ORIGINAL ARTICLE

PARAMETERS OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS WITH HYPERTENSION DISEASE WITH CONCOMITANT TYPE 2 DIABETES

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ABSTRACT

The aim: To study the parameters of the left ventricular (LV) diastolic function in patients with HT with concomitant T2DM and without it before and after complex treatment with the inclusion of Eplerenone 50 mg per day and Trimetazidine 80 mg per day during 3 months.

Materials and methods: The study included 50 patients, aged 45–54 years (mean age 51.3±1.5 years), women – 24 and men 26 with HT stage II. All patients were divided into 2 groups: 1 group (n=25) – patients with HT stage II (HbA1c level of 5.01±0.13%) and 2 group (n=25) – patients with HT stage II and concomitant T2DM (HbA1c level of 7.6±0.34%). The control group consisted of 20 healthy individuals (HbA1c level of 4.68±0.49%).

Results: When analyzing the findings on left atrial volume index (LAVI), the highest indicators were observed in patients with HT with T2DM, but slightly lower in HT, and even lower in the control group, but the differences at this stage were not significant. This suggests that functional changes in cardiomyocyte kinetics, which develop in patients with comorbid pathology and are caused by metabolic and hemodynamic disorders, can progress steadily.

Conclusions: After a three-month course of treatment with Eplerenone and Trimetazidine, the rate of myocardial relaxation in diastole likely increased in both groups of those examined. The prescribed treatment with Eplerenone and Trimetazidine has led to a decrease in the rate of progression of heart failure and a reduction in cardiovascular risks.

KEY WORDS: hypertension, type 2 diabetes mellitus, Eplerenone, Trimetazidine, diastolic flow, comorbid pathology

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INTRODUCTION

Nowadays, hypertension (HT) remains the most widespread non-communicable pandemic in human history, which causes cardiovascular morbidity and mortality. [1] Cardiovascular mortality holds a leading position in the overall mortality of the world's population. This is attributed to the high comorbidity of cardiovascular pathology with other diseases. [2,3] The correlation between HT and various pathological conditions, which largely determine its progression and development of cardiovascular complications, is evident and well-proven. One of these conditions or diseases is type 2 diabetes mellitus (T2DM), with about 400 million patients worldwide, which is projected to increase to 700 million by 2030. [4,5] The aggregate impact of HT and T2DM greatly impairs the quality of life of patients and leads to increased disability and fatal cardiovascular outcomes. [6,7]

Comorbid patients are becoming more prevalent in modern clinical practice, which brings certain difficulties in the diagnosis and treatment of such patients [8-10]. Timely diagnosis and treatment of cardiovascular complications in T2DM patients in the early stages refer to important tasks both from the point of view of prevention and improvement of the course of comorbidities. T2DM dramatically reduces both the quality of life and its average duration. The reason for such an adverse effect of T2DM consists in the alterations it causes in the cardiovascular system, kidneys, and other systems. Alterations in the cardiovascular system in the diabetic population can trigger significant disorders in various organs and systems of the body and have a negative mutual influence. [7]

Timely diagnosis and treatment of cardiovascular and nephrological alterations in diabetic patients in the early stages are among the major tasks both from the point of view of prevention and improvement of the course of comorbidities. [7]

THE AIM

To study the parameters of the left ventricular (LV) diastolic function in patients with HT with concomitant T2DM and without it before and after complex

treatment with the inclusion of Eplerenone 50 mg per day and Trimetazidine 80 mg per day during 3 months.

MATERIALS AND METHODS

The study was conducted according to the main provisions of the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki of the World Medical Association with an overview of the ethical principles for medical research involving human subjects (1964-2004), the requirements of Good Clinical Practice (GCP) from 1996, and the Order of the Ministry of Health of Ukraine No. 690 as of 23.09.2009.

The study included 50 patients, aged 45–54 years (mean age 51.3±1.5 years), women – 24 and men 26 with HT stage II. All patients were divided into 2 groups: 1 group (n=25) – patients with HT stage II (HbA1c level of 5.01±0.13%) and 2 group (n=25) – patients with HT stage II and concomitant T2DM (HbA1c level of 7.6±0.34%). The patients were comparable in terms of age, sex, duration of the disease on HT, they were being treated at the clinic of the GI "L.T. Malaya Therapy National Institute of the NAMS of Ukraine". The control group consisted of 20 healthy individuals (HbA1c level of 4.68±0.49%). All patients were examined in accordance with the recommendations of the European Society of hypertension and the European Society of Cardiology (ESH/ESC, 2019). All respondents signed an informed consent to participate in the study. The diagnosis of T2DM was established according to the recommendations of the American Diabetes Association (ADA, 2020)

The inclusion criteria were patients with HT stage II and patients with HT stage II and concomitant T2DM. The non-inclusion criteria were patients with type 1 diabetes mellitus, congenital heart, and urinary tract defects, presence of an artificial pacemaker, presence of artificial heart valves, heart failure stage II B and III, acute myocardial infarction, infectious and severe inflammatory processes, hematological and oncological diseases.

All patients and control subjects underwent general clinical and laboratory examination (clinical and biochemical blood and urine tests, albuminuria, carbohydrate metabolism, etc.), electrocardiography (ECG), and anthropometric measurements.

Research hypothesis is a positive effect of treatment with Eplerenone and Trimetazidine for 3 months on the state of cardiohemodynamics is expected.

