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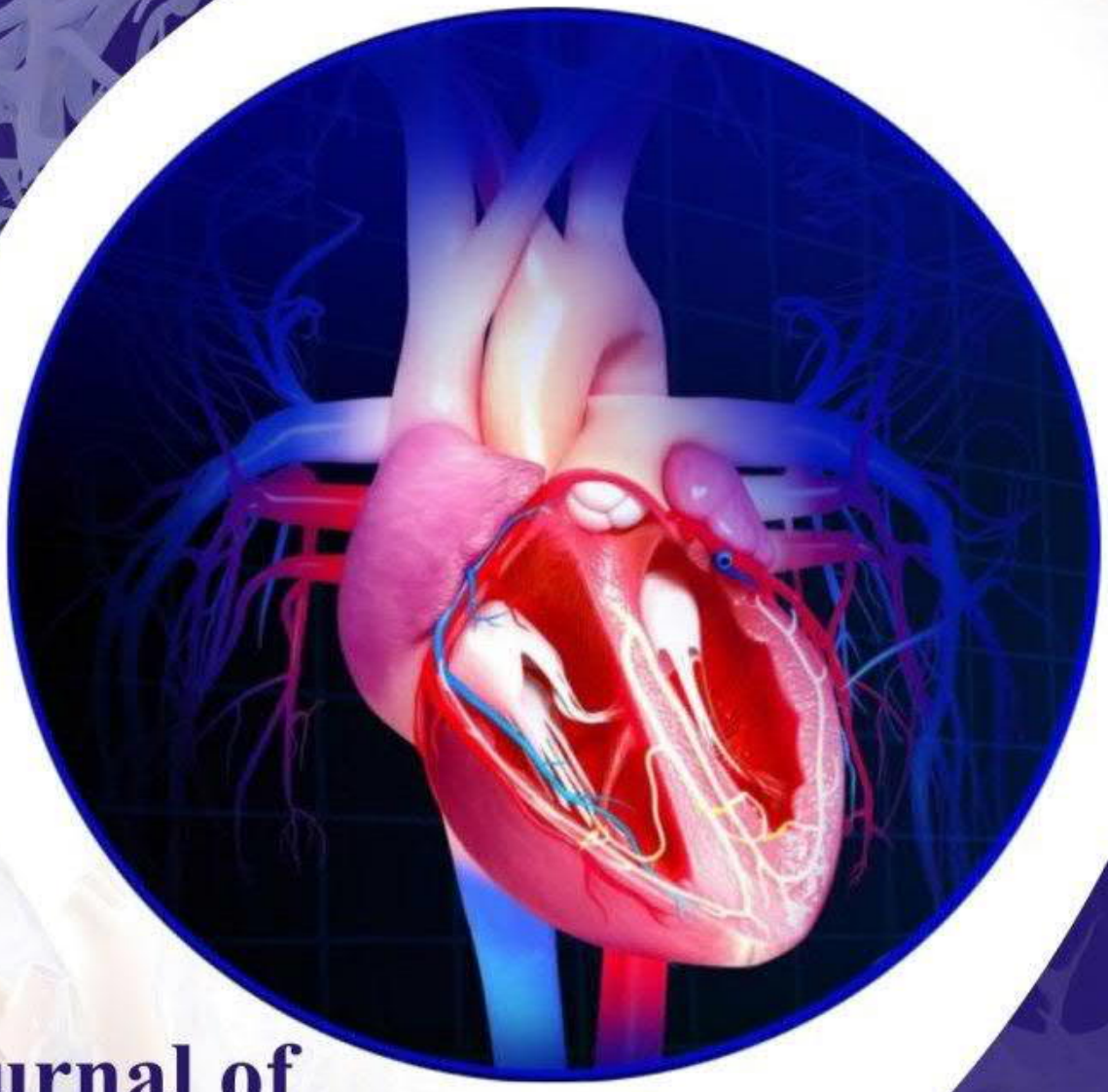

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CHANGES IN THE CYTOKINE STATUS WITH STABLE ANGINA (REVIEW)

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ANNOTATION

This review summarizes the current evidence on the role of cytokines in the pathogenesis of ischemic myocardial damage. It described the important role of inflammation in the development of coronary heart disease. The role of individual cytokines in the pathogenesis of coronary artery disease and the most frequent forms of it - angina. It is shown that in patients with coronary heart disease progression of the disease is due to an imbalance in cytokine system, elevated pro-inflammatory cytokines (TNF, IL-1β, IL-6). Anti-inflammatory cytokines (IL-4, IL-10) inhibit the secretion of proinflammatory cytokines by limiting excessive intensity of the immune response. Revealed increasing levels of TGF-β1 as a key cytokine that promotes the development of fibrosis in the wall of the heart and blood vessels. The interrelation between improving markers of inflammation and the development of coronary heart disease, the predictive value of these markers of inflammation in patients with stable coronary heart disease: angina of effort of different functional classes.
Key words: ischemic heart disease, stable angina, cytokines.

