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Cytokine Levels in Patient with Chronic Heart Failure

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Plasma concentrations of cytokins TGF-β1, IL-10, TNF-α in patient with heart failure on the basis of coronary heart disease and myocardial infarction according to the type of left ventricular dysfunction were studied. The aim of research was to improve treatment of chronic heart failure patients by regulating the levels of cytokins by adding to basic therapy medicines Imunofan and Metamax. It was found the increased levels of TGF-β1, TNF-α, IL-10 in all patients. The level of TGF-β1 in patients with preserved left ventricular ejection fraction and systolic dysfunction of the left ventricle increased after treatment. We found the increased level of IL-10 in patients. After treatment a clear decrease of IL-10 is typical for patients with preserved ejection fraction of left ventricular, whereas in patients with systolic dysfunction of left ventricular IL-10 levels remain more constant. Observed increasing of TNF-α, which decreased after treatment in all groups, but most definitely in patients with preserved ejection fraction of left ventricular.

Keyword: Chronic Heart Failure, Preserved Ejection fraction of left Ventricular, Systolic Dysfunction of left Entricular, Cytokins.

1. Introduction

Advances in molecular biology, genetics and immunology of recent decades suggest an important role of immune activation and systemic inflammation in the new theory of the pathogenesis of chronic heart failure (CHF). They are not only markers of disease progression and adverse prognosis, but independent factors of the high cardiovascular risk. [1,2]. Found that regardless of the etiology of heart failure, immune activation is supported by a number of mechanisms, among which the most important is the hyperproduction of cytokines, increased concentrations of autoantibodies and disturbance of cellular immunity [1,4]. Among cytokines that play an important role are tumornekrosis factor-α (TNF-α); interleukins (IL) - IL-1β, IL-4, IL-6, IL-8, IL-10; cell adhesion molecules - VCAM 1, ICAM1, VE-cadherin; selectins - L-selectin, P-selectin, integrins; growth factors - transforming growth factor (TGF β1), fibroblast growth factor, etc [4]. The increase of CHF symptoms accompanied by activation of the systemic inflammatory response, including the elevation of cytokines like TGF-β1, IL-10, TNF-α, which we decided to investigate, choosing them from cytokine network.

It is known that TGF-β1 is involved in the processes of inflammation, tissue repairing, collagen synthesis. It plays an important role in the hyperplasia and hypertrophy of tissues but at the same time it increases survival of cardiomyocytes during ischemia, reduces the activity of apoptosis [1,3,9]. As far as IL-10 is concerned it is known to suppress the synthesis of proinflammatory cytokines. It can promote or inhibit apoptosis, depending on the interaction with other growth factors. IL-10 suppresses

macrophage function and inhibits the production of proinflammatory cytokines as well as matrix metalloproteinases [1,2,8]. Among proinflamatory cytokins, which play role in the pathogenesis of CHF TNF-α is one of the most studied. TNF-α can cause violation of contractile ability of the heart, myocardial hypertrophy and remodeling [1,4]. Furthermore, trial such as the Studies of the Left Ventricular Dysfunction database showed an increased rate of mortality with increasing levels of TNF-α in patients with CHF [1].

2. Materials and Methods of Research: To study plasma concentrations of cytokins, we conducted dynamic observation of 152 patients with heart failure III class by NYHA with preserved ejection fraction of the left ventricular (PEFLV) and systolic dysfunction left ventricular (SDLV). CHF developed on the background of ischemic heart disease and myocardial infarction (100%). Evaluation and monitoring of patients were conducted at the Regional Cardiology Clinic in Ivano-Frankivsk (clinical base of the department of internal medicine #2 of Ivano-Frankivsk national medical university) in the period from 2008 to 2012. Diagnoctics and medication of the patients were conducted according to existing standarts of heart failure treatment. Diagnosis of CHF was put on the data of complaints, anamnesis of disease, physical examination, data of electrocardiography, echocardiography. Criteria for inclusion of patients in the study were as follows: chronic heart failure III class by NYHA, Q-wave myocardial infarction various locations in the anamnesis. Exclusion criteria: age over 75 years, uncontrolled hypertension, atrioventricular block, supraventricular and ventricular paroxysmal tachycardia, chronic diseases in acute phase, acute stroke, intolerance to medicines Imunofan and Metamaks, patient reluctance to participate in the study. Among the examined patients in 78 patients (51.3%) heart failure with preserved ejection fraction of the left ventricular was diagnosed and 74 patients (48.4%) had heart failure with systolic dysfunction of the left ventricular. Among the patients examined male dominated - 127 persons (83.6%) and there were 25 women (16.3%). The average age of the patients was 56,1 ± 0,4 years. 15 healthy individuals of the same age were examined to control normal ranges of the studied parametres. All patients received standart basic therapy (BT) according to standarts. In order to potentiate the therapeutic efficacy of BT medical complex was complemented by immunostimulant Imunofan and antioxidant Metamax. Imunofan (I) – 0.005% solution - 1.0 mL was administered at a dose of 1.0 ml intramusculary every other day ten times (production of "Bionox", Russia, registration certificate number UA/0318/01/01 from 02.02.2009 to 02.02.2014). Medicine Metamax (M) - capsules 250 mg, patients received 3 times a day every day orally, 20 days (production "Darnitsya", Ukraine, Registration certificate № UA/3572/01/01 from 06.08.2010 to 06.08.2015). The patients were divided into groups: patients with preserved ejection fraction of the left ventricular who received basic therapy, another group received combination of BT and Imunofan, next group of patients were treated by combination of BT and Metamax and the last group - combination of BT, Imunofan and Metamax. Another big group were patients with systolic dysfunction of the left ventricular, who were divided in the same way: patients of the first group received only BT, another were treated by combination BT and I, the next – received BT+M and the last were treated by combination of drugs - BT+I+M. Levels of cytokins TGF-β1, TNF-α, IL-10 as immunological factors that are involved in the pathogenesis of CHF were determined by ELISA. Statistical processing of the study materials was performed using the methods of biostatistics in software packages EXCEL-2003, STATISTICA 7.0 Statsoft Inc., USA).

