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RESEARCH ARTICLE

COMPARATIVE ANALYSIS OF INFLAMMATION MARKERS IN PATIENTS WITH ISCHEMIC HEART DISEASE OF STABLE AND UNSTABLE FLOW

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ABSTRACT

Aim: Of the study was to conducta comparative analysis of inflammatory markers in patients with coronary heart disease of stable and unstable flow. **Methods:** 78 patients aged 36 to 75 years were enrolled in this study (mean age 58.2±12.6 years). Laboratory and instrumental data were obtained and assessed. IL-6, TNF-α in blood plasma was carried out by the method of enzyme immunoassay on a solid-phase analyzer «Humareader Single». Statistical processing of the obtained results was carried out using vibrational statistics methods recommended for biomedical research on the IBM PC AT Pentium IV. **Results:** In patients with unstable angina (UA), the frequency of elevated levels of CRP, TNF-α, and leukocytes was statistically significantly higher than in the group with stable ischemic heart disease (P<0.05).The mean levels of these markers were statistically significantly higher in patients with UA compared with patients with stable form of coronary heart disease (CHD, P<0.05): CRP (4.3 ± 2.4 and 2.9 ± 2.3 mg / L, p <0.05, respectively), TNF-α (10.5 ± 2.5 and 7.7 ± 3.4 pg / ml, p <0.05) and leukocytes (9.2 ± 2.5 6.9 ± 2.3x109 / l, p <0.05). The level of interleukin-6 in patients with UA was higher in comparison with patients with stable angina (SA, 3.4 ± 1.7 and 2.9 ± 0.5 pg/ml), but the difference was statistically not significant (p>0.05). There were no significant differences in the level of fibrinogen and ESR between patients with UA and SA. **Conclusion:** It was noted that the signs of inflammation are detected both in patients with unstable forms and in patients with stable form of CHD, but the degree of inflammation in patients with UA (level of TNF-α, CRP and leukocytes) is higher than in patients with stable ischemic heart disease.

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INTRODUCTION

Coronary heart disease (CHD) is one of the most dangerous diseases, which account for one of the highest death rates from diseases of the circulatory system, which makes it necessary to seek new opportunities for diagnosis, prognosis, risk assessment and prevention (Alyavi, 2017; Aukrust *et al*., 2009; Serkova *et al*., 2007). Among the strategies for its solution is the identification of high-risk groups for the conduct of preventive drug and non-pharmacological interventions (Belenkov Yu, 2002).Despite the improvement in the condition of patients and the slowing down of the pathological cardiac remodeling process, the reduction in the risk of cardiovascular changes with the use of modern neuromodulators, ischemic heart disease continues to progress, albeit less intensively. This may be due to immunoinflammatory activation mediated by proinflammatory cytokines (Becker, 2010).If to date, some researchers have obtained convincing experimental and clinical evidence of the role of tumor necrosis factor-a (TNF-α) in the pathogenesis of IHD (5,8,12,15), then the nature and significance of changes in the activity of other pro-inflammatory cytokines playing a leading role in inflammatory response - interleukin-1b (IL-1b), interleukin-6 (IL-6), remain little studied. A small number of studies devoted to the simultaneous assessment of changes in IL-6, IL-1β and TNF-α concentrations in patients with CHD of different functional classes. The relationship of the cytokines studied to the main clinical indicators and risk factors (age, heredity, duration of the disease, severity of CHF, smoking, body weight, blood lipid level, outcome of the disease) has not been adequately studied.

Purpose of the study: Conduct a comparative analysis of markers of inflammation in patients with coronary heart disease of stable and unstable flow.

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MATERIALS AND METHODS

A total of 78 patients aged 36 to 75 years were examined (mean age was 58.2 ± 12.6 years), of which 50 (64.1%) men and 28 (35.8%) women in inpatient cardio logical department of the center. Of these, stable angina (SA) was diagnosed in 48 patients, unstable angina (UA) in 30 patients. The clinical characteristics of the examined patients are reflected in Table 1.Diagnosis of CHD was established on the basis of clinical, instrumental, laboratory data. Attention was drawn to the typicality of the anginal syndrome, the specificity of changes in ECG parameters at rest, with daily monitoring and with a load on a veloergometer (VEM) and echocardiography (EchoCG) data. Blood sampling for biochemical analyzes was carried out by puncture of the ulnar vein in the morning, on an empty stomach. The determination of IL-6, TNF-α in blood plasma was carried out by the method of enzyme immunoassay on a solid-phase analyzer «Humareader Single» (Germany). The concentration of CRP in serum was determined by a highly sensitive method on the Humareader Single analyzer (Germany).