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РОЛЬ ЦИТОКИНОВ ПРИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА (ОБЗОР)

АННОТАЦИЯ

В обзоре обобщены современные данные, касающиеся роли цитокинов в патогенезе ишемических поражений миокарда. Описана важная роль воспаления в развитии ишемической болезни сердца. Определена роль отдельных цитокинов в патогенезе ИБС и самой часто встречающейся ее формы - стенокардии. Показано, что у больных ишемической болезнью сердца прогрессирование заболевания связано с дисбалансом в цитокиновой системе, повышением содержания провоспалительных цитокинов (ФНОα, ИЛ-1β, ИЛ-6). Противовоспалительные цитокины (ИЛ-4, ИЛ-10) угнетают секрецию провоспалительных цитокинов, ограничивая чрезмерную интенсивность иммунного ответа. Выявлено повышение уровня ТФР-β1 как ключевого цитокина, способствующего развитию фиброза в стенке сердца и сосудов. Обсуждается взаимосвязь повышения уровня маркеров воспаления и развития ишемической болезни сердца, прогностическая ценность этих маркеров воспаления у пациентов, страдающих стабильными формами ишемической болезни сердца: стенокардией напряжения различных функциональных классов.

Ключевые слова: ишемическая болезнь сердца, стабильная стенокардия напряжения, цитокины.

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YURAK ISHEMIK KASALLIGIDA SITOKINLARNING ROLI (ADABIYOTLAR TAHLILI)

ANNOTATSIYA

Ushbu maqolada miokardni ishemik jarohatlanishida sitokinlarni ahamiyati haqida eng yangi ma’lumotlar ko’rsatilgan. Yurak ishemik kasalligining rivojlanishida yallig’lanishni o’rni to’liq yoritilgan. Yurak ishemik kasalligi ya’ni ko’p uchrovchi stenokardiya patogenezida ayrim sitokinlarni o’rni aniqlandi. YIK bor bemorlarda kasallikni zo’rayishi sitokinlar disbalansi bilan bog’liqligi,

ayniqsa yallig'lanishiga qarshi sitokinlar (FNOα, IL-1β, IL-6) miqdorini oshishi ko'rsatildi. Yallig'lanishga qarshi sitokinlar (IL-4, IL-10) yallig'lanish sitokinlar ishlab chiqarish sitokinlari kamaytiradi. TFR-β1 sitokini miqdorini oshishi yurak va qon tomir devorida fibrozni rivojlanishidan dalolat beradi. Yallig'lanish markerlari miqdorini oshishi yurak ishemik kasalliga rivojlanishida bog'liqlik borligini, va yurak ishemik kasalligining barcha shakllari bilan kasallangan bemorlar uchun muhim ahamiyatga egaligi muhokama qilinmoqda.
Kalit so'zi: yurak ishemik kasalligi, stabil zo'riqish stenokardiyasi, sitokinlar

Cardiovascular disease (CVD) remains the main cause of morbidity and mortality in the world [1]. Coronary heart disease (CHD) gets the most significant part in the structure of cardiovascular diseases, which maintains one of the leading places among the causes of mortality among the adult population [2]. According to estimates by the World Health Organization (WHO), more than 17 million people die from CVD every year in the world, including more than 7 million from CHD [3]. Reports of the State Research Center for Preventive Medicine in 2013, the mortality rate of the population at an economically powerful age (15-72 years) in the Russian Federation from IHD amounted to 181.36 per 100 thousand people aged 15–72 years, among men - 269.23 and 103.01 - among women [4]. In Russia, coronary heart disease is the most common reason for referring to medical institutions for all CVDs and accounts for 28% of cases. Stable angina pectoris is the most prevalent form of chronic coronary heart disease [5,6]. According to the State Research Center for Preventive Medicine, in Russia 10 million able-bodied people suffer from coronary heart disease, more than a third of them in the form of stable angina pectoris. The annual mortality of patients with stable angina is 2%.

The role of inflammation in the pathogenesis of atherosclerosis of coronary arteries and coronary artery disease

Many data show that systemic inflammation is frequent CVD and implicate that inflammation contributes to damage and dysfunction of the cardiovascular system. In the pathogenesis of atherosclerosis and exacerbation of coronary heart disease, the role of the main link is assigned to the inflammatory reaction. The inflammatory process develops at the local level, which is determined by the basic mechanisms of inflammation, and the systemic is the systemic inflammatory response syndrome (SIRS). Atherosclerosis of the coronary arteries is the pathomorphological basis of IHD. With atherosclerosis, signs of a local and systemic non-specific inflammatory process are observed already in the early stages of damage to the blood vessel wall. Atherosclerosis is known to be a chronic inflammatory process, and even in the early stages of atherogenesis - intracellular and extracellular deposition of lipids and formation of lipid spots, inflammatory cells (macrophages and T-lymphocytes) are already present [6,7]. These cells produce a large number of cytokines, chemokines, and matrix metalloproteinases, which cause the development of atherosclerotic foci [8,9].

