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DYNAMICS OF SST2 AND NT-PROBNP IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS BASED ON COMBINED THERAPY WITH EPLERENONE AND TRIMETASIDINE ADDITION

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The purpose of our study was to investigate the effect of complex therapy with the addition of eplerenone and trimetazidine on the state of left ventricular diastolic function, as well as levels of soluble growth-stimulatingreceptor expressed by gene 2 and N-terminal fragment of brain natriuretic propeptide in patients with arterial hypertension with type 2 diabetes mellitus. After registration baseline data were recorded, 42 patients (group 1) were prescribed baseline therapy and 38 patients (group 2) were prescribed eplerenone 25-50 mg once daily and trimetazidine 80 mg once daily in addition to antihypertensive therapy for 3 months. The control group consisted of 20 practically healthy individuals. After the treatment, a significant decrease in the level of soluble growth-stimulatingreceptor expressed by gene 2 in the blood of patients in both groups was found, but in group 2 this indicator did not differ from the control group, while in group 1 it remained significantly higher than in healthy individuals. At the same time, the level of N-terminal fragment of brain natriuretic propeptide significantly decreased by 1.3 times and 1.6 times in groups 1 and 2, respectively, but remained significantly higher than in the control group. A significant decrease E/e`mean was determined in both groups of patients, but in group 2 by 8.9 % less than in group 2 and a decrease in the geometric parameters of the left atrium, more pronounced in group 2. Thus, the addition of eplerenone and trimetazidine to the complex therapy of patients with arterial hypertension and type 2 diabetes mellitus during 3 months improved diastolic function, and also had a positive effect on the biomarker of myocardial stress and fibrosis soluble growth-stimulatingreceptor expressed by gene 2 level and myocardial dysfunction N-terminal fragment of brain natriuretic propeptide concentration in serum

Key words: soluble growth-stimulatingreceptor expressed by gene 2, N-terminal fragment of brain natriuretic propeptide, diastolic function, arterial hypertension, type 2 diabetes mellitus, eplerenone, trimetazidine

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ДИНАМІКА SST2 ТА NT-PROBNP У ПАЦІЄНТІВ З ГІПЕРТОНІЧНОЮ ХВОРОБОЮ ТА ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ НА ФОНІ КОМБІНОВАНОЇ ТЕРАПІЇ З ДОДАВАННЯМ ЕПЛЕРЕНОНУ ТА ТРИМЕТАЗИДИНУ

Метою нашого дослідження було вивчення впливу комплексної терапії з додаванням еплеренону та триметазидину на стан діастолічної функції лівого шлуночка, а також вміст розчинного рецептор стимулюючого чинника зростання, що експресується геном 2, та N-термінального фрагмента мозкового натрійуретичного пропептида у хворих на артеріальну гіпертензію з супутнім цукровим діабетом 2 типу. Після реєстрації вихідних даних 42 пацієнтам (1 група) призначали базисну терапію та 38 пацієнтам (2 група) додатково до антигіпертензивної терапії призначали еплеренон 25-50 мг 1 раз на день та триметазидин 80 мг 1 раз на день протягом 3 місяців. Контрольну групу склали 20 практично здорових осіб. Після проведеного лікування встановлено суттєво зниження рівня розчинного рецептор стимулюючого чинника зростання, що експресується геном 2, в крові у пацієнтів обох груп, але в групі 2 цей показник не відрізнявся від групи контролю, тоді як в групі 1 залишався вірогідно вищим даних здорових осіб. При цьому рівень N-термінального фрагмента мозкового натрійуретичного пропептида достовірно знижувався у 1,3 рази та 1,6 разів у групах 1 і 2 відповідно, але залишався суттєво вищим групи контролю. Визначено достовірне зниження показника діастолічної функції E/e`mean в обох групах пацієнтів, але в групі 2 на 8,9 % менше ніж в групі 2 та зменшення геометричних параметрів лівого передсердя, більш виражене в групі 2. Таким чином, включення еплеренону та триметазидину в комплексну терапію хворих з артеріальною гіпертензією з супутнім цукровим діабетом 2 типу протягом 3 місяців сприяло покращенню показників діастолічної функції, а також позитивно впливало на біомаркер міокардіального стресу і фіброзу вміст розчинного рецептор стимулюючого чинника зростання, що експресується геном 2 та дисфункції міокарда концентрацію N-термінального фрагмента мозкового натрійуретичного пропептида в сироватці крові, поряд з безпечністю і хорошою переносимістю.

