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THE MARKERS OF INFLAMMATION AS PREDICTORS OF CARDIOVASCULAR EVENTS AFTER PRIMARY MYOCARDIAL INFARCTION

МАРКЕРЫ ВОСПАЛЕНИЯ КАК ПРЕДИКТОРЫ СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПОСЛЕ ИНФАРКТА МИОКАРДА.

Abstract. The aim of the study was to determine the potential of inflammatory processes such as interleukin-6, interleukin-10, C-reactive protein, tumor necrosis factor alpha, as predictors of cardiovascular events after primary myocardial infarction.

Резюме. целью нашего исследования было определение возможности воспалителььынх маркерок таких как интерлейкин-6, интерлейкин-10, С-реактивный белок, фактор некроза опухоль альфа, как предикторов сердечно сосудистых событий после первичного инфаркта миокарда.

Ключевые слова: инфаркт миокарда, воспаление, интерлейкин,С-реактивный протеин.
Key words: myocardial infaction, inflammation, interleukin, C-reactive protein

Relevance. Despite all the preventive, diagnostic and therapeutic possibilities of our time, diseases of the circulatory system are the leading causes of adult mortality in the world. The emergence and development of reperfusion centers significantly reduced mortality because of acute myocardial

infarction and its complications to 4.0 % in developed countries. Meanwhile, the high probability of repeated cardiovascular events and the development of life-threatening rhythm disorders are the main cause of death in this category of patients [1, 2].

According to studies, patients with acute myocardial infarction with stable ST segment elevation (STEMI) have an increased level of inflammation, and it is higher than in stable CHD. In addition, after primary percutaneous coronary intervention and stenting with mechanical damage to the intima, it contributes to the development of plaque instability in the entire coronary tree, and may affect the occurrence of adverse events [3, 4].

Currently, the role of statin therapy in this category of patients is being actively studied. Small pilot studies show that intensive statin therapy in the acute phase after STEMI reduces not only oxidized low-density lipoprotein cholesterol (LDL-C), but also markers of inflammation, as well as inflammatory cytokines [5, 6].

The proinflammatory cytokines are directly involved in the development of acute coronary events. However, the contribution of inflammatory mediators to the mechanism of development of complications, in particular among patients with AMI, in real clinical practice, requires further study. Their diagnostic and prognostic significance among patients with STEMI remains debatable. Analysis of the relationship between cytokine imbalance and recurrent cardiovascular events is particularly relevant [7, 8].

The aim of the study. To determine the possibilities of inflammatory markers as predictors of cardiovascular events after primary myocardial infarction.

Materials and methods. The study is based on data obtained during a comprehensive examination of 141 patients with acute myocardial infarction with stable ST segment elevation (STEMI). The sample of patients was carried out in the period from 2015 to February 2018. The patients were delivered by ambulance staff to the reception and diagnostic Department of the Municipal institution "Regional medical center of cardiovascular diseases" of Zaporizhzhia Regional Council. All patients included in the study were taken to the hospital before 12 hours from the start of STEMI.

Criteria for inclusion in the study: male and female patients from 46 to 75 years of age; for women postmenopausal period is more than 1 year; presence of STEMI in the first 12 hours from the onset of the disease; informed consent of the patient to participate in the study.

Criteria for exclusion from the study: atrioventricular block of II-III degree; permanent form of atrial fibrillation; detection of congenital and acquired hemodynamically significant heart defects; III stage of chronic heart failure; detected left ventricular aneurysm; decompensated concomitant pathology; acute inflammatory diseases or exacerbation of chronic ones; history of coronary artery bypass grafting; oncological diseases.

All patients underwent a comprehensive clinical, instrumental and laboratory examination. AMI diagnosis verification was performed based on the ESC/ACCF/AHA/WHF Third universal definition of myocardial infarction (2012), taking into account the recommendations of the ESC Fourth universal definition of myocardial infarction (2018) [9, 10]. The distribution of patients into groups was performed depending on the development of a cardiovascular event after primary myocardial infarction.

- the first group included 23 patients who had event (median age 60,00 [52,00 ; 65,00] years);
- in the second group, there were 118 patients without event (median age 58,50 [52,00 ; 64,00] years).

All the patients had been collected blood samples for determination of the level of creatinine phosphokinase-myocardial band (CPK-MB) and troponin I (TnI) at the first contact. All patients underwent a lipidogram during screening and after 12 months. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride (TG) levels were determined. The safety of statin treatment was determined by the level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) during screening and in dynamics.

