DYNAMICS OF THE LEVEL OF PRO-INFLAMMATORY CYTOKINES IN VARIOUS VARIANTS OF ACUTE MYOCARDIAL INFARCTION

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INTRODUCE

At present, it is inflammation that is considered as one of the leading links in the pathogenesis, course, and prognosis of coronary heart disease (CHD) [1, 2]. It also plays a significant role in the development of acute myocardial infarction (MI) and the outcome of the disease, namely, in the formation of atherothrombosis, alteration, necrosis, and repair, followed by myocardial remodeling [3–5]. As shown by numerous recent studies, the severity of immunoinflammatory reactions in patients with unstable forms of coronary heart disease is higher than in patients with a stable course of the disease [6]. At the same time, overexpression of pro-inflammatory agents during the development of myocardial infarction can lead to the development of systemic inflammatory response syndrome (SIRS) and complications, in particular, cardiogenic shock (CS) [7–10]. In this regard, the study of histohormones of a protein nature, cytokines, attracts great attention of researchers [11–12].

Considering that the outcome of myocardial infarction is determined both by the degree of myocardial damage and by complications developing at different periods of the course of the disease, primarily heart failure, studies aimed at identifying indicators that can be used in the clinic to predict and prevent the development of complications are of particular relevance. myocardial infarction and determining the tactics of their treatment [6, 13–16].

The aim of this study was to study the dynamics of changes in pro-inflammatory cytokines in patients with myocardial infarction, depending on the variant of its course, the presence and severity of acute left ventricular failure (ALHF).

MATERIAL AND METHODS

Study design: open, cohort, prospective. The study included 82 patients of both sexes with verified myocardial infarction, admitted within 24 hours from the onset of the disease to the cardiac intensive care unit of the infarction department of the city hospital and the intensive care and resuscitation department. The diagnosis of myocardial infarction was established in accordance with the diagnostic criteria of the European Society of Cardiology, the American Heart Association, the World Heart Federation (ESC/ACCF/AHA/WHF) [17, 18], based on clinical, electrocardiological and laboratory data [19].

The study did not include patients with concomitant acute infectious, inflammatory, autoimmune, allergic, oncological and chronic diseases in the acute stage, persons with

blood diseases, as well as patients who had chronic heart failure above functional class I before the development of the index event - myocardial infarction.

In the studied sample of patients, males predominated (n = 55; 67.07%), the average age was (67.87 ± 2.29) years (44–87 years). The observation period was (14 ± 4) days.

Clinical examination included assessment of complaints, collection of anamnesis of the underlying disease and concomitant pathology, standard physical examination, dynamic electrocardiography (ECG), standard laboratory examination, echocardiography. Acute left ventricular failure was verified by clinical, radiological and echocardiographic data. To assess the severity of acute left ventricular failure, the Killip classification was used [20, 21]. For all patients with documented myocardial infarction, the prognostic index was calculated according to the GUSTO risk stratification scale [22] upon admission to the hospital. The GUSTO risk stratification scale suggests using additional clinical factors, such as tachycardia, increased cardiac biomarkers, along with age, certain data from a cardiovascular history (presence of a stroke or myocardial infarction, heart failure), to assess the 30-day prognosis in acute coronary syndrome. S-reactive protein, creatinine, and the presence of anemia.

Depending on the variant of the clinical course of myocardial infarction, patients were divided into four groups: group 1 (n = 27) consisted of patients (18 men and 9 women) with myocardial infarction without Q wave without complications (mean age (62.7 ± 1 .65) years); group 2 (n = 30) included patients (25 men and 5 women) with Q-forming myocardial infarction and acute left ventricular failure of classes I–II according to Killip (mean age (63.13 ± 1.68) years); group 3 (n = 17) included patients (11 men and 6 women) with Q-forming myocardial infarction and acute left ventricular failure of III–IV classes according to Killip (mean age (68.65 ± 2.37) years) ; Group 4 consisted of 8 patients (4 women and 4 men; mean age (74.50 ± 3.48) years) who died within 48–60 hours from the onset of myocardial infarction due to the development of refractory cardiogenic shock.

