

## **Association of genetic polymorphism of tumor necrosis factor- $\alpha$ in the development of coronary heart disease in elderly patients**

### **Abstract**

The research project outlines a new look at the concept of "inflammaging" and the role of the subclinical inflammatory process in various age-associated pathology, in particular coronary heart disease. Particular attention is paid to the tumor necrosis factor- $\alpha$  -cytokine, which plays an important role in the pathogenesis of chronic inflammatory processes and in the aging process. The increased content of tumor necrosis factor- $\alpha$  leads to the emergence and accumulation of various diseases, disability and mortality of elderly and senile people.

Tumor necrosis factor- $\alpha$  influences various risk factors for cardiovascular pathology. This substance aggravates various breakdowns in metabolism, primarily causing insulin resistance. Tumor necrosis factor- $\alpha$  is a key cytokine that stimulates bone resorption (osteoporosis) and sarcopenia. Currently available data prove the important role of tumor necrosis factor- $\alpha$  in various age-associated pathologies.

**Keywords:** *cytokines, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), atherosclerosis, aging, senile age, comorbid patients, longevity, coronary heart disease*

### **Introduction**

In Russia, "emergency medicine" is well developed - the treatment of a problem that is already clearly making itself felt in the form of symptoms and a burdened condition. At the same time, preventive medicine based on fundamental knowledge of the molecular biochemistry of the body is gaining momentum in the world. As a result of scientific and research progress over the past few years, the Russian medical community has significantly revised its views on therapy and anticipatory diagnosis of this cohort of pathologies. Especially regarding the

dominant leader of the complex spectrum of manifestations of coronary heart disease - acute coronary syndrome.

For example, a "vascular program" is being conducted in many regions of the country, and an increasing number of patients are undergoing interventional treatment and careful monitoring. Such measures provide new opportunities and chances for a more successful reduction of mortality and prolongation of patients' lives (not just prolongation, but comfortable life support for years to come). The patterns of course and prognosis for patients of the older age group differ from younger groups, which means that each patient is considered as an independent clinical history. In these conditions, the prognosis of the course of coronary heart disease (especially after episodes of exacerbation of unstable angina or infarction) according to a set of clinical, instrumental, biochemical and genetic indicators is of great importance, as it allows you to make a personalized approach to each individual.

According to official statistics of the Ministry of Health of the Russian Federation, pathologies of the cardiovascular system occupy a leading position among organ diseases in the country, and this trend has been growing exponentially for the last 20-25 years. **More than half of cases end in developmental death and coronary heart disease.** Coronary heart disease (also called coronary arterial disease or coronary atherosclerosis) is an independent nosological unit caused by absolute or relative insufficiency of coronary circulation, Coronary heart disease is the leading cause of death for both men and women worldwide (approximately 7 million people die annually). This is the collective name of a group of pathophysiologically related syndromes resulting from myocardial ischemia (an imbalance between perfusion and the need of the heart for oxygenated blood). Ischemia not only causes oxygen deficiency, but also reduces the availability of nutrients and the removal of metabolites. As a result, the heart tolerates ischemia worse than isolated hypoxia, for example, with severe anemia, congenital heart disease of the blue type or long-term lung disease [1, 2].

## **A new look at the factors of development of coronary heart disease**

In the last few years, scientists and clinicians have expanded their understanding of the genesis of heart disease. And if earlier doctors did not recognize many "elements", today doctors pay close attention to the correlation between inflammatory processes (for example, rheumatoid arthritis), migraines, headaches and even living in the immediate vicinity of the highway and diseases of the heart [3, 4].

The situation of the male population aged 40-65 years in economically developed countries with a high level of urbanization is especially sad. But what's even worse: CHD is getting younger. And if 5-10 years ago it was nonsense to meet a person with a myocardial infarction at the age of 25, today such cases are more and more common. The threat has never been so terrible, and the need for action has never been so urgent. The statistics of cardiovascular diseases in general and heart diseases in particular are terrifying. At the beginning of the last century, 11% of all deaths were registered from heart attack in Russia. In the middle of the 20th century - 25%. In the early 90s - 50%. In 2007, their number reached 57% and continues to hold approximately at this level.