3. Results and Discussion:

Analyzing the impact of the proposed treatment options on indices of immune status in patients with chronic heart failure III class (NYHA) with preserved left ventricular ejection fraction and systolic dysfunction of the left ventricle we found the following changes. The level of anti-inflammatory cytokine TGF-β1 was studied.

According to the results obtained in all patients revealed elevated levels of TGF-β1 relative performance in the group of healthy individuals, where it was 156,56 ± 4,79 pg / ml. In particular, patients with preserved LV ejection fraction had the next levels of TGF-β1 which is shown in the Table 1. In patients who received basic therapy level of TGF-β1 increased by 3.9% ($P>0,05$). Adding to the basic therapy Imunofan, boosted TGF-β1 level by 19.1% ($P<0.001$) and addition to BT Metamax increase the TFG-β1 level only by 7.7% ($P<0,05$). While patients who received the combination of BT+Imunofan+Metamax, production of TGF-β1 increased most definitely - by 19.2% ($P<0.001$). So, in all clinical groups anti-inflammatory cytokine TGF-β1 rapidly increased, more in patients, who received combination treatment. Analyzing the data of Table 2, we see that in patients with LV systolic dysfunction dynamic growth of TFG-β1 was less pronounced. In patients who received basic therapy observed increased production of TFG-β1 by 6.2% ($P>0,05$), whereas in patients who received the combination of BT+Imunofan, TFG-β1 levels increased by 19.1% ($P<0.001$). Using a treatment scheme with the addition of Metamax the production of TFG-β1 grew only by 10.7% ($P<0,05$).

Table 1: The influence of basic therapy, basic therapy+ Imunofan, basic therapy+Metamax, basic therapy+Imunofan+Metamax on the levels of cytokins in the patiens with preserved ejection fraction of left ventricle (M±m).

Index	Normal ranges in healthy individuals	BT (n=22)		BT+I (n=22)		BT+M (n=17)		BT+I+M (n=17)	
		before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
IL-10, pg/ml, Δ%, p	17,96±2,09	35,72±2,1	30,41±1,8 -14,9 >0,05	36,54±2,03	22,72±1,2 -37,8 <0,001	34,11±1,9	28,47±1,1 -16,7 <0,05	36,38±2,2	22,56±1,1 -38,0 <0,001
TGF-β, pg/ml, Δ%, p	156,56±19,21	372,32±3,06	386,86±6,85 +3,9 >0,05	368,91±4,07	439,77±7,91 +19,1 <0,001	361,82±4,96	389,65±8,68 +7,7 <0,05	364,18±4,89	433,94±8,02 +19,2 <0,001
TNF-α, pg/ml, Δ%, p	23,71±2,63	119,5±5,5	95,5±8,1 -20,1 <0,05	124,3±3,8	49,5±7,1 -60,2 <0,001	121,48±8,7	93,87±7,5 -22,7 <0,05	125,25±8,4	48,11±7,7 -61,6 <0,001

Notices: Δ – increasing (+) or decreasing (-) of index in percent;
p – value of the difference data in comparison with the values before treatment.

Table 2: The influence of basic therapy, basic therapy+ Imunofan, basic therapy+Metamax, basic therapy+Imunofan+Metamax on the levels of cytokins in the patiens with systolic dysfunction of left ventricle (M±m).