When conducting the study, data on minimal gender differences were taken into account, indicating that in women, primary myocardial infarction often occurs against the background of concomitant arterial hypertension, diabetes mellitus, anemia and hypercreatininemia and, on average, 8 years older [23, 24]. At the same time, there was no significant difference in male and female hospital mortality with acute coronary syndrome [25, 26].

The control group included 12 practically healthy individuals without cardiovascular pathology and, in terms of age and sex composition, corresponded to groups of patients with myocardial infarction. Treatment and observation of patients of all groups was carried out according to the treatment and diagnostic standards for the management of patients with myocardial infarction [19].

The material for laboratory studies was venous blood samples, which were obtained from a peripheral vein in a conventional way. The quantitative content of pro-inflammatory cytokines (interleukin (IL): IL-1β, IL-6 and tumor necrosis factor α (TNF-α)) in

the blood serum was assessed upon admission of patients to the hospital and verification of the diagnosis of myocardial infarction. The time of blood sampling was 18–28 hours from the onset of the development of symptoms of the disease. Monitoring of immunological parameters was carried out in dynamics on the 3rd and 14th days of infarction. The concentrations of IL-1β, IL-6 and tumor necrosis factor α in blood serum were determined by enzyme immunoassay using Vector-Best reagent kits. The results were recorded using a Multiskan FC immunoassay analyzer (Thermo Fisher Scientific) at a wavelength of 450 nm.

Statistical processing of the research results was performed using the Statistica 6.0 software package (StatSoft, Inc., USA). All data are presented as mean and standard error, M ± m. Comparison between groups of patients was carried out using Student's parametric test, taking into account a preliminary check of the data for normal distribution. When assessing the significance of differences in the studied indicators in the dynamics of the study, the nonparametric Mann-Whitney U-test for related samples was used. The presence and strength of the relationship between the studied parameters was assessed using the nonparametric Spearman rank correlation coefficient r. Results and correlations were considered statistically significant at $p < 0.05$ [27].

RESULTS

As the results of the study showed, the distribution of patients into groups with different variants of the course of myocardial infarction corresponded to the value of the GUSTO risk stratification scale index. Already in the 1st group with non-Q-forming myocardial infarction, the GUSTO risk stratification scale index was 8.67 ± 0.4 ($p < 0.001$) and progressively increased with an increase in the class of acute left ventricular failure, reaching maximum values of 16.63 ± 1, 10 in the 4th group of patients who died due to the development of cardiogenic shock.

The division of patients with myocardial infarction into groups depending on the variant of the course of the disease made it possible to identify some patterns in the levels of pro-inflammatory cytokines (table) in the blood serum of patients.

