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PHARMACOLOGICAL CORRECTION OF IMMUNE DISORDERS IN PATIENTS WITH CHRONIC HEART FAILURE AND ISCHEMIC HEART DISEASE

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Summary. Currently, there are few data on the effect of cardiovascular drugs on the immune status of patients with heart failure (HF). This paper provides information on the impact of ß-adrenergic blocking agent (BAB), angiotensin-converting enzyme inhibitors (ACEI) on the maintenance of markers of immune inflammation in the blood, as well as on inhibition of synthesis of tumor necrosis factor-α (TNF-α) and on blocking of interaction between TNF-α and membrane receptors.

Keywords. Immune inflammation, chronic heart failure, coronary heart disease, tumor necrosis factor-α, ß-blockers, angiotensin-converting enzyme inhibitors.

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МЕДИКАМЕНТОЗНАЯ КОРРЕКЦИЯ ИММУННЫХ НАРУШЕНИЙ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ ПРИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА

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Аннотация. В настоящее время имеется немного данных о влиянии сердечно-сосудистых препаратов на иммунный статус больных с сердечной недостаточностью (ХСН). В данной статье освещены аспекты влияния ß-адреноблокаторов (БАБ), ингибиторов ангиотензинпревращающего фермента(ИАПФ) на содержание в крови маркеров иммунного воспаления, а так же на ингибирование синтеза фактора некроза опухоли-α (ФНО-α) и блокирующих взаимодействие ФНО-α с мембранными рецепторами.
Ключевые слова. Иммунное воспаление, хроническая сердечная недостаточность, ишемическая болезнь сердца, фактор некроз опухоли-α, ß-адреноблокаторы, ингибиторы ангиотензинпревращающего фермента.

A congestive chronic heart failure is a clinical syndrome characterized by malaise, shortness of breath, swelling and other symptoms, primarily associated with the impairment of tissue perfusion, resulting from many cardiovascular diseases of both inflammatory (myocarditis, dilated cardiomyopathy), and non-inflammatory (coronary artery disease, arterial hypertension, hypertrophic and restrictive cardiomyopathy, etc.) nature [9.21]. Until recently, the pathophysiological processes that lead to the development of heart failure were considered primarily from the perspective of neurohormonal hypothesis based on concepts of overexpression of neurohormones initiating remodeling and progression of dysfunction of the left ventricle (LV) and desensitization of the cardiomyocyte (CMC) b1-receptor-G-protein complex, which results in weakness of myocardial contractility [15].

The role in the congestive chronic heart failure progression is assigned to the neurohormonal activation, and the sense of sympathoadrenal nervous system (SAS) becomes more and more clear. The literature presents data on changes in the level of catecholamines, renin, angiotensin and aldosterone at various stages of ischemic CHF progression, starting from the occurrence of acute myocardial infarction (AMI) and until the end-stage of heart failure [8, 19, 20]. It is known that patients with CHF have significantly higher SAS values with the increase in TNF-α level in plasma than the patients with CHF who have normal levels of TNF-α [6]. It was found that the levels of adrenaline, noradrenaline, aldosterone, and cortisol was higher in patients with cardiac cachexia as compared with patients without cachexia [17]. However, there are another data, for example, G. Torre-Amione et al., using a SOLVD database, found no intensity correlation between the inflammatory response and neurohormonal activity of plasma in patients with chronic heart failure [14].

A starting moment in the mechanism of neurohormonal activation is the reduction in cardiac output at LV dysfunction, which leads to a decrease

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in blood pressure (BP), stimulating in turn the baroreceptors (blood high-pressure receptors and cardiopulmonary low-pressure receptors). As a result, the flow of impulses into the central nervous system increases, causing the rise in both the SAS and renin-angiotensin-aldosterone system (RAAS) activity, which is accompanied by increased cardiac output (positive inotropic effect of catecholamines) and improved blood supply to vital organs and skeletal muscles (the effect of vasoconstriction).

