of life expectancy (Acar *et al*., 2019).

Among economically developed nations, coronary heart disease stands out as a prevalent health issue,

ranking high among the causes of mortality related to the circulatory system. A severe complication of coronary heart disease is Acute Myocardial Infarction (AMI), which can lead to the development of chronic left ventricular aneurysm and subsequent Congestive Heart Failure (CHF) due to left ventricular remodeling, which refers to changes in Left Ventricular (LV) geometry, mass and volume in response to myocardial injury or alterations in load. Surgical reconstruction of the left ventricle is the primary method for treating post-infarction Left Ventricular (LV) aneurysms, which are caused by a focal protrusion of all 3 layers of the LV wall (the endocardium, myocardium and epicardium) ensuring stability (Benz *et al*., 2019).

The long-term progression of congestive heart failure is largely influenced by the development of fine-focal fibrosis in the extracellular matrix, particularly the replacement of damaged cardiomyocytes with scar tissue. Various studies have highlighted a clear correlation between the extent of post-infarction remodeling, the severity of heart failure symptoms and the heightened risk of acute heart failure following LV reconstruction (Blankenberg *et al*., 2003).

Currently, there is insufficient exploration of predictors for adverse outcomes and risk factors associated with the progression of CHF. Therefore, it is imperative to identify specific predictors that contribute to the long-term progression of LV remodeling post-surgical reconstruction, ultimately leading to a recurrence of chronic heart failure.

Matrix Metalloproteinase-9 (MMP-9) is a crucial enzyme involved in the degradation of extracellular matrix components, playing a significant role in tissue remodeling processes. In patients with Coronary Artery Disease (CAD), MMP-9 has garnered attention as a potential prognostic marker for Left Ventricular (LV) remodeling, especially post-Myocardial Infarction (MI) and the subsequent development of heart failure.

Studies have shown that increased levels of MMP-9 are associated with adverse cardiovascular outcomes, including LV dysfunction, increased LV volumes and progression of heart failure symptoms post-MI. Elevated MMP-9 levels have been correlated with pathological remodeling processes in the myocardium, leading to impaired cardiac function and structural changes in the heart.

Research has demonstrated the utility of analyzing MMP-9 expression in myocardial tissues and blood plasma to predict adverse outcomes in patients undergoing surgical interventions for CAD, such as myocardial revascularization and LV reconstruction. By assessing MMP-9 levels before and after surgery, researchers have been able to monitor the progression of LV remodeling and identify patients at higher risk of developing chronic heart failure.

The use of MMP-9 as a prognostic marker offers valuable insights into disease progression, treatment response and long-term outcomes in patients with CAD. By understanding the role of MMP-9 in LV remodeling, clinicians can make informed decisions regarding patient management strategies, risk stratification and personalized treatment plans to improve clinical outcomes and quality of life in individuals with coronary artery disease.

Materials and Methods

This study was conducted in accordance with the ethical principles of the Helsinki Declaration of the World Medical Association (1964, 2004) and written voluntary informed consent from all patients was obtained. Approval for the study was granted by the ethics committee of the Moscow regional research clinical institute No. 6 on July 14, 2017. All patient data was strictly confidential.

The study included 28 patients with multivessel coronary artery disease and Left Ventricular aneurysm (LV) who were divided into two groups. The first group consisted of 18 patients who underwent surgical myocardial revascularization and surgical LV reconstruction five years ago. The second group comprised 10 patients with coronary artery disease complicated by LV aneurysm who underwent planned surgical LV reconstruction with coronary artery bypass grafting. Participants in both groups were selected based on similar clinical diagnoses, age, concomitant pathology and surgical treatment methods.

The small sample in both groups is due to the pilot study, with further expansion of this cohort of patients, as well as the development of the study design.