Index	MI development time day	Patient groups			
		Group 1 (n = 27)	Group 2 (n = 30)	Group 3 (n = 17)	Group 4 (n = 8)
IL-1β, pg/ml	Control 1,62 ± 0,21 (n = 12)				
	1-st	3,37 ± 0,28 p1 < 0,001 p2 < 0,001	2,75 ± 0,19 p1 < 0,001 p2 < 0,001	2,99 ± 0,23 p1 < 0,001 p2 < 0,01	3,18 ± 0,46 p1 < 0,001
	3-rd	2,60 ± 0,17 p1 < 0,05 p2 < 0,001	2,21 ± 0,14 p1 < 0,001 p2 < 0,001	2,61 ± 0,23 p1 < 0,001 p2 < 0,01	3,70 ± 0,42*º• p1 < 0,001
	14-th	1,97 ± 0,13 p1 < 0,001	1,68 ± 0,16	2,29 ± 0,27 p1 < 0,001	-
IL-6, pg/ml	Control 12,40 ± 1,1				
	1-st	16,04 ± 1,3 p1 < 0,01 p2 < 0,001	20,16 ± 1,91 p1 < 0,001 p2 < 0,001	26,16 ± 3,24* p1 < 0,001	27,45 ± 1,83*º• p1 < 0,001
	3-rd	14,14 ± 1,05 p1 < 0,01 p2 < 0,01	16,23 ± 1,09• p1 < 0,001, p2 < 0,001	24,03 ± 2,96*º p1 < 0,001	39,63 ± 5,63*º• p1 < 0,001
	14-th	12,52 ± 1,11	13,71 ± 0,95• p1 < 0,01	22,85 ± 3,66*º p1 < 0,001	-
	Control 9,70 ± 0,92				
	1-st	19,58 ± 1,43 p1 < 0,001 p2 < 0,01	20,57 ± 1,02 p1 < 0,001 p2 < 0,001	22,81 ± 1,05 p1 < 0,001 p2 < 0,01	24,74 ± 2,91 p1 < 0,001
	3-rd	16,56 ± 0,8 p1 < 0,001 p2 < 0,01	18,20 ± 0,88 p1 < 0,001 p2 < 0,001	20,24 ± 1,03* p1 < 0,001 p2 < 0,01	29,38 ± 1,84*º• p1 < 0,001
	14-th	13,54 ± 0,85 p1 < 0,01	15,93 ± 0,92 p1 < 0,001	18,10 ± 1,44* p1 < 0,001, p2 < 0,01	-

Note. p1 is the significance of differences in relation to the control group, p2 is the significance of differences in relation to the 14th day of myocardial infarction. * significant difference from group 1 ($p < 0.05$). º significant difference from group 2 ($p < 0.05$). • significant difference from group 3 ($p < 0.05$)

The results obtained indicate a significant increase in serum concentrations of IL-1β, IL-6 and tumor necrosis factor α in the development of myocardial infarction. Thus, on the 1st day of myocardial infarction, patients showed a significant increase in the content of all pro-inflammatory cytokines in the blood serum compared to the control group. In all presented groups, a significant increase in serum levels of IL-1β and tumor necrosis factor α was detected, which were increased by more than two times in relation to the value of these indicators in the control group ($p < 0.001$). But if the concentration of IL-1β in all variants of myocardial infarction remained approximately at the same level, then the concentrations of IL-6 and tumor necrosis factor α gradually increased as acute left ventricular failure worsened. On the 1st day of myocardial infarction in patients of the 4th group, serum concentrations of IL-6 significantly differed not only from the control, but also from all groups of surviving patients ($p < 0.001$). At the same time, the concentrations of IL-6 and tumor necrosis factor α equally correlated with the value of the GUSTO stratification risk scale index ($r = 0.40$ and $r = 0.40$, respectively; $p < 0.05$). A direct correlation was also found between the level of IL-6 and the number of leukocytes in peripheral blood ($r = 0.31$; $p < 0.05$).

There was a gradual decrease in serum concentrations of pro-inflammatory cytokines on the 1–14th day of infarction in all groups, except for the 4th group, in which on the 3rd

