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Regulation of extracellular matrix in patients with Q-wave myocardial infarction after thrombolytic therapy

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Key words: *matrix metalloproteinase, myocardial infarction, heart aneurysm.*

Aims. In order to study the levels of matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, intracardiac hemodynamics, frequency of acute cardiac aneurysm development in patients with Q-wave myocardial infarction after thrombolysis, 74 patients were examined.

Methods and results. All participants underwent clinical and laboratory examination, echocardiography, determination of serum levels of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1.

Conclusion. Patients, who got thrombolysis in 6 to 12 hours period, had excessive activation of the proteolysis system on the background of relative deficit of tissue inhibitor of metalloproteinase-1, the prevalence of dilatation and restrictive diastolic dysfunction, cardiac aneurysm was detected frequently and thrombogenic potential was higher.

Регуляція екстрацелюлярного матриксу у хворих на Q-інфаркт міокарда після тромболітичної терапії

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З метою вивчення рівнів матриксної металопротеїнази-9, тканинного інгібітора металопротеїнази-1, стану внутрішньосерцевої гемодинаміки, частоти виникнення гострої післяінфарктної аневризми серця у хворих на Q-інфаркт міокарда після тромболізису обстежено 74 хворих. Усім пацієнтам проведено клініко-лабораторне обстеження, ехокардіографію, визначено сироваткові рівні матриксної металопротеїнази-9 та тканинного інгібітора металопротеїнази-1. У хворих, яким проводили тромболізис у строки від 6 до 12 годин, встановили надмірну активацію системи протеолізу на тлі відносного дефіциту тканинного інгібітора металопротеїнази-1, перевагу процесів дилатації та рестриктивний тип діастолічної дисфункції лівого шлуночка, частіше виявляли аневризму серця та визначили більший тромбогенний потенціал.

Ключові слова: *матриксна металопротеїназа, інфаркт міокарда, аневризма серця.*

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Регуляция экстрацелюлярного матрикса у больных Q-инфарктом миокарда после тромболитической терапии

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С целью изучения уровней матриксной металлопротеиназы-9, тканевого ингибитора металлопротеиназы-1, состояния внутрисердечной гемодинамики, частоты возникновения острой постинфарктной аневризмы сердца у больных Q-инфарктом миокарда после тромболизиса обследовано 74 больных. Всем пациентам проведено клинико-лабораторное обследование, эхокардиографию, определены сывороточные уровни матриксной металлопротеиназы-9 и тканевого ингибитора металлопротеиназы-1. У больных, которым проводили тромболизис в сроки от 6 до 12 часов, установили чрезмерную активацию системы протеолиза на фоне относительного дефицита тканевого ингибитора металлопротеиназы-1, преобладание дилатации и рестриктивный тип диастолической дисфункции левого желудочка, чаще обнаруживали аневризму сердца и определили больший тромбогенный потенциал.

Ключевые слова: *матриксная металлопротеиназа, инфаркт миокарда, аневризма сердца.*

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Achievements and successes of modern cardiology in recent years have led to a significant reduction in morbidity and mortality from myocardial infarction (MI), as in Ukraine, as abroad [3, 4, 5]. However, remains a high probability of myocardial infarction complicated course, even if the modern treatment strategy isused [3]. One of the most dangerous complications of MI is the occurrence of an aneurysm of the left ventricle (LV) [10]. In this course of postinfarction remodeling in the pathological process involved both cellular and extracellular morphologic substrate [5]. Modification of extracellular matrix in the myocardium leads to increased rigidity and changes in cardiac chamber geometry [7]. As a consequence of changes in the spatial organization of the heart chambers, disrupt filling and expulsion of blood from the heart, leading to the development of systolic and diastolic dysfunction [6]. At present time, it is well known fact, that the synthesis and degradation of extracellular substance is controlled by systems MMP/TIMP, the ratio of which influence to the character of extracellular matrix of myocardium restructuring [8]. The study of the diagnostic and prognostic value of MMP-9 showed increased activity of this gelatinase in serum of patients with myocardial infarction compared with controls and patients with unstable angina and preference of proteolytic processes during postinfarction remodeling [7, 8, 9]. Similar effects were found after experimental myocardial infarction in mice with deficit of TIMP-1 [4]. Still unclear is the impact of treatment strategy on the state of the MMP/TIMP system and development of postinfarction remodeling.

The purpose of the study

To investigate the levels of MMP-9, TIMP-1, the status of intracardiac hemodynamics, frequency of acute postinfarc-

tion left ventricular aneurysm development in patients with Q-wave myocardial infarction after thrombolytic therapy.

