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THE ROLE OF MATRIX METALLOPROTEINASES IN THE DEVELOPMENT OF CHRONIC HEART FAILURE

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Abstract: the progression of chronic heart failure in patients with myocardial infarction is accompanied by changes in the structure and function of the cardiovascular system. The results of this work made it possible to establish the pattern of participation of MMP-9 and TIMP-4 in the processes accompanying the rearrangement of the extracellular matrix of the heart during postinfarction remodeling of the left ventricle, the development and progression of chronic heart failure.

Key words: matrix metalloproteinases, tissue inhibitors of metalloproteinases, cardiovascular system, chronic heart failure.

Relevance. Despite significant achievements in the study of the pathogenesis, diagnosis and treatment of chronic heart failure (CHF), it still occupies a leading position in the structure of cardiovascular diseases, continuing to grow, reaching 1.5-2.0% in the general population, and 6-10% among people over 65 years of age [7-12]. Currently, it has become obvious that changes in the structure of the extracellular matrix and cell death by apoptosis play an important role in the formation of chronic heart failure. Among the mechanisms of the damaging effect of systemic inflammation factors in CHF, attention is drawn to the state of activity of the matrix metalloproteinase (MMR) system and tissue metalloproteinase inhibitors (TIMR) [1,6]. Matrix metalloproteinases (MMPs) are the main regulators of myocardial extracellular matrix metabolism during postinfarction LV remodeling, and MMP-9, in turn, is the main metalloproteinase of human neutrophils and monocytes [2.11]. There are very few studies examining the clinical significance of MMP and TIMMP concentrations in cardiovascular diseases. Therefore, the study of the serum concentration of MMP/TIMP will determine their place in assessing the prognostic significance of degradation of the extracellular matrix of the myocardium for the development of cardiovascular complications in patients who have suffered an acute myocardial infarction.

Objective: to study the activity level of MMP-9 and TIMP-4 in patients with postinfarction cardiosclerosis at different stages of chronic heart failure.

Research methods and materials. The study included 39 patients who were treated for CHF against the background of postinfarction cardiosclerosis in the 1 hospital of the Samarkand State Medical University in the period from 2022-23. The diagnosis of CHF was made on the basis of the classification proposed by the Society of Specialists in Heart Failure, which provides for the unification of the currently existing classification of stages of CHF according to N.D. Strazhesco and V.H. Vasilenko (1935) and FC according to the classification of the New York Association of Cardiologists (NYHA, 1964). These moments were decisive for the inclusion of patients in this group. The average duration of CHF was 4.14+0.40 years. As it was noted, the main cause of CHF in patients was acute myocardial infarction. All patients with coronary heart disease

included in the study had suffered a myocardial infarction and suffered from postinfarction angina pectoris. The functional class of angina pectoris and the variant of unstable angina pectoris was determined according to the classification of angina pectoris of the Canadian Cardiovascular Society and the classification of E.Braunwald. Metalloproteinase-9 (MMP-9) and its type 4 tissue inhibitor (TIMP-4) were determined using a sandwich version of solid-phase enzyme immunoassay (ELISA), according to the attached instructions using specific reagents from Vector-Best CJSC (Russia). The results were recorded using an enzyme immunoassay analyzer - MINDRAY (China). Calculations of the number of indicators were carried out by constructing a calibration curve using a computer program, expressed in ng/ml. The obtained data were subjected to statistical processing. The results of the study: When analyzing the content of the metalloproteinase-9 system in patients with CHF, it was revealed that the level of MMR-9 was more than twice higher than that of healthy donors, which reflects its participation in myocardial damage. At the same time, no significant difference in TIMP-4 was found in comparison with the control group, only a tendency to increase TIMP-4 was recorded in the general group of patients with CHF, which can be regarded as compensatory activity.

Table 1. The content of MMP-9 and its tissue inhibitor TIMP-4 in patients with CHF

Indicators	Patients with CHF – a common group	Healthy donors	Significance level (P)
MMP-9 ng/ml	24,51±0,21	10,91±0,17	0,01
TIMP-4 ng/ml	1,26±0,06	2,15±0,05	0,01

When analyzing metalloproteinase-9 indices, depending on age, we revealed slightly reduced values of MMR-9 in the blood serum of patients under 50 years of age (19.91±0.76), compared with patients after 50 years of age (23.67±0.17 ng/ml). The TIMP-4 index in patients, depending on age, also had distinctive features, which was manifested by a significant increase in this indicator in the group of patients under 50 years of age compared with the group of patients with CHF after 50 years ($p>0.05$).

