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Correction of Cytokine Imbalance in the Treatment of Stable Angina Pectoris

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Abstract: Coronary heart disease (CHD) is one of the most common causes of death in developed countries. This is due to the attention paid to the study of the pathogenesis of coronary heart disease. The main mechanisms leading to the development of acute coronary syndrome (ACS), unstable angina and acute myocardial infarction (AMI), are atherosclerosis and thrombosis. Despite the fact that atherosclerotic plaques narrowing the lumen of the coronary arteries cause inadequate myocardial perfusion and, consequently, the development of stable angina, ACS occurs only when these plaques are damaged and ruptured, followed by thrombosis. Many risk factors for the development and progression of coronary heart disease are known, but so far it has not been possible to fully explain what is the cause and trigger of acute coronary complications. Recently, the inflammatory theory of atherosclerosis has been widely discussed. The inflammatory theory of atherogenesis is confirmed by an increase in the concentration of markers of the inflammatory response in the blood of patients with coronary artery disease – C-reactive protein (CRP), neopterin, interleukin-6 (IL-6), fibrinogen, etc. Destabilization of the atherosclerotic plaque is determined by the high activity of the chronic inflammatory process. Neopterin is also a marker of activation of human cellular immunity. By its structure, neopterin is a condensed heterocyclic compound consisting of two parts – pyrimidine and pyrazine. Its main source is blood cells. IL-6 is a multifunctional cytokine and stimulates the proliferation of T-lymphocytes, macrophages, and endothelial cells. With the help of IL-6, endothelial cells, monocytes are activated and procoagulative reactions occur. Cytokines have a strong effect on the production of each other. In this network of mutual influences, almost all effects are stimulating, and only IL–6 suppresses the production of IL-1 and TNF-α. This feature of IL-6 determines its dual role in the development of inflammation: being a typical pro-inflammatory cytokine in its effects, it also has an anti-inflammatory effect.

Keywords: angina pectoris, TES therapy, cytokines, ACTH, cortisol, β-endorphin

Introduction

Inflammation occupies a key position in the pathogenesis of atherosclerosis of the coronary arteries, which forms the pathomorphological basis CHD. The development of the inflammatory process occurs at the local and systemic level – a systemic inflammatory reaction (SIR). SIR is the main factor in the formation of atherosclerotic plaque, its destabilization and rupture. It most

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often occurs subclinically. At the initial stages of atherosclerosis, signs of a local and systemic nonspecific inflammatory process are already developing in the walls of blood vessels.
Inflammatory cells (macrophages and T-lymphocytes) are detected already at the initial stages of atherogenesis, when intra- and extracellular deposition of lipids occurs and lipid spots are formed. When activated, these cells secrete a large number of cytokines, chemokines and matrix metalloproteinases that cause the progression of the formation of atherosclerotic foci.
In patients with coronary heart disease, inflammation is not limited to the area of atherosclerotic lesion of the vascular wall. The inflammatory reaction is accompanied by an increase in the level of markers and mediators of inflammation in the blood and is systemic in nature. The activity of the inflammatory response is assessed by the level of biomarkers. According to numerous studies, interleukins (IL) are inflammatory markers associated with atherosclerosis.
Cytokines are conditionally divided into: pro-inflammatory (IL-1, IL-6, IL-8, TNFa, IL-12) and anti-inflammatory (IL-4, IL-10, TFR-β) depending on the effect on the development of the inflammatory process. Cytokines modulate the functions of the cardiovascular system. They have a negative inotropic effect, activate remodeling of the heart muscle and trigger apoptosis of cardiomyocytes. Anti-inflammatory cytokines, inhibiting the secretion of pro-inflammatory cytokines, reduce the severity of the inflammatory response and reduce tissue damage.
The strategy of treatment of angina pectoris is based on improving the prognosis and quality of life of the patient by reducing the frequency of angina attacks and episodes of myocardial ischemia. It is possible to distinguish two main directions of treatment of angina pectoris: drug therapy according to international standards and coronary revascularization. However, to date, all available methods of treatment are not effective enough. Even modern, well-chosen drug therapy does not always allow to achieve an acceptable quality of life for the patient. In addition, long-term use of medications is accompanied by the development of a number of side effects. Surgical methods are not always technically applicable, have a number of complications and a high frequency of relapses of the disease: in 32-40% of patients after CAH for 6 months and in 20-25% of patients after CABG for 8-10 years old, angina attacks resume, which is due to the progression of coronary sclerosis. In connection with the above, the development of new approaches to the treatment of stable angina is an urgent task.
Coronary heart disease is considered from the position of stress damage to the heart. At the same time, adaptive-compensatory reactions of TES therapy are included, accompanied by selective activation of protective (antinociceptive) mechanisms of the brain. This method has a complex, systemic, homeostatic effect, increasing the ability of the body to adapt to damage. Currently, antihypoxic, anti-inflammatory and immunomodulatory effects are known. In addition, the effect on the synthesis of pituitary hormones has been established.
The target of the therapeutic effect of TES therapy in the treatment of angina pectoris is the effect on cytokine networks, stress-implementing and stress-limiting systems.
The aim of the study was to study the cytokine status and hormonal profile in patients with stable angina pectoris of functional class II-III and the possibility of their correction when added to the standard treatment of TES therapy.