The role of genetic factors in the development of exacerbations of coronary heart disease has not been studied enough to date, although there is a lot of fresh data in this regard [5].

It is known that allelic polymorphism of cytokine and mediator genes affects the expression of protein conglomerates, thereby determining the outcome of a cardiovascular catastrophe. Taking into account other risk factors, hospital mortality increases by 70% for every 10-year increase in age. In addition, the treatment of this pathology in patients is complicated by high-grade rhythm disturbances, heart failure and polymorbidity due to combination with type II diabetes mellitus, dyscirculatory encephalopathy, bronchoobstructive syndrome [6].

The most important negative factor is that ACS in elderly patients develops against the background of existing organic and functional changes in the heart and blood vessels of an age-related nature.

### **Polymorphism of tumor necrosis factor- $\alpha$ in the development of age-associated pathologies, in particular, coronary heart disease in elderly patients**

"Inflammaging" is increasingly viewed in the context of one of the most significant points in the aging process and the development of chronic diseases. Unlike the usual response to a particular pathogenic agent, inflammation does not disappear with aging, but persists stably, leading to various pathological changes [7, 8].

Both clinical and experimental studies have established that proinflammatory cytokines (primarily tumor necrosis factor- $\alpha$  and interleukin-6) play an important role in the occurrence and progression of subclinical inflammation associated with aging processes. An increase in the content of these cytokines in the blood serum of elderly and senile people is associated with an increase in morbidity, disability and mortality [9, 10]. With aging, the expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 increases. The imbalance between pro-inflammatory and anti-inflammatory cytokines leads to subclinical inflammation, accelerates the aging process and contributes to the emergence of various age-associated diseases. Pro-inflammatory cytokines cause cellular aging by stimulating hyperproduction of reactive oxygen species, while damage to deoxyribonucleic acid activates, in turn, pro-inflammatory cytokines, blocks the cell cycle and supports cellular aging [11]. The classical proinflammatory cytokine TNF- $\alpha$  plays an important role in the immune response in the elderly.

The TNF- $\alpha$  family is considered as a group of cytokines with important functions in various immune reactions, in the process of inflammation, differentiation, control of proliferation of various cells and their apoptosis [12, 13]. TNF- $\alpha$  is regarded as the main pro-inflammatory mediator responsible for the

activation of the immune system in infectious processes. Bacterial agents and many other stimuli induce the synthesis of TNF- $\alpha$ , which recruits and activates neutrophils, macrophages and lymphocytes at the sites of tissue damage and infection [14].

The study of TNF- $\alpha$  genetic polymorphisms in people over 75 years of age revealed no differences in the distribution of TNF- $\alpha$  genotypes, however, the GA genotype (TNF- $\alpha$ -308AG) was associated with a lower incidence of dementia in centenarians.

A few centenarians (carriers of the AA genotype) had a higher risk of mortality and, as a rule, an increased level of TNF- $\alpha$  in blood plasma was observed [15]. Some authors have noted a longer life expectancy of women with the TNF- $\alpha$ -308AG genotype, compared with women with the GG genotype [16].

Genetic studies have also found that the allele A of the TNF- $\alpha$ -308 gene (TNF- $\alpha$ -308A) is associated with the risk of coronary heart disease [16, 17]. The multifunctional proinflammatory cytokine TNF- $\alpha$  influences several risk factors for cardiovascular diseases, in particular, insulin resistance, dyslipidemia, endothelial dysfunction and endothelial activation of cell adhesion molecules [18]. A high level of TNF- $\alpha$  in centenarians is associated with a low ankle-shoulder index, indicating peripheral atherosclerosis. Other effects of TNF- $\alpha$  may also contribute to the development and progression of atherosclerosis and a high risk of thromboembolic complications. We are talking about the stimulation of TNF- $\alpha$  synthesis of other pro-inflammatory mediators, for example, interleukin-6, C-reactive protein, fibrinogen, as well as leukocytes [19].