Patients and methods

74 patients (43 males and 31 females, mean age – 61.2 ± 3.5 years) were examined. They were delivered to the intensive care unit of Municipal Institution «City Clinical Hospital of Emergency and Urgent Care of Zaporizhzhya» with a diagnosis of acute Q-wave myocardial infarction of anterior wall of left ventricle (LV). The diagnosis was determined according to the recommendations of the Association of Cardiologists of Ukraine (2013). Drug treatment was performed according to the order of Ministry of Public Health of Ukraine №436 from 03.07.2006 «Protocols of care for patients with Acute Coronary Syndrome with segment ST elevation (Q-wave myocardial infarction). All patients received thrombolytic therapy (TLT) using Streptokinase (Farmakinase, Farmak, Ukraine) and basic therapy that included statins, anticoagulants (unfractionated or low molecular weight heparin), antiplatelet agents (aspirin and clopidogrel), beta-blockers, ACE inhibitors at target doses, nitrates by demand. Depending on the exposure of onset of thrombolytic therapy all patients were divided to such groups: the first group consists of 24 patients who received thrombolytic therapy within the first 2 hours from onset, the second – 32 patients with an exposure of 2 to 6 hours, third – 18 persons who got thrombolytic therapy from 6 to 12 hours.

Groups were comparable by age, sex and comorbidities. All patients were examined by clinical, laboratory, ECG and echocardiography methods on the fifth day. ECG was recorded using diagnostic complex «Cardiolab» («HAI – Medica», Kharkov, Ukraine). Intracardiac hemodynamics was investigated using two-dimensional transthoracic echocardiography with the help of ultrasound diagnostic scanner MyLab 50 CV XVision (Esaote, Italy). Using echocardiography we assessed such parameters of the heart, as diastolic diameter of left atrium (LA), interventricular septum in diastole (IVSd), end-diastolic diameter of LV (LVIDd), posterior wall of LV in diastole (PWLV), end-systolic diameter of LV (LVIDs), relative thickness of walls of LV (RTW), LV myocardium mass index (LVMMI), ejection fraction (EF), stroke volume (SV), stroke index (SI), cardiac output (CO), cardiac index (CI), early LV filling velocity (VE), atrial systole flow velocity (VA) and their ratio (VE/VA), deceleration time of E velocity (DT), isovolumic relaxation time (IVRT), pressure in pulmonic artery (Pr. A.pulm.). Serum levels of matrix metalloproteinases-9 (MMP-9) and tissue inhibitor of metalloproteinases-1 (TIMP-1) were determined using ELISA kits reagents of «Elisa» company (Austria) microplate photometer DigiScan-400 in the Central Research Laboratory of Zaporizhzhya State Medical University (Head - Prof. A.V. Abramov).

Statistical analysis of the results was performed on a personal computer using the licensed program "Statistica" (version 6.0, StatSoftInc, USA). The distribution of the variables in the ranks of variation was determined by Shapiro-Wilk test. With a normal distribution of signs descriptive statistics presented as mean and standard deviation (M ± SD), with an abnormal distribution - as the median and interquartile range - Me (IQR). The significance of differences was evaluated by parametric (t-test, ANOVA) and nonparametric (Wald-Wolfowitz test, Kolmogorov-Smirnov two-sample test, Mann-Whitney U-test). Significant differences were in case of $p<0.05$.

Results and discussion

Analysis of indicators which characterize the MMP/TIMP system (*tabl. 1*) showed the lowest level of MMP-9 in patients of the first group. The level of MMP-9 was significantly higher in the second (25.7%, p = 0.01) and third (47.5%, p = 0.001) groups than in the first. The level of MMP-9 in the third group prevailed also in comparison with the second group (17.3%, p = 0.04). Serum level of TIMP-1 in the first group was the highest and dominated in comparison with patients of the second (33.8%, p = 0.03) and third (58.3%, p = 0.006) groups. In the second group the level of TIMP-1 was higher than the same index in the third group (36.9%, p = 0.05).

Table 1

MMP/TIMP system characteristic

Index	1 group n=24	2 group n=32	3 group n=18
MMP-9, ng/ml	73.4±2.1	92.3±5.4*	108.3±1.7*#
TIMP-1, pg/ml	113500.4±269.3	75150.8±74.2*	47350.2±126.3*#

Note: * – differences are significant in comparison with the first group ($p<0.05$), # – differences are significant in comparison with the second group ($p<0.05$).

Obtained data, in case of thrombolytic therapy application in later periods, are the evidence of excessive activation of proteolysis on the background of relative deficiency of TIMP-1, which is an inhibitor of excessive activity of MMP-9. However, in patients with less period before the beginning of thrombolytic therapy lower levels of MMP-9 in the background of increased activity TIMP-1 were observed. By data of Ferrony P. et al. (2003), high activity of proteolysis associated with the processes of disintegration of extracellular matrix [7].