Materials And Methods

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In this work, the dynamics of cytokines (IL-1β,-4,-6,-10) and hormones (cortisol, ACTH, β-endorphins) were evaluated in 60 patients who were hospitalized for planned treatment of stable angina pectoris II-III FC.
Criteria for inclusion in the study:
• age 50-75 years, coronary history of at least 2 years, the presence of dyslipoproteinemia;
• stable HF II-III FC, verified by a characteristic pain syndrome, according to the treadmill test;
• having the right heart rate;
• availability of informed consent of the patient to conduct the study.
Exclusion criteria from the study:
• GM tumors, mental illness, epilepsy, skin damage at the sites of electrode application;
• * presence of complex cardiac arrhythmias, history of MI, DM, condition after surgical treatment (coronary artery bypass grafting);
• the presence of GB of the 3rd degree, in which, against the background of treatment, the patient's blood pressure does not reach the target values, CHF III-IV FC (NYHA);
• lack of informed consent of the patient for research.
All patients with SSN II-III FC were randomly assigned to two groups. The following groups of patients were identified: group 1 – 30 patients with angina who received standard treatment according to the protocol (Clinical recommendations Stable Coronary Heart Disease, 2016), group 2 – 30 patients who received TES therapy along with standard treatment.
The course of transcranial electrical stimulation was carried out by the TRANSAIR-03 apparatus, which provides stimulation with rectangular pulses of electric current (frequency 77 Hz, pulse duration – 3.5-4 ms, current strength from 1 to 2.4 m A). The cathode was placed on the forehead, and the double anode was placed on the mastoid processes. Electrostimulation sessions were performed daily during the daytime for 8 days, from the 1st day of stay in the hospital.
Biochemical studies were carried out upon admission to the hospital and in dynamics on 8th day upon discharge from the hospital. Blood sampling from patients was carried out strictly on an empty stomach, in the morning. Blood in the volume of 4 ml was collected from the cubital vein into plastic vacuum tubes "Vacuette" with a stopper containing EDTA. Then the samples were centrifuged (OP-12 centrifuge, Russia) for 15 minutes at a speed of 1500 rpm./min. The infusion fluid was collected and frozen in cryoprobes, stored in the refrigerator at –70°C. Statistical data processing was carried out by nonparametric statistics methods – the program "Statistica 6.0 for Windows" of the company "Stat Soft, Inc." and "Microsoft Office Excel 2010". The results, after statistical processing, were expressed as the mean value (M) and the error of the mean (m). The comparison of dependent samples was carried out by the nonparametric Wilcoxon criterion, independent samples – by the nonparametric criterion Manna-Whitney with the establishment of the level of significance *p≤0.05 and **p≤0.01.