The inclusion criteria for patients in the main group were: Hemodynamically significant stenoses of the main coronary arteries confirmed by angiography, presence of LV aneurysm, planned surgery (surgical revascularization of the myocardium combined with LV reconstruction), age between 45 and 65 years and informed consent. Exclusion criteria included acute myocardial infarction, chronic heart failure of functional class III-IV, oncological diseases and blood diseases. The control group consisted of 5 healthy volunteers aged 45-60 years, meeting the inclusion criteria of the absence of cardiovascular pathology confirmed by angiography, blood diseases, oncological diseases and narcotic drug intake. Table 1 presents the clinical data of the patients.

Patients from the first study were under constant supervision after surgery, with regular instrumentation and laboratory monitoring, once every 6 months. This included EchoCG, MRI of the heart with contrast, ECG and standard laboratory tests. In the first study, intraoperative biopsy sampling was conducted from both normal and hypokinesis zones to assess the pathomorphological content of MMP-9 and type 4 collagen. In the long-term postoperative period, specifically after 5 years, a blood test for MMP-9 was administered.

Table 1: Clinical data of patients

Indicators	Group 1 Follow-up 5 years after surgery		Group 2 Observation before and after surgical treatment		
	Before the surgery	Long-term	Before the Surgery	In the early postoperative period	Control group
Average age, years	56,1±6,8	61,5±04,1	57,2±05,8	57,2±05,8	54,2±2,8
Sex (M), %	100	100	100	100	100
Diabetes mellitus, %	50	50	60	60	-
Angina pectoris III-IV FC, %	100	50	100	40	-
Heart failure, I-II FC%	60	80	60	60	-
EDD LV, cm	6,1±2,3	6,6±03,4	6,1±02,3	5,1±03,4	4,1±3,4
EDV LV (Simpson), ml	206,0±43,1	244,8±58,2	216,0±43,1	157,8±58,2	127,8±38,2
EF (Theiholz), %	51,3±18,3	44,2±06,7	51,3±18,3	54,2±06,7	59,2±6,7
EF (Simpson), %	41,7±7,2	32,8±05,2	41,7±07,2	45,8±05,2	65,8±5,2
LV thrombus, (no)	8	-	3	-	-
Pulmonary artery pressure, mm Hg	36,2±5,4	22,3±14,6	37,2±6,6	21,3±10,6	20,3±5,6
Number of distal anastomoses	3.2	-	2.5	-	-

FC-Functional Class, EDD LV-End-Diastolic Dimension of the Left Ventricle, EF-Ejection Fraction, EDV LV-End-Diastolic Volume of the Left Ventricle

In the second study, patients underwent surgical remodeling of the myocardium combined with surgical revascularization. A blood test for MMP-9 was performed before and after the operation.

Methods

Commercial kits from two different companies were utilized to quantify the level of circulating MMP-9 in the patients' blood: RnD Systems, Inc. (Human MMP-9 immunoassay Cat. # DMP900) and thermo fisher scientific (human MMP9 ELISA Kit Cat.# BMS2016-2). Blood samples were collected from the patients using vacuum tubes (Vacuette) containing lithium-heparin, followed by centrifugation at 1000 g for 15 min to obtain plasma. The selected plasma was further centrifuged at 10,000 g in a cold rotor for 10 min to eliminate platelets. For the enzyme immunoassay conducted with the RnD kit, the patient's plasma was diluted 40 times, whereas, with the Thermo fisher scientific kit, it was diluted 25 times. The concentration of MMP-9 was determined using standard calibration curves, as per the recommendations provided by the kit manufacturers.

Morphological Examination

Myocardial biopsies were categorized based on their location in the LV and sent for pathomorphological examination. The biopsy specimens intended for examination were fixed in 10% neutral (buffered) formalin. Following sectioning, the tissue fragments were processed using a Leica TP1020 histoprocessor (Leica Biosystems, Germany) according to a standard protocol and subsequently embedded in paraffin blocks. Histological sections measuring 2-3 microns in thickness were obtained using a Leica RM2245 microtome (Leica Biosystems, Germany).