Currently, there are already-formed ideas about the negative role of SAS chronic hyperactivation in patients with CHF due to its main mechanism of action via stimulation of catecholamine beta-receptors (primarily noradrenaline) and activation of adenylate-cyclase mechanism that increases the content of cyclic AMP (cAMP). This mechanism enhances calcium entering into the cell and its mobilization from sarcoplasmic reticulum, which is accompanied by increased contractility. Chronic activation leads to a gradual overflow of myocardial cells with calcium, their contracture, a impairment of electrical stability and membrane integrity, and the CMC necrosis, which is manifested by toxic effects of catecholamines on the myocardium. Hyperactivity of neurohumoral systems stimulates the production of other neurohormones and mediators, including some cytokines that have proinflammatory action, which predetermines the development of pathological changes in the peripheral tissues. Furthermore, noradrenaline together with angiotensin-II (A-II) stimulate the activation of growth factor and increase the synthesis of cytokines, which is accompanied by the development of hypoxic stress, the stimulating development of myocardial hibernation, and eventually increased cell mortality caused by apoptosis. It is known that the main effector RAAS A-II, in turn, increases the production and release of noradrenaline. Thus, the reciprocal activation of the RAAS and SAS generates a vicious circle. Elevated concentrations of catecholamines also gives indirect effect through RAAS, in the renal juxtaglomerular apparatus where the ß-adrenergic receptors are located, the stimulation of which enhances the release of renin. Finally, noradrenaline increases the pacemaker activity of cells of the cardiac conduction system by increasing the heart rate (HR), myocardial oxygen demand, and the risk of arrhythmias [5].

It is now apparent that, in addition to the classic neurohormones, the overexpression of another class of biologically active substances – cytokines – can make a significant contribution to the development and progression of chronic heart failure. Indeed, along with circulatory disorders observed in patients with CHF, there are clinical symptoms observed, typical of chronic inflammatory diseases and malignancies. These primarily include cardiac cachexia syndrome, which is manifested by progressive weight loss, anorexia and a number of biochemical abnormalities typical of malnutrition (anemia, hypoalbuminemia, leukopenia, hypocholesteremia) and inflammation (increase in erythrocyte sedimentation rate, fibrinogen, and acute-phase proteins). Materials relating to the participation of pro-inflammatory cytokines in the development of heart failure, may be of practical importance for the development of new approaches to the treatment of this pathology and decryption of mechanisms of action of already applied pharmacological agents. Currently, there are few data on the effect of cardiovascular drugs on the immune-inflammatory status of patients with chronic heart failure. Features of the pathogenesis of this state, including cytokinin aggression, necessitate the development of new approaches to its pharmacological correction with the use of modulators of the cytokine, and neurohormonal systems, as well as investigation of the influence of drugs used in standard CHF therapy on the level of pro- and anti-inflammatory cytokines [4].

A particular importance is attached to TNF-a, which at its low concentration plays an important physiological role in tissue homeostasis regulation, and at high concentrations has a pathological endocrine-similar effect, causing metabolic exhaustion, microvascular hypercoagulability, and hemodynamic disturbances. As early as in 1985 J. Parillo et al. found in the sera of patients with septic shock a «myocardial depressive substance», which was later identified as TNF-a. In 1990 B. Levine et al. first discovered the increased levels of TNF-a in patients with CHF. TNF-a has the ability to increase the catabolism of proteins, but, however, along with other cytokines, in particular interleukin-1b (IL), increases the protein synthesis and causes myocardial hypertrophy of CMC. TNF-a and IL-1 are synthesized simultaneously, have the ability to induce the production of each other, and demonstrate numerous general effects. TNF-a is synthesized by monocytes, macrophages, and lymphocytes under the influence of endotoxins, viruses, and other cytokines. TNF-a and TNF-b bind to two high-affinity surface cell receptors with molecular weights of 55 kd and 75 kd, respectively, that are expressed on the membranes of many cells (T-lymphocytes, macrophages, neutrophils, etc.), which are released into body fluids during activation of mononuclear cells and involved in the implementation of the biological effects of TNF-a. Recent studies have shown that TNF-a and IL-1b have the ability to disrupt the function of cardiac muscle in patients with