Results And Discussion

In patients of group 1, on the 1st day of hospital stay, a statistically significant (p≤0.01) increase in the content of IL-1ß to 2.14±0.87 pg/ml was noted - by 7.1 times. On the 8th day of therapy , the level of IL-1ß was 2.19±0.68 pg/ml.
Thus, during the entire period of treatment, there were no statistically significant changes in the level of IL-1ß in group 1 patients who received only standard treatment for angina pectoris according to the protocol. In the 2nd group of patients on the 1st day, the level of IL-1ß it was

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2.36±1.05 pg/ml, which was statistically significantly (p≤0.01) higher (7.9 times) in relation to by the control, and on the 8th day of observation, it decreased statistically significantly (p≤0.01) to 1.05±0.07 pg/ml. Thus, the use of TES therapy along with standard treatment contributed to a statistically significant decrease in the level of IL-1ß by 2.2 times compared to the 1st day in patients of this group.

The content of IL-6 in the blood serum of group 1 patients on the 1st day in the hospital was 10.51±1.88 pg/ml. This is statistically significant (p≤0.01) 7.5 times higher than normal. On the 8th day of observation of patients of the 1st group, the level of IL-6 in the blood, it decreased statistically significantly (p≤0.01) by 1.6 times and amounted to 6.62±2.64 pg/ml; however, it remained statistically significantly (p≤0.01) by 4.7 times above the norm. In the 2nd group of patients on day 1, the level of IL-6 was 10.68±6.83 pg/ml, which was statistically significantly (p≤0.01) higher (7.6 times) in relation to the control, by the end of the follow-up for In patients, its content decreased statistically significantly (p≤0.01) (2.2 times) in relation to the 1st day and amounted to 4.75±1.87 pg/ml, but remained statistically significantly higher (3.4times) in relation to the control (1.4±0.28 pg/ml).Thus, the use of TES therapy in the 2nd group of patients together with standard therapy provides a statistically significant significant decrease in the level of IL-6, which reduces its damaging effect.

The level of IL-4 in the blood serum of patients on the 1st day of hospital stay was 5.66±1.25 pg/ml, which is statistically significant (p≤0.05) is 3.8 times higher than normal. On the 8th day of standard therapy, it did not change statistically significantly and amounted to 5.13±1.40 pg/ml. In group 2, on day 1, the IL-4 content was 5.10±1.04 pg/ml, which was statistically significantly (p≤0.01) higher (3.4 times) in relation to the control. By the end of the observation of patients, its level statistically significantly (p≤0.01) decreased (by 2.5 times) in relation to the 1st day and amounted to 2.07±0.50 pg/ ml, i.e. it was 1.4 times higher in relation to the control value.

In patients of group 1, the level of IL-10 in the blood serum was 5.02±1.25 pg/ml. This was statistically significant (p≤0.01) 3.3 times higher than normal. On the 8th day of observation of patients, its content did not change statistically significantly and amounted to 4.10±1.10 pg/ml (2.7 times above control). In the 2nd group, where the TES therapy, the level of IL-10 on the day of hospitalization was 4.26±0.91 pg/ml, which is statistically significantly (p≤0.01) higher (2.8 times) relative to the control. In the same group, on the 8th day of observation, it decreased statistically significantly (p≤0.01) (1.9 times): up to 2.21±0.24 pg/ml. Thus, the use of TES therapy along with standard therapy contributed to a decrease in the level of IL-10 by almost 2 times in relation to the first days in this group.

