The Features of Cytokine Status in Patients with Coronary Heart Disease

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Abstract
This article is about the role of cytokines in the pathogenesis of ischemic myocardial damage. It describes 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 pectoris. It is shown that TGF-β exhibits its anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory cytokines, such as IL-1α, β, TNF-α. The increase in the level of TGF-β1 as a key profibrotic cytokine leads to the development of fibrosis processes in the walls of the heart and vessels. A decrease in the level of anti-inflammatory cytokines in the blood plasma and an increased content of proinflammatory cytokines and acute phase proteins indicate a higher risk and an unfavorable CVD prognosis.

Keywords: Coronary Heart Disease; Stable Angina; Cytokines

Abbreviations: CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; WHO: World Health Organization; SIR: Systemic Inflammatory Response; VCAM-1: Vascular Cell Adhesion Molecule 1; CAIS: Compensatory Anti-Inflammatory Syndrome; MARS: Mixed Antagonistic Response Syndrome; CMC: Cardiac Muscle Cells; TNF: Tumor Necrosis Factor; TGF: Transforming Growth Factor; MMPs: Matrix Metalloproteinases; IL: Interleukin; IHD: Ischemic Heart Disease.

Introduction
Cardiovascular diseases (CVD) are the main cause of morbidity and mortality in the world. In the structure of cardiovascular diseases, the most significant is coronary heart disease (CHD), which occupies one of the leading places among causes of adult mortality [1]. According to the estimates of the World Health Organization (WHO), more than 17 million people die of CVD each year, of which more than 7 million are from CHD [2]. The most frequent form of chronic ischemic heart disease is stable angina [3,4]. According to the State Research Institute for Preventive Medicine, 10 million working-age people in Russia suffer from ischemic heart disease, more than a third of them in the form of stable angina. The annual mortality of patients with stable angina is 2% [5].
The Role of Inflammation in the Pathogenesis of Atherosclerosis of Coronary Arteries and Ischemic Heart Disease

Inflammation is the most common typical pathological process that underlies most human diseases. In the pathogenesis of atherosclerosis and exacerbation of coronary artery disease, the role of the main link is assigned to the inflammatory response. The inflammatory process develops at the local level, which is determined by the basic mechanisms of inflammation, and the systemic inflammatory response (SIR). Atherosclerosis of the coronary arteries is the pathomorphological basis of CHD. In atherosclerosis, signs of local and systemic nonspecific inflammatory processes are already observed in the early stages of the destruction of the blood vessels wall. It is known that atherosclerosis is a chronic inflammatory process and even in the early stages of atherogenesis - intra- and extracellular lipid deposition and formation of lipid spots - inflammatory cells (macrophages and T-lymphocytes) already exist [6,7]. These cells, by activating, secrete a large number of cytokines, chemokines and metalloproteinases that cause the progression of atherosclerotic foci [8,9]. Atherosclerosis, an increase in the expression of Vascular cell adhesion molecule 1 (VCAM-1) adhesion molecules on endotheliocytes is noted, which under the influence of pro-inflammatory chemoattractants results in the migration of monocytes into the intima of the arteries and their subsequent transformation into foam cells. T-lymphocytes also migrate, secreting cytokines that enhance local inflammation. After the formation of the plaque, the constant interaction of lymphocytes and macrophages supports the inflammatory process [5]. It is known that cytokines have multidirectional regulatory effects on the atherosclerotic process. Proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) are considered as atherogenic and anti-inflammatory cytokines (IL-4 and IL-10) as anti-atherogenic mediators [10]. In patients with ischemic heart disease, inflammation is a non-local process limited by the zone of atherosclerotic vascular wall lesion; inflammatory reactions are systemic, accompanied by an increase in blood level of markers and mediators of inflammation [11]. Syndrome of systemic inflammatory reaction is usually identified with systemic inflammation. Systemic inflammation is a typical, multi syndrome, phase-specific pathological process that develops at the organism level 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 dysfunctions [12]. SIR is represented by several clinical and immunological phenomena: systemic inflammatory response (SIRS), compensatory anti-inflammatory syndrome (CAIS) and mixed antagonistic response syndrome (MARS). In the experiments, it was shown that, following the increase in the production of cytokines characteristic of SIRS (TNF-α, IL-1β), inflammatory mediators characteristic of CAIS (TGFβ, IL-4, IL-10) are produced and are antagonists of the first phase. Both responses eventually form MARS, which is characterized by the simultaneous production of pro- and anti-inflammatory cytokines [13]. Development of CAD is accompanied by activation of the atherosclerotic process. According to modern ideas, an important component of the pathogenesis of CAD is systemic inflammatory activity. SIRS most often proceeds subclinically and is the main factor underlying the formation of atherosclerotic plaque, its destabilization and subsequent rupture [14]. The severity of CAD is determined by the level of immunological biomarkers. Based on the results of numerous studies, inflammatory markers associated with atherosclerosis are interleukins IL-6 [15], IL-8 [16], IL-1-β, and TNF-α [17].