Ключові слова: розчинний рецептор стимулюючий чинник зростання, що експресується геном 2, N-термінальний фрагмент мозкового натрійуретичного пропептида, діастолічна дисфункція, артеріальна гіпертензія, цукровий діабет 2 типу лікування

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Arterial hypertension (AH) is the largest non-communicable pandemic in the history of humanity, which determines the structure of cardiovascular morbidity and mortality [12]. The relationship between hypertension and various pathological conditions that largely determine its progression and the development of cardiovascular complications is obvious and proven. One of these conditions or diseases

is type 2 diabetes mellitus. The number of patients with type 2 diabetes in the world is currently about 400 million people, and it is projected to increase to 700 million by 2030 [14]. The combination of hypertension and type 2 diabetes significantly worsens the quality of life of patients, leading to increased disability and fatal cardiovascular complications [2].

In this regard, the search for non-invasive biomarkers that reflect early changes in target organs in the comorbidity of hypertension and type 2 diabetes is of special importance. Taking into account the mechanisms of cardiac heart failure (CHF) formation and progression, biomarkers of myocardial fibrosis are extremely important [9]. It has been shown that the content of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) is useful in the diagnosis of heart failure (HF) and in determining the prognosis of patients with cardiovascular disease [8]. Among the biomarkers of myocardial fibrosis, the growth factor receptor expressed by the gene 2 (sST2) is being actively studied, but the data on the possibility of its use as a predictor of the preclinical stage of CHF are controversial [13]. However, there is no unequivocal opinion in the available literature regarding the diagnostic value of NT-proBNP of these biomarkers in the initial myocardial changes in patients with comorbidity of hypertension and type 2 diabetes.

The purpose of the study was to investigate the effect of complex therapy with the addition of eplerenone and trimetazidine on the content of sST2 and NT-proBNP in the blood, as well as the state of diastolic LV function in patients with HTN with concomitant type 2 diabetes mellitus.

Materials and methods. The study included 80 patients (54 men and 26 women) aged 45-54 years (mean age 52.5±2.5 years) with grade 2 hypertension and type 2 diabetes mellitus of moderate severity, subcompensated. The diagnosis of hypertension was made in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH/ESC, 2018). The diagnosis of type 2 diabetes was made in accordance with the general recommendations of the American Diabetes Association (ADA) in 2019 and the International Diabetes Federation (IDF) in 2018.

The control group consisted of 20 healthy individuals (9 women and 11 men, mean age 51.9±2.3 years).

All subjects have signed an informed consent to participate in the study.

The exclusion criteria were as follows: Type 1 diabetes mellitus, congenital heart disease, presence of an artificial pacemaker, presence of artificial heart valves, heart failure of stages II B and III, acute myocardial infarction, infectious and severe inflammatory processes, haematological and oncological diseases.

All subjects underwent a general clinical and laboratory examination (clinical and biochemical blood and urine tests, albuminuria, carbohydrate metabolism, etc.), office blood pressure, heart rate, electrocardiography (ECG), and anthropometric measurements. The state of diabetes compensation was assessed by the concentration of glycated haemoglobin (HbA1c).