For the Immunohistochemical (IHC) analysis, consecutive sections with a thickness of 2-3 microns were affixed to adhesive-coated slides and the reaction was performed manually. Antibodies to type IV collagen (cell Margue, USA; monoclonal mouse antibodies, clone CIV22) and Matrix Metalloproteinase 9 (MMP-9) (Epitomics, USA; monoclonal rabbit antibodies, clone EP 127) were employed for the IHC studies.

The restoration of antigenicity for type IV collagen was carried out using a pH 9.0 buffer (Trilogy) for 20 min at 97°C in the PT module (Thermo Scientific, UK). For MMP-9, the antigenicity restoration process was performed using a pH 6.0 buffer (Declere) for 20 min at 95°C in the PT Module (Thermo scientific, UK). Both kits have undergone certification and sample preparation.

The IHC reaction intensity of MMP-9 in the Cytoplasm of Cardiomyocytes (CMC) was assessed using a semi-quantitative method: No reaction-0; weak reaction, indicated by the presence of a small amount of finely-grained material in the cytoplasm of CMC-1+; moderate reaction, characterized by medium-sized granules (occasionally large) in the cytoplasm of most CMC-2+; intense reaction, denoted by the presence of a significant number of large-sized granules-3+, in the majority of observed CMC.

Regarding the IHC reaction of type IV collagen, the evaluation was based on the staining characteristics of the Basal Membranes (BM) of CMC: Complete membrane staining of BM in all CMC, following a "grid" pattern-3+; incomplete (partial) staining of BM in most CMC-2+; weakly expressed staining in the form of small fragments on individual CMC-1+; complete absence of staining in all CMC-0.

Results

Patients who participated in the initial study and underwent surgical treatment were safely discharged from the clinic for further observation.

The expression of type IV collagen and MMP-9 in myocardial regions categorized as normokinesis and hypokinesis zones was examined. Our findings demonstrated that in the hypokinetic myocardial zones, the Basement Membranes (BM) of most Cardiomyocytes (CMC) exhibited either complete disappearance or fragmented structures of type IV collagen. Conversely, there was a significant accumulation of MMP-9-positive granules in the cytoplasm of CMC, with the intensity of accumulation correlating to the extent of type IV collagen destruction in the BM (Fig. 1). In contrast, in the normokinesis zones, a distinct and continuous collagen "framework" in the form of "honeycombs" surrounding the CMC was observed (Fig. 2).

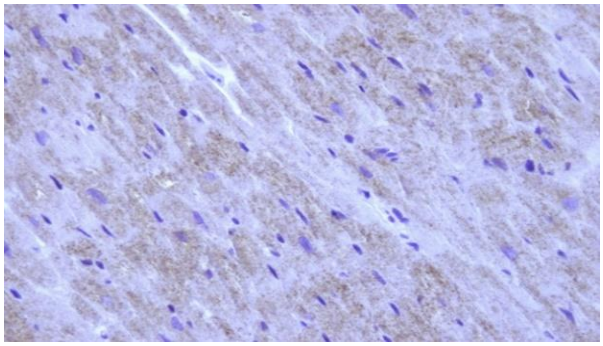

Fig. 1: Cardiac muscle tissue in left ventricular aneurysm: There were significant accumulations of MMP-9 in the cytoplasm of cardiomyocytes in areas where the Basement Membrane (BM) was absent and a structured network of type IV collagen was not formed. The accumulation of metalloproteinases indicates ischemic changes in the extracellular matrix

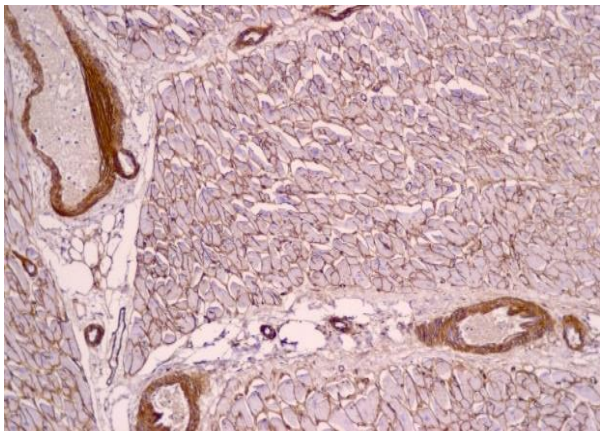

Fig. 2: Normokinesis zone: There was a distinct and well-defined expression of type IV collagen in the form of a solid, clearly colored "grid" or honeycomb pattern observed on both the basement membrane of cardiomyocytes and the walls of blood vessels. The absence of a large amount of MMP-9 and preserved matrix indicates the preserved contractile function