Immunoenzyme analysis. Blood sampling was carried out from the ulnar vein into 50 mg EDTA tubes, it was centrifuged at 3000 RPM for 15 minutes. The obtained plasma was separated, and then were immediately freezed and stored at a temperature not less than -24 °C degrees until the time of the study. The level of highly sensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-10 (IL-10) in blood plasma were determined by enzyme-linked immunosorbent assay method using standard «ELISA-Best» kits (Vektor-Best, Russia) according to the method described in the test systems instructions. The analysis was carried out using the «SUNRISE TS» enzyme immunoassay (Austria). The content of interleukin-6 (interleukin-10, TNF-α) in blood plasma was expressed in PG/ml.

Treatment of patients. Patients were treated according to current European recommendations (2012, 2017) for the treatment of patients with STEMI. In the group of patients with STEMI, the following therapy was performed: a combination of systemic thrombolytic therapy (TLT) and stent implantation was performed in 34 (24.1 %) patients, systemic TLT was performed in 32 (22.7 %) patients, stent implantation - 71 (50.4 %) and 4 individuals (2.8 %) underwent conservative treatment. Further treatment of patients was performed using antiplatelet agents, selective beta-blockers, and ACE inhibitors. Statin was prescribed at an average dose of 88 (62.4 %) patients atorvastatin (Torvacard, Zentiva) 40 mg or rosuvastatin (Rosuvard, Zentiva) 20 mg 1 time per day 27 (19.1 %) patients, taking into account the level of LDL-C in a high dose was prescribed 8 (5.7 %) patients atorvastatin 80 mg or rosuvastatin 40 mg inside 1 time per day 18 (12.8 %) patients. The cardiovascular event including a condition that required emergency medical attention: repeated myocardial infarction, ventricular tachycardia, angina attack.

Statistical processing of the obtained results. Statistical processing of the received data was

performed on a personal electronic computer using the PSPP application software package (version 1.0.1, GNU Project, 1998-2017, GNU GPL license) and Apache OpenOffice (version 4.1, GNU GPL license). The obtained data are presented as the median and interquartile range of IU [Q25 ; Q75]. When testing statistical hypotheses, the null hypothesis was rejected at a level of statistical significance (p) below 0.05.

The processing of quantitative data was carried out by nonparametric or parametric methods depending on the distribution of the sample. The student's criterion (t-criterion) was used for parametric distribution: odd - for comparing independent samples. Nonparametric methods were used for distribution other than normal if two independent samples were compared, the Mann-Whitney method (U-criterion) was used.

For dichotomous division of variables, ROC analysis (Receiver Operating Characteristic curve analysis) was used. We calculated the area under the ROC curve (AUC - Area under the ROC curve), the model was considered reliable when the AUC value is more than 0.5. The cut-off point was found using the J-Youden index.

The relative risk (RR, Relative Risk and its 95% confidence interval) was calculated using table 2x2 as the ratio of the frequency of cases among patients exposed to the studied factor to the frequency of cases among subjects who were not affected by this factor. The 95 % CI RR value that did not intersect 1 was considered reliable.

Results and discussion. Baseline characteristics for patients with STEMI included: age, sex, body mass index (BMI), the lipidogram, the level of creatinine phosphokinase-myocardial band and cardiac troponin I, the markers of inflammation, calculated the left ventricle ejection fraction (LVEF) using Simpson's method. The data obtained is presented in table 1.

Table 1.

Baseline characteristics for all STEMI patients

Characteristics	All patients (n = 141)	Event group (n = 23)	No-event group (n = 118)
Age, years	59.00 [52,00 ; 64,00]	60.00 [52,00 ; 65,00]	58.50 [52,00 ; 64,00]
BMI, kg/m^2	27.06 [24,82 ; 30,42]	25.50 [23,88 ; 30,72]	27.11 [24,98 ; 30,42]
CPK-MB, U/l	45.24 [22,46 ; 81,70]	74.30 [27,63 ; 143,72]	41.30 [21,84 ; 73,98]*
TnI, ng/ml	4.65 [0,85 ; 6,80]	5.80 [0,89 ; 6,89]	3.83 [0,84 ; 6,80]
HS-CRP, mg/l	10.57 [9,52 ; 13,26]	12.09 [10,05 ; 29,47]	10.35 [9,26 ; 13,22]*
TNF-α, PG/ml	1.95 [1,44 ; 2,72]	1.91 [1,42 ; 3,22]	1.96 [1,44 ; 2,69]
IL-6, PG/ml	11.34 [8,06 ; 15,06]	13.15 [9,10 ; 16,30]	10.97 [7,75 ; 14,85]
IL-10, PG/ml	3.87 [2,56 ; 6,70]	3.95 [2,72 ; 5,93]	3.83 [2,52 ; 7,07]
IL-6/IL-10	2.78 [1,78 ; 4,34]	2.82 [2,07 ; 5,67]	2.65 [1,72 ; 4,17]
LVEF, %	55.56 [50,99 ; 62,00]	55.56 [50,60 ; 61,80]	55.67 [51,42 ; 62,08]

