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CYTOKINE STATUS IN MIDDLE-AGED MEN WITH ACUTE CORONARY SYNDROME AFTER CORONARY ARTERY STENTING

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Background. Inflammatory cytokines and growth factors are involved in various mechanisms of coronary artery disease. Clinical studies have shown the correlation between the increase in the level of proinflammatory cytokines and the severity of coronary artery disease, while the data on the role of proinflammatory interleukin IL-8 and anti-inflammatory interleukin IL-4 are contradictory.

The aim of the study is to assess the levels of proinflammatory cytokines (IL-8, TNF-α) and anti-inflammatory interleukin (IL-4) in patients with various forms of coronary artery disease who underwent coronary artery stenting.

Materials and methods. By the method of enzyme-linked immunosorbent assay, the levels of cytokines were determined in 30 patients with acute coronary syndrome who underwent primary stenting of the coronary arteries and in 24 patients with chronic coronary syndrome who had previously had myocardial infarction with stenting of an infarction-associated artery, who were admitted to the clinic for staged stenting of the coronary arteries.

Results. In patients with chronic coronary syndrome the levels of IL-4 a do not exceed the reference values, in patients with acute coronary syndrome the levels of IL-4 there was an increase 3,70 ± 0,24 and 240,85 ± 49,25 pg/ml, $p \leqslant 0{,}001$. In patients with chronic coronary syndrome the levels of IL-8 a do not exceed the reference values, in patients with acute coronary syndrome the levels of IL-8 there was an increase 7,34 ± 1,29 and 110,33 ± 27,67 pg/ml, $p \leqslant 0{,}001$.

Conclusion. Most likely the increase in the level of IL-4 has a compensatory character and, along with a slight increase in TNF-α, can be considered as a positive factor stabilizing the course of the disease. There may be some relationship between of the increase in the level of interleukins in patients with acute coronary syndrome on the degree of stenosis of the coronary arteries (90–95%) and impaired myocardial contractility was established.

Keywords: acute coronary syndrome; chronic coronary syndrome; stenting of coronary arteries; interleukin-4; interleukin-8; tumor necrosis factor alpha; myocardial infarction.

ЦИТОКИНОВЫЙ СТАТУС У МУЖЧИН СРЕДНЕГО ВОЗРАСТА С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ ПОСЛЕ СТЕНТИРОВАНИЯ КОРОНАРНЫХ АРТЕРИЙ

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Актуальность. Воспалительные цитокины и факторы роста участвуют в различных механизмах развития ишемической болезни сердца. Клинические исследования показали корреляцию повышения уровня провоспалительных цитокинов с тяжестью ишемической болезни сердца, при этом данные о роли провоспалительного интерлейкина IL-8 и противовоспалительного интерлейкина IL-4 противоречивы.

Цель исследования — оценить уровни провоспалительных цитокинов (IL-8, TNF-α) и противовоспалительного интерлейкина (IL-4) у пациентов, страдающих различными формами ишемической болезни сердца, которым было выполнено стентирование коронарных артерий.

Материалы и методы. Методом твердофазного иммуноферментного анализа определены уровни цитокинов у 30 пациентов с острым коронарным синдромом, которым было выполнено первичное стентирование коронарных артерий, и у 24 — с хроническим коронарным синдромом, ранее перенесших инфаркт миокарда со стентированием инфаркт-связанной артерии, которые поступили в клинику для этапного стентирования коронарных артерий.

Результаты. Уровень IL-4 у больных хроническим коронарным синдромом находился в пределах референсных значений, в то время как у пациентов с острым коронарным синдромом отмечалось его повышение — 3,70 ± 0,24 и 240,85 ± 49,25 пг/мл, при $p \leqslant 0{,}001$. Уровень IL-8 у пациентов с хроническим коронарным синдромом также находился в пределах референсных значений, тогда как в группе с острым коронарным синдромом отмечалось его повышение — 7,34 ± 1,29 и 110,33 ± 27,67 пг/мл, при $p \leqslant 0{,}001$.

Заключение. Вероятнее всего повышение уровня IL-4 имеет компенсаторный характер и, наряду с незначительным повышением TNF-α, может рассматриваться как положительный фактор, стабилизирующий течение заболевания. Может существовать определенная зависимость между повышением уровня интерлейкинов у пациентов с острым коронарным синдромом от степени стенозирования коронарных артерий (90–95 %) и нарушения сократимости миокарда.

Ключевые слова: острый коронарный синдром; хронический коронарный синдром; стентирование коронарных артерий; интерлейкин-4; интерлейкин-8; фактор некроза опухоли альфа; инфаркт миокарда.