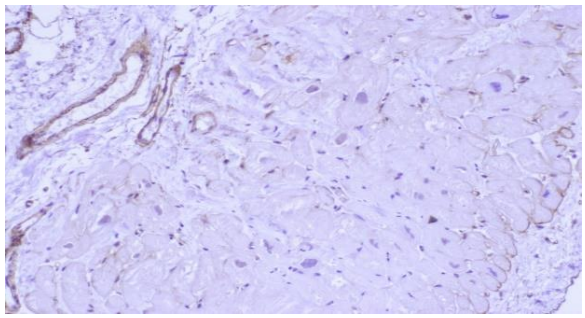

Fig. 3: Hypokinesis zone. The expression of type IV collagen was observed in the walls of blood vessels; however, there was an absence of a solid collagen mesh or fragments of type IV collagen in specific areas of the basal membranes of cardiomyocytes. As a result of such changes, the contractile function of the myocardium suffers and diastolic dysfunction worsens

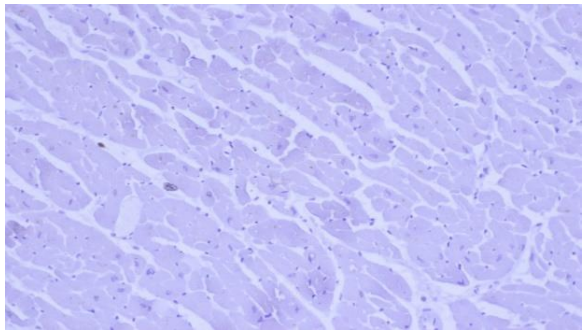

Fig. 4: Healthy myocardium. No MMP9 expression in the cytoplasm of cardiomyocytes, ×250 A, B-IHC assay with antibodies to type IV collagen, ×250. C, D-IHC assay with antibodies to MMP9

Prominent clusters of MMP-9 with large-sized granules were often detected in the hypokinesis zones, where CMC exhibited almost complete absence of type IV collagen in the BM (Fig. 3). Meanwhile, in the normokinesis zones, the expression of MMP-9 in the cytoplasm of the majority of CMCs was not detected, mirroring observations in the control group (Fig. 4), or only minuscule dust-like clusters of this enzyme were observed in individual cells.

When assessing the level of MMP-9 in the patient's blood plasma five years after surgery, the following data were obtained and are presented in Table 2. Based on the 5-year follow-up and analysis of long-term treatment outcomes, the patients could be divided into two groups: Group 1, consisting of 10 patients displaying negative dynamics, with an average MMP-9 concentration of 240 ng/mL; and group 2, comprising 8 patients exhibiting stabilization of the condition, with an average MMP-9 concentration of 128 ng/mL (Table 2). By comparison, in the control group of patients without signs of Congestive Heart Failure (CHF), the average MMP-9 concentration in blood plasma was 74 ng/mL.

Table 2: Clinical and morphological characteristics and long-term results of treatment of patients with coronary heart disease

Patients (No.)	MMP9 expression in the hypokinesis zone normokinesis zone	Expression of type 4 collagen in BM in the	Long-term result (after 5 years)	Concentration of MMP-9 in blood serum, 5 years after surgery (p1-2 = 0,0287)
Group 1, n = 10	2+/3+ (abundant accumulations of large and medium-sized granules)	0-1+ (missing, single fragments of BM)	Negative dynamics in the form of a decrease in the ejection fraction, expansion of the heart cavities	240 ng/mL
Group 2, n = 8	0-1+ (granules are absent or present in the form of dust-like clusters in individual cells)	2-3+ (The BM is preserved of whole or in part on most KMTs)	Stable post-surgical course, preserved ejection fraction, slight increase in heart cavities	128 ng/mL

