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OSTEOPONTIN, INTERLEUKIN-15 AND DYSFUNCTION OF LEFT VENTRICULAR MYOCARDIUM IN HYPERTENSIVE PATIENTS WITH CHRONIC HEART FAILURE

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Based on a survey of 108 patients with hypertension complicated by chronic heart failure, studied the connection concentration of osteopontin, interleukin-15 in serum and morpho-functional characteristics of the left ventricle of the heart. In patients with CHF osteopontin levels were significantly higher, it revealed a relationship between adverse LV filling state and knots in serum osteopontin, while the level of IL-15 did not show such a relationship. The results indicate the potential value of osteopontin as a biomarker for the diagnosis of CHF.

KEY WORDS: osteopontin, interleukin-15, hypertension, left ventricular myocardial dysfunction, chronic heart failure

ОСТЕОПОНТИН, ИНТЕРЛЕЙКИН-15 ТА ДИСФУНКЦІЯ МІОКАРДА ЛІВОГО ШЛУНОЧКУ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ

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На підставі обстеження 108 пацієнтів з гіпертонічною хворобою, ускладненою хронічною серцевою недостатністю, вивчений зв'язок концентрації остеопонтину, інтерлейкіна-15 в сироватці крові і морфофункціональних особливостей лівого шлуночку серця. У пацієнтів з ХСН рівень остеопонтину був достовірно вище, виявлений взаємозв'язок між несприятливим станом наповнення ЛШ та зростанням концентрації остеопонтину в сироватці крові, в той час, як рівень інтерлейкіна-15 не продемонстрував таку залежність. Отримані результати свідчать про потенційну цінність остеопонтину, як біомаркера діагностики ХСН.

КЛЮЧОВІ СЛОВА: остеопонтин, интерлейкин-15, гипертонична хвороба, дисфункция миокарду ЛШ, хронична серцева недостатність

ОСТЕОПОНТИН, ИНТЕРЛЕЙКИН-15 И ДИСФУНКЦИЯ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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На основании обследования 108 пациентов с гипертонической болезнью, осложненной хронической сердечной недостаточностью, изучена связь концентрации остеопонтину, интерлейкина-15 в сыворотке крови и морфо-функциональных особенностей левого желудочка сердца. У пациентов с ХСН уровень остеопонтину был достоверно выше, выявлена взаимосвязь между неблагоприятным состоянием наполнения ЛЖ и нарастанием сывороточной концентрации остеопонтину, в то время как уровень интерлейкина-15 не продемонстрировал такую зависимость. Полученные результаты свидетельствуют о потенциальной ценности остеопонтину, как биомаркера диагностики ХСН.

КЛЮЧЕВЫЕ СЛОВА: остеопонтин, интерлейкин-15, гипертоническая болезнь, дисфункция миокарда ЛЖ, хроническая сердечная недостаточность

INTRODUCTION

Among the causes of death of middle and elderly patients cardiovascular diseases (CVD)

are the first priority. The overall incidence of them also makes a considerable share among the population of Ukraine. Considering, in particular, essential hypertension (EH), in 2015, have been registered in 788214 patients in Ukraine [1]. A serious complication of EH, coming to the risk of cardiovascular events, is chronic heart failure.

CHF occurs as a consequence of the remodeling of the left ventricle (LV). Structural and functional reorganization of the left ventricle is one of the earliest manifestations of systemic EH [2]. Remodeling involves changing the geometrical shape and structure of the heart muscle [3] and leads to myocardial dysfunction.

The main mechanisms of cardiac remodeling in hypertension complicated by heart failure are inflammation and fibrosis. The role of osteopontin, which is a recognized marker of fibrosis, and pro-inflammatory cytokine interleukin-15 (IL-15) has not been studied in the formation of heart failure. Osteopontin is a secretory sialoprotein belonging to the class of matrix protein cells [4]. Proved his involvement in the inflammatory processes with increasing rigidity of the vascular wall, calcification of atheroma [5]. The interrelation level of osteopontin with LV myocardial changes and the development of hypertension in children and adolescents [6]. One of the mechanisms mediating the remodeling of the myocardium is overproduction of cytokines [7]. IL-15 pro-inflammatory cytokine involved in the autoimmune inflammation, proliferation of T-lymphocytes and natural killer cells [8]. His role in the development of structural and functional changes of left ventricular myocardium little studied and is of interest for further research.