Note. * - an indicator of the significant y difference of two independent samples it event and no-event groups.

The number of patients with STEMI was 141, the event group group included 23 patients, and the no-event group - 118 patients. All the surveyed persons were comparable in age, social status and sex (the ratio of men and women was 4 to 1). The *body mass index* value in the event group was 25,50 [23,88 ; 30,72] kg/m^2 versus 27,11 [24,98 ; 30,42] kg/m^2 in the no-event group and had no significant difference ($p > 0.05$).

The CPK-MB level among patients with STEMI with the event was 74.30 [27,63 ; 143,72] U/l and was significantly higher than 41.30 [21,84 ; 73,98] U/l in the group the STEMI without the event group ($p < 0.05$). The HS-CRP level in the event group of patients was significantly higher and amounted to 12.09 [10,05 ; 29,47] mg/l versus 10.35 [9,26 ; 13,22] mg/l in the no-event group of patients ($p < 0.05$).

The cTnI, TNF-α, IL-6, IL-10 and the IL-6 / IL-10 ratio levels had no statistically significant difference between the patient groups ($p > 0.05$). The median LVEF in the event group was 55.56 [50.60 ; 61.80] % and was comparable to 55.67 [51.42 ; 62.08] % in the no-event group ($p > 0.05$).

Further, using two data sets: the first group of patients with STEMI with event (n = 23) and the second one with STEMI without event (n = 118) are performed ROC-analysis. The results are presented in table 2.

Table 2.

The cut off of indicators of immuno-inflammatory response for event

Variable	Cut-off	AUC	95 % CI AUC	Se, %	Sp, %
CPK-MB, U/l	>73.98	0.644	0.559 – 0.722	52.17 %	75.42 %
TnI, ng/ml	>4.46	0.566	0.480 – 0.649	69.57 %	53.39 %
HS-CRP, mg/l	>9.95	0.633	0.548 – 0.712	82.61 %	43.22 %
TNF-α, PG/ml	>2.72	0.542	0.456 – 0.626	39.13 %	77.97 %
IL-6, PG/ml	>11.53	0.607	0.521 – 0.688	69.57 %	56.78 %
IL-10, PG/ml	>2.32	0.508	0.422 – 0.593	91.30 %	22.03 %
IL-6 / IL-10	>5.46	0.586	0.500 – 0.668	30.43 %	88.14 %

The results of the ROC analysis showed that for CPK-MB significantly (AUC = 0.644) at the cut-off >73.98 U/l, the sensitivity value was 52.17 % and specificity was 75.42 % for the event. The largest area under the ROC curve (AUC = 0.633, 95% CI 0.559 – 0.722) among the analyzed parameters of immuno-inflammatory response had an indicator of the hs-CRP level. At the cut-off point >9.95 mg/l sensitivity was 82.61 % and specificity was 43.22 % for the event.

The average quality of the model (AUC = 0.607, 95% CI AUC 0.521 – 0.688) had the IL-6 level. For the cut-off >11.53 PG/ml sensitivity was 69.57 % and specificity was 56.78 % for the event. The immuno-inflammatory response markers such as the levels TNF-α, IL-10 and the IL-6/IL-10 ratio although they had significant prognostic value according to ROC-analysis (AUC > 0.5) for event prediction, however, their models were unsatisfactory (AUC 0.5-0.6).

Using the cut-off values, relative risk was calculated for analyzed the indicators. Obtained result are shown in the table 3.

Table 3.