Table 3: Cardiac ultrasound data before and after surgery

	Group 2 (n = 10)	
Cardiac ultrasound data	Before the surgery	7 days after surgery
EDD LV, cm	6,6±03,4	5,4±02,2
EDV LV (S), mL	264,8±58,2	167,1±44,9
EF (Theiholz), %	44,2±06,7	49,3±10,5
EF (Simpson), %	32,8±05,2	41,8±05,5

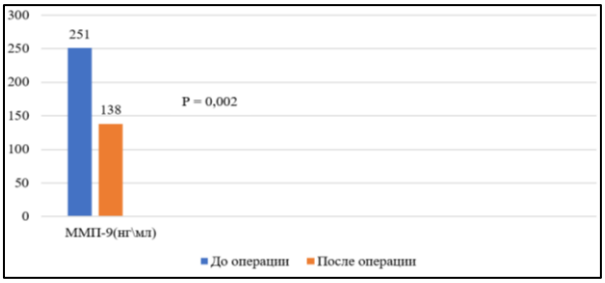

Fig. 5: MMP-9 before and after surgery. A statistically significant decrease in MMP-9 after myocardial revascularization was shown, probably due to an improvement in left ventricular systolic function

The second study aimed to compare the concentration of MMP-9 between the preoperative and early postoperative periods. The patients underwent complete myocardial revascularization along with surgical LV remodeling. Analysis of echocardiographic parameters in the early postoperative period revealed a significant improvement in LV pumping function due to myocardial revascularization. The corresponding data is presented in Table 3. Additionally, the patients experienced a disappearance of angina pectoris symptoms and a reduction in the severity of heart failure.

The analysis of MMP-9 was performed before and after the operation, the data are presented in Fig. 5.

Limitations of the Study

Sample size Our study included a small number of patients, but despite this, we obtained results that require further consideration of this issue.

The use of semi-quantitative methods for determining the expression of MMP-9-despite the routine nature of the method, the presence of the human factor imposes its own disadvantages.

Discussion

Despite satisfactory hemodynamic parameters and quality of life after surgical treatment, the remodeling process becomes pathologically irreversible over time due to fibrosis progression (Brunner *et al*., 2010). This leads to further dilation of the left ventricular cavity, worsening the course of chronic heart failure. Therefore, it is important to identify predictors of long-term LV remodeling progression after surgical reconstruction, which can contribute to a relapse of chronic heart failure (Ezhov *et al*., 2019). This highlights the need for closer monitoring of this patient population to prevent irreversible consequences of chronic heart failure and identify indications for heart transplantation consideration (Ferraris, 2021; Gu *et al*., 2017).

In recent years, MMPs have been extensively studied as markers for predicting LV remodeling following Myocardial Infarction (MI) and the subsequent development of heart failure (Guizani *et al*., 2022; Jha *et al*., 2015; Kloner, 2020; Konstantino *et al*., 2009; 2007). MMP-9, also known as gelatinase B, is one of the most widely studied proteases involved in pathological remodeling processes. MMP-9 plays a major role in the degradation of extracellular matrix in various physiological and pathophysiological processes, including tissue remodeling. It is secreted by various cell types, including

cardiomyocytes, endothelial cells, neutrophils, macrophages and fibroblasts (Kremastiotis *et al*., 2021; Kwon *et al*., 2008; Mosterd and Hoes, 2007; Popov *et al*., 2023; Sahle *et al*., 2017; Squire *et al*., 2004).

Blankenberg *et al*. (2003) were the first to utilize MMP-9 as a prognostic biomarker for the development of LV dysfunction and cardiovascular mortality. In a study of 1127 patients with confirmed atherosclerotic coronary artery disease, they investigated baseline plasma levels of MMP-9 over an average follow-up period of 4.1 years. Concentrations of MMP-9 were significantly higher among patients who experienced fatal cardiovascular events compared to those who did not (62.2 vs. 47.8 ng/mL; $p<0.0001$). The authors concluded that plasma concentration of MMP-9 can serve as a novel predictor of cardiovascular mortality in patients with coronary heart disease (Xin *et al*., 2013).