Statistical processing of the obtained results was carried out using variational statistics methods recommended for biomedical research on the IBM PC AT Pentium IV. The results are processed using Microsoft Excel 2002 and Statistica 6.0 under Windows XP. The indicators are presented as the average of the arithmetic variation series and its standard error (M ± m). The reliability of differences in the mean values was estimated using Student's t-test. For the level of statistical significance, $p < 0.05$ was taken. In the group of patients with unstable angina were: 50% - patients with progressive angina pectoris, 20% - patients with first-onset angina pectoris and 30% - early postinfarction angina pectoris. In the group of patients with stable CHD, 50% of patients had angina pectoris, 29% had angina pectoris with cardiac arrhythmias and 21% had isolated cardiac arrhythmias. 63% of patients had a history of myocardial infarction, in 17% the course of CHD was complicated by chronic heart failure II FC. In the group of patients with stable coronary artery disease the majority of patients had angina pectoris of tension II and III FC (I FC - 1 person (2%), II FC - 27 persons (56%), III FC - 19 persons (40%), IV FC - 1 person (2%).The study did not include patients who underwent stroke or thromboembolism of the pulmonary artery; people with alcohol dependence; patients with liver pathology (chronic hepatitis, cirrhosis); patients with oncological pathology or blood diseases; chronic lung diseases; mental disorders; with acute concomitant pathology.

RESULTS

The study of the content of inflammatory markers in blood plasma in patients with stable and unstable angina revealed elevated levels of inflammatory in both study groups. In patients with UA, the frequency of elevated levels of CRP, TNF-α, and leukocytes was statistically significantly higher than in the group with stable ischemic heart disease (Table 2), and the mean levels of these markers were statistically significantly higher in patients with UA compared with patients with stable form of CHD: CRP (4.3 ± 2.4 and 2.9 ± 2.3 mg / L, $p < 0.05$, respectively), TNF-α (10.5 ± 2.5 and 7.7 ± 3.4 pg / ml, $p < 0.05$, respectively) and leukocytes (9.2 ± 2.5 6.9 ± 2.3x109 / l, $p < 0.05$, respectively). The level of interleukin-6 in patients with UA was higher in comparison with patients with SA (3.4 ± 1.7 and 2.9 ± 0.5 pg / ml, respectively), but the difference was statistically not significant ($p > 0.05$). There were no significant differences in the level of fibrinogen and ESR between patients with UA and SA. The obtained data can testify that in the vascular wall an inflammatory process can be noted, despite the clinically stable state of the patients, and with an exacerbation of the course of CHD, the inflammation becomes more active. When comparing the levels of inflammatory markers in the group of patients with UA, it was found that patients with early postinfarction angina have significantly higher levels of leukocytes (9.3 ± 5.3 and 7.7 ± 2.1 x109 / L, $p < 0.05$ respectively) and (on the verge of statistical significance) TNF-α (11.0 ± 2.8 and 9.0 ± 1.1 pg / ml, $p < 0.05$, respectively) compared with patients with progressive angina pectoris. This may indicate that the severity of inflammatory reactions is associated with the severity of the course of angina pectoris. There were no significant differences between patients with progressive angina and early post infarction angina in terms of CRP, IL-6, fibrinogen, and ESR. In patients with UA, the following indicators were included in the correlation analysis: levels of CRP, TNF-α, IL-6, fibrinogen, ESR, leukocytes, cholesterol, TG, LDL, HDL; age, male gender, body mass index, smoking; myocardial infarction, diabetes mellitus, arterial hypertension in the anamnesis. In the group of patients with UA, a reliable association with the prognosis of the appearance of adverse cardiovascular events was found for four variables: TNF-α, age, type 2 diabetes mellitus, and myocardial infarction in the anamnesis (Table 3). Patients over 65 years of age had a 3.4-fold higher risk of developing cardiovascular events than those under the age of 65, MI had a 4.4-fold increase in cardiovascular risk, a 4.66-fold decrease in diabetes, and patients with a TNF-α level> 9 pg / ml had a 4.98-fold risk of developing adverse cardiovascular events compared with patients with a TNF-α level <9 pg / ml.

