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THE ROLE OF GROWTH FACTORS IN THE DEVELOPMENT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS

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The role of insulin-like growth factor-1 and transforming growth factor-β1 in the pathogenetic mechanisms of the formation of diastolic dysfunction of the left ventricle of the heart in patients with arterial hypertension and with type 2 diabetes mellitus were studied. 67 patients with type 2 diabetes mellitus and 46 with arterial hypertension and without diabetes mellitus patients were examined. Patients with arterial hypertension with concomitant diabetes mellitus were more marked than the diastolic function of the left ventricle. The relationship between the level of the transforming growth factor-β1 and the diastolic function of the left ventricle is established. In the presence of signs of diastolic dysfunction, the level of this growth factor was significantly higher in both groups of patients. The relationship between the level of insulin-like growth factor-1 and the indicators of diastolic function of the heart has not been established.

Key words: arterial hypertension, diabetes mellitus type 2, diastolic function of the left ventricle, insulin-like growth factor-1, transforming growth factor-β1.

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РОЛЬ ФАКТОРІВ РОСТУ В РОЗВИТКУ ДІАСТОЛІЧНОЇ ДИСФУНКЦІЇ ЛІВОГО ШЛУНОЧКА У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Вивчали роль інсуліноподібного фактора росту-1 та трансформуючого фактора росту-β1 в патогенетичних механізмах формування діастолічної дисфункції лівого шлуночка серця у хворих на гіпертонічну хворобу з цукровим діабетом 2 типу. Обстежено 67 хворих на гіпертонічну хворобу з цукровим діабетом 2 типу і 46 хворих на гіпертонічну хворобу без цукрового діабету. Хворі на гіпертонічну хворобу з супутнім цукровим діабетом 2 типу відрізнялись більш вираженими порушеннями діастолічної функції лівого шлуночка. Встановлено взаємозв'язок між рівнем трансформуючого фактора росту-β1 і показниками діастолічної функції лівого шлуночка. При наявності ознак діастолічної дисфункції лівого шлуночка рівень даного ростового фактора був достовірно вище в обох групах хворих. Взаємозв'язок між рівнем інсуліноподібного фактора росту-1 з показниками діастолічної функції серця не встановлений.

Ключові слова: артеріальна гіпертензія, цукровий діабет 2 типу, діастолічна функція лівого шлуночка, інсуліноподібний фактор росту-1, трансформуючий фактор росту-β1.

The study is a fragment of the research project "To develop methods for improving the treatment of arterial hypertension in patients with obesity based on the study of humoral and epigenetic factors and intestinal microbiota parameters", state registration No. 0120U000070.

Arterial hypertension (AH) is one of the most common cardiovascular diseases and significantly influences the disease's forecast and mortality rate. The heart and blood vessels suffer most frequently due to it. Identifying left ventricle hypertrophy in these patients and assessing its influence on disease development remains an important scientific and clinical problem. It is known that the patients with AH, especially when combined with type 2 diabetes mellitus (DM), considerably change not only structural but also functional left ventricle parameters [11–13]. There is evidence that diastolic dysfunction (DD) may be determined by myocyte hypertrophy and cardiac fibrosis [1]. DM patients suffer these changes

to a great extent due to the hyperglycemia and insulin resistance. Along with that the importance of studying the growth factors in the hypertrophy mechanisms and left ventricular fibrosis process is indicated in the patients with AH and DM, entailing the disruption in its functional specifications [2, 3, 8]. The left ventricle hypertrophy regress and, consequently, the improvement of its diastolic function will promote the survival rate of patients with AH. Therefore, it is justified to study the mechanisms of developing left ventricular diastolic dysfunction, specify the role and significance of the growth factors in these processes as they have not been sufficiently considered yet.

The purpose of the study was to establish the role of insulin-like growth factor-1 and transforming growth factor-β1 in the pathogenic mechanisms of developing cardiac left ventricular diastolic dysfunction in patients with arterial hypertension and type 2 diabetes mellitus.

Materials and methods. 67 AH patients with type 2 DM and 46 AH patients without DM were examined in State Institution "L.T. Malaya National Therapy Institute of the National Academy of Medical Sciences of Ukraine" (Kharkiv). The average age of the AH patients with type 2 DM was 62(3.2) years old, while AH patients without type 2 DM – 59 (4.0) years old. All patients underwent standard clinical laboratory and instrumental examinations, enabling to confirm the AH and type 2 DM diagnosis. The left ventricle diastolic function was assessed according to the Doppler sonography data of the transmitral flow in the pulse mode in the cardiac cross-section four-chamber view with sample volume being at the ends of mitral leaflets. The maximum speed of early diastolic filling (E, m/sec), the maximum speed of the wave of the late diastolic filling (A, m/sec), their ratio (E/A), left ventricle isovolumic relaxation time (IVRT, ms), as well as flow deceleration time to the early diastolic phase (DcT) were evaluated.