Table 2. The content of MMP-9, its tissue inhibitor TIMP-4, depending on the age of patients with CHF

Indicators	Patients with CHF – up to 50 years old	Patients with CHF – after 50 years of age	Significance level (P)
MMP-9 ng/ml	19,91±0,76	23,67±0,17	0,05
TIMP-4 ng/ml	1,89±0,04	1,18±0,02	0,05

When distributing patients with CHF by gender, it was found that the level of MMR-9 was slightly higher in men than in women and reached statistical significance ($p<0.05$). An increase in the formation of MMR-9 in men can also be associated with sexual reactivity or, possibly, with the predominance of smokers among men, who, according to the literature, have pronounced activity of MMR-9 [18]. The content of TIMP-4 in the male population was also higher than that of the female group, the differences also reached statistical significance, amounting to 1.31±0.03 ng/ml compared with 1.17±0.04 ng/ml (Table 3).

Table 3. The content of MMP-9, its tissue inhibitor TIMP-4, depending on the gender of patients with CHF

Indicators	Patients with CHF – Male	Patients with CHF – Female	Significance level (P)
MMP-9 ng/ml	24,07±0,31	13,21±0,48	<0,05
TIMP-4 ng/ml	1,31±0,03	1,17±0,04	<0.05

When studying the MMP-9 index, depending on the time interval after the MI, we found the highest values of MMP-9 in the period up to 12 months after MI (Table 4). At the same time, the level of TIMP-4 was higher than the control level during this period after MI ($p<0.05$), which reflects activation of TIMP-4 aimed at binding excess MMP-9 (Table 4).

Table 4. The content of MMP-9, its tissue inhibitor TIMP-4 in patients with CHF, depending on the prescription of MI

Indicators	Patients with CHF – up to 12 months after MI	Patients with CHF – more than 12 months after MI	Significance level (P)
MMP-9	25,21±0,24	21,87±0,41	<0,05
TIMP-4	1,72±0,08	1,15±0,05	<0,05

The MMR-9 index was also high for a period of more than 12 months and amounted to 21.87±0.41 ng/ml, reaching statistical significance compared with this indicator in the control group ($p<0.05$). The content of TIMP-4 in the period more than 12 months after MI was lower than in the period up to 12 months after MI, which does not exclude the interruption of the use of recommended postinfarction therapy by patients and the development of reactivation of inflammation and myocardial damage.

Next, we studied the average values of MMR-9 and TIMP-4 indicators depending on the severity of CHF. It was recorded that with an increase in the degree of CHF, there was an increase in the level of MMR-9, and vice versa, a decrease in TIMP-4. Thus, the level of MMR-9 in stage IIB CHF was 26.46±0.24 ng/ml against stage IIA CHF 24.31±0.17 ng/ml and against stage I CHF 22.77±0.30 ng/ml. The values of TIMP-4 at grade IIB CHF amounting to 1.21±0.02 ng/ml were significantly lower than at grade IIA CHF 1.34±0.04 ng/ml and grade I CHF 1.25±0.03 ng/ml (Table 5).

Table 5. The content of MMP-9, its tissue inhibitor TIMP-4, depending on the severity of CHF

Indicators	CHF I	CHF IIA	CHF IIB	Healthy donors
MMP-9 ng/ml	22,77±0,30	24,31±0,17	26,46±0,24	10,91±0,17
TIMP-4 ng/ml	1,25±0,03	1,34±0,04	1,21±0,02	2,15±0,05

Conclusions. Thus, our studies have established a progressive increase in the systemic level of MMP-9, a decrease in the content of TIMP-4 with an increase in the severity of CHF, depending on the time interval after IT, which indicates the activation of inflammatory reactivity mechanisms and a lack of specific tissue inhibitors aimed at binding excess metalloproteinases in ischemic myocardial tissue damage.

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