In atherosclerosis, there is an increase in the expression of VCAM-1 adhesion molecules on endotheliocytes, which, under the influence of pro-inflammatory chemoattractants, leads to the migration of monocytes to intima of the arteries and their subsequent transformation into foam cells. T-lymphocytes also migrate, secreting cytokines that enhance local inflammation. After plaque formation, the constant interaction of lymphocytes and macrophages supports the inflammatory process [10]. Cytokines are known to have multidirectional regulatory effects on the atherosclerotic process. So, proinflammatory cytokines (TNFα, IL-1β, IL-6, IL-8) are considered atherogenic, and anti-inflammatory cytokines (IL-4 and IL-10) as anti-atherogenic mediators [11]. In patients with coronary artery disease, inflammation is a nonlocal process limited to the zone of atherosclerotic lesion of the vascular wall, inflammatory reactions are systemic, accompanied by an increase in blood levels of markers and mediators of inflammation [12].

Systemic Inflammatory Response Syndrome (SIRS) is usually identified with systemic inflammation (SI). Systemic inflammation is a typical, multisyndromic, phase-specific pathological process that develops at the body and is characterized by total inflammatory activity of endotheliocytes, plasma factors, blood cells and connective tissue, as well as microcirculatory disorders in vital organs and tissues with the development of multiple organ failure [13]. CBO is represented by several clinical and immunological phenomena: systemic inflammatory response (SIRS), compensatory anti-inflammatory syndrome (CARS) and mixed antagonistic response syndrome (MARS). It was shown in experiments that, following an increase in the production of cytokines characteristic of SIRS (TNFα, IL-1β), inflammatory mediators characteristic of CARS (TGFβ, IL-4, IL-10) are produced and are antagonists of the first phase. Both responses ultimately form MARS, which is characterized by the simultaneous production of pro- and anti-inflammatory cytokines [14].

Systemic Inflammatory Response Syndrome (SIRS) is usually identified with systemic inflammation (SV). Systemic inflammation is a typical, multiple syndrome, a phase-specific pathological process that develops at the body level and is characterized by the total inflammatory activity of endotheliocytes, plasma factors, blood cells, and connective tissue, as well as microcirculatory disorders in vital organs and tissues with the development of multiple organ failure [13]. SIRS is represented by several clinical and immunological phenomena: systemic inflammatory response (SIRS), compensatory anti-inflammatory syndrome (CARS), and mixed antagonistic response syndrome (MARS). It was shown in experiments that, following an increase in the production of cytokines characteristic of SIRS (TNFα, IL-1β), inflammatory mediators characteristic of CARS (TGFβ, IL-4, IL-10) are produced and are antagonists of the first phase. Both responses ultimately form MARS, which is characterized by the simultaneous production of pro- and anti-inflammatory cytokines [14].

The development of SIRS is accompanied by the activation of the atherosclerotic process. According to modern concepts, an important component of the pathogenesis of coronary heart disease is a systemic inflammatory activity. SIRS most often proceeds subclinically and is the main factor underlying the formation of atherosclerotic plaque, its destabilization, and subsequent rupture [15]. The severity of SIRS is determined by the level of immunological biomarkers. According to the results of numerous studies, inflammatory markers associated with atherosclerosis are IL-6 [16], IL-8 [17], IL-1-β, and TNF-α [18].

The cytokine status changes in patients with coronary artery disease

Violation of the synthesis of cytokines or the expression of receptors for them has a damaging effect on the myocardium. Pro-inflammatory cytokines have a negative inotropic effect, cause cardiac remodeling (irreversible cavity dilatation and cardiomyocytes hypertrophy), impaired endothelium-dependent dilatation of arterioles, and increased cardiomyocytes apoptosis. The decrease in cardiac output that occurs after myocardial damage stimulates the extramyocardial production of these mediators. The components of humoral and cellular immunity are involved in the development of immuno-inflammatory activation. Besides, the function of the heart can change not only due to damage to the cardiomyocytes, but also a change in the activity of cardiofibroblasts. Cardiofibroblasts provide physiological post-stress remodeling. The participation of pro-inflammatory cytokines in the formation of chronic inflammation in coronary artery disease is confirmed in the experiment [19]. Depending on the effect on the inflammatory process, cytokines are divided into