The assessment of structural and functional parameters of the heart was performed using a GE Medical Systems (Germany) device with a Doppler sensor that allows operation in M- and B-modes, as well as an energy Doppler sensor that allows determining the diastolic function of the LV in the pulse-wave mode. To assess the diastolic function of the LV by pulsed Doppler echocardiography [1]. To determine LV diastolic function in patients with hypertension and diabetes, we analyzed the main parameters of transmitral blood flow: E, A, E/A; and indices of the kinetics of the fibrous ring of the mitral valve; the early speed of diastolic movement of the lateral (e`lateral) and septal (e`septal) parts with calculation of the average value of the speed of the early diastolic movement of the fibrous ring (e`mean); and left atrial volume (LVA) and indexed volume of the left atrium( iLVA). The ratio of the speed of the transmitral flow to the average speed of the fibrous ring of the mitral valve E/e` was calculated, that indirectly reflects the filling pressure of the left ventricle [5].

Using enzyme-linked immunosorbent assay kits, soluble growth factor receptor expressed by gene 2 (sST2, Critical Diagnostics, USA) and N-terminal fragment of brain natriuretic propeptide (NT-proBNP, Biomedica Slovakia, Slovakia) were measured in the blood serum. These biomarkers play an important role in both the immunological and fibrotic response of the myocardium to injury.

After recording the baseline data, 42 patients (group 1) were prescribed basic antihypertensive therapy (combination of lisinopril and amlodipine in medium therapeutic doses) and 38 patients (group 2) were prescribed eplerenone (Epletor, Borshchagivsky Plant, Ukraine) at a dose of 25-50 mg once daily and trimetazidine (Preductal OD, Servier Industry, France) at a dose of 80 mg once daily for 3 months Patients in both groups also received statins and antiplatelet therapy. A combination of metformin and gliclazide was prescribed for glycaemic control. These groups of patients were comparable in terms of age and gender.

All patients successfully finished the study according to the protocol. Clinical examinations and serum potassium measurements were performed after 4 and 12 weeks of treatment. No side effects or adverse events were reported during this period.

Statistical computer processing of the study results was carried out using the software package Statistica 10.0 (StatSoft Inc, USA). The mean (M), variance, standard deviation, median (m), probability and significance level (p) were calculated. Differences between the groups of mean values and their errors (M±m) were assessed using the Student-Fisher test. A probable error of less than 5 % ($p<0.05$) was considered reliable. The normality of the distribution of indicators was checked using the Kolmogorov-Smirnov test.

Results of the study and their discussion. The dynamics of diastolic function during treatment are presented in Table 1.

It was established that in all patients with hypertension and type 2 diabetes mellitus at baseline, the mean value of the kinetics of diastolic movement of the mitral valve fibrous ring was significantly lower than in the control group. Also, the level of e`mean was significantly lower in patients with hypertension and diabetes mellitus compared with controls.

Table 1.

Indices of the LV diastolic function in patients with CHF and type 2 diabetes mellitus (M±m)

Parameters	Before treatment n=80	Group 1 after the treatment n=38	Group 2 after the treatment n=42	Control group n=20
E, sm/s	59.91±5.42	62.47±6.29	64.81±6.25	77.44±5.04
A, sm/s	82.05±4.38	59.43±4.78	67.48±5.48	55.11±4.63
E/A	0.73±0.15	1.05±0.14	0.99±0.32	1.44±0.16
LVA, ml	58.64±4.31	56.73±4.56*	54.83±5.06*	44.00±3.83
iLVA, ml/m^2	29.33±4.26	27.88±4.42	26.31±3.73	23.63±3.91
e`mean, sm/s	7.34±1.33	8.26±2.23*	9.34±2.16*	14.26±1.90
E/e`mean	8.38±1.42	7.62±1.85*	6.94±1.42*	6.07±1.16

Note * - the difference in indicators is likely compared to the control group, $p<0.05$

The mean values of the kinetics of diastolic motion of the mitral valve fibrous ring increased significantly after treatment, especially in group 2, but even after 3 months of treatment remained significantly lower than in the control group. The level of e`mean in patients with diabetes mellitus and hypertension also increased, but did not fully recover to the levels of healthy subjects. After treatment, the rate of myocardial relaxation in diastole was significantly accelerated in both groups compared with the pretreatment values.