PURPOSE OF THE STUDY

The study of the relationship between the concentration of osteopontin, IL-15 serum, remodeling and changes in left ventricular cardiac function in hypertensive patients complicated with chronic heart failure (CHF).

MATERIALS AND METHODS

The study included 108 hypertensive patients complicated with heart failure who have given informed consent to survey and the use of survey data in the publication. The first clinical group consisted of 44 hypertensive patients with concomitant heart failure I stage,

the second – 64 hypertensive patients with concomitant heart failure II A-B stage. The control group consisted of 12 healthy people.

Exclusion criteria of patients from the study were: secondary hypertension; heart rhythm disturbances, AB conduction; presence of chronic heart failure stage IIB-III (NY classification); acute myocardial infarction or stroke in history, a sharp left or right heart failure; traumatic lesions of the central nervous system; comorbid psychiatric disorders, alcoholism, drug addiction; decompensated of liver disease (increased AST, ALT more than 3 times); diffuse connective tissue diseases; infectious diseases and cancer.

Verification of the diagnosis, staging and the degree of hypertension, were carried out according to the criteria recommended in 2013 by the European Society of Hypertension (ESH)/and the European Society of Cardiology (ESC). Verification of the diagnosis, determine the degree of heart failure, were performed according to the criteria recommended in 2012 by the Association of Ukrainian specialists in heart failure.

The blood was taken to the biochemical and enzyme immunoassay research is done with the ulnar vein in the morning on an empty stomach is not earlier than after 12-hour fast. Research methods included the collection of complaints and anamnesis, anthropometry (BMI, waist circumference, hip circumference, height).

All patients were determined osteopontin levels (ng/ml) in serum by enzyme immunoassay using a set of «Human Osteopontin Assay Kit -IBL Co., Ltd» Japan, IL-15 (pg/ml) in blood serum using a set «RayBio® Human IL-15 Elisa Kit» USA.

Ultrasound of the heart study was conducted using an ultrasound scanner RADMIR Ultima PA (Ukraine, Kharkov) in a recognized procedure in M-, B- and D- modes echolocation, as recommended by the American Society echocardiographic (Americansociety of Echocardiography – ASE), with the definition of the following indicators: the mass of the left ventricle (LV MM), g.; myocardial mass index (IMM), g/m²; myocardial mass index on growth (IMMr^{2.7}) g/m^{2.7}; interventricular septum thickness (IVST) mm; the thickness of the rear wall of the left ventricle (LV CTM) mm; the relative thickness of the left ventricular wall (LV UTS), mm; - End-diastolic dimension (CRA), mm; ejection fraction (EF), %. For the purpose of a detailed

assessment of left ventricular diastolic filling state of patients underwent echocardiography protocol with in-depth study of transmitral flow parameters and motion of the mitral valve fibrous ring tissue Doppler mode: Peak E cm/s; Peak A, cm/s; E/A; Peak E' – cm/s; E/E'.

Statistical processing of the results was performed using standard methods of nonparametric statistics using Statsoft STATISTICA statistical software package v. 10.0 on personal home computers. As the parameters of descriptive statistics used median (Me), the bottom (the LQ) and the upper (UQ's)

quartile of the sample. Significant differences between the figures that have been studied, was determined using the Mann - Whitney. To determine the relationship between the studied parameters, carried out a correlation analysis with the calculation of Pearson correlation coefficients of pair.

RESULTS AND DISCUSSION

The study results of osteopontin concentration in serum IL-15 in hypertensive patients complicated with CHF given in tab. 1.

Table 1

The concentration of osteopontin in the blood serum IL-15 in patients with EH complicated by heart failure, Me (LQ; UQ)

Level of serum markers	Clinical patients group		
	Control (n = 12)	Hypertensive patients complicated with heart failure I stage (n = 44)	Hypertensive patients complicated with heart failure IIA-B stage. (n = 64)
Osteopontin, ng/ml	10,0 (7,69;12,8)	14,3 (8,25; 19,1) p > 0,05	15,3 (12,4; 18,5) p > 0,05 p* = 0,002
IL-15, pg/ml	88,6 (57,1; 103,8)	93,1 (79,8; 106,8) p > 0,05	87,7 (82,2;100,4) p > 0,05 p* > 0,05

Note: p – confidence level compared to the control group performance; p* – confidence level in comparison with indicators of group 1.