two groups - pro-inflammatory (IL-1, IL-6, IL-8, TNFα, IL-12) and anti-inflammatory (IL-4, IL-10, TGF-β) [20]. Pro-inflammatory cytokines are an important and well-studied class of biologically active substances that have an immunoregulatory and inflammatory effect. The main pro-inflammatory cytokines include TNFα, IL-1, and IL-6, IL-8. Tumor necrosis factor α (TNFα) is a cytokine with pronounced inflammatory properties. It plays a decisive role in the development of inflammation, is an active participant in the immune response, and takes part in the regulation of cell apoptosis [21]. TNFα is synthesized mainly in monocytes and macrophages, as well as in mast cells, fibroblasts, endothelial cells. It stimulates the expression of the production of IL-1β, IL-6, IL-8. This cytokine affects the functional properties of the endothelium, affects coagulation, disrupts lipid metabolism, stimulating atherogenesis. TNFα is considered one of the key factors that ensure the interaction of endothelium and white blood cells. Bozkurt et al. Found that prolonged infusion of TNFα leads not only to a decrease in myocardial contractility but also to irreversible dilatation of the ventricles of rat hearts [22]. The cardiodepressive effect of TNFα is probably associated with a change in calcium cell homeostasis [23], activation of metalloproteinases that induce the destruction of the fibrillar collagen matrix [24]. The researchers found that in patients with coronary artery disease there is an increase in the level of TNFα associated with the severity of the course of angina pectoris [25]. IL-1β, one of the main pro-inflammatory cytokines, is produced primarily by phagocytes, macrophages, as well as fibroblasts, lymphocytes, and epithelial cells. IL-1β activates and regulates inflammatory, immune processes, activates neutrophils, T- and B-lymphocytes stimulates the synthesis of proteins of the acute phase of inflammation, pro-inflammatory cytokines (TNFα), adhesion molecules, prostaglandins. IL-1β increases chemotaxis, vascular wall permeability, cytotoxic and bactericidal activity, which has a pyrogenic effect. The synthesis of IL-1β is suppressed by anti-inflammatory cytokines such as IL-4 and IL-10. An increase in the content of IL-1β was noted in many diseases, including IHD. Violation of coronary blood flow, accompanied by myocardial ischemia, leads to an increase in the content of IL-1β in the blood. The researchers found that the severity of IL-1β expression depends on the severity of the course of angina pectoris and is most significant in severe angina pectoris IV FC [25]. IL-1β takes an active part in the development of atherosclerosis and the formation of the clinical course of coronary heart disease, due to its effect on the function of the endothelium and the blood coagulation system, the ability to induce the synthesis of pro-inflammatory cytokines and expression of adhesive molecules, stimulate procoagulant activity and affect lipid metabolism. IL-6 pro-inflammatory cytokine plays an important role in systemic inflammation, is the main activator of the synthesis of acute-phase proteins in the liver. Using IL-6, endothelial cells, monocytes are also activated, and procoagulant reactions occur. Some studies [26] show the importance of IL-6 as a predictor of the development of clinical manifestations of atherosclerotic vascular lesions in healthy individuals without signs of disease. IL-6 is produced by activated monocytes or macrophages, fibroblasts, endotheliocytes. In inflammation, TNF-α, IL-1β, and IL-6 are sequentially secreted. Then, IL-6 begins to inhibit the secretion of TNF-α and IL-1β, activate the production of proteins of the acute phase of inflammation by the liver and stimulate the hypothalamic-pituitary-adrenal system, which contributes to the regulation of the inflammatory process, and therefore IL-6 can also be considered pro-inflammatory, and as an anti-inflammatory cytokine. The main effect of IL-6 is associated with its participation as a cofactor in the differentiation of B-lymphocytes, their maturation, and conversion into plasma cells that secrete immunoglobulins. Besides, IL-6 promotes the expression of the IL-2 receptor on activated immunocytes and also induces the production of IL-2 by T cells. This cytokine stimulates the proliferation of T-lymphocytes and the reaction of hematopoiesis. In the invitro study, an increase in the level of IL-6 was accompanied by a decrease in the contractile function of myocytes [27].

It has been shown that the ability of IL-6 to transfer inflammation from the acute phase to the chronic with the involvement of mononuclear cells. It was proved that a high level of IL-6 is associated with an unfavorable prognosis and an increased level of TNF-α– with an increase in mortality of patients. IL-8, a pro-inflammatory cytokine, plays an important role in the initiation and maintenance of inflammation, is responsible for the induction of adhesive molecules involved in the interaction of leukocytes and endothelium and subsequent extravasation of leukocytes at the site of the inflammatory reaction. Induces the production of IL-8 damage to the vascular endothelium. The main producers of IL-8 are activated monocytes/macrophages and endothelial cells. According to the authors of clinical trials, IL-8 is the only pro-inflammatory cytokine that is associated with cardiovascular events independently of other cytokines. Since IL-8 stimulates directed migration of neutrophils, these results indicate that neutrophil activation may be associated with the occurrence of cardiovascular events [28]. It is known that cytokines can modulate the functions of the cardiovascular system. Adverse effects of pro-inflammatory cytokines are negative inotropic effects, remodeling of the heart, activation of apoptosis cardiomyocytes, and peripheral muscles.