As a result of multivariate regression analysis (taking into account the influence of factors such as age, MI and type 2 diabetes in the anamnesis), TNF-α remained the strongest and most independent prognostic factor of adverse cardiovascular events: patients with TNF-α> 9.0 pg / ml in the long term had a risk of unfavorable cardiovascular events 5 times higher compared with patients with a TNF-α level <9 pg / ml. When analyzing the data, it was noted that adverse cardiovascular events occur significantly more frequently and earlier in patients with a TNF-α level> 9 pg / ml ($p < 0.05$). In patients with adverse cardiovascular events that occurred during the time of observation, the level of TNF-α> 9 pg / ml was 78% of patients (14 patients out of 18), while in the group of patients who had no recorded cardiovascular events, the level of TNF-α> 9 pg / ml was observed in 34% of patients (4 patients out of 12). When analyzing the survival rate in patients with UA, it was noted that the level of TNF-α significantly affects the time of onset of events. In patients in the UA group with a TNF-α level> 9 pg / ml, the median survival time without unwanted cardiovascular outcomes was 1.5 years, while in the group of patients with a TNF-α level <9 pg / ml in 60% patients to five years of observation adverse cardiovascular events have not yet occurred. In patients with stable ischemic heart disease, the following indicators were included in the single-factor regression analysis: CRP, TNF-α, IL-6, fibrinogen, ESR, leukocytes, cholesterol, TG, LDL, HDL; age, male gender, body mass index, smoking; myocardial infarction, diabetes mellitus, arterial hypertension in the anamnesis. In the group of patients with stable CHD one-factor regression analysis revealed a reliable association with an unfavorable

Table 1. Clinical characteristics of patients with ischemic heart disease

Indicator	Unstableangina(n = 30)	Stable angina pectoris (n = 48)	P
Age, years	62,3 ± 11,9	64,6 ± 8,9	> 0,05
Men	21 (70%)	29 (60%)	> 0,05
BMI, kg / m2	27,7 ± 3,0	28,3 ± 4,6	> 0,05
Postinfarctioncardiosclerosis	10 (33%)	30 (63%)	<0,01
Thehistoryof NASMI	5 (17%)	7 (15%)	> 0,05
AG	27 (90%)	44 (92%)	> 0,05
Type 2 DM	2 (7%)	7 (15%)	> 0,05
Hyperlipidemia	20 (67%)	36 (75%)	> 0,05
Smoking	17 (57%)	34 (71%)	> 0,05
Myocardialrevascularizationinhistory	1 (3%)	9 (19%)	> 0,05

Note: the data are presented in the form of mean and standard deviation, as well as in absolute figures (in brackets -% of the total number of patients in the group); n-number of patients in groups; the difference is not statistically significant (p> 0.05);

Table 2. Elevated indicators of inflammatory markers in patients with stable and unstable angina

Indicator	Unstableangina(n = 30)	Stable angina pectoris (n = 48)	p
CRP> 3.0 mg / l	18 (60%)	18 (37%)	< 0,05
TNF-γ> 6.3 pg / ml	30 (100%)	27 (56%)	<0,05
IL-6> 3.3 pg / ml	6 (20%)	4 (8%)	> 0,05
Fibrinogen> 4 g / l	9 (30%)	10 (21%)	> 0,05
ESR> 10 mm / h (m)	11 (37%)	14 (29%)	> 0,05
Leukocytes> 10x10*9 / l	9 (30%)	4 (8%)	< 0,05

Note. The data are presented in absolute figures (in brackets -% of the total number of patients in the group), n - the number of patients in the group, p> 0.05 - the difference is not statistically significant.