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burn and septic shocks, myocarditis, graft rejection, and chronic heart failure [29]. Along with cardiotropic effects, TNF-a is involved in the development of cachexia in cancer patients and in patients with severe heart failure. According to the findings of experimental studies, TNF-a and IL-1b inhibit myocardial contractility in vivo when administered to intact animals, and in vitro when to the models of isolated heart, isolated papillary muscles, and in the CMC culture, contributing to LV remodeling by breaking and inducing the CMC apoptosis. Low concentrations of TNF-a cause rapid, reversible, independent of nitric oxide and prostaglandins decrease in intracellular calcium content. High concentrations of TNF-a otherwise induce a rapid and reversible decrease in the contractile ability of CMC, and this effect is canceled by inhibitors of nitric oxide synthetase. In the study, the administration of TNF-a caused a 15-20% reduction in ejection fraction (EF) under the absence of the dynamics of blood pressure and heart rate. Moreover, continuous infusion of TNF-a induced a time-dependent impairment of LV remodeling, manifesting itself in increased LV dilatation along with the decreased LV thickness, and these changes were not fully reversible after discontinuation of TNF-a, or during administration of fc-receptors. These findings suggest that the impaired LV remodeling is associated with TNF-induced degradation of the fibrillar collagen matrix. It is known that the TNF has the ability to activate the expression of matrix metalloproteinases (MMPs), which cause the degradation of extracellular matrix proteins. It was established that CMC of patients with heart failure and sepsis are capable of expression and synthesis of TNF-a, while CMC of people without heart failure do not have this ability. Thus, TNF-a, along with noradrenaline, endothelin, and A-II, is involved in the progression of myocardial dysfunction and remodeling in patients with chronic heart failure [12]. Since TNF-α plays a central role in the mechanism of development and progression of chronic heart failure, search for drugs is aimed mainly at the synthesis of drugs with the ability to inhibit the TNF-α synthesis or block the TNF-a interaction with membrane receptors.

Application of ß-blockers in CHF break a vicious circle ending with SAS chronic hyperactivation, by blocking all the above mechanisms of negative impact of the increased catecholamine content. Positive effects of ß-blockers in patients with chronic heart failure are as follows: a reduction in heart rate, ischemia (myocardial hypoxia), myocardial hypertrophy, the CMC death (by necrosis and apoptosis), dimensions (dilatation) of left ventricle, the restoration of ß-receptors sensitivity and response to external stimuli, an improvement of diastolic relaxation, and reduction in CMC electrical instability (arrhythmias). But not all ß-blockers can have a beneficial effect on the clinical signs and hemodynamic disorders in patients with CHF. Summing up the findings obtained in large randomized trials like CIBIS, CIBIS-II, MERIT-HF and COPERNICUS Q, we can conclude that currently there are at least 3 BABs able to significantly improve the efficiency of traditional therapy. The most promising BABs for long-term use in nowadays are four drugs such as bisoprolol, bucindolol, carvedilol and metoprolol.

For example, a 4-week use of carvedilol in CHF contributed to significant reduction in the levels of proinflammatory cytokines IL-1β, IL-6, a fibrogenic cytokine, and a transforming growth factor-β1 in the myocardial tissue, and was associated with reduction of MMP activity, fewer myocardial collagen and increased expression of IL-10.

The level of proinflammatory IL-6 decreased by more than 5 times in the course of therapy with carvedilol. Plasma content of γ-interferon has reached the control values. Reduction in IL-6 content in the course of carvedilol therapy may result not only from the hypotensive action of the drug, but also its vasoprotective properties [1]. The use of Carvedilol for 4-6 weeks in the treatment of CHF due to ischemic heart disease combined with type 2 diabetes and the ejection fraction >40%, showed in comparison with metoprolol a significant decrease in aldosterone level by 20%, and brain natriuretic peptide – by 30 % [16]. The influence of 24-week pharmacotherapy with Bisoprolol in patients with chronic heart failure with the activation of cytokines led to the decrease in TNF-a concentration in blood plasma by 87% [7, 10].

A mandatory group of drugs used in the treatment of chronic heart failure that improves survival of patients is ACE inhibitors. The positive effects of enalapril ACE inhibitors on further life of patients with chronic heart was demonstrated for the first time during the CONSENSUS in 1987. It was found that the mortality in the group treated with enalapril is significantly lower than in the control group. These results were later confirmed in subsequent major randomized trials in relation to other ACE inhibitor drugs [12].

All positive pharmacological effects of ACE inhibitors observed in heart failure can be divided into cardiovascular and neuroendocrine ones. For example, cardiovascular effects include a decrease in total peripheral vascular resistance, drop of pulmonary capillary-wedge pressure, reduction in regional vascular resistance in the heart, kidneys, brain, and skeletal muscles; a reduction in systolic and diastolic volumes of the left ventricle; increase in stroke volume and

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cardiac output, as well as regression of LV hypertrophy. Neuroendocrine effects of ACE inhibitors are as follows: a reduction in the formation of A-II, aldosterone, noradrenaline, arginine-vasopressin, and endothelin-1, increase in the tissues and blood content of bradykinin and other kinins, potassium retention, and the increased excretion of water, sodium, and uric acid. ACE inhibitors also inhibit the proliferation and migration of smooth muscle vascular cells, contribute to the stabilization of atherosclerotic patch, have antiplatelet action and antioxidant properties, and activate endogenous fibrinolysis.