Squire *et al*. (2004) demonstrated that increased levels of MMP-9 are associated with large volumes of left ventricle and LV dysfunction following MI. In a study involving 60 patients with acute myocardial infarction, the quantitative level of MMP-9 was assessed within 5 days after MI. The authors concluded that MMP-9 can provide insights into myocardial remodeling after MI (Ya, 2015).

Based on the findings of the first study, we demonstrated that the pair of type 4 collagen and MMP-9 from intraoperative biopsies can be a reliable predictor ($p = 0.001$) of adverse prognoses following surgical myocardial remodeling (Zeng *et al*., 2005).

Analysis of MMP-9 indicators from blood samples after 5 years revealed negative dynamics, indicated by a high plasma concentration of MMP-9, likely associated with ongoing ischemic changes in the myocardium despite myocardial revascularization and consequently, the progression of chronic heart failure. Therefore, plasma MMP-9 can serve as a reliable marker for adverse outcomes in this patient population.

Additionally, when analyzing MMP-9 in patients from the second study before surgery and in the early postoperative period, we observed a statistically significant decrease ($p = 0.002$) in MMP-9 levels, directly indicating the benefits of myocardial revascularization. Monitoring the dynamics of MMP-9 concentration is planned for future assessments.

The clinical implications of our findings highlight the significance of MMP-9 as a valuable biomarker for predicting adverse outcomes following surgical myocardial remodeling and myocardial infarction. Elevated levels of MMP-9 have been associated with increased left ventricular volumes, dysfunction and progression of chronic heart failure. Monitoring plasma concentrations of MMP-9 can aid in identifying patients at risk of adverse cardiovascular events, guiding closer monitoring and potentially altering treatment strategies. The use of MMP-9 as a prognostic tool provides insight into myocardial remodeling post-MI, allowing for timely interventions and personalized approaches to patient care. These findings underscore the importance of incorporating MMP-9 assessment into clinical practice for better risk stratification and improved management of patients undergoing surgical myocardial reconstruction and revascularization.

Conclusion

The presented results demonstrate certain successes achieved in the search for a predictor of adverse events after myocardial revascularization, in combination with surgical remodeling of the myocardium. In the future, MMP-9 can also be used at the pre-hospital stage, when selecting candidates for surgical revascularization. With an increased content above certain values, the patient may be denied surgical treatment, taking into account unfavorable outcomes and a more gentle personalized approach is offered.

Acknowledgment

Thank you to the publisher for their support in the publication of this research article. We are grateful for the resources and platform provided by the publisher, which have enabled us to share our findings with a wider audience. We appreciate the effort.

Funding Information

This research was supported by Russian science foundation grant number 20-15-00264.

Author's Contributions

Mikhail Aleksandrovich Popov: Conceptualization, written-original draft preparade.

Anastasia Vladimirovna Poznyak, Elizaveta Mikhailovna Pleshko, Victor Yurievich Glanz, Natalia Mikhailovna Kashirina, Vasily Nikolaevich Sukhorukov, Dmitry Felixovich Beloyartsev and Alexander Nikolaevich Orekhov: Written-review and edited.

Dmitry Valerievich Shumakov: Conceptualization.

Dmitry Igorevich Zybin, Liudmila Nikolaevna Lipatova, Mikhail Mikhailovich Peklo and Pavel Nikolaevich Rutkevich: Investigation.

Elena Vadimovna Yanushevskaya: Investigation, written-original draft preparade.

Ethics

Institutional review board statement this study was conducted in accordance with the ethical principles of the Helsinki declaration of the world medical association (1964, 2004) and written voluntary informed consent

from all patients was obtained. Approval for the study was granted by the ethics committee of the Moscow regional research clinical institute No. 6 on July 14, 2017.