Changes in Cytokine Status in Patients with CHD

Violation of cytokines synthesis or the expression of receptors to them has a damaging effect on the myocardium. Proinflammatory cytokines have a negative inotropic effect, cause heart remodeling (irreversible dilatation of the cavities and hypertrophy of Cardiac muscle cells (CMC)), disturbance of endothelium-dependent dilatation of arterioles, intensification of the process of apoptosis of CMC. The drop in cardiac output following myocardial damage stimulates the extramyocardial production of these mediators. Components of humoral and cellular immunity participate in the development of immuno-inflammatory activation. In addition, the function of the heart, apparently, can change not only due to damage to the CMC, but also by altering the activity of the cardio-fibroblasts. Cardiofibroblasts provide physiological post stress remodeling. The participation of proinflammatory cytokines in the development of chronic inflammation in CHD was confirmed in an experiment [18]. Depending on the effect on the inflammatory process, cytokines are divided into two groups: proinflammatory (IL-1, IL-6, IL-8, TNF-α, IL-12) and anti-inflammatory (IL-4, IL-10, TGF-β) [19]. Proinflammatory cytokines are an important and well-studied class of biologically active substances that have an immunoregulatory and pro-inflammatory effect.
The main pro-inflammatory cytokines include TNF-α, IL-1 and IL-6, IL-8. The tumor necrosis factor α (TNFα) is a cytokine with pronounced pro-inflammatory properties. It plays a crucial role in the development of inflammation, is an active participant in the immune response, and takes part in the regulation of apoptosis of cells [20]. TNF-α is synthesized mainly in monocytes and macrophages, as well as in mast cells, fibroblasts, endothelial cells. It stimulates the expression of IL-1β, IL-6, and IL-8 products. This cytokine affects the functional properties of the endothelium, affects coagulation, disrupts lipid metabolism, stimulating the processes of atherogenesis. TNF-α is considered one of the key factors that ensure the interaction of endothelium and leukocytes. 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 [21].

The cardiodepressant effect of TNFα is probably associated with a change in the calcium homeostasis of the cells [22], activation of metalloproteinasises inducing destruction of the fibrillar collagen matrix [23]. The researchers found that CHD patients have an increase in the level of TNFα, associated with the severity of angina pectoris [24]. IL-1β, one of the main pro-inflammatory cytokines, is produced mainly by phagocytes, macrophages, as well as by fibroblasts, lymphocytes and epitheliocytes. 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, exerts a pyrogenic effect. Synthesis of IL-1β is suppressed by such anti-inflammatory cytokines as IL-4 and IL-10. An increase in IL-1β was observed in many diseases, including CHD. Coronary blood flow disorder, accompanied by myocardial ischemia, leads to an increase in the content of IL-1β in the blood. The researchers found that expression of IL-1β depends on the severity of angina pectoris and is most significant in severe angina pectoris IV [24]. IL-1β takes an active part in the development of atherosclerosis and the formation of the clinical course of IHD, which is due to its effect on endothelial function and the blood coagulation system, the ability to induce the synthesis of pro-inflammatory cytokines and the expression of adhesive molecules, stimulate procoagulant activity and affect lipid metabolism. IL-6 proinflammatory cytokine plays an important role in systemic inflammation; it is the main activator of the synthesis of acute phase proteins in the liver. With the help of IL-6, endothelial cells, monocytes are activated as well, and occurs procoagulant reactions.