Other indicators in the analysis of each other had the same tendency as before treatment, but there was no significant difference between the indicators before and after treatment. At the same time, the absolute values of the E/e`mean, (LVA) and (iLVA) ratios were still slightly lower compared with their values before treatment.

An important aspect of the management of patients with comorbidities is the development of treatment stratification, which is carried out to prevent destabilisation of the disease and the development of possible complications. One of the most promising ways that has been developed recently in this area is to study the level of various biomarkers in the patient's body. Among them, much attention is paid to sST2 and NT-proBNP, which are considered highly informative markers in the prediction of adverse cardiovascular events.

Part of our study was aimed at studying the clinical and prognostic role of these factors and the impact of treatment on the course of the disease in patients with hypertension and type 2 diabetes.

The data in Table 2 show that before treatment, patients with comorbidities had high serum concentrations of the above biomarkers. Thus, the level of sST2 was increased by 88 %, and the content of NT-proBNP was twice as high as in the control group.

Table 2.

The effect of different treatment regimens on the content of biomarkers in the blood serum of patients with hypertension and type 2 diabetes (M±m)

Parameters	Before treatment n=80	Group 1 after the treatment n=38	Group 2 after the treatment n=42	Control Group n=20
sST2, ng/ml	39.2±4.4*	28.7±3.5*	21.5±2.2#	20.8±2.6
NT-proBNP, pg/ml	337.6±54.1*	253.7±41.8	212.3±44.5	164.2±38.5

Note * – the difference in indicators is likely compared to the control group, $p<0.05$; # – the difference in indicators is likely compared to group 1, $p<0.05$.

The 3-month treatment resulted in positive changes in the clinical condition and cardiac performance of most patients. This was accompanied by a decrease in the blood concentrations of the biomarkers studied in our study. Thus, in patients of group 1, the level of sST2 was significantly reduced by 50 % compared with the data before treatment but remained significantly higher than in the control group. In patients of group 2, the sST2 level decreased to the level of healthy individuals (control group).

After the treatment, the level of NT-proBNP, which is a marker for assessing the functional state of the contractile potential of the heart muscle, decreased by 1.3 times in group 1 and 1.6 times in group 2 compared with the initial data (before treatment). However, even after 3 months of treatment, its concentration remained significantly higher than the control.

Analysing the data obtained, it can be said that type 2 diabetes mellitus in combination with arterial hypertension is accompanied by a significant increase in the level of biochemical compounds that indicate the development of heart failure in the early stages of the disease. This primarily concerns the concentration of biomarkers such as sST2 and NT-proBNP in the blood of patients. Their determination has potential significance in the diagnosis and prognosis of asymptomatic remodelling, cardiac fibrosis, and the development of chronic heart failure.

The size and volume of the left atrium are recognised as powerful indicators of LV diastolic function [4]. Clinical studies have demonstrated the relationship between left atrial volume and LV diastolic function [10]. Left atrial volume is a sensitive morphological indicator of the severity of LV dysfunction and is expected to be a useful index for assessing cardiovascular risk [4]. It has been shown that atrial enlargement is a powerful marker of poor prognosis in patients with CHF [10].

One of the main components of structural remodelling of the heart in CHF is fibrosis. Fibrosis is an important cause of organ dysfunction in many different diseases, including hypertension and diabetes mellitus, and indicates an unfavourable prognosis [15]. It has been established that hypertension is associated with progressive interstitial and perivascular deposition of extracellular matrix proteins that increase myocardial stiffness and cause diastolic dysfunction [7]. Ageing, obesity, and diabetes mellitus can also contribute to the development of interstitial myocardial fibrosis and reduce ventricular compliance, potentially contributing to the development of HF with preserved ejection fraction [3]. Some established treatments for HF targeting neurohumoral pathways (such as angiotensin-converting enzyme (ACE) inhibition, angiotensin II AT1 receptor blockade, mineralocorticoid antagonism, and β-adrenergic blockade) may reduce mortality and event rates in patients with HF, at least in part by inhibiting fibrosis [6]. It is of interest to study the effectiveness of therapy with the addition of the mineralocorticoid receptor antagonist (MRA) eplerenone in early and subclinical changes in the structural and functional state of the heart. This approach is fundamentally important from a practical point of view, as it opens up new opportunities in the search for ways to personalise therapy and slow the progression of target organ damage and cardiovascular complications in patients with hypertension in combination with type 2 diabetes.