Anti-inflammatory cytokines Anti-inflammatory cytokines (IL-4, IL-10) inhibit the secretion of pro-inflammatory cytokines, inhibit macrophage activity, reduce the expression of adhesion molecules and reduce cytotoxicity [29]. IL-4, an anti-inflammatory cytokine, is produced by activated T-lymphocytes of type 2 helpers, basophils, mast cells, eosinophils. IL-4 is a stimulator of the humoral link of immunity and allergies, plays the role of one of the main negative regulators of the development of cellular immunity reactions, by directly suppressing the immunological reactions caused by cytokines of type I helper T lymphocytes (INF-γ, IL-2, TNF) [30]. Anti-inflammatory cytokines, in particular IL-4, are involved in limiting the activity of the inflammatory response, inhibiting the secretion of pro-inflammatory cytokines and thus regulating the severity of tissue damage. According to modern data, in patients with coronary artery disease the highest level of IL-4 was determined in the group of patients with angina pectoris in comparison with the control. The highest content of this cytokine was observed in patients with angina pectoris II-III FC against the background of post-infarction cardiosclerosis in comparison with the group of patients with angina pectoris II-III FC without it [31]. An increase in the level of IL-4 in patients with coronary heart disease seems to be compensatory in response to the activation of pro-inflammatory cytokines and acts as a factor stabilizing the course of the disease. A relationship was found between an increase in the level of pro-inflammatory cytokines (IL-6, TNFα) and the severity of coronary heart disease. As the angina FC increases, the level of pro-inflammatory cytokines increases, and the concentration of IL-4 and IL-10 decreases [25].

There is a certain balance between pro- and anti-inflammatory cytokines, it determines the activity of atherosclerotic plaque and affects the course of IHD. In a stable level of angina pectoris II FC, physiological mechanisms of regulating the balance between pro- and anti-inflammatory cytokines are activated, which makes it possible to suppress inflammation in the atheromatous plaque due to blockage of the secretion of pro-inflammatory cytokines with increased production of IL-4 and IL-10. In angina pectoris IV FC, the regulatory mechanisms in the cytokine network are violated and an imbalance develops overexpression of IL-1β, IL-6, and TNF-α, which can have a cardiodepressive effect [32], increase myocardial ischemia and, thus, significantly change the clinical course of the disease. IL-10, the main anti-inflammatory cytokine and one of the most sensitive markers of inflammation in CVD,

reduces the secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNFα), limits the excessive immune response [33]. IL-10 can inhibit damage and thrombosis of an atherosclerotic plaque because it inhibits the activity of macrophages, the main triggers of hypercoagulation. IL-10 reflects the reserve capacity of the body. According to reported reviews, the content of IL-10 in the blood of patients with CVD decreases [34]. Stable angina pectoris IV is characterized by minimal concentrations of IL-4 and IL-10, and a maximally elevated level of pro-inflammatory cytokines [25]. Clinical studies have shown that factor risks of poor prognosis of CVD were decreased levels of anti-inflammatory cytokines (IL-10) and increased content of pro-inflammatory cytokines (IL-8) and acute-phase proteins. In chronic SI, the level of IL-10 exceeding 5 pg/ml was detected in a small part of patients, and the critical level for acute SI of IL-10 of more than 25 pg/ml was recorded only in two cases. Therefore, other cytokines act as an inhibitory mechanism in the SIRS structure, one of which may be TGF-β1 [35]. Transforming growth factor-β1 (TGF-β1) and the process of fibrosis in the cardiovascular system TGF-β, an anti-inflammatory cytokine, regulates the process of fibrosis in the cardiovascular system [36]. TGF-β is involved in the regulation of cell growth, proliferation, differentiation, apoptosis, extracellular matrix production, inflammation, angiogenesis, and tissue healing through exposure to various types of cells [37].

TGF-β exists in 5 isoforms, three of them are expressed in normal mammalian tissues and are designated as TGF-β1, TGF-β2, and TGF-β3. The most pronounced expression and significant role in inflammation, remodeling, and fibrosis of blood vessels and myocardium have TGF-β1. TGF-β is produced by inflammatory cells like a cytokine. The sources of TGF-β are mainly monocytes and macrophages, fibroblasts, endotheliocytes, neutrophils, eosinophils, mast cells, smooth muscle cells [30]. For the same physiological processes, the stimulating and inhibitory effects of TGF-β1, and in some cases the absence of its influence, were revealed. The effect of TGF-β on a cell depends on its type, stage of differentiation, and the presence of other cytokines. There is evidence that TGF-β has both pro-inflammatory and anti-inflammatory functions [36]. TGF-β helps resolve inflammation and repair tissue. TGF-β exhibits its anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory cytokines, such as IL-1 α, β, TNF-α [36]. A literature review shows that a local or systemic excess of this growth factor is associated with unresolved inflammation [38]. Long-term chronic hyperproduction of TGF-β1 leads to hyperplasia of smooth muscle cells, the progression of remodeling of the cardiovascular bed. A reduced level of TGF-β1 can lead to an increase in systemic inflammation (for example, an increase in the level of IL-6), arterial stiffness, and hypertension [39]. Domestic scientists have shown that myocardial ischemia is accompanied by a decrease in the level of anti-inflammatory cytokine TGF-β1 in blood serum [40]. The researchers found an increase in the concentration of TGF-β1 in the blood serum of patients with coronary artery disease compared with the control group. The highest content of this cytokine was observed in patients with angina pectoris II-III FC against the background of post-infarction cardiosclerosis in comparison with the group of patients with angina pectoris II-III FC without it. Therefore, an increase in TGF-β1 in the blood serum of patients with coronary heart disease can be considered as a compensatory reaction aimed at decreasing the activity of proinflammatory cytokines TNF-α, IL-8 [31]. TGF-β1 is involved in the remodeling of blood vessels and myocardium, and also takes part in the process of neoangiogenesis. The development of fibrosis is associated with excessive formation of connective tissue as a result of increased collagen production and impaired degradation of extracellular matrix proteins. TGF-β1 increases the collagen content due to a direct effect on myofibroblasts, contributing to the fibrosis process. The process of heart remodeling is realized due to the influence of many factors, including the death of cardiomyocytes by necrosis, apoptosis, and violation of the structural and functional state of the extracellular matrix against the background of increased fibrosis processes. This cytokine mediates the many effects of angiotensin II, promotes the development of fibrosis by inhibiting the activity of matrix metalloproteinases (MMPs), and the induction of the synthesis of tissue inhibitors of metalloproteinases. An increase in the level of TGF-β1 as a key pro-fibrotic cytokine leads to the development of fibrosis in the walls of the heart and blood vessels. Severe fibrosis of the myocardium and vascular walls prevents them from stretching during blood supply. On the one hand, this complicates the blood supply to the LV and leads to an increase in diastolic insufficiency, but on the other hand, it can protect the remaining muscle fibers of the myocardium from overstretching during the diastole for some time, which allows them to function with increased efficiency by the Starling law. Limiting the extensibility of blood vessels, especially in arteries of the elastic type, leads to an acceleration of the return of blood and an additional burden on the heart.