The pharmacological effects of ACE inhibitors are based on their ability to inhibit the activity of angiotensin-1-converting enzyme (or kininase II) and thus at the same time affect the functional activity of the RAAS and the kallikrein-kinin system. Inhibiting the activity of angiotensin-1-converting enzyme, ACE inhibitors reduce the formation of A-II and eventually weaken the major cardiovascular effects of RAAS including arterial vasoconstriction and aldosterone secretion. Inhibiting the activity of kininase II, ACE inhibitors reduce inactivation of bradykinin and other kinins and contribute to the accumulation of these substances in the tissues and blood. Kinins themselves or through the release of prostaglandins E2 and 12 have a vasodilatory and natriuretic effect. The ACE inhibitor therapy helps to recover an impaired endothelial function, i.e., its ability to release nitric oxide (endothelial relaxation factor) and tissue plasminogen activator. ACE inhibitors reduce afterload on the left ventricle of the heart, causing vasodilatation of systemic arteries and reducing the total peripheral vascular resistance, and thus improve its pumping function.

ACE inhibitors can positively affect the immune system. For the first time in 1993, an immunomodulatory effect of captopril ACE inhibitor was shown on monocytes cells. Then, it was confirmed by a series of other clinical studies. For example, Liu found a significant decrease in the level of TNF-α in patients with chronic heart failure during therapy with four different ACE inhibitors – perindopril, benasepril, enalapril, and fosinopril, which indicates the systemic nature of anti-cytokine action of this class of drugs. In addition, it was noted that the use of high doses of enalapril ACE inhibitor in patients with CHF was accompanied by a significant reduction in levels of IL-6, and the thickness of the interventricular septum of the heart. Anticytokine effect of ACE inhibitors in patients with CHF is likely mediated by a reduction of synthesis A-II – neurohormone that increases the production of cytokines, including TNF-α and

adhesive molecules through activation of the nuclear kappa-B factor playing an important role in the regulation of transcription of cytokines and adhesive molecules. In general, the increased levels of TNF-α, IL-6 and antinuclear factor are considered «biochemical markers» of LV insufficiency. According to R. Ferrari et al. an increase in the TNF levels is observed mainly in patients with functional class IV chronic heart failure. The experimental animal studies revealed that ACE inhibition reduces some of the parameters associated with inflammation in the atherosclerotic lesions and controlled by nuclear kappa-B factor, which helps to stabilize the patches. High efficiency of ACE inhibitors, is most likely caused both by modulating neurohumoral and partially by anti-inflammatory effects [3]. It should be also noted that the literature presents the results of some studies on the ability of agents of standard CHF therapy, such as cardiac glycosides, diuretics, calcium antagonists and some antiarrhythmic drugs, in particular, amiodarone, at least partially, to reduce the level of cytokines.

One also distinguishes drugs such as pentoxifylline and vesnarinone that increase intracellular cAMP levels and prevent transcription of TNF-α by blocking the intracellular accumulation of RNA and TNF-α. It should be noted that the positive effect of pentoxifylline is additionally accompanied by increased levels of inflammatory mediators, including IL-10, antagonists to both IL-1 receptors and soluble TNF-α receptors. These drugs undergo approbation in patients with chronic heart failure, although some studies have produced results showing that vesnarinone worsens the survival ability of patients with CHF. It is known that glucocorticoids can also inhibit the synthesis of TNF-α at the transcriptional and translation levels [2]. Studying the efficacy of biological drugs specifically inhibiting the activity of TNF-α is of particular interest. One of them is Enbrel. This drug binds to a biologically active TNF-α and prevents its interaction with membrane TNF-a receptor. The drug efficacy has been demonstrated by the preliminary minor placebo-controlled trials in patients with CHF. However, the large-scale, randomized, placebo-controlled studies of Etanercept, such as RENAISSANCE (Randomized Endrel North American Strategy to Study Antagonism of Cytokines) and RECOVER (Research into Antagonism of Cytokines), has recently been stopped because of the lack of positive results [13].

Despite the advances made in the treatment of patients with chronic heart failure, there is a steady progress of disease and a high level of mortality and disability. This allows suggesting that the most

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important pathogenetic mechanisms of disease either retain their activity or slightly change in the course of treatment. These «immutable» mechanisms can also include both immune activation and inflammation. Involvement of inflammatory mediators in the pathogenesis of chronic heart failure opens new prospects for increasing the effectiveness of treatment of decompensated patients [18, 22, 23]. We should note that the immunoinflamatory concept of formation and progression of chronic heart failure remains understudied and valid.

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