DYNAMICS OF PROINFLAMMATORY CYTOKINES ON THE BACKGROUND OF DRUG THERAPY IN PATIENTS WITH CHRONIC HEART FAILURE

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Impact of pharmacotherapy on the concentration of pro-inflammatory cytokines and C-reactive protein in chronic heart failure patients caused by ischemic heart disease was studied. 126 patients, who were divided into 4 groups were examined. Group 1 received ß-blockers; the second group received angiotensin-converting enzyme inhibitors. While Group 3 received the combined therapy with both ß-blockers and angiotensin-converting enzyme inhibitors. Group 4 received only standard therapy. The concentration of cytokines (Tumor Necrosis Factor-α, interleukin-1β, interleukin-6) and C-reactive protein was determined both before and after 9 weeks of treatment. Thus, it was revealed that angiotensin-converting enzyme inhibitor (perindopril 2,5–10 mg daily) reduces the concentration of Tumor Necrosis Factor-α by 76,3 %, interleukin-1β – by 77,9 %, and interleukin-6 – by 63,0 %. Moreover, the combined therapy with angiotensin-converting enzyme inhibitors and β-blockers (2,5–10 mg perindopril and metoprolol succinate 12,5–100 mg daily) reduce C-reactive protein levels by 43,1 %.

Keywords: pro-inflammatory cytokines, C-reactive protein, angiotensin-converting enzyme inhibitors, Chronic Heart Failure

Prevalence of chronic heart failure (CHF) in the Russian Federation is quite high. Around 3–3,5 million patients suffer from symptomatic heart failure (Functional Class – III–IV) [1]. Currently, to determine the tactics of patients with heart failure, as well as to prevent its development in patients with ischemic heart disease (IHD), it is necessary to consider the pathogenesis of this process.

Formation of the left ventricle (LV) dysfunction with the transformation from asymptomatic to severe CHF is expressed not only by the activation of neurohormonal systems such as sympathetic-adrenal and renin-angiotensin-aldosterone, but also by immune activation and systemic inflammation [2]. Pro-inflammatory cytokines are important components of this process [3]. Tumor Necrosis Factor-α (TNF-α) and interleukin 6 (IL-6) are recognized as the most important of this class [4]. The subject of debate is the degree of cytokines increase in blood and evaluation of their role in patients with ischemic heart disease, as well as data about the changes of plasma levels of pro-inflammatory cytokines under the impact of CHF therapy, which in its turn requires further study.

Objective. To determine drug therapy impact on the concentration of pro-inflammatory cytokines and C-reactive protein (CRP) levels in blood serum of patients with ischemic heart disease, postinfarction cardiosclerosis.

Materials and methods of research

In randomized open study 126 patients were examined, 109 males (86,5 %) and 17 females (13.5 %), mean age 56,6 ± 10,8 years. All the patients suffered from myocardial infarction 4 months ago. To determine the Functional Class (FC) of CHF the New York Heart Association (NYHA) classification using 6 minute walk test was used. Thus, CHF FC-I was detected in 29 patients (23 %), CHF FC-II was revealed in 45 (36 %) patients, CHF FC-III – in 42 patients (33 %) and CHF FC-IV – in 10 patients (8 %). Control group comprised 30 apparently healthy individuals (mean age 49,9 ± 6,4 years), in which after clinical and laboratory studies no diseases of cardiovascular or other systems were revealed. All the patients were divided into four groups according to stratification method. Group 1 ($n = 35$) included patients who on the basis of standard therapy received ß-blockers (BB) (metoprolol succinate 12,5–100 mg daily). In Group 2 ($n = 25$) patients received angiotensin-converting enzyme (ACE) inhibitor (perindopril 2,5–10 mg daily). The patients in Group 3 ($n = 50$) received a combined therapy with both BAB and ACE inhibitors. The fourth group ($n = 16$) consisted of patients received only standard therapy, neither beta blockers nor ACE inhibitors were included in the scheme of their treatment (because of contraindications or side effects). As for standard therapy it included lipid-lowering agents (razuvastatin 10 mg daily), nitrates (nitrosorbid 20 mg daily) if necessary, antiplatelet agents (aspirin 75–150 mg per day/chimes 200 mg daily), sydnonimine (1–4 mg molsidomine 2–3 times daily), as well as calcium antagonists (diltiazem 120 mg daily). A survey of patients was conducted both before and after 9 weeks of treatment. Cytokines (TNF-α, IL-1β, IL-6) and CRP plasma levels were measured with ELISA using «Vector-Best» (Russia) reagent. The results of cytokines were expressed in pg/ml, CRP – mg/l.

Statistical analysis of the data was held on a personal computer using Median test and such programs as «Microsoft Excel» and «Statistica 6.0». The results are presented as Me (25–75 %) (Median, interquartile range (25–75 percentile)). Differences were considered significant at $p < 0,05$.