Thus, in the pathogenesis of atherosclerosis of coronary arteries, as the pathomorphological basis of coronary heart disease (CHD), inflammatory reactions occupy a key position. With atherosclerosis, the inflammatory process develops both at the local, but at the systemic level, systemic inflammatory response (SIRS). The systemic inflammatory process most often proceeds subclinically and is the main factor underlying the formation of atherosclerotic plaque, its destabilization, and rupture. Signs of local and systemic non-specific inflammatory processes are observed already in the early stages of damage to the blood vessel wall. The severity of the inflammatory response is determined by the level of immunological biomarkers. As the angina FC increases, the level of pro-inflammatory (TNFα, IL-1, IL-6, IL-8) cytokines increases, and the concentration of anti-inflammatory (IL-4 and IL-10) cytokines decreases. With stable angina pectoris of FC II, physiological mechanisms of regulating the balance between pro- and anti-inflammatory cytokines are activated, inflammation in the atheromatous plaque is suppressed due to blockage of the secretion of pro-inflammatory cytokines and increased production of IL-4 and IL-10. With angina pectoris IV FC, the regulatory mechanisms in the cytokine network are violated and an imbalance develops between pro- and anti-inflammatory cytokines with overexpression of IL-1β, IL-6, and TNF-α, which have a cardiodepressive effect, enhance myocardial ischemia and, therefore, change the clinical course of the disease. high angina pectoris is associated with increased expression of pro-inflammatory cytokines, which confirms the presence of persistent inflammation, which increases the risk of thrombotic complications and acute coronary syndrome, as in step stable angina. TGF-β exhibits its anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory cytokines, such as IL-1 α, β, TNF-α. An increase in the level of TGF-β1 as a key pro-fibrotic cytokine leads to the development of fibrosis in the walls of the heart and blood vessels. Anti-inflammatory cytokines are involved in limiting the activity of the inflammatory response, inhibit the secretion of pro-inflammatory cytokines, and regulate the severity of tissue damage. A decrease in plasma levels of anti-inflammatory cytokines and an increased content of pro-inflammatory cytokines and acute-phase proteins indicate a higher risk and poor prognosis of CVD [41]. The number of markers of inflammation (pro- and anti-inflammatory cytokines) is constantly increasing. The introduction of measurements of their level in practice will improve the quality of diagnosis, identify risk groups, and more accurately evaluate treatment outcomes and prognosis.