Thus, we can see that both haemodynamic and metabolic changes affect the kinetic capabilities of the myocardium. The lowest rates of myocardial diastolic relaxation were found in patients with hypertension and diabetes mellitus. This indicates that the combination (comorbidity) of these negative factors has the greatest impact on myocardial function.

The data obtained showed that the kinetic capabilities of the myocardium improved significantly after treatment, which may indicate the absence of significant fibrosing changes and the possibility of reversal of the functional state of cardiomyocytes at this stage of the disease.

The biological action of sST2 plays an important role in both immunological and fibrotic response of the myocardium to injury. ST2 is expressed in the myocardium in response to pathological changes caused by chronic diseases and acute injuries caused by internal or external factors [15]. NT-proBNP is considered to be the most indicative marker of ventricular dysfunction in the early stages of heart failure [15]. This marker is also a regulator of water and salt balance in the body, which is very important for blood pressure regulation. In left ventricular dysfunction and CHF, an increase in serum NT-proBNP is detected earlier than the signs determined by instrumental examinations, including echocardiography.

Determination of diastolic function parameters at the stage of myocardial dysfunction and treatment contributed to the inhibition or reversal of the initial manifestations of heart failure in patients with comorbidities (HF and diabetes mellitus). The inclusion of trimetazidine and eplerenone in the drug therapy helped to restore the energy balance in cells to a greater extent, reduce the manifestations of hypertension and mobilise compensatory capabilities to normalise myocardial haemodynamic and metabolic disorders, which was the key to improving the cardiovascular prognosis.

Over the course of three months of treatment, haemodynamics and metabolic processes were normalised, and myocardial functionality improved (increased myocardial relaxation rate in diastole). This

support allowed to slow down or stop further development of adverse changes in cardiohemodynamics in the form of increased left ventricular filling pressure (E/e`mean) and disturbances in the geometric parameters of the heart (LVA).

Determination of specific biomarkers sST2 and NT-proBNP in the blood serum helps to assess the severity of CHF, predict further development of the disease, and evaluate the effect of the therapy being performed.

Thus, the inclusion of a combination of eplerenone and trimetazidine in the complex therapy of patients with CHF with type 2 diabetes for 3 months helps to slow down the damage to the heart as a target organ, as evidenced by the positive dynamics of diastolic function parameters and biomarkers the content of sST2 and NT-proBNP in the blood serum, along with safety and good tolerability.

Conclusions

1. In patients with grade 2 hypertension and type 2 diabetes mellitus, the addition of eplerenone and trimetazidine to antihypertensive therapy promotes a more pronounced reduction in the level of sST2 and NT-proBNP in the blood compared with the group receiving basic antihypertensive therapy.

2. The inclusion of eplerenone and trimetazidine in the complex therapy of patients with grade 2 hypertension in combination with type 2 diabetes mellitus has a pronounced positive effect on the structural and geometric parameters of the myocardium, parameters of diastolic function, along with good tolerability.

Prospects for further research. The data obtained and the world experience [11] clearly confirm the need for prevention, early diagnosis, clarification of mechanisms and adequate treatment of cardiac disorders in patients with hypertension and diabetes mellitus before the onset of cardiac remodelling. Further research in this area is needed to find new pathogenetic mechanisms of cardiac lesions, duration and scope of treatment in patients with comorbidities.

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