Some studies [25] have demonstrated the importance of IL-6 as a predictor of the development of clinical manifestations of atherosclerotic vascular disease 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 TNFα and IL-1β, activate the production of acute inflammation proteins by the liver and stimulate the hypothalamic-pituitary-adrenal system, which contributes to the regulation of the inflammatory process, so that IL-6 can be considered both 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 transformation into plasma cells secreting immunoglobulins. In addition, 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 hemopoiesis reaction. In an in vitro study, an increase in the level of IL-6 was accompanied by a decrease in the contractile function of the myocytes [11]. The ability of IL-6 to translate inflammation from the acute phase to the chronic one with the involvement of mononuclears is also shown. It was proved that a high level of IL-6 is associated with an unfavorable prognosis, and an elevated 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. In the opinion of the authors of clinical studies, IL-8 is the only pro-inflammatory cytokine that is associated with cardiovascular events independently of other cytokines. Since IL-8 stimulates targeted neutrophil migration, these results suggest that activation of neutrophils can be associated with the occurrence of cardiovascular events [17]. It is known that cytokines are capable of modulating the functions of the cardiovascular system. Adverse effects of proinflammatory cytokines are negative inotropic action, cardiac remodeling, activation of apoptosis of 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 [9]. IL-4, an anti-inflammatory cytokine, is produced by activated T-lymphocytes of type 2 helper, basophils, mast cells, eosinophils. IL-4 is a stimulator of humoral immunity and allergy, plays a role as one of the major negative regulators of cellular immune reactions, this being done by direct suppression of immunological reactions caused by cytokines T-lymphocyte helper type 1 (IFN-γ, IL-2, TNF) [14]. Anti-inflammatory cytokines, in particular IL-4, participate in limiting the activity of the inflammatory response by suppressing the secretion of pro-inflammatory cytokines and thus regulating the severity of tissue damage. According to modern data, the highest level of IL-4 in patients with IHD was determined in the group of patients with angina in comparison with the control. The greatest content of this cytokine was observed in patients with stable angina II-III FC on the background of postinfarction cardiosclerosis in comparison with the group of patients with stable angina II-III FC without it [17]. The increase in the level of IL-4 in patients with IHD appears to be compensatory in response to the activation of pro-inflammatory cytokines and acts as a stabilizing factor in the course of the disease. The relationship between the increase in the level of pro-inflammatory cytokines (IL-6, TNF-α) and the severity of IHD has been revealed. With the increase in angina pectoris, the level of pro-inflammatory cytokines increases, and the concentration of IL-4 and IL-10 decreases [7]. There is a certain balance between pro- and anti-inflammatory cytokines, which determines the degree of activity of atherosclerotic plaque and affects the course of IHD. With stable angina FC II include physiological mechanisms regulating the balance between pro- and anti-inflammatory cytokines, which enables suppression of inflammation in atheromatous plaque by blocking the secretion of pro-inflammatory cytokines in increased production of IL-4 and IL-10. Angina IV FC regulation mechanisms in the cytokine network violated and develops imbalance between pro- and anti-inflammatory cytokines with excessive IL-1β, IL-6 and TNF-α, capable of providing cardio depressive effects [11], to enhance myocardial ischemia and thus significantly alter clinical course of the disease. IL-10, anti-inflammatory cytokine primary and one of the most sensitive markers of inflammation CVD reduces secretion of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNF-α) limits excessive immune response [12]. IL-10 is able to inhibit the damage and thrombosis of atherosclerotic plaque due to the fact that it inhibits the activity of macrophages, which are the main triggers of hypercoagulability. IL-10 reflects the reserve capabilities of the body. Stable angina pectoris FC IV is characterized by minimal concentrations of IL-4 and IL-10, with the highest level of pro-inflammatory cytokines [4]. Clinical studies have shown that a decrease in the level of anti-inflammatory cytokines (IL-10) in the blood plasma and an increased content of pro-inflammatory cytokines (IL-8) and acute phase proteins indicate a higher risk and an unfavorable CVD prognosis. In chronic CB, the level of IL-10, exceeding 5 pg / ml, was detected in a small part of the patients, and the level of IL-10 critical for acute MI was more than 25 pg / ml only in two cases. The transforming growth factor-β1 (TGF-β1) and the fibrosis process in the cardiovascular system of TGF-β, an anti-inflammatory cytokine, regulate the fibrosis process in the cardiovascular system. TGF-β is involved in the regulation of cell growth, proliferation, differentiation, apoptosis, and production of extracellular matrix, inflammation, angiogenesis, and tissue healing through exposure to various cell types [16]. TGF-β exists as 5 isoforms, three of which are expressed in normal mammalian tissues and are referred to as TGF-β1, TGF-β2 and TGF-β3. The most pronounced expression and significant role in inflammation, remodeling and fibrosing of blood vessels and myocardium is possessed by TGF-β1. TGF-β is produced by inflammatory cells like a cytokine. The sources of TGF-β are mainly monocytes and macrophages, fibroblasts, endothelialocytes, neutrophils, eosinophils, mast cells, smooth muscle cells [21]. For the same physiological processes, the stimulating and inhibitory effects of TGF-β1 were revealed, and in some cases, the absence of its effect. The effect of TGF-β on a cell depends on its type, the state of differentiation and the presence of other cytokines. There is evidence that TGF-β has both pro-inflammatory and anti-inflammatory functions [15].