Список литературы/Iqtiboslar/References

1. Zhou, P., Hua, F., Wang, X. et al. Therapeutic potential of IKK-b inhibitors from natural phenolics for inflammation in cardiovascular diseases. Inflammopharmacol 28, 19–37 (2020). https://doi.org/10.1007/s10787-019-00680-8
2. Raish M (2017) Momordica charantia polysaccharides ameliorate oxidative stress, hyperlipidemia, inflammation, and apoptosis during myocardial infarction by inhibiting the NF-kB signaling pathway. Int J Biol Macromol 97:544–551
3. WorldHealthOrganizationStatisticalInformationSystem (WHOSIS) [Elektronnyy resurs]: Statisticheskaya informatsionnaya sistema Vsemirnoy organizatsii zdravookhraneniya. – rezhim dostupa k zhurn.: http: /www.who.int/ mediacentre/factsheets/fs310/ru/index2.html
4. Gosudarstvennyy nauchno-issledovatel'skiy tsentr profilakticheskoy meditsiny Ministerstva zdravookhraneniya Rossiyskoy Federatsii (GNITS profilakticheskoy meditsiny) [Elektronnyy resurs]: Statisticheskiye materialy po zabolevayemosti i smertnosti. - Samorodskaya I.V., Pustelenin A.V., S.A. Boytsov I.V. Smertnost' i dolya umershikh v ekonomicheski aktivnom vozraste ot prichin, svyazannykh s alkogolem (narkotikami), IM i IBS ot vsekh umershikh v vozraste 15-72 za 2013 god. – rezhim dostupa k zhurn.: http: /www.gnicpm.ru/PublicHealth/326 (data obrashcheniya: 23.12.15).
5. Rekomendatsii po vedeniyu stabil'noy koronarnoy bolezni serdtsa Yevropeyskogo obshchestva kardiologov. – Moskva: 2013.
6. Diagnostika i lecheniye khronicheskoy ishemicheskoy bolezni serdtsa/ Klinicheskiye rekomendatsii. – Moskva: 2013.
7. Armstrong E.J. et al., Inflammatory biomarkers in acute coronary syndromes: part I: introduction and cytokines // Circulation, 2006, 113 (6): e72–75.
8. Fruchart J.-C. Pathophysiology of stages of development of atherosclerosis / Handbook of dyslipidemia and atherosclerosis // France, University of Lille, 2003; Part 1, p. 1–65.
9. Armstrong E.J. et al., Inflammatory biomarkers in acute coronary syndromes: part IV: matrix metalloproteinases and biomarkers of platelet activation // Circulation, 2006, 113 (9): e382–385.
10. Bucova M. et al., C-reactive protein, cytokines and inflammation in cardiovascular diseases //Bratisl. Lek.Listy., 2008, 109 (8): 333–340.
11. Libby P. Inflammation and cardiovascular disease mechanisms. // Am J ClinNutr 2006; 83:456S – 460S.
12. Atrial fibrillation pathophysiology: implications for management / Y.K. Iwasaki et al.,] // Circulation. 2011; 124: 2264–2274.
13. Pavlov O.N. Svyaz' vospaleniya s rostom titra antitel k helicobacterpylori pri ostrom koronarnom sindrome// Rossiyskiy kardiologicheskiy zhurnal №6(92)/2011. – S.43-46.
14. Gusev Ye.YU., Osipenko A.V. Immunologiya sistemnogo vospaleniya / Immunologiya Urala. – 2001. – T.1, №1. – S.4-8.
15. Belotskiy, S.M., Avtalion, R.R. Vospaleniye. Mobilizatsiya kletok i klinicheskiye effekty. – M.: Izdatel'stvo BI- NOM, 2008. – 240 s.
16. Rukovodstvo po kardiologii v chetyrekh tomakh. Tom 2: Metody diagnostiki serdechno-sosudistykh zabolevaniy /Pod redaktsiyey akademika Ye. I. Chazova. – M.: Praktika, 2014.
17. Sukhija R. et al., Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome // Am. J. Cardiol., 2007, 99 (7): 879–884.
18. Boekholdt S.M. et al., IL-8 plasma concentrations and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk prospective population study // Arterioscler. Thromb.Vasc.Biol., 2004, 24 (8): 1503–1508.
19. Ragino YU.I. i soavt., Aktivnost' vospalitel'no-destruktivnykh izmeneniy v protsesse formirovaniya nestabil'noy aterosklerotic heskoy blyashki // Kardiologiya, 2007; 9: 62–67.
20. Hansson GK. Inflammation, atherosclerosis and coronary artery disease.//NEnglJMed 2005; 352 (16): 1685–95.
21. Koval'chuk L.V. i soavt., Klinicheskaya immunologiya i allergologiya s osnovami obshchey immunologii, - GEOTAR-Media, 2014. – 640s.
22. Packard R, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. //Clin.Chem. 2008; 54(1): 24-38.
23. BozkurtB., KribbsS.B., ClubbF.J. etal. Pathophysiologically relevant concentrations of tumor necrosis factor-a promote progressive left ventricular dysfunction and remodeling in rats. // Circulation 1998; 97: 1382-91.
24. TeplyakovA.T. Khronicheskayaserdechnayanedostatochnost. Tsitokinovayaekspressiya, immunnayaaktivatsiya I zaschitaorganovmisheney. Tomsk: Izd-vo Tom. Un-ta, 2012. rp. 294.
25. Anker S.D. et al., Elevation soluble CD14 receptore and altered cytokines in chronic heart failure // Am. J. Cardiol. 1997. no. 79. pp. 1426–1430.
26. Zakirova, N.E. Immunovospalitel'nyye reaktsii pri ishemicheskoy bolezni serdtsa / N.E. Zakirova, N.KH. Khafizov, A.N. Zakirova // Ratsional'naya farmakoterapiya v kardiologii.-2007.- №2.-S.16-19.
27. Paleyev, F.N. Izmeneniya interleykina-6 pri razlichnykh formakh ishemicheskoy bolezni serdtsa //F.N.Paleyev, I.S. Abudeyeva, O.V. Moskalets, I.S. Belokopytova / Kardiologiya.- 2010.-№ 2.- S. 69-72. 28. RathanN., HemingwayC.A., AlizadehA.A., StephensA.C., BoldrickJ.C., OraguiEE, McCabeC., WelchS.B., WhitneyA., O'Gara
28. PathanN., HemingwayC.A., AlizadehA.A., StephensA.C., BoldrickJ.C., OraguiEE, McCabeC., WelchS.B., WhitneyA., O'GaraP., NadelS., RelmanD.A., HardingS.E., LevinM. Roleofinterleukin 6 inmyocardialdysfunctionofmeningococcalsepticshock //Lancet. 2004. no. 363. pp. 203–209.
29. Inoue T., Komoda H., Nonaka M. et al. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease // Int. J. Cardiol. 2008. V. 124. № 3. P. 319–325.
30. Kukharchuk V.V., Zykov K.A., Masenko V.P. i dr. Dinamika vospalitel'nogo protsessa u bol'nykh s ostrym koronarnym sindromom i bol'nykh so stabil'noy stenokardiyey. Kardiolvestn // 2007; 2.
31. KetlinskiyS.A., Simbirtsev A.S. Tsitokiny — SPb., Foliant 2008.— 552 s.
32. Prasolov A.V., Knyazeva L.A., Knyazeva L.I., Zhukova L.A. Izmeneniye pokazateley tsitokinovogo statusa u bol'nykh IBS: stabil'noy stenokardiyey napryazheniya II-III funktsional'nogo klassa v zavisimosti ot terapii // Vestnik novykh meditsinskikh tekhnologiy – 2009 – T.KHVI, №2 – s.146-147.
33. Zakirova A.N., Mukhametrakhimova A.R., Zakirova N.E. Sostoyaniye sistolicheskoy funktsii levogo zheludochka i aktivnost' provospalitel'nykh tsitokinov pri ostrom infarkte miokarda. // ZhurnalSerdechnayanedostatochnost' 2005;6(4):162-5.

