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Research Article

Influence mechanisms of mineralocorticoid receptor antagonist (spironolactone) among elderly patients with chronic heart failure against ischemic disease

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ABSTRACT
They examined 120 elderly patients with chronic heart failure (CHF) against ischemic heart disease (IHD), the mean age of the patients was 66.6 ± 6.8 years. The patients were divided into 4 groups. The 1st group consisted of the patients who had planned therapy with ß-adrenoblocker (BAB) (metoprolol succinate 12.5-100 mg per day); 2nd group - angiotensin-converting enzyme (ACE inhibitor) inhibitor (perindopril - 4-8 mg per day); 3rd group - combination of BAB and ACE inhibitors; 4th group - BAB, ACEI and the competitive antagonist of aldosterone spironolactone with the daily dose of 25-50 mg per day. The effect of therapy on C-reactive protein and cytokines (TNF-α, IL-1ß, IL-6) was determined. The content of CRP and TNF-α, IL-1β and IL-6 cytokines in all groups decreased in different degrees. It was determined that a significant positive dynamics of TNF-synthesis suppression by 67.0% (p‧ 0.0001) was established in the 4th group of patients taking combined therapy with the blocker of mineralocorticoid receptors with spironolactone.

Key words: chronic heart failure, elderly patients, TNF-α, the blocker of mineralocorticoid receptors, spironolactone

INTRODUCTION.
The prevalence of chronic heart failure (CHF) in Russian Federation is quite high and amounts at least to 3-3.5 million patients with clinically significant CHF (III-IV functional class) [1]. Modern approaches require take into account the pathogenesis of this process for the determination of management tactics for the patients with CHF as well as to prevent its progress among the patients with coronary heart disease (CHD) [2]. The appearance of left ventricular (LV) dysfunction and its transformation from asymptomatic to clinical CHF occurs with the participation of neural humoral systems: sympathetic adrenal, renin-angiotensin-aldosterone (RAAS) and immuno-inflammatory one [3, 4]. In recent years the evidence emerged about the parallel existence of tissue RAAS in a heart, kidneys, liver, pancreas and about the additional synthesis of angiotensin fragments, which confirms the role of tissue RAAS in growth regulation, proliferation and the apoptosis of cardiomyocytes (CMC), as well as inflammation increase and, as a consequence, the development of fibrosis [5].

The strengthening of proinflammatory cytokine synthesis is one of the significant components of this process. Such cytokines as TNF-α (TNF-α) and IL-6 (IL-6) [6,7,8] are confirmed as the leading ones in the pathogenesis of systemic inflammation induction among the patients with CHF. The determination of proinflammatory cytokine value and C-reactive protein (CRP) in the serum of elderly patients with CHF and coronary heart disease and their change under the influence of pharmacotherapy deserve a separate examination.

Purpose. To study the effect of spironolactone mineralocorticoid receptor antagonist on the

level of neurohormones, cytokines and CRP among elderly patients with the CHF of ischemic genesis.

MATERIALS AND METHODS.

120 elderly CHF patients were examined on the background of ischemic heart disease. 120 men (100%) with the average age of 66.6 ± 6.8 years had a myocardial infarction more than 4 months ago. The New York Heart Association (NYHA) used the classification to determine the functional class (FC) of CHF using a 6-minute walk test. CHF I FC was detected in 37 patients (31%), CHF II FC was detected in 43 (36%) patients, CHF III FK - in 40 patients (33%). The control group consisted of 20 conditionally healthy individuals (mean age - 48.9 ± 7.3 years), who did not have cardiovascular system and other organ and system dysfunction at a careful clinical laboratory and instrumental examination. All patients, depending on the treatment, were divided into 4 groups. Group 1 (n = 35): the planned therapy included ß-adrenoblockers (BAB) (metoprolol succinate 12.5-100 mg per day); 2nd group (n = 25) - the patients who received the angiotensin-converting enzyme inhibitor (ACEI) (perindopril - 4-8 mg per day); 3rd group (n = 40) - the patients who took combined treatment of BAB and ACEI; Group 4 (n = 20) consisted of the patients receiving the combination of BAB, ACEI and a competitive antagonist of aldosterone (mineralocorticoid receptor antagonists) spironolactone in a daily dose of 25-50 mg per day.