Table 3. Single-factor and multifactorial regression analysis in patients with UA and SA pectoris

Patientswithunstableangina				
Single-factor analysis			Multivariate analysis	
Variable	RR (95% CI)	p	RR (95% CI)	p
MI inanamnesis	4,4 (3,38 -5,42)	0,004	3,8 (2,7 - 4,9)	0,02
Age> 65 years	3,4 (2,34 - 4,45)	0,02	2,7 (1,5 - 3,9)	0,11
Diabetesinanamnesis	4,66 (3,07- 6,25)	0,05	1,9 (0,3 - 2,5)	0,40
TNF-α> 9 pg / ml	4,98 (3,73 - 6,23)	0,01	5,0 (3,6 - 6,4)	0,02
Patientswithstableangina				
Single-factor analysis			Multivariate analysis	
CRP> 3 mg / l	4,36 (3,26-5,44)	0,009	3,5 (2,3 - 4,7)	0,03
Diabetesinanamnesis	3,3 (2,3 - 4,0)	0,029	2,72 (1,64 - 3,8)	0,07
Cholesterol> 5.2 mmol / l	3,5 (2,2 - 4,8)	0,053	2,75 (1,45 - 4,05)	0,12

Note: abbreviations - see the list of abbreviations, RR - relative risk, CI - confidence interval.

cardiovascular prognosis for three variables: the level of C-reactive protein and total cholesterol (on the verge of statistical significance), as well as the presence of type 2 diabetes mellitus, with the strongest prognostic factor was the C-reactive protein.The risk of developing adverse cardiovascular events during the observation period in patients with a C-reactive protein level> 3 mg / l was 4.36 times higher than in patients with a C-reactive protein level <3 mg / L, patients with a level total cholesterol> 5.2 mmol / l had a risk of developing adverse cardiovascular events 3.5 times higher than patients with total cholesterol level <5.2 mmol / l, and the presence of type 2 diabetes in patients with stable CHD increased cardiovascular risk by 3.3 times compared with patients not suffering from type 2 diabetes mellitus. As a result of multivariate regression analysis (with the influence of factors such as cholesterol level and the presence of type 2 diabetes), the C-reactive protein remained the strongest and most independent prognostic factor of adverse cardiovascular events. Patients with a C-reactive protein level> 3.0 mg / L in the long-term period had a risk of developing adverse cardiovascular outcomes 3.5 times higher than patients with a C-reactive protein level <3 mg / L. When analyzing the data, it was noted that unfavorable cardiovascular events occur more often (p = 0.03) and earlier (p = 0.005) in patients with CRP> 3 mg / l.

In the group of patients with adverse cardiovascular events that occurred during the observation period, the level of CRP> 3 mg / l was 77% of patients (10 patients out of 13), while in the group of patients who did not have cardiovascular events were recorded, CRP> 3 mg / l was observed in 23% of patients (8 patients out of 35). When comparing survival curves without adverse cardiovascular events in patients with C-reactive protein levels> 3 mg / L and <3 mg / L in patients with stable CHD, it was noted that the level of C-reactive protein significantly influenced the time of onset of events.

DISCUSSION

Cardiovascular diseases continue to be the main cause of death in the developed countries of the world. The prevalence of coronary heart disease (CHD) in Europe and the US varies from 1 to 1.5%, significantly increasing with age and reaching 10% among people over 60 years of age (1). CHD is a disease that requires extremely high costs. This situation indicates that questions about the accuracy and timeliness of diagnosis, the adequacy of treatment and prevention of cardiovascular disease require careful study.It was noted that the signs of inflammation are detected both in patients with unstable forms and in patients with stable form of CHD, but the degree of inflammation in patients with UA (level of TNF-α, CRP and