During Doppler echocardiography (*mabl. 2)* in the third group in comparison with the first and second groups were registered higher indexes of LVIDd (14.3%, p = 0.03 and 9.6%, p = 0.05), LVIDs (23.8%, p = 0.01 and 18.9%, p = 0.04 appropriately), the frequency of left ventricular aneurysm detection (85.2%, p = 0.03 and 66,4%, p = 0.001 appropriately) and the phenomenon of spontaneous ventricular contrasting (44.1%, p = 0.03 and 74.4%, p = 0.001 appropriately), higher than in the first group were such indexes as LVMMI (15.2%, p = 0.05), SV (31.2%, p = 0.008), SI (30.4%, p = 0.02), CO (19.2%, p = 0.05), CI (25.2%, p = 0.04), VE (42.4%, p = 0.001) , VT/VA ratio(51.5%, p = 0.006), left ventricular aneurysm (85.2%, p = 0.001) , smaller than the first and second groups values of LV EF (23.3%, p = 0.04 and 11.2%, p = 0.05, appropriately), lower than in the first group of indicators VA (25.0%, p = 0.002), DT (25.0% p = 0.002) and IVRT (94.3%, p = 0.001) of LV. In the second group, compared with the first, there were determined higher values of SV (26.5% , p = 0.03), SI (22.1 %, p = 0.01), CI (17,2%, p = 0.05) VE (31.1%,

p = 0.02) , VE/VA ratio (40.2%, p = 0.04) and lower values of LV EF (10.8%, p = 0.05), VA (61.2%, p = 0.05), DT (29.4%, p = 0.008) and IVRT(69.9%, p = 0.002) of LV.

Table 2

Doppler echocardiography indexes

Index	1 group n=24	2 group n=32	3 group n=18
LA, sm	3.94±0.31	4.12±0.36	4.29±0.18
IVSd, sm	0.94±0.17	1.04±0.10	0.98±0.09
LVIDd,sm	5.34±0.12	5.63±0.20	6.23±0.11*#
PWLVd,sm	1.10±0.07	1.12±0.05	1.14±0.12
LVIDs,sm	3.06±0.15	3.26±0.11	4.02±0.12*#
RTW, U	0.45±0.03	0.42±0.04	0.38±0.06
LVMMI,g	119.3±4.1	129.5±5.7	140.7±3.4*
EF, %	48.2±0.2	43.5±0.3*	39.1±1.0*#
SV,ml	52.3±3.7	71.2±6.2*	76.0±3.2*
SI, ml/m^2	32.5±3.1	41.7±1.8*	46.7±2.4*
CO,l/min	4.83±0.33	5.61±0.13	5.98±0.16*
CI,l/min/m^2	2.78±0.18	3.36±0.22*	3.72±0.38*
VE, m/sec	0.42 (0.40; 0.51)	0.61 (0.50; 0.64)*	0.73 (0.66; 0.74)*
VA,m/sec	0.50 (0.47; 0.56)	0.31 (0.29; 0.37)*	0.40 (0.38; 0.44)*
VE/VA, U	0.79±0.08	1.32±0.04*	1.63±0.07*
DT, msec	152.4±1.3	117.8±1.0*	128.5±1.3*
IVRT, msec	121.3±3.4	71.4±4.2*	62.4±3.8*
PrA.pulm,mmHg	27.5±5.2	31.9±3.4	41.5±2.3
Phenomenon of spontaneous contrast	8.1%	3.7%	14.5%*#
Aneurism of LV	4.1%	9.3%	27.7%*#
Thrombus of LV	4.1%	6.2%	16.6%

Note: * - differences are significant in comparison with the first group (p<0.05), # - differences are significant in comparison with the second group (p<0.05).

From the obtained material it is understandable, that an increase of time before the TLT, directs the LV remodeling mainly to dilatation way and associate it with lower LV systolic function on the background of higher volume values of intracardiac hemodynamic indexes. The same results were obtained by Shliahto E.V. et al. (2007), who showed that overload by volume is associated with elevation of MMP-9/TIMP-1 ratio predominantly due to MMP-9 [5]. At the same time Blenkenberg S. et al. (2003) showed that prevalence of proteolytic processes followed to the development of prognostically unfavorable types of LV remodeling [6].Violation of diastolic function of LV typical for all patients, but its type varied from impaired relaxation in the first group to the restrictive type with increasing of exposure before usage of thrombolytic therapy. On the background of described disturbances in patients, with the longest period before usage of thrombolytic therapy, often showed an aneurysm of left ventricle and the phenomenon of spontaneous ventricular contrast, that confirms the high thrombogenic potential. In this cohort of patients was also found a precise tendency to thrombus formation in the left ventricle cavity. Our observations were confirmed in works of other scientists (Berezin A.E. at.al., 2011), who proved the high risk of complications of Q-wave MI in patients with high level of MMP-9 [1].

Conclusions

In patients with Q-wave myocardial infarction, who got thrombolytic therapy in 6 to 12 hours period, excessive activation of proteolysis system on the background of relative deficit of TIMP-1was revealed.

Increasing of time before usage of thrombolytic therapy till 12 hours, in patients with Q-wave myocardial infarction, directs LV remodeling to dilation way predominantly.

Violation of diastolic function of LV typical for all patients with Q-wave myocardial infarction, but in exposure prolongation before usage of thrombolytic therapy changes it from impaired relaxation till the restrictive type.

In patients with Q-wave myocardial infarction with longest period before usage of TLT most frequently was revealed aneurysm of left ventricle and the phenomenon of spontaneous ventricular contrast, that confirms the high thrombogenic potential.

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