The study of C-reactive protein, cytokines (TNF-α, IL-1ß (IL-1ß), IL-6 (IL-6)) was carried out using the special sets for the determination of TNF-α, IL-1ß (IL-1ß), IL-6 (IL-6) content manufactured by VECTOR-BEST (Russia) for CRP by "Eucardio" (USA), guided by the manufacturer's instructions. The results of cytokines were expressed in pg/ml, CRP - mg/l.

"Statictica 6.0" software package was used for the statistical processing of data. The indicators are presented as medians (Me) with interquartile range (25% and 75% percentile) using the median test. The differences were considered as reliable at $p < 0.05$.

RESULTS.

The activation of tissue myocardial RAAS promotes the development of hypertrophy and cardiomyocyte fibrosis [9]. If in the short term the activation of the neurohumoral system allows to improve the perfusion of organs and compensate for circulatory insufficiency, then after a certain period the mechanisms begin to increase the work of a heart muscle, which is the trigger mechanism for the progression of heart failure. The activation of cytokine system also acts within the same trend.

The content of CRP and TNF-α, IL-1β and IL-6 cytokines among elderly patients with CHF on the background of IHD under the influence of differentiated treatment in all groups decreased in different degrees (Table 1). Thus, the 1st group of patients during the treatment of BAB, showed CRP level decrease by 21.6% ($p<05.05$), and TNF-α by 6.0% and IL-1β by 2.0% ($p> 0.05$). In the second group of treated ACE inhibitors, the dynamics of CRP content after the treatment was reduced by 30.6%, TNF-α by 24.0%, IL-1β by 10.0% and IL-6 by 21.7%, which significantly differed from the baseline level. In the blood of patients who received the combination therapy of BAB and ACEI against standard therapy, the levels of CRP, TNF-α and IL-1β also decreased and significantly differed from the baseline data. Thus, the content of CRP in serum decreased by 43.1% ($p<0.001$), TNF-α by 25.0% ($p <0.01$), IL-1β by 11% ($p <0.05$). The concentration of IL-6 in this group also decreased by 23.3% ($p<0.05$). In the fourth group of patients taking combination therapy, ACE inhibitors, BAB and spironolactone, the positive dynamics of CRP decrease was 44% ($p<0.01$). The attention is drawn to the decrease of TNF-□ by 67.0% (p▪ 0.0001) with respect to pre-treatment concentration, which is statistically significant in relation to all groups of drug therapy (p▪ 0.001).

There is the decrease of IL-1β indicators (r▪ 0.05) by 9.0%, but no statistical difference with the group of ACEI + BAB is revealed ($p>0.05$). IL-6 decreased by 58% (p▪ 0.001), which is 34.7% higher than the group of taking IPF with BAB (p▪ 0.01).

Summary. Such cytokines as TNF-α, IL-1β, IL-6 enhancing the expression and detected among the patients with CHF represent the class of biologically active substances responsible for the development of inflammation and the heart failure progression [5,10]. Many CHF mechanisms may be explained by well-known pharmacodynamic effects of proinflammatory cytokines, particularly TNF-α, which induces other cytokines, playing an important role in inflammation, such as IL-1α, IL-1β and IL-6 [11]. The factors inhibiting apoptosis are represented by transforming growth factor-α (TRF-α), secreted in immune reactions and which has anti-inflammatory properties, but enhancing the progression of organ fibrosis [4,12]. Experimental and clinical studies showed that the potential adverse effects of proinflammatory cytokines at CHF are the following ones: left ventricular dysfunction, pulmonary edema, cardiomyopathy, decreased blood flow in legs, cell metabolism abnormalities, anorexia and cachexia, impaired beta-receptor capture of adenylate cyclase, the abnormalities of mitochondrial energy and the activation of apathosis gene programs [13,14].
Cytokine release, like the release of neurohormones, is the biochemical mechanism responsible for the development of symptoms among the patients with CHF [15,16,17].