leukocytes) is higher than in patients with stable ischemic heart disease (Zorina *et al*., 2012; Uzokov *et al*., 2017).A direct correlation between the levels of inflammation markers and a number of factors has been revealed: the presence of excess body weight (CRP) and bad habits (leukocytes), age (fibrinogen) and sex of the patient (IL-6), treatment before hospitalization (CRP, leukocytes).In patients with UA, unlike patients with stable CHD, there is a moderate positive correlation between cytokines and lipid profile of the blood: TNF-α and cholesterol (r = 0.46, p = 0.009), TNF-α and LDL (r = 0.42, p = 0.02, IL-6 and CS (r = 0.47, p = 0.008), IL-6 and LDL (r = 0.39, p = 0.03). It was found that with stable CHD, CRP> 3.0 mg / l is the strongest and most independent prognostic factor of adverse cardiovascular events. In patients with UA the strongest independent prognostic factor of adverse cardiovascular events is the level of TNF> 9 pg / ml (RR = 5.0, 95% CI = 3.6-6.4, p = 0.02).It was found that patients with a level of TNF-α> 9 pg / ml in the group of patients with UA and with CRP> 3 mg / l in the group of patients with stable course of IHD repeat cardiovascular events occur significantly more often and earlier than in patients with lower indicators of these markers.

There is evidence that the degree of increase in blood concentrations of such cytokines as interleukin-1β (IL-1β) and tumor necrosis factor (TNF-α) is directly related to the stages of CHF (6). This makes it possible to use them as markers of severity of CHF. Several studies have demonstrated that patients with CHF are characterized by persistent immune activation in vivo. This is reflected in increased levels of pro-inflammatory cytokines in the blood (TNF-a, interleukins-IL-1β and IL-6) and chemokines (monocyte chemoattractant protein-1 and IL-8), as well as enhanced expression of various inflammatory mediators (TNF- IL-6 and adhesion molecules) in the myocardium, regardless of the etiology of CHF (Kukharchuk, 2015). The results of several studies showed a direct relationship between elevated plasma levels of inflammatory cytokines and changes in the functional class of CHF and heart condition (left ventricular ejection fraction) (Eiken, 2009). More importantly, these inflammatory mediators carry important prognostic information about patients with CHF. For example, in the SOLVD study, patients with a plasma TNF-a level of less than 6.5 pg / ml had a better prognosis than patients with a higher level (Torre-Amione, 1996). Moreover, according to data from a large population of patients with CHF (cytokine database from the VEST study) (10), circulating levels of pro-inflammatory cytokines (TNF-a and IL-6) and cytokine receptors (soluble receptors for TNF-a) are independent predictors of mortality in patients with severe CHF. These new clinical data support the view that elevated levels of cytokines in CHF reflect important pathogenetic mechanisms in such patients.Thus, according to the publication of B. Bozkurt *et al*., prolonged administration of TNF-α in the experiment led to a decrease in myocardial contractility and, subsequently, to irreversible dilation of the cavity (LV) (9).

L.J. Jobe *et al*. showed that in rats with experimentally induced heart failure due to volume overload, the administration of the TNF-α inhibitor led to a decrease in LV remodeling (13). These and a number of other effects are realized through interaction with specific TNF receptors (TNF-α, R-1, TNF-R-2). TNF-α induces the process of programmed death of cardiomyocytes (apoptosis) (Masenko and others // Cardiological bulletin. 2007). In patients with CHF, a decrease in the number of viable cardiomyocytes as a result of their apoptosis leads to a decrease in the contractile function of the myocardium and the progression of the disease. The tumor necrosis factor enhances the processes of oxidative stress of cardiomyocytes. Binding of TNF-α to receptors and oxidative stress processes trigger the caspase cascade in the cardiomyocyte. In turn, the enzyme caspase-3 triggers a genetic program of cell death. Activation of the cytokine system is accompanied by pathochemical and pathomorphological changes at the level of various organs and tissues. Thus, information concerning the participation of pro- and anti-inflammatory cytokines in the development and progression of CHD is of great practical importance for the development of new approaches to the treatment of this disease.

Conclusion

It was noted that the signs of inflammation are detected both in patients with unstable forms and in patients with stable form of CHD, but the degree of inflammation in patients with UA (level of TNF-α, CRP and leukocytes) is higher than in patients with stable ischemic heart disease. A direct correlation between the levels of inflammation markers and a number of factors has been revealed: the presence of excess body weight (CRP) and bad habits (leukocytes), age (fibrinogen) and sex of the patient (IL-6), treatment before hospitalization (CRP, leukocytes).

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