The insulin-like growth factor-1 (IGF-1) level in blood was found using the immunoenzymometric method with sets from DSL (USA).

The transforming growth factor-β1 (TGF-β1) level in the blood serum was found using the immunoenzymometric method with a test system from DRG Instruments GmbH (Germany).

The examination protocol was approved by the local ethical commission of the Malaya Public National Institute of Therapy of the National Academy of Medical Sciences of Ukraine. The examination was performed in compliance with the principles of the Declaration of Helsinki. All patients signed their consent to participate in the examination.

For the statistical data processing the general software package Statistica for Windows version 6.0 was used. The data were presented as M(m). When the distribution was not normal, the data were presented as median (Me) (50^{th} percentile), 25^{th} (LQ) and 75^{th} percentiles (UQ) (upper and lower quartiles), hereinafter referred to as: Me (LQ ÷ UQ). To study the influence of the independent variable on the dependent one non-parametric analogues of the variance analysis – Kruskal-Wallis test (KKW) were used.

Results of the study and their discussion. The analysis of the obtained transmitral flow indicators points to the deepest disorders of the left ventricular diastolic function in patients with AH and concomitant type 2 DM compared to the patients with AH and the normal carbohydrate metabolism.

For example, comparing the average values of the left ventricular functional characteristics it was found out that the E/A ratio was statistically lower in the patients with AH and type 2 DM 0.98(0.02) versus the patients with AH and without type 2 DM – 1.26(0.07), $p<0.05$. The average values of another indicator of the left ventricular diastolic function – DcT, showing the deceleration time of the early transmittal flow, in the group of patients with AH and concomitant type 2 DM were 203.9(10.6) ms, in the group of patients with AH and without DM – 192.6 (7.6) ms, and they did not reliably differ in both groups of patients, $p>0.05$. The average IVRT values were statistically reliably higher in the patients with AH and concomitant type 2 DM – 102.0 (0.6) ms compared to the AH patients without DM – 86.1 (1.0) ms, $p<0.01$.

Basing on the analysis of E/A, DcT and IVRT indicators in the patients under examination the following types of the left ventricular diastolic dysfunction were singled out: abnormal left ventricular relaxation and left ventricular pseudonormal filling pattern (Table 1).

Table 1

Types of left ventricular diastolic dysfunction in patients with AH and concomitant type 2 DM and without type 2 DM (%)

Diastolic function type	AH with type 2 DM (n=67)	AH without DM (n=46)
Norm	36	63**
Abnormal relaxation	39	33
Pseudo-normalization	25**	4

Note: 1. * – the differences are reliable between the indicators in the groups of patients with AH and type 2 DM and patients with AH and without DM ($p<0.05$); 2. ** – the differences are reliable between the indicators in the groups of patients with AH and type 2 DM and patients with AH and without DM ($p<0.05$) ($p<0.01$).

Patients with AH and concomitant type 2 DM compared to those without DM differed in the higher rate of left ventricular diastolic dysfunction – 43 persons (64%) and 17 persons (37%), respectively, $p<0.01$. In the structure of different diastolic dysfunction options both groups of patients featured the prevalence of the abnormal left ventricular myocardium relaxation type. At the same time the group of patients with AH and concomitant type 2 DM showed a higher number of more severe diastolic dysfunction type – left ventricular pseudo-normal filling pattern, $p<0.01$. The results of analyzing the IGF-1 level showed that its content in the blood of patients with AH and type 2 DM (130.3(98.1÷140.1) ng/ml) was reliably lower compared to the patients with AH and without DM (146.0(138.5 ÷ 201.3) ng/ml, the dependence was reliable under the KKW criterion, $p <0.05$. The IGF-1 level in blood of the persons with normal left ventricular diastolic function and in those with different types of the left ventricular diastolic dysfunction did not show statistic discrepancy in the patients with AH and without type 2 DM. According to the data of the 1D correlation analysis the dependence between the IGF-1 level in the blood of patients with AH and DM men positive and the E/A ratio ($r=+0.56$, $p<0.01$) was found.