Table 2: Changes of cytokine and CRP content, depending on the type of received therapy (Me ($Me_н$-$Me_в$))

Indicators		Metoprolol succinate	Perindopril	Perindopril, metoprolol succinate	Perindopril, metoprolol succinate, spironolactone
		n=35	n=25	n=40	n=20
CRP, mg/l	Before treatment	3.7 (3.5-6.5)	4.9 (3.3-6.3)	5.1 (3.4-7.2)	5.0 (3.3-7.0)
	After treatment	2.9 (1.6-4.1)	3.4 (2.8-4.0)	2.9 (1.9-5.2)	2.8 (1.8-5.1)
	p	<0.05	<0.01	<0.01	<0.01
TNF -α, pg/ml	Before treatment	17.0 (7.6-18.7)	18.2 (7.4-26.2)	17.4 (7.2-29.1)	16.9 (7.8-20.7)
	After treatment	15.9 (5.4-22.4)	13.8 (6.6-25.3)	13.1 (8.2-21.6)	5.6 (3.5-7.8)
	p	>0.05	<0.01	▪ 0.01	<0.0001
IL-1ß, pg/ml	Before treatment	183.0 (102.9-255.6)	186.6 (110.2-254.7)	179.8 (120.8-349.3)	180.4 (120.2-305.1)
	After treatment	179.3 (147.3-255.4)	167.9 (130.8-256.3)	160.0 (132.9-250.5)	164.2 (127.3-207.1)
	p	▪ 0.05	<0.05	<0.05	<0.05
IL-6, pg/ml	Before treatment	46.0 (31.9-59.6)	44.7 (35.1-66.2)	44.1 (25.8-69.7)	45.0 (33.8-57.9)
	After treatment	45.1 (16.9-78.1)	35.3 (21.8-68.8)	33.8 (20.7-71.1)	18.9 (15.6-50.6)
	p	▪ 0.05	<0.01	<0.01	<0.001

In order to interpret the biological activity of any cytokine, the concentration of a measured cytokine in blood is very important. It determines the extent of its involvement, the presence or the absence of any circulating antagonists, and the concentration of soluble and membrane low affinity and high affinity receptors in the blood. Circulating soluble receptors for cytokines serve as biological buffers capable to modulate their cytotoxic effects. Cytokines can also enter the bloodstream and cause secondary activation of an immune system, amplifying the signal to the periphery [7.17]. In recent years, it has been established that TRP-α and IL-6 determine the release of stress-activated cytokines in large amounts during a heart failure [18, 19, 20]. In our studies, the use of ACE inhibitors (perindopril), as well as the combination of perindopril and spironolactone, resulted in the decrease of pro-inflammatory cytokine release, in particular TNF-□ and IL-6, among the patients with CHF on the background of post-infarction cardiosclerosis. Apparently, the decrease of TNF-□ concentration can be explained by the effect of spironolactone.
Clinical and experimental data, as well as the results obtained by us, indicate that CHF depends on immunoinflammatory cytokine activation. The biomarkers of inflammation can

be used for diagnostic and prognostic purposes, as well as for the monitoring of CHF course and the evaluation of therapeutic effects, especially among severely injured patients. The determination of cytokine expression can be one of effective ways for therapeutic interventions, including various classes of ACE inhibitors and beta-adrenoreceptor blocking agents.

CONCLUSIONS

1. Chronic heart failure during ischemic heart disease and postinfarction cardiosclerosis is characterized by the activation of proinflammatory mechanisms. The effect of spironolactone was established on the decrease of TNF-□ level by 67.0% with respect to the concentration before treatment.
2. The determination of cytokine expression can be one of the ways to assess the severity of disease course and the effectiveness of therapeutic interventions, including various classes of ACE inhibitors and beta-adrenoreceptor blocking agents.

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