Results of research and their discussion

Concentration of cytokines and CRP in patients with chronic heart failure changed as

follows. Levels of pro-inflammatory cytokines and CRP were higher and significantly differed as compared to control group. Thus, CRP levels increased by 3,9 times, TNF-α – by 3,1 times, IL-1β – by 4,6 times, and IL-6 – by 5,6 times (Tab. 1).

Table 1

The content of pro-inflammatory and anti-inflammatory cytokines and serum CRP levels on the background of the therapy (Me (25% 75%))

Data	Control group, $n = 30$	Patients with CHF, $n = 126$		p before and after treatment *
		before treatment	after treatment	
CRP, mg/l	1,15 (0,49–1,72)	4,52 (3,46–6,51)	3,35 (2,55–4,32)	$p < 0,01$
TNF-α, pg/ml	36,51 (32,73–39,66)	113,35 (72,2–219,7)	62,91 (32,67–102,4)	$p < 0,001$
IL-1ß, pg/ml	34,34 (31,71–36,67)	156,71 (110,4–275,45)	82,43 (47,75–118,83)	$p < 0,001$
IL-6, pg/ml	17,24 (14,75–20,42)	97,01 (68,65–149,75)	79,02 (55,6–118,2)	$p < 0,05$

N o t e : * – significance of differences was tested based on Kruskal-Wallis test for related samples.

Under the influence of differential treatment concentration of cytokines and CRP in patients with chronic heart failure decreased to a great extent in all groups (Table. 2).

Table 2

Changes in the content of inflammatory markers levels, depending on the type of receiving therapy (Me (25% of 75%))

Data		Therapy			
		Standard therapy $n = 16$	Metoprolol succinate $n = 35$	Perindopril $n = 25$	Perindopril + Metoprolol succinate $n = 50$
CRP, mg/ml	before treatment	4,7 (4,3–6,3)	3,7 (3,4–6,5)	4,8 (3,2–6,3)	5,1 (3,4–7,1)
	after treatment	5,4 (2,9–8,2)	2,9 (1,6–4,1)	3,4 (2,7–4,0)	2,9 (1,9–5,1)
	p	< 0,05	< 0,05	< 0,01	< 0,01
TNF-α, pg/ml	before treatment	100,0 (72,3–85,7)	100,1 (56,0–187,9)	138,2 (74,7–338,1)	157,4 (82,9–241,2)
	after treatment	94,7 (86,1–105,8)	84,6 (54,9–102,4)	32,6 (13,2–89,2)	67,4 (44,4–218,3)
	p	> 0,05	< 0,05	< 0,001	= 0,001
IL-1ß, pg/ml	before treatment	210,8 (102,9–292,6)	133,0 (87,9–155,6)	284,6 (134,7–338,1)	174,6 (110,3–335,7)
	after treatment	199,4 (56,5–569,3)	113,1 (84,7–384,7)	63,5 (45,4–95,3)	68,9 (47,2–101,8)
	p	> 0,05	< 0,05	< 0,001	< 0,01
IL-6, pg/ml	before treatment	89,9 (81,4–101,6)	92,0 (54,8–111,6)	122,1 (75,0–186,2)	102,4 (75,7–170,7)
	after treatment	85,6 (78,6–96,1)	90,5 (76,9–128,1)	45,2 (31,8–88,8)	79,0 (68,2–118,2)
	p	> 0,05	> 0,05	< 0,01	< 0,05

N o t e : * – Significant difference was tested based on Kruskal-Wallis test for related samples.

In patients of Group 1 under β-blockers treatment CRP levels decreased by 21,4 %, TNF-α – by 19,5 %, and IL-1β – by 14,9 %, which significantly differ from baseline. In the second group after treatment with ACE inhibitors dynamics of CRP concentration decreased by 30,1 %, TNF-α – by 76,3 %, IL-1β – by 77,9 %, and IL-6 – by 63,0 %, which also significantly differ from baseline. In blood of patients who received both standard treatment and combined therapy with beta blockers and ACE inhibitors (Group 3), the levels of CRP, TNF-α and IL-1β have also become less. Thus, CRP levels in blood serum decreased by 43,1 % ($p < 0,01$), TNF-α – by 57,2 % ($p < 0,001$), IL-1β – by 60,0 % ($p < 0,001$).

Moreover, IL-6 concentration in this group also decreased by 22,9 % ($p < 0,05$). In Group 4, in which patients under standard therapy receive neither β-blocker nor ACE inhibitor, CRP levels increased by 14,8 %, while the concentration of pro-inflammatory cytokines decreased as follows TNF-α by 5,31 %, IL-1β by 5,4 %, IL-6 by 4,7 %. No significant changes were observed ($p > 0,05$).

Conclusions

1. In chronic heart failure patients caused by ischemic heart disease and myocardial infarction ACE inhibitor (perindopril 2,5–10 mg daily) reduces the concentration of TNF-α by 76,3 %, IL-1β – by 77,9 %, and IL-6 – by 63,0 %.

2. The combined therapy with both ACE inhibitors and β-blockers (2,5–10 mg perindopril and metoprolol succinate 12,5–100 mg daily) reduce CRP levels by 43,1 %.

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