34. KrishnamurthyP. IL-10 inhibits inflammation and attenuates left ventricular remodeling after myocardial infarction via activation of STAT-3 and suppression of HuR / P. Krishnamurthy, J. Rajasingh, E. Lambersetal //CircRes. - 2009. -Vol.104. - P.9– 18.
35. Kofler S., Nickel T., Weis M. Role of cytokines in cardiovascular diseases: a focus on endothelial responses to inflammation // Clinical Science. —2005. — Vol. 108.—P. 205—213.
36. Gusev Ye.YU., Yurchenko L.N., Chereshnev V.A., Zotova N.V. Metodologiya izucheniya sistemnogo vospaleniya // Tsitokiny i vospaleniye. – 2008. – T. 7, № 1. – S. 15-23.
37. In vivo pro- and anti-inflammatory cytokines in normal and patients with rheumatoid arthritis // S. P. Sivalingam, J. Thumboo, S. Vasoo, S. T. Thio [et al.] / Ann. Acad. Med. Singapore. 2007. Vol. 36. N 2. P. 96–99.
38. Association between transforming growth factor-b1 T869C polymorphism and rheumatoid arthritis: a meta-analysis / W. W. Chang, H. Su, L. He, K.-F. Zhao [et al.] // Rheumatology. 2010. Vol. 49. N 4. P. 652–656.
39. Thrombospondin-1 and transforming growth factor b are proinflammatory molecules in rheumatoid arthritis / M. C. Rico, J. M. Manns, J. B. Driban, A. B. Uknis [et al.] // Transl. Res. 2008. Vol. 152.N 2. P. 95–98.
40. Transforminggrowthfactor-b1 869T/C, butnotinterleukin-6 — 174G/ C, polymorphismassociateswithhypertensioninrheumatoidarthritis / V. F. Panoulas, K. M. Douglas, J. P. Smith, A. Stavropoulos-Kalinoglou [etal.] // Rheumatology. 2009. Vol. 48.N 2.P. 113–118.
41. Sergeyenko I.V., Semenova A.Ye., Masenko V.P., Khabibullina L.I., Gabrusenko S.A., Kukharchuk V.V., Belenkov YU.N. Vliyaniye revaskulyarizatsii miokarda na dinamiku sosudistogo endotelial'nogo i transformiruyushchego faktorov rosta u bol'nykh ishemicheskoy bolezn'yu serdtsa // Kardiovaskulyarnaya terapiya i profilaktika. – 2007. – T. 6, № 5. – S. 12-17.
42. Nazheva M.I., Demidov I.A. Diagnosticheskoye znacheniye opredeleniya bazovykh kontsentratsiy S-reaktivnogo belka i interleykina-6 v krovi dlya otsenki riska serdechno-sosudistykh zabolevaniy // Meditsinskiy vestnik Yuga Rossii. – 2015. - № 3. – S.86–91.

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