The relative risk of occurrence for event among patients with STEMI

Variable	Cut-off	RR	95 % CI RR
CPK-MB, U/l	>73.98	2.571	1.234 - 5.359
TnI, ng/ml	>4.46	1.902	0.861 - 4.199
HS-CRP, mg/l	>9.95	3.038	1.091 - 8.456
TNF-α, PG/ml	>2.72	1.947	0.924 - 4.102
IL-6, PG/ml	>11.53	2.525	1.107 - 5.757
IL-10, PG/ml	>2.32	0.402	0.100 - 1.612
IL-6 / IL-10	>5.46	2.500	1.172 - 5.333

In the without the event group were 88 patients below 73,98 U/l and 30 ones had a level higher than 73,98 U/l, in the event group respectively 11 patients below 73,98 U/l and 12 above 73,98 U/l. Relative risk for event was 2.571, 95 % CI 1.234 - 5.359. For variables TnI, TNF-α and IL-10 the value of RR was unreliable because 95 % CI of RR crossed a 1. In the group with STEMI and the event were 4 patients with hs-CRP below 9.95 mg/l and 19 ones had a level higher than 9.95 mg/l, in the group with STEMI without the event, respectively 51 patients below 9.95 mg/l and 67 above 9.95 mg/l. Relative risk for hs-CRP was 3.038, 95 % CI 1.091 - 8.456. The relative risk for the event was related to the IL-6 / IL-10 ratio 2.500, 95% CI 1.172 - 5.333, cut-off point >5.46.

The processes of destruction and repair caused by myocardial necrosis are inextricably linked with the concept of «inflammation». They play an important role in post-infarction remodeling of the heart. The immuno-inflammatory response of various degrees is determined in almost all major forms of cardiac pathology, and AMI is a classic example of an aseptic inflammatory reaction that develops after the development of necrosis. Although there are certain limitations of the study, which is that until now, there is no standard cut-off point for the inflammatory process behind the IL-6, IL-10 markers [11], [12].

Prognostic value of the immuno-inflammatory response markers at the present time remains understudied. The role of higher level hs-CRP as a predictor of unfavorable prognosis was demonstrated in the population of patients with myocardial infarction. Particular importance is the stratifying the risk of the event among patients who have undergone STEMI [13].

Currently, there are no data from specialized clinical studies on secondary prevention of cardiovascular diseases, which indicate the benefits of reducing the level of inflammation. To solve this problem, studies are currently being conducted which evaluate the effectiveness of therapeutic agents aimed at reducing inflammation among patients with AMI. Determination of the C-reactive protein concentration is proposed to improve risk stratification and improve the effectiveness of treatment of this category of patients [14].

The results of our work correlate with data from other studies. So in the work of D. R. P. Ribeiro et al. hs-CRP levels were shown to be independently associated with 30-day mortality after STEMI (odds ratio 1.27, 95% CI 1.07-1.51). In a study by Y. Kobayashi et al. it was determined that hs-CRP is one of the independent predictors of in-hospital recurrent ventricular tachycardia [15, 16].

Thus, our data suggest that a systemic inflammatory response is involved in the occurrence of event after AMI. However, today there are certain discrepancies regarding the activity of cytokines in the daily period after STEMI, which demonstrates the lack of consensus on this issue. Our understanding of the factors that lead to an event after an AMI is still evolving. Also, the most optimal diagnostic time frame for evaluating markers of systemic inflammatory response in patients with acute myocardial infarction remains uncertain.

Conclusions.

1. The systemic inflammatory response behind the value of hs-CRP levels is more pronounced in patients with STEMI and the event than in those without the event.

2. The relative risk of the event increases in 3.038 times among patients with acute myocardial infarction with an increase in the level hs-CRP higher than 9.95 mg/l.

Conflict of interest statement. The authors report that there is no conflict of interest.

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ОРТОПЕДИЧЕСКАЯ КОНСТРУКЦИЯ ДЛЯ ШИНИРОВАНИЯ ЗУБОВ ПРИ ХРОНИЧЕСКОМ ЛОКАЛИЗОВАННОМ ПАРОДОНТИТЕ СРЕДНЕЙ СТЕПЕНИ ТЯЖЕСТИ НА НИЖНЕЙ ЧЕЛЮСТИ.

Аннотация. Лечение заболеваний пародонта является одной из актуальных проблем современной стоматологии. Пародонтит-это многофакторное заболевание и является одним из самых распространенных заболеваний, встречающихся в стоматологической практике. Клинические проявления хронического локализованного пародонтита разнообразны, что требует комплексного подхода в лечении. Целью исследования является создание ортопедической конструкции, позволяющей повысить качество