Osteopontin concentration in serum increased with the accession of CHF and reliably reached the highest values in patients with HF II AB stage, whereas serum IL-15 did not show such a relationship.

The correlation coefficients between the levels of osteopontin and IL-15 in serum and

echocardiographic parameters (tab. 2) showed lower strength of correlations osteopontin serum and IL-15 with the linear dimensions of the LV, absolute and relative thickness of its walls, the calculated indices and myocardial mass fraction LV ejection.

Table 2

The correlation coefficients between osteopontin, IL-15 and PV characteristics of LV morphology in hypertensive patients complicated with heart failure

Index	Osteopontin	IL-15
CRA	-0,095	0,250
IVST	-0,065	-0,103
LV TZS	-0,118	-0,096
LV UTS	-0,076	-0,326
MM LV	-0,205	0,001
IMM	-0,164	0,059
IMMr2,7	-0,145	0,128
FW	-0,011	-0,076

In our opinion, this fact can be explained by the fact that in hypertensive patients in the formation of heart failure in the early stages of a typical violation of diastolic function [9]. Previous studies [10–12] show that even in cases where the central hemodynamics has not changed at patients already diagnosed with hypertension heart failure is due to the appearance of diastolic LV myocardial dysfunction. The number of such patients, including patients with hypertension and heart failure is approximately 30–40 % [13].

Reduction of myocardial contractile function, determined by the ejection fraction, joins in the later stages of the disease and is often associated with the manifestations of comorbid pathology, primarily, coronary heart disease [14].

Analysis of the data shown in table 3 shows a lack of significant association between serum IL-15 levels and features of diastolic filling. At the same time, it revealed a negative correlation between the average powers in the serum concentration of osteopontin and peak E' ($r = -0,049$), ($p > 0.05$), reflecting a decrease in left ventricular relaxation properties of the myocardium in patients with higher levels of osteopontin. At the same time between the E/E' and osteopontin direct correlation medium strength ($r = 0,500$), ($p > 0.05$), which indicates an increase in stiffness and increase in myocardial LV filling pressure in patients with high levels of osteopontin.

Table 3

The correlation coefficients between osteopontin, IL-15 and functional features of the left ventricle in hypertensive patients complicated with heart failure

Index	Osteopontin	IL-15
Peak E	-0,049	0,059
Peak A	-0,065	0,016
E/A	0,107	0,082
Peak E'	-0,429	-0,036
E/E'	0,500	0,107

The above data confirm the results of earlier studies conducted, during which a direct relationship between the concentration of osteopontin and myocardial stiffness change [14–16] was detected, which leads to the development of left ventricular dysfunction and, as a consequence, CHF.

An analysis of the literature regarding the sources of pro-inflammatory cytokines evidence of their involvement in the LV remodeling [17], but the analysis of data is an IL-15 did not reveal data on the direct interconnection of IL-15 with a clinical picture of heart failure, prognosis of myocardial remodeling. As in this study, the relationship between serum levels of IL-15 and severity of heart failure has not been identified.

Considering the above, it seems appropriate to search for new biomarkers, a change in the level which would have made it possible to predict the development of diastolic dysfunction at the stage prior to its manifestation. Our findings suggest the

potential value of osteopontin, which is a proven marker of fibrosis, in predicting the development of myocardial dysfunction.

CONCLUSIONS

1. In hypertensive patients in combination with CHF revealed significantly elevated levels of osteopontin in the blood serum, reaching maximum severity in patients with heart failure stage II. IL-15 level in these patients does not depend on the presence and severity of heart failure.

2. Increased serum levels of osteopontin in hypertensive patients is associated with a relatively unfavorable LV filling state, both in the early and late in diastole, the manifestation of which is the negative correlation with the values of osteopontin peak E, and a positive attitude to the E/E'.

3. The established relationship concentration of osteopontin in the blood serum with functional myocardial changes in hypertensive patients complicated with heart failure, an opportunity to recognize the

important role of this maker of fibrosis in myocardial remodeling and heart failure severity.

PROSPECTS FOR FUTURE STUDIES

In hypertensive patients with levels of osteopontin study established its dependence

on the degree of severity of heart failure. Given the correlation between the concentration of serum osteopontin and diastolic myocardial dysfunction, it seems appropriate to consider it as a predictor of functional disorders of the myocardium in hypertensive patients.

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