BACKGROUND

Cardiovascular system diseases currently rank first in mortality and disability in all economically developed countries [2, 4, 16].

Coronary heart disease (CHD) affects a large proportion of the population in industrialized countries and causes more than a third of deaths among people aged >35 years [14]. According to Federal State Statistics Service, as of June 22, 2019, in the structure of mortality from diseases of the blood circulatory system, more than half (52.6%) of the cases accounted for CHD in 2018 [24]. In the same year, myocardial infarction as the cause of death was recorded in 54,427 people (6.5% in the structure of mortality in diseases of the blood circulatory system). With the widespread introduction of invasive treatment for patients with CHD, mortality from myocardial infarction is decreasing [5]; however, its indicators in Russia exceed those in Europe and North America [4].

Risk factors for CHD include obesity, diabetes, hypertension, high levels of low-density lipoprotein (LDL), tobacco smoking, cocaine or amphetamine abuse, family history, chronic kidney disease, human immunodeficiency virus infection, autoimmune disorders, and anemia [11]. The main etiological factors in the CHD development include atherosclerosis, chronic inflammatory lesion with infiltration of mononuclear leukocytes, proliferation of vascular smooth muscle cells, and accumulation of extracellular matrix [13, 23].

Acute coronary pathology includes unstable angina, myocardial infarction (acute coronary syndrome, ACS) with and without ST segment elevation, and acute myocardial infarction, which differ in the degree of myocardial damage and level of cardiac markers [5].

Acute coronary pathology is most commonly caused by atherothrombosis, which is triggered by damage to the atherosclerotic plaque. Moreover, the initial degree of coronary artery stenosis can be different, in some cases not reaching hemodynamic significance. A less common cause is coronary artery vasospasm (a variant of Prinzmetal angina pectoris) caused by endothelial or vascular dysfunction [12].

Multivessel coronary artery disease (MVCAD) is defined as significant stenosis (>70%) of two or more large coronary arteries (≥2.5 mm in diameter) [8]. Approximately 40%–60% of patients with ST-segment elevation myocardial infarction have multivessel coronary disease [21, 22]. However, the strategy of myocardial revascularization in patients with MVCAD has not yet been ultimately determined. Simultaneous stenting of all hemodynamically significant stenoses of the coronary arteries or only infarction-related artery with subsequent stenting of hemodynamically significant stenoses within

the same hospitalization or staged revascularization continues to be a subject of discussion [7, 9]. A recent meta-analysis (which included 7423 patients from 10 randomized trials) confirmed a significant reduction in the incidence of major adverse cardiovascular events in patients with a history of complete coronary revascularization (CR) compared with infarction-related arterial revascularization. The significant decrease was mainly caused by the low rate of repeated revascularization in the CR group, and a decrease was more pronounced when CR was performed during ST-segment elevation myocardial infarction rather than in stages [20].

Inflammatory cytokines and growth factors are involved in various pathways of CHD, including transcription activator, mitogen-activated protein kinase, and SMAD (transcription factor family) [1, 10, 18]. Clinical studies have shown a direct correlation between an increase in the level of proinflammatory cytokines (interferon-γ, tumor necrosis factor [TNF]-α, and interleukin [IL]-2, IL-6, IL-9, and IL-17) and CHD severity, determined by coronary angiography. Data on the level of anti-inflammatory IL-4 in patients with CHD are contradictory [17]. Various studies have highlighted the ambiguous role of IL-8 as an indicator of CHD risk. IL-8 is a leukocyte chemoattractant that is also present in atherosclerotic plaque and can contribute to the development of plaque instability by increasing leukocyte extravasation and endothelial cell adhesion [3, 15]. Moreover, in ischemic tissues, IL-8 accelerates neovascularization and promotes angiogenesis. Some authors have reported that high levels of IL-8 cannot be considered a marker of the risk of cardiovascular diseases in the future, while they are associated with an increased risk of death, regardless of the underlying cause. The main properties of IL-8, i.e., being pro-inflammatory and anti-ischemic, noted in experimental studies may partially explain the discordant association of IL-8 with the risk of cardiovascular diseases associated with atherosclerosis [6, 19].

Thus, inflammatory biomarkers, in particular pro- and anti-inflammatory cytokines, play essential roles in the initiation and development of CHD. Their analysis can provide a better understanding of the mechanism of vascular lesions and offer the most objective markers for predicting outcomes of CHD treatment.

The study aimed to assess the levels of pro-inflammatory cytokines (IL-8 and TNF-α) and anti-inflammatory cytokines (IL-4) in patients with various forms of CHD, who underwent coronary artery stenting.