References

Acar, E., Aksu, A., Akkaya, G., & Çapa Kaya, G. (2019). Prevalence and Localization of Hibernating Myocardium Among Patients with Left Ventricular Dysfunction. *Current Medical Imaging*, *15*(9), 884-889. https://doi.org/10.2174/1573405615666190701110620

Benz, D. C., Von Dahlen, A. P., Huang, W., Messerli, M., Von Felten, E., Benetos, G., Giannopoulos, A. A., Fuchs, T. A., Gräni, C., Gebhard, C., Pazhenkottil, A. P., Gaemperli, O., Kaufmann, P. A., & Buechel, R. R. (2019). No Differences in Rest Myocardial Blood Flow in Stunned and Hibernating Myocardium: Insights into the Pathophysiology of Ischemic Cardiomyopathy. *European Journal of Nuclear Medicine and Molecular Imaging*, *46*, 2322-2328. https://doi.org/10.1007/s00259-019-04440-2

Blankenberg, S., Rupprecht, H. J., Poirier, O., Bickel, C., Smieja, M., Hafner, G., Meyer, J., Cambien, F., & Tiret, L. (2003). Plasma Concentrations and Genetic Variation of Matrix Metalloproteinase 9 and Prognosis of Patients with Cardiovascular Disease. *Circulation*, *107*(12), 1579-1585. https://doi.org/10.1161/01.cir.0000058700.41738.12

Brunner, S., Kim, J.-O., & Methe, H. (2010). Relation of Matrix Metalloproteinase-9/Tissue Inhibitor of Metalloproteinase-1 Ratio in Peripheral Circulating CD14+ Monocytes to Progression of Coronary Artery Disease. *The American Journal of Cardiology*, *105*(4), 429-434. https://doi.org/10.1016/j.amjcard.2009.10.013

Ezhov, M., Safarova, M., Afanasieva, O., Mitroshkin, M., Matchin, Y., & Pokrovsky, S. (2019). Matrix Metalloproteinase 9 as a Predictor of Coronary Atherosclerotic Plaque Instability in Stable Coronary Heart Disease Patients with Elevated Lipoprotein(a) Levels. *Biomolecules*, *9*(4), 129. https://doi.org/10.3390/biom9040129

Ferraris, V. A. (2021). Commentary: Recovering Ischemic Myocardium-Hibernation, Autophagy, Preconditioning, Mitochondria, Stem Cells and More. *The Journal of Thoracic and Cardiovascular Surgery*, *162*(1), E17-E18. https://doi.org/10.1016/j.jtcvs.2020.01.002

Gu, C., Wang, F., Hou, Z., Lv, B., Wang, Y., Cong, X., & Chen, X. (2017). Sex-Related Differences in Serum Matrix Metalloproteinase-9 Screening Non-Calcified and Mixed Coronary Atherosclerotic Plaques in Outpatients with Chest Pain. *Heart and Vessels*, *32*, 1424-1431. https://doi.org/10.1007/s00380-017-1014-3

Guizani, I., Zidi, W., Zayani, Y., Nesrine, F., Douik, H., Sanhaji, H., Mourali, M. S., Feki, M., & Allal-Elasmi, M. (2022). Matrix Metalloproteinase 3 and 9 as Genetic Biomarkers for the Occurrence of Cardiovascular Complications in Coronary Artery Disease: A Prospective Cohort Study. *Molecular Biology Reports*, *49*, 9171-9179. https://doi.org/10.1007/s11033-022-07742-1

Jha, S. R., S. K. Ha, H., Hickman, L. D., Hannu, M., Davidson, P. M., Macdonald, P. S., & Newton, P. J. (2015). Frailty in Advanced Heart Failure: A Systematic Review. *Heart Failure Reviews*, *20*, 553-560. https://doi.org/10.1007/s10741-015-9493-8

Kloner, R. A. (2020). Stunned and Hibernating Myocardium: Where Are We Nearly 4 Decades Later? *Journal of the American Heart Association*, *9*(3), e015502. https://doi.org/10.1161/jaha.119.015502