At the same time, TNF- $\alpha$  induces smooth muscle cell proliferation and increases leukocyte adhesion to endothelial cells by inducing the expression of cell adhesion molecules (E-selectin, ICAM-1 (CD54) and VCAM-1 (CD106)), as well as the expression of various cytokines by endothelial cells, including interleukin-6 [20]. It has been shown that TNF- $\alpha$  stimulates endothelial dysfunction at an early stage of atherosclerosis, increases endothelial permeability, and promotes leukocyte migration into the vascular wall. Increased vascular permeability

contributes, in turn, to the formation of atherosclerotic plaques. At later stages, this proinflammatory cytokine increases apoptosis of vascular smooth muscle cells and macrophages (which contributes to the rupture of atherosclerotic plaque), induces synthesis of matrix metalloproteinases and procoagulant activity, reducing transcription of anticoagulant genes - thrombomodulin and protein-C [19]. TNF- $\alpha$  contributes to dyslipidemia by increasing the level of triglycerides, total cholesterol, as well as low-density lipoprotein cholesterol and reducing the concentration of high-density lipoproteins. TNF- $\alpha$  participates in lipid metabolism, reducing the activity of 7-hydroxylase and lipoprotein lipase and stimulating the production of triglycerides in the liver [20].

The results of clinical and experimental studies indicate the important role of TNF- $\alpha$  in atherogenesis and the occurrence of vascular dysfunction in arterial hypertension and pathological remodeling of the myocardium [9, 20].

Over the past 20 years, cardiology has firmly established the concept that not only dyslipidemia, but also inflammation are actively involved in the atherosclerotic process and in the development of cardiovascular diseases, including coronary heart disease (CHD) [21, 22]. Both chronic coronary heart disease and acute myocardial infarction are inflammatory processes in which such pro-inflammatory cytokines as TNF- $\alpha$ , as well as acute-phase proteins, for example, C-reactive protein, play an important role [22, 23].

TNF- $\alpha$  is considered as a key pro-inflammatory cytokine involved in the processes of atherogenesis and supporting mild systemic inflammation in the cardiovascular system. The effects of TNF- $\alpha$  on the cardiovascular system include not only its effect on vascular dysfunction, but also its effect on cardiomyocytes [18].

Direct evidence of stimulated TNF- $\alpha$  vascular dysfunction is presented in a study on healthy volunteers: intraarterial administration of a high dose of this cytokine for 30 minutes led to acute local vascular inflammation. At the same time, violations of endothelium-dependent vasodilation and a persistent increase in the release of plasminogen activator from endothelial cells were noted [24].

Administration of a lower dose of TNF- $\alpha$  to healthy volunteers was accompanied by an increase in basal vascular resistance, which was blocked by pretreatment with a nonselective cyclooxygenase inhibitor [25].

It can be assumed that the observed effects of TNF- $\alpha$  are mediated not only by a decrease in the bioavailability of nitric oxide, but also by an increase in cyclooxygenase-dependent production of vasoconstrictors [26]. In healthy people, TNF- $\alpha$  concentrations in the heart are low and do not affect contractile function. However, the introduction of exogenous TNF- $\alpha$  inhibits the contractile activity of cardiomyocytes. This pro-inflammatory cytokine is also able to reduce the absorption of calcium ions by the sarcoplasmic reticulum and the sensitivity of myofilaments to calcium.

In addition to reducing the contractility of cardiomyocytes, TNF- $\alpha$  is able to induce their hypertrophy [16]. Occlusion of the coronary arteries in myocardial infarction causes a rapid increase in the content of proinflammatory cytokines, including TNF- $\alpha$ . Although an early increase in TNF- $\alpha$  after myocardial infarction helps to stabilize the function of the left ventricle, prolonged stimulation of TNF- $\alpha$  provokes its dysfunction in later phases after acute coronary syndrome.

Chronic exposure to high concentrations of TNF- $\alpha$  leads to left ventricular dysfunction and increased activity of matrix metalloproteinases, contributing to matrix degradation and, ultimately, an increase in cardiomyocyte apoptosis [27].