MATERIALS AND METHODS

The study was performed in accordance with Good Clinical Practice and the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Scientific Medical Research Involving Human Subjects, as amended in 2000. The study protocol was approved by the Ethics Committees of all participating centers. Written informed consent was obtained from all patients before inclusion in the study.

The study enrolled 54 male patients aged 52–59 years (ACS group) and those aged 45–59 years (chronic coronary syndrome [CCS] group). The exclusion criteria were type I and II diabetes mellitus, chronic kidney disease requiring renal replacement therapy, ongoing inflammatory diseases that could affect an additional change in the cytokine status, as well as vasospastic and non-coronarogenic CHD.

All patients examined were distributed into two groups. The ACS group included 30 (55.6%) male patients admitted to the clinic with a diagnosis of ACS that subsequently progressed to unstable angina pectoris, without a history of myocardial infarction, with a single-vessel coronary artery disease, who underwent primary stenting of the coronary arteries. The CCS group consisted of 24 (44.4%) male patients who were admitted to the clinic with CCS and had a history of ST-segment elevation myocardial infarction with revascularization of the infarct-dependent artery with drug-eluting stents within the previous 2–6 months. This group underwent staged (planned) stenting of hemodynamically significant stenoses.

All patients underwent a comprehensive clinical examination. Before coronary angiography, the blood levels of pro-inflammatory cytokines (TNF-α and IL-8) and anti-inflammatory interleukin (IL-4) were measured. The enzyme-linked immunosorbent

assay with the use of reagents (indirect fluorescent antibody [IFA]-IL-4, IFA-IL-8, and IFA-TNF-α] produced by Cytokin (St. Petersburg) was applied on the Uniplan apparatus (CJSC Picon, Russia). The degree of stenosis of the coronary arteries was assessed using the standard Stenosis Analysis software installed on GE Healthcare angiography (Chicago, IL, USA). The ejection fraction was calculated with a two-dimensional Echo-CG according to the Simpson method.

Obtained data were processed on a personal computer using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Student's *t*-test was used to assess the differences between the two groups of values of indicators with normal distribution. Differences were considered significant at $p \leq 0.01$.

RESULTS AND DISCUSSION

Patients from both groups were distributed according to the degree of stenosis and localization of coronary artery lesions. Circumflex artery stenosis was recorded more often in the CCS group than in the ACS group ($p \leq 0.01$). Moreover, 80%–90% stenosis of the coronary artery was diagnosed in 83% of the cases ($p \leq 0.01$). In the ACS group, 90%–95% stenosis of the coronary artery ($p \leq 0.01$) was revealed in 60%, anterior interventricular artery in 40%, and right coronary artery in 50% of all cases (Table 1).

The degree of stenosis was higher in patients with ACS and single-vessel coronary artery disease, who underwent primary stenting of the coronary arteries, than in patients with CCS having a history of ST-segment elevation myocardial infarction with revascularization of the infarction-dependent artery with drug-eluting stents within the previous 2–6 months (Table 1). Moreover, circumflex artery lesion was noted less often in the ACS group.

Left ventricular ejection fraction was preserved in all patients of the CCS group (54%–63%). The ACS group had preserved and an intermediate left ventricular ejection fraction (48%–62%). The average group value of the ejection fraction in the ACS group with unstable angina pectoris was significantly lower than in the CCS group with stable angina pectoris (50.5 ± 0.7 versus $59 \pm 0.6\%$) ($p \leq 0.001$). Impaired myocardial contractility was recorded in 18 (60%) patients of the ACS group

Table 1 / Таблица 1

The degree of stenosis coronary arteries in different patients groups with acute coronary syndrome and chronic coronary syndrome

Степень стеноза коронарных артерий в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

The degree of stenosis coronary arteries / Степень стеноза коронарных артерий	Group / Группа	Left anterior descending artery / Передняя межжелудочковая артерия	Left circumflex artery / Огибающая артерия	Right coronary artery / Правая коронарная артерия	Outcome / Итого
70–80%	1	3 (10%)	0	3 (10%)	6 (20%)
	2	0	0	0	0
80–90%	1	3 (10%)	3 (10%)	0	6 (20%)
	2	4 (17%)	12 * (50%)	4 (17%)	20 * (83%)
90–95%	1	6 (20%)	0	12 (40%)	18 (60%)
	2	0	0	4 (17%)	4 * (17%)
Total / Всего	1	12 (40%)	3 (10%)	15 (50%)	30 (100%)
	2	4 (17%)	12 * (50%)	8 (33%)	24 (100%)

* Differences with group 1 are statistically valid at $p \leq 0.01$.

* Различия относительно 1-й группы статистически значимы при $p \leq 0{,}01$.