Upon admission to the hospital, group 1 patients showed a statistically significant (p≤0.01) decrease in the content of ACTH to 3.31± 0.81 pg/ml, i.e. by 1.5 times. On the 8th day of therapy, the level of ACTH it was 2.26±0.63 pg/ml. Thus, for the entire period of treatment in group 1 patients who received only standard treatment of angina pectoris according to the protocol, there was a statistically significant (p≤0.01) decrease in the level of ACTH by 1.5 times in relation to its level at admission. In patients of the 2nd group on the 1st day, the level of ACTH was 3.41±2.10 pg/ml, which was statistically significant (p≤0.01) is lower (1.4 times) in relation to the control, and on the 8th day of follow-up, it increased statistically significantly (p≤0.01) to 5.30±3.46 pg/ml (1.6 times in relation to the 1st day in patients of this group). The content of cortisol in the blood serum of group 1 patients upon admission to the hospital was 519.41±68.37 nmol/l. This is

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statistically significant (p≤0.01) 1.5 times higher than normal. Cytokines, mainly IL-1, -6, penetrate into the brain through the blood-brain barrier, increase the secretion of KTRG and further cortisol in the bundle zone of the adrenal cortex. In addition, IL1ß, TNF-α, IL-6 are able to directly stimulate the synthesis of cortisol in the adrenal glands and enhance its effect [10]. On the 8th day of observation of group 1 patients, the level of cortisol in the blood statistically significantly (p≤0.01) decreased by 1.7 times and amounted to 311.16±73.96 nmol/L. Under the influence of an excess of released IL-1β, IL-6 suppresses cortisol production [3, 10]. In the 2nd group of patients, upon admission to the hospital, the cortisol level was 524.79±151.44 nmol/l, which was statistically significant (p≤0.01) higher (1.6 times) with respect to to control. By the end of the patient follow-up, its content significantly (p≤0.01) increased (by 1.2 times) in relation to the 1st day and amounted to 648.90±180.58 nmol/l, but remained statistically significantly higher (by 1.9 times) in relation to the control (336.8±34.33 nmol/L). This is due to a decrease in the level of IL-1ß and IL-6.

Thus, the use of TES therapy in The 2nd group of patients, together with standard therapy, ensures the maintenance of cortisol levels. Cortisol prevents the development of all phases inflammation (exudation, proliferation, scarring). The synthesis of arachidonic acid and inflammatory mediators such as prostaglandins and leukotrienes decreases. A decrease in the anti-inflammatory effect of cortisol leads to an increase in the level of pro-inflammatory factors, for example IL-6.

Cortisol also has a negative feedback effect on IL-1. In patients of group 1, the level of beta-endorphin in the blood serum was 2.51±0.67 pg/ml (with a norm of 7.22±1.75 pg/ml). It was statistically significant (p≤0.01) 2.9 times lower than normal. On the 8th day of patient observation, its content statistically significantly (p≤0.01) decreased and amounted to 1.77±0.46 pg/ml (4.1 times lower than the control). In the 2nd group of patients who underwent TES therapy, the level of β-endorphin on the day of hospitalization was 2.89±1.23 pg/ml, which was statistically significantly (p≤0.01) lower (2.5 times) relative to the control. In the same group , on the 8th day of observation, it increased statistically significantly (p≤0.01) (1.6 times) to 4.54±1.64 pg/ml in relation to the first days in this group. Thus, the use of TES therapy, along with standard therapy, contributed to a significant (p≤0.01) increase in the level of β-endorphin.

Conclusion

Standard treatment of group 1 patients with angina pectoris of functional class II-III does not cause normalization of the level of the main proinflammatory cytokines IL-1ß and IL-6. In the 2nd group of patients, when TES therapy was added to the standard treatment, the levels of the main proinflammatory cytokines (IL-1ß, IL-6) were significantly (p≤0.01) lower. The results obtained indicate that the combined use of TES therapy reduces the degree of activity of the systemic inflammatory response in angina more pronounced than one standard treatment, preventing the continuation of the damaging effect of proinflammatory cytokines.

Thus, in patients with angina pectoris of tension II-III functional class during, along with standard treatment, TES therapy showed a statistically significant (p≤0.01) increase in the level of ACTH, cortisol and beta-endorphin in blood plasma and their approximation to the normal level. Therefore, the use of TES therapy combined with standard treatment of patients with stable angina pectoris is justified.

Literature

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