A number of studies have shown that high levels of TNF- $\alpha$  in the blood serum can persist for many months after a myocardial infarction [22,28]. According to the observations of some authors, long-term maintenance of high TNF- $\alpha$  content becomes a risk factor for the development of repeated cardiovascular events. Proinflammatory cytokines (including TNF- $\alpha$ ) are produced mainly in the periinfarction zone, therefore, a persistent increase in cytokine levels after myocardial infarction may be the result of increased infiltration of the heart muscle by inflammatory cells.

Expression of TNF- $\alpha$  after myocardial infarction may persist over time in intact cardiomyocytes, which suggests a possible long-term role of this cytokine in

myocardial and vascular remodeling [28]. In general, the effect of TNF- $\alpha$  on cardiomyocytes is quite multifaceted and depends on the effect on a certain type of receptor and on the form of the cytokine (membrane-bound or soluble).

When exposed to type 1 receptors, TNF- $\alpha$  causes inhibition of myocardial contractility. This dysfunction can occur due to the stimulation of oxidative stress during the formation of reactive oxygen species and increased production of nitric oxide synthase (accompanied by the production of nitric oxide and peroxynitrite), activation of phospholipase A2, arachidonic acid and sphingomyelinase [9, 29].

TNF- $\alpha$  may have independent negative inotropic effects and inhibit the expression of contractile proteins (in particular, heavy chains of  $\alpha$ -myosin and cardiac  $\alpha$ -actin). In addition, TNF- $\alpha$  can cross-interact with the system of  $\beta$ -adrenergic receptors and inhibit the contractility of cardiomyocytes by changing the transmission of signals to these receptors [29]. In addition to reducing contractility, TNF- $\alpha$  enhances the transcription of genes that contribute to myocardial hypertrophy in heart failure. At the same time, this pro-inflammatory cytokine stimulates cardiomyocyte apoptosis, cardiac fibrosis, and pathological remodeling of the myocardium, which contributes to the progression of heart failure [30, 31].

Under the influence of TNF- $\alpha$ , the activation of the renin-angiotensin-aldosterone system (RAAS) is observed in the heart, which leads to increased remodeling of the left ventricle, an increase in collagen content and apoptosis of cardiomyocytes [32]. An increase in the content of TNF- $\alpha$  in patients with chronic heart failure (CHF) has been demonstrated in a number of studies that have confirmed the role of this pro-inflammatory cytokine in the pathogenesis of CHF, especially with preserved ejection fraction [29, 33]. Expression of TNF- $\alpha$  by cardiomyocytes leads to inhibition of their contractile activity. At the same time, TNF- $\alpha$  can interact with  $\beta$ -adrenergic receptors and thereby aggravate the negative inotropic effect [9,29,34]. TNF- $\alpha$ , along with other proinflammatory cytokines, plays a role in the pathogenesis of atrial fibrillation. In a number of recent studies, it has been found that the risk of atrial fibrillation with elevated TNF- $\alpha$  increases

markedly [31]. The specific pathogenetic relationship between proinflammatory cytokines (including TNF- $\alpha$ ) and atrial fibrillation is not yet clear, however, a number of concepts have been proposed linking chronic inflammation with the development and progression of structural and electrophysiological remodeling of the atria [30].

Both in clinical and experimental studies, TNF- $\alpha$  has been found to have a negative effect on the remodeling of the left ventricle and other chambers of the heart through induction of matrix metalloproteinases and activation of proteolytic processes [35]. Along with this, a reliable direct correlation was found between the level of TNF- $\alpha$  in the blood serum and the diameter of the left atrium [36].

### **Conclusion**

Thus, it remains extremely important to search for risk factors for adverse outcomes of exacerbations of coronary heart disease in patients of the older age group. This will allow us to identify a group of patients who need more active tactics of invasive and conservative treatment. It is also proved that in the pathogenesis of the development of exacerbation of coronary heart disease, the central role is assigned to the processes of inflammation.

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