Table 2 / Таблица 2

Risk Factors CAD in different patients groups with acute coronary syndrome and chronic coronary syndrome
Факторы риска ишемической болезни сердца в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

Indication / Показатели	Group 1 / 1-я группа (n = 30)		Group 2 / 2-я группа (n = 24)		Statistics significance of differences (t) / Статистическая значимость различий (t)
	n	%	n	%	
Hyperlipidemia (LDL > 1.8 mmol/L) / Гиперлипидемия (ЛПНП > 1,8 ммоль/л)	24	80	6	25	$p \leq 0.001$ (4.7)
Hypertensive disease 3 stage / Гипертоническая болезнь 3-й стадии	5	16.7	24	100	$p \leq 0.001$ (4.4)
Chronic obstructive pulmonary disease / Хроническая обструктивная болезнь легких	7	23	3	12.5	$p > 0.05$ (1.0)
Smoking / Табакокурение	23	76.7	10	41.7	$p \leq 0.05$ (2.7)
Obesity I–II stage / Ожирение I–II степени	14	46.7	6	25	$p > 0.05$ (1.7)

Note. LDL – low density lipoproteins.
Примечание. ЛПНП — липопротеиды низкой плотности.

Table 3 / Таблица 3

Level of cytokine in different patients groups with acute coronary syndrome and chronic coronary syndrome
Уровень цитокинов в группах пациентов с острым коронарным синдромом и хроническим коронарным синдромом

Indication / Показатели	Group 1 / 1-я группа (n = 30)	Group 2 / 2-я группа (n = 24)	Statistics significance of differences (t) / Статистическая значимость различий (t)
IL-4 (0–4 pg/ml / пг/мл)*	240.85 ± 49.25	3.70 ± 0.24	$p \leq 0.001$ (4.8)
IL-8 (0–10 pg/ml / пг/мл)*	110.33 ± 27.67	7.34 ± 1.29	$p \leq 0.01$ (3.7)
TNF-α (0–6 pg/ml / пг/мл)*	0.81 ± 0.45	0.04 ± 0.004	$p > 0.05$ (1.7)

Note. * Reference interval according to laboratory data.
Примечание. * Референсный интервал по данным лаборатории.

and only in 4 (17%) patients of the CCS group ($p \leq 0.01$).

According to the anamnesis, the risk factors for CHD were established in patients with ACS and CCS (Table 2).

Hyperlipidemia and tobacco smoking significantly more often occurred in the ACS group ($p \leq$ 0.05–0.001). In the CCS group, the stage 3 hypertensive disease was noted in all patients with CCS ($p \leq 0.001$). The presence of chronic obstructive pulmonary disease and obesity grades I–II was not significantly different between the groups, and a tendency to their increase was only found in the ACS group (Table 2).

In the CCS group, a more favorable situation with regard to hyperlipidemia was associated with maintenance therapy with statins, which included in the complex treatment of myocardial infarction complications.

The CCS group had no significant change in the level of both pro-inflammatory and anti-inflammatory cytokines (Table 3). Their IL-4, IL-8, and TNF-α levels were within the reference interval. By contrast, the ACS group had very high mean group indicators of both pro-inflammatory IL-8 and anti-inflammatory IL-4 (Table 3).

As a result, the differences in the IL-8 and IL-4 levels between the groups were significant ($p \leq 0.01$–0.001) with an increase in the IL level

in the ACS group. Moreover, in 18 (60%) patients with ACS, the levels of IL-4 and IL-8 were higher than the reference values. The increase in the IL-4 level was probably of a compensatory property to proinflammatory cytokines and can be considered a positive factor in stabilizing the disease course. No significant change was noted in the levels of TNF-α in patients with ACS, which can also be considered a factor that facilitates the course of ACS.

According to echocardiography data, all patients with increased IL levels had 90%–95% coronary artery stenosis and impaired myocardial contractility. By contrast, IL levels in patients with ACS having 70%–90% stenosis did not increase. In the clinical analysis of blood in patients with increased IL levels, the erythrocyte sedimentation rate was higher in patients with ACS having normal IL level than in those with CCS.

CONCLUSIONS

1. In patients with ACS, levels of both pro-inflammatory IL-8 and anti-inflammatory IL-4 were increased. The increase in IL-4 level was most probably of a compensatory nature. In patients with CCS, the levels of IL-4 and IL-8 were within the reference values.
2. In patients with ACS, which subsequently progressed into unstable angina pectoris, and in patients with CCS, the level of TNF-α was not increased.
3. A higher degree of stenosis of the coronary arteries in combination with a disorder of local myocardial contractility leads to higher levels of IL-4 and IL-8, which may indicate a more extensive inflammatory response that resulted in the development of ACS.

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