When studying the TGF-β1 level in the patients with AH and DM it was found its reliable rise compared to the patients with AH and without DM – (16.3±1.14) ng/ml and (11.8±1.21) ng/ml, respectively, $p<0.01$. The interdependence between the TGF-β1 level and left ventricular functional indicators were found in both groups of patients with AH, with and without type 2 DM. For instance, the patients with left ventricular diastolic dysfunction were associated with reliably higher TGF-β1, both with AH, and with HT with concomitant type 2 DM. The AH patients with type 2 DM and LV DD the TGF-β1 level was (17.30±0.68) ng/ml, with normal left ventricular DF - (12.80±0.65) ng/ml, $p<0.05$. In the AH patients without DM and left ventricular DD the TGF-β1 level was (12.20±0.91) ng/ml, with the normal left ventricular DF – (9.30±0.82) ng/ml, $p<0.05$. The TGF-β1 level correlated with such cardiac DF indicators as DcT (in AH patients with type 2 DM ($r=0.49$; $p<0.05$), in the AH patients without DM - ($r=0.39$; $p<0.05$)) and the E/A ratio (in AH patients with type 2 DM ($r=-0.45$; $p<0.05$), in AH patients without DM ($r=-0.32$; $p<0.05$)). The availability of the E/A and DcT correlation between the TGF-β1 level and such left ventricular diastolic dysfunction indicators in patients with AH, with type 2 DM, and without type 2 DM point to the significant role of this growth factor in the mechanisms of developing left ventricular diastolic dysfunction under hypertension.

Thus, patients with AH and type 2 DM were characterized by more expressed disorder of the myocardial diastolic function left ventricular than those with AH and without concomitant type 2 DM. The IGF-1 level was also reliably lower in patients with AH and type 2 DM, unlike in patients without DM. In this research, no statistically significant dependence between the IGF-1 level and left ventricular diastolic function indicators in patients with AH, with type 2 DM, and without type 2 DM was not found. However, it is known that teenage patients with weak growth hormone generation and low IGF-1 levels are associated with the left ventricular diastolic function, whose manifestations are reduced provided substitution treatment [4, 9]. In addition, the experiment showed that the hyper-expression of IGF-1 decelerates the progression of age-related left ventricular diastolic dysfunction changes [6]. There is a suggestion that the protective effect of IGF-1 is tightly related to its competitive relations with myocardial angiotensin-renin system. For example, it was found that IGF-1 inhibits the apoptosis of cardiomyocytes by angiotensinogen gene transcription silencing and angiotensin II receptors of type 1 [7]. Besides, certain attention should be paid to the literary data on the interrelation between IGF-1 and another growth factor – TGF-β1, involved in the processes of pathological myocardial alteration, but unlike IGF-1, the effect of the latter is mainly aimed at the hypertrophy of cardiomyocytes and interstitial fibrosis [10].

TGF-β1 regulates physiological and pathological processes in the cardiovascular system, and its role in the initiation and progression of AH is confirmed by the relationship between the signaling pathways of this cytokine and a number of biologically active substances. Receptors for TGF-β1 are localized practically in all tissues, which confirms their importance in the diversity of processes occurring in humans. The dynamic of TGF-β1 index in the patients with AH and with type 2 DM and without type 2 DM, found in this research, confirms the significant contribution of this growth factor into the mechanisms of developing pathological changes in the left ventricular functional characteristics, which is in line with the data of other studies [5, 15]. It is known that the TGF-β1 hyper-expression increases the content of collagen, that by influencing the fibroblasts, it activates fibrosis process. These processes are deeply determined by the regulation of the expression of genes that encode collagen types I and III, and also by abnormal extracellular matrix protein degradation [14]. The pathogenic mechanism for the development of myocyte hypertrophy may be the activation of angiotensin-11, which TGF-β1 relates – via signals. Accordingly, TGF-β1 may be referred to as an important and significant factor for the left ventricular diastolic dysfunction development, since it promotes the development of pathological proliferative processes in the

cardiac muscle, strengthened due to the metabolic changes along with hyperinsulinemia and hyperglycemia, and entailing myocardial dysfunction.

Conclusions

1. Patients with AH and with concomitant type 2 DM compared to the patients with AH and without DM are characterized by deeper left ventricular diastolic function disorders. AH patients with type 2 DM have higher frequency rate of left ventricular diastolic dysfunction. In the structure of various types of the left ventricle hypertrophy in both groups of patients the prevailing type is with the abnormal left ventricular myocardial relaxation. However, in the group of patients with AH and with concomitant 2 DM there is a higher frequency of the more severe diastolic function type – pseudo-normal left ventricular filling pattern.

2. High TGF - β1 level in the AH patients with type 2 DM and in those without DM with the left ventricular diastolic function disorder shows the participation of this growth factor in the pathogenic mechanisms of left ventricular diastolic dysfunction development.

3. No dependence was found between the IGF-1 level and the left ventricular diastolic function indicators in both groups of patients under examination.

Prospects for further research. Studying the effect of antihypertensive drugs on the morphological and functional characteristics of the left ventricle of the heart and the production of growth factors will allow us to develop optimal approaches to the correction of detected disorders.

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