Index	BT (n=22)		BT+I (n=19)		BT+M (n=17)		BT+I+M (n=16)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
IL-10, pg/ml, Δ%, p	34,45±2,3	31,32±2,04 -9,1 >0,05	36,16±1,7	28,37±1,8 -21,5 <0,01	34,82±1,6	29,82±1,08 -14,5 <0,05	36,73±1,6	26,94±1,9 -26,7 <0,01

TGF-β, pg/ml, Δ%, p	351,19±5,55	373,09±10,58 +6,2 >0,05	345,89±6,34	390,05±11,95 +12,8 <0,01	348,41±6,83	385,71±12,07 +10,7 <0,05	351,94±6,35	408,13±15,23 +16,0 <0,01
TNF-α, pg/ml, Δ%, p	123,8±6,2	100,7±7,2 -18,7 <0,05	123,8±4,3	85,6±7,1 -31,0 <0,01	122,21±8,1	98,79±7,5 -19,2 <0,05	123,68±8,1	84,52±6,88 -31,7 <0,001

Notices: Δ – increasing (+) or decreasing (-) of index in percent;
p – value of the difference data in comparison with the values before treatment.

However, in patients who received BT with combination Imunofan and Metamax concentration of TGF-β1 increased by 16.0% (P<0,01). We can assume that elevated levels of TGF-β1 in patients examined positive impact on the course of coronary artery disease, reducing cases of decompensation of chronic heart failure. TGF-β1 is involved postinfarction myocardial remodeling processes, in particular, its effect is found to increase rigidity, inflexibility infarction, there is evidence of his property to prevent ventricular dilatation and on the same time, patients with low levels of TGF-β1, destabilization of ischemic heart disease held more frequently than in patients with elevated levels of this cytokine (Sadovyi V.I., 2012). However, the diagnostic and prognostic significance level elevation TGF-β1 in patients with heart failure remains a subject of scientific discussion is interesting for further study.

We studied the levels of anti-inflammatory cytokine IL-10. Data from the Table 1 shows that in patients with preserved LV ejection fraction using BT resulted in an insignificant decrease of IL-10 to -14.9% (P>0,05). Similar results were obtained when using BT+metamax - we saw the significant reduction of antiinflammatory cytokine, in particular, by 16.7% (P<0,05). Application of the treatment scheme with the addition of imunofan helped to reduce IL-10 to -37.8% (P<0.001). Patients who received basic therapy in combination with two study drugs, observed decrease of IL-10 by 38.0% (P<0.001). The data in Table 2 show that in patients with LV systolic dysfunction who received basic treatment, the concentration of IL-10 did not significantly decreased - only by 9.1% (P>0,05), and in patients who received with BT Imunofan, the level of IL-10 decreased by 21.5% (P<0,01). Introduction to basic therapy Metamax led to reduced production of IL-10 by 14.5% (P<0,05). However, treatment with a combination BT+Imunofan+ Metamax helped reduce the concentration of IL-10 to 26.7% (P<0,01). Due to the described data we see that a clear reduction of IL-10 is typical for patients with preserved LV ejection fraction, whereas in patients with LV systolic dysfunction IL-10 levels remain more constant. Maybe, these features are associated with more persistent violations that led to reduced cardiac pump function and therefore are less therapeutic effect.

The most studied pro-inflammatory cytokine involved in the pathogenesis of myocardial injury and the development and progression of heart failure is TNF-α. In all patients the level of this cytokine was increased, indicating that the immunoinflammatory activation is present in patients with CHF. In patients with preserved ejection function of LV who were treated by basic therapy the level of TNF-α decreased by 20.1% (P<0,05). In patients treated with BT+I, TNF-α production decreased after treatment by 60.2% (P<0.001). An introduction to basic therapy Metamax helped reduce concentrations of TNF-α only by 22.7% (P<0,05). The most pronounced effect of the treatment, as shown in Table 1, was observed in patients who received treatment with BT+Imunofan+Metamax - the level of TNF-α decreased by 61.6% (P<0.001). For patients with LV systolic dysfunction, the dynamics of changes in the level of TNF-α in patients who received basic therapy was small - its production declined by 18.7% (P<0,05).

Adding to the basic therapy Imunofan contributed more better reducing of the concentration of TNF-α - by 43.3% (P<0.001). Patients, treated by the scheme with the addition of Metamax to BT, TNF-α production declined by 19.2% (P<0,05). The most active reduction of cytokine occurred in patients treated with the addition to BT Imunofan and Metamax to BT, resulting in reduction of TNF-α by 43.3% (P<0.001). So, better results of the decreasing of TNF-α were shown in the patients with preserved LV ejection fraction, more in patients, who received combination of basic therapy+Imunofan+Metamax.

4. Conclusions: As can been seen from the data, the regulation of plasma concentrations of cytokines is more active in patients with preserved ejection function of left ventricle, whereas patients with left ventricular systolic dysfunction have levels of cytokins closer to the initial data, that is more constant. We saw that adding to the basic therapy Imunofan, especially combination of basic therapy with Imunofan and Metamax, regulate plasma concentrations of cytokines more active. Pronounced effect of treatment was observed in patients treated with basic therapy+Imunofan and basic therapy with Imunofan and Metamax (P<0.001), which resulted not only accurate dynamics, but closer to the reference values of concentration of TNF-α and IL-10. Anti-inflammatory cytokine TGF-β1 applied after treatment increased, due to ability to inhibit the activity of TNF-α and fibrogenic properties.

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