TGF-β promotes the resolution of inflammation and tissue repair. TGF-β exhibits its anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory cytokines, such as IL-1α, β, TNF-α [6]. The literature data show that a local or systemic excess of this growth factor is associated with unresolved inflammation [17]. Prolonged chronic hyperproduction of TGF-β1 leads to hyperplasia of smooth muscle cells, the progression of remodeling of the cardiovascular bed. Reduced levels of TGF-β1 may lead to an increase in systemic inflammation (eg, an increase in IL-6), arterial stiffness and hypertension [9]. Domestic scientists have shown that myocardial ischemia is accompanied by a decrease in the level of anti-inflammatory cytokine TGF-β1 in the blood serum [5]. The researchers found an increase in the concentration of TGF-β1 in the serum of patients with CHD in comparison with the control group. The greatest content of this cytokine was observed in patients with
stable angina II-III FC with postinfarction cardiodesclerosis in comparison with the group of patients with stable angina II-III FC without it. Therefore, the increase in TGF-β1 in the blood serum of patients with IHD can be considered as a compensatory reaction aimed at decreasing the activity of proinflammatory cytokines TNF-α, IL-8 [3]. TGF-β1 participates in vascular and myocardial remodeling, and also participates 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 degradation of extracellular matrix proteins. TGF-β1 increases the collagen content by directly affecting myofibroblasts, contributing to the fibrosis process. The process of cardiac remodeling is realized due to the influence of many factors, including the death of cardiomyocytes by necrosis, apoptosis and disturbance of the structural and functional state of the extracellular matrix against the background of intensification of fibrosis processes. This cytokine serves as a mediator of many effects of angiotensin II, promotes the development of fibrosis by suppressing the activity of matrix metalloproteinases (MMPs) and induction of the synthesis of tissue inhibitors of metalloproteinases. The increase in the level of TGF-β1 as a key profibrotic cytokine leads to the development of fibrosis processes in the walls of the heart and vessels. The pronounced fibrosis of the myocardium and the walls of the vessels impede their stretching during blood filling. On the one hand, it complicates LV filling and leads to an increase in diastolic insufficiency, but on the other hand, it can for some time protect the remaining muscle fibers of the myocardium from overstretching during diastole, which allows them to function with increased efficiency in accordance with Starling’s law. Restriction of vasodilatation, especially in the arteries of the elastic type, leads to an accelerated return of blood and an additional burden on the heart.

Thus, in the pathogenesis of coronary artery atherosclerosis, which is the pathomorphological basis of coronary heart disease, inflammatory responses take a key position. With atherosclerosis, the inflammatory process develops both at the local and systemic level - a systemic inflammatory reaction (SIR). 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 nonspecific inflammatory process are observed already in the early stages of the destruction of the wall of blood vessels. The severity of the inflammatory response is determined by the level of immunological biomarkers. As the angina pectoris increases, the level of proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8) increases, and the concentration of anti-inflammatory (IL-4 and IL-10) cytokines decreases. With stable angina II FC, physiological mechanisms for regulating the balance between pro- and anti-inflammatory cytokines are included suppression of inflammation in the atheromatous plaque due to blockade 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 disrupted and an imbalance develops between pro- and anti-inflammatory cytokines with over expression of IL-1β, IL-6 and TNF-α, which have a cardiodepressant effect, which increase myocardial ischemia and, consequently, change the clinical course of the disease. So, 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, already at the stage of stable angina. TGF-β exhibits its anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory cytokines, such as IL-1α, β, TNF-α. The increase in the level of TGF-β1 as a key profibrotic cytokine leads to the development of fibrosis processes in the walls of the heart and vessels. Anti-inflammatory cytokines participate 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 the level of anti-inflammatory cytokines in the blood plasma and an increased content of proinflammatory cytokines and acute phase proteins indicate a higher risk and an unfavorable CVD prognosis. The number of markers of inflammation (pro- and anti-inflammatory cytokines) is constantly increasing [25]. The introduction of measurements of their level in practice will improve the quality of diagnosis, identify risk groups, and more accurately assess the results of treatment and prognosis [26].

References