day of the disease there was a pronounced increase in the studied parameters. Further monitoring of immunological parameters in group 4 was not possible due to the lethal outcome of the disease due to the development of refractory cardiogenic shock. In this group, attention is drawn to the overexpression of pro-inflammatory cytokines; thus, the serum concentration of IL1β by the 3rd day of the disease exceeded the values of the comparison group by more than two times, and the levels of IL-6 and tumor necrosis factor α were more than three times higher than those of the control group. On the 3rd day of the disease, all the studied blood serum cytokines reached their maximum values and significantly differed not only from the control group and from the indices in the groups of surviving patients, but also from the concentrations of cytokines on the 1st day of myocardial infarction. A more significant direct correlation between the levels of IL-6 and tumor necrosis factor α with the GUSTO scale index was also found compared with the 1st day of myocardial infarction ($r = 0.51$ and $r = 0.40$, respectively). On the 14th day of myocardial infarction, serum concentrations of IL-1β, IL-6, tumor necrosis factor α in the 1st group approached those of the control group. In patients with myocardial infarction complicated by acute left ventricular failure of III-IV classes according to Killip, there was also a gradual decrease in serum concentrations of the studied cytokines, but less significant: by the end of the 2nd week from the development of myocardial infarction. In this group, serum concentrations of cytokines exceeded those of the control group by almost two times. On the 14th day of the development of myocardial infarction, a correlation was found between the levels of IL-1β with the levels of IL-6 and tumor necrosis factor α ($r = 0.39$ and $r = 0.39$; $p < 0.01$), as well as the levels of IL -6 and tumor necrosis factor α ($r = 0.45$; $p < 0.01$), which indicates a unidirectional change in the cytokine profile. Hypercytokinemia correlated with the index of the GUSTO scale, with the strongest direct correlation observed for IL-6 ($r = 0.54$). For tumor necrosis factor α: $r = 0.40$; for IL-1β: $r = 0.26$; $p < 0.001$.

The obtained results show that in groups of patients with a more severe class of acute left ventricular failure, a more intensive increase in pro-inflammatory cytokines is observed, and the trend towards a progressive increase in serum concentrations of pro-inflammatory cytokines in the course of myocardial infarction may indicate a threat of developing fatal complications, such as cardiogenic shock, and the risks increase as the pathology progresses.

The presented data are consistent with the results of other researchers, who also revealed an increase in serum concentrations of pro-inflammatory cytokines on the 1st day of myocardial infarction [2, 11, 12, 28]. Their level progressively increased and reached its maximum in the group of patients with an unfavorable outcome of the disease, which can be used as a predictor of the development of fatal complications. It should be noted that this group of patients consisted of older patients, which looks quite logical and corresponds to the literature data [29]. In elderly and senile patients, myocardial infarction often proceeds atypically, with a large number of complications (than in younger patients),

against the background of a large number of comorbid conditions, which may be due to the depletion of the morphofunctional reserve of the cardiovascular system. This predetermines a more severe course of pathology and an increase in mortality.

On the other hand, a significant increase in the concentration of proinflammatory cytokines in the blood serum in patients with myocardial infarction indicates, apparently, the activation of a systemic inflammatory response due to aseptic myocardial necrosis [30, 32]. A number of studies have shown that a high level of IL-1β and IL-6 in blood plasma is an independent and reliable predictor of the development of myocardial infarction, and the maximum increase in their concentrations is associated with a lethal outcome of the disease [33, 34]. This study also noted that an increase in the serum concentration of tumor necrosis factor-α in patients with myocardial infarction significantly correlates with the occurrence of complications or the presence of severe acute left ventricular failure (III–IV classes according to Killip) [35]. However, the most sensitive independent predictors of death during hospitalization were the GUSTO scale index ($p < 0.001$) and serum IL-6 concentration ($p < 0.01$).

CONCLUSION

The development of myocardial infarction is accompanied by an increase in serum concentrations of IL-1β, IL-6, tumor necrosis factor α, the degree of activation of which depends on the severity of signs of myocardial damage and the nature of complications. At the same time, an increase in the severity of acute left ventricular failure is accompanied by a more pronounced activation of cytokines.

The dynamics of changes in pro-inflammatory cytokines (IL-6, tumor necrosis factor α and IL-1β) in blood serum during myocardial infarction is characterized by a progressive decrease in their levels by the 3rd and 14th days of the disease. In the group of patients with developed cardiogenic shock and death, in contrast to the groups of surviving patients, there is a progressive increase in serum concentrations of the studied cytokines.

The level of interleukin-6 in blood serum, along with the risk stratification index, determined by the GUSTO scale, most reliably reflects the severity of hemodynamic disorders, namely acute left ventricular failure, in myocardial infarction and predetermines an unfavorable prognosis.

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