Konstantino, Y., Nguyen, T. T., Wolk, R., Aiello, R. J., Terra, S. G., & Fryburg, D. A. (2009). Potential Implications of Matrix Metalloproteinase-9 in Assessment and Treatment of Coronary Artery Disease. *Biomarkers*, *14*(2), 118-129. https://doi.org/10.1080/13547500902765140

Konstantino, Y., Wolk, R., Terra, S. G., Nguyen, T. T., & Fryburg, D. A. (2007). Non-Traditional Biomarkers of Atherosclerosis in Stable and Unstable Coronary Artery Disease, do they Differ. *Acute Cardiac Care*, *9*(4), 197-206. https://doi.org/10.1080/17482940701474486

Kremastiotis, G., Handa, I., Jackson, C., George, S., & Johnson, J. (2021). Disparate Effects of MMP and TIMP Modulation on Coronary Atherosclerosis and Associated Myocardial Fibrosis. *Scientific Reports*, *11*, 23081. https://doi.org/10.1038/s41598-021-02508-4

Kwon, S. H., Ju, S. A., Kang, J. H., Kim, C. S., Yoo, H. M., & Yu, R. (2008). Chemokine Lkn-1/CCL15 Enhances Matrix Metalloproteinase-9 Release from Human Macrophages and Macrophage-Derived Foam Cells. *Nutrition Research and Practice*, *2*(2), 134-137. https://doi.org/10.4162/nrp.2008.2.2.134

Mosterd, A., & Hoes, A. W. (2007). Clinical Epidemiology of Heart Failure. *Heart*, *93*(9), 1137-1146. https://doi.org/10.1136/hrt.2003.025270

Popov, M. A., Shumakov, D. V., Gurevich, L. E., Fedorov, D. N., Zybin, D. I., Ashevskaya, V. E., Korosteleva, P. A., & Tyurina, V. M. (2023). The Evaluation of Hibernating Myocardium Function. *Clinical and Experimental Morphology*, *12*(1), 59-67. https://doi.org/10.31088/cem2023.12.1.59-67

Sahle, B. W., Owen, A. J., Chin, K. L., & Reid, C. M. (2017). Risk Prediction Models for Incident Heart Failure: A Systematic Review of Methodology and Model Performance. *Journal of Cardiac Failure*, *23*(9), 680-687. https://doi.org/10.1016/j.cardfail.2017.03.005

Squire, I. B., Evans, J., Ng, L. L., Loftus, I. M., & Thompson, M. M. (2004). Plasma MMP-9 and MMP-2 Following Acute Myocardial Infarction in Man: Correlation with Echocardiographic and Neurohumoral Parameters of Left Ventricular Dysfunction. *Journal of Cardiac Failure*, *10*(4), 328-333. https://doi.org/10.1016/j.cardfail.2003.11.003

Xin, X., Lihan, W., Changfu, X., Peng, Z., Fendi, Y., Haibo, L., Jianan, W., & Yuping, S. (2013). Variations in Matrix Metalloproteinase-1, -3 and -9 Genes and the Risk of Acute Coronary Syndrome and Coronary Artery Disease in the Chinese Han Population. *Coronary Artery Disease*, *24*(4), 259-265. https://doi.org/10.1097/mca.0b013e32835ea3af

Ya, L. (2015). Correlation Analysis of Levels of Adiponectin and Matrix Metalloproteinase-9 with Stability of Coronary Heart Disease. *Technology and Health Care*, *23*(s1), S95-S98. https://doi.org/10.3233/thc-150937

Zeng, B., Prasan, A., Fung, K. C., Solanki, V., Bruce, D., Freedman, S. B., & Brieger, D. (2005). Elevated Circulating Levels of Matrix Metalloproteinase-9 and-2 in Patients with Symptomatic Coronary Artery Disease. *Internal Medicine Journal*, *35*(6), 331-335. https://doi.org/10.1111/j.1445-5994.2005.00822.x