The diastolic function of the heart was assessed by transthoracic echocardiography, which was performed on the ULTIMA PA ultrasound machine ("Radmir", Ukraine) using a phased array transducer with a frequency range of 2-3 MHz according to the standard method of the American Society of Echocardiography [11].

To assess the LV diastolic function by pulsed-wave Doppler echocardiography, transmitral blood flow parameters were determined: E/A ratio (where E is the peak flow velocity of the early filling period, and A is the peak flow velocity of the late filling period). Furthermore, according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging in 2016, the left atrial volume (LAV), left atrial volume index (LAVI) were measured using tissue Doppler in pulsed-wave mode, and the mean value of the early diastolic velocity of the fibrous ring (e`mean) was calculated [11-12]. E/e` (the ratio between the transmitral flow velocity and the average velocity of the fibrous ring of the mitral valve) was calculated as well. This indicator reflects indirectly the filling pressure of the left ventricle [13-15].

Statistical analysis of the data was performed using Statistica, 8.0 (Stat Soft Inc, USA), Microsoft Office Excel 2003. The Kolmogorov-Smirnov test was used to assess the nature of the aggregate distribution of the sample data. Between-group differences in mean values and their errors (M ± m) were evaluated using the Student's t-test. A probable error of less than 5 % ($p < 0.05$) was considered reliable.

The main parameters of transmitral blood flow were analyzed to determine the LV diastolic function in patients with HT and T2DM and HT: E, A, E/A, kinetics parameters of the fibrous ring of the mitral valve: early diastolic velocity e' of the lateral (e`lateral) and septal (e`septal) parts and calculating the mean value of the early diastolic velocity of the fibrous ring (e`mean); LAV, LAVI. The ratio between the transmitral flow velocity and the average velocity of the fibrous ring of the mitral valve E/e` was calculated, which reflects indirectly the filling pressure of the left ventricle.

RESULTS

The data in Table I suggest that in patients with HT and HT with comorbid T2DM, the mean kinetics of diastolic flow of the fibrous ring was significantly lower in comparison with the control group. While the e`mean level in patients with T2DM and HT was significantly lower in comparison with patients with HT. Thus, the findings indicate that aggregate hemodynamic and metabolic alterations adversely affect the kinetic capabilities of the myocardium. Moreover, the lowest rates of the myocardial diastolic relaxation rate were probably found in patients with HT with T2DM. The latter proves that the comorbidity of these negative factors significantly reduces the functional capacity of the myocardium.

Table I. Indicators of LV diastolic function in patients with HT and type 2 DM before treatment (M±m)

Indicators	HT and T2DM n = 25	2 grade HT n = 25	Control n = 20
E, cm/s	59.91±5.42*	64.81±6.25	77.44±5.04
A, cm/s	82.05±4.38*	67.48±5.48*	55.11±4.63
E/A	0.73±0.15*	0.99±0.32*	1.44±0.16
LAV, ml	54.83±6.86*	58.33±5.31*	44.00±3.83
LAVI, ml/m²	29.33±2.05*	26.31±1.84	23.63±1.65
e`mean, cm/s	7.76±1.33	8.98±1.44	14.26±1.90
E/e`mean	7.88±2.16*	7.14±1.44	6.07±1.16

Note. *Significant difference in indicators compared to the control, $p < 0,05$

Table II. Indicators of LV diastolic function in patients with HT and type 2 DM after treatment (M±m)

Indicators	HT and T2DM n = 25	2 grade HT n = 25	Control n = 20
E, cm/s	59.91±5.42	64.81±6.25	77.44±5.04
A, cm/s	82.05±4.38	67.48±5.48	55.11±4.63
E/A	0.73±0.15	0.99±0.32	1.44±0.16
LAV, ml	52.83±6.86	49.33±5.31	44.00±3.83
LAVI, ml/m²	28.91±1.95*	26.31±1.84	23.63±3 .91
e`mean, cm/s	8.64±1.33*	9.92±1.44	14.26±1.90
E/e`mean	7.23±2.16	6.77±1.44	6.07±1.16

Note. *Significant difference in indicators compared to the control, $p < 0,05$

One of the key criteria for assessing LV diastolic function is the ratio of the peak flow velocity of the early filling period E to the mean value of the early diastolic velocity of the fibrous ring of the mitral valve e`mean (E/e`mean reflects indirectly the increase in pressure in the LV cavity).

An increase in parameters indicating elevated pressure in the LV cavity may result in changes in the volumetric parameters of the left atrium (LA). Therefore, the next major parameter in the analysis of diastolic dysfunction, which may indicate the development of diastolic heart failure, is an increase in left atrial volume (LAV). Thus, a significant increase in the left atrial volume was found in both groups (HT and HT with T2DM) compared to the control group ($p<0.05$), while this indicator did not differ significantly between the groups.

When analyzing the findings on left atrial volume index (LAVI), the highest indicators were observed in patients with HT with T2DM, but slightly lower in HT, and even lower in the control group, but the differences at this stage were not significant. This suggests that functional changes in cardiomyocyte kinetics, which develop in patients with comorbid pathology and are caused by metabolic and hemodynamic disorders, can progress steadily. Eventually, these changes may progress to dystolic and systolic dysfunction and further worsening of heart failure.

The analysis of LV diastolic function parameters after a three-month treatment with Eplerenone 50 mg per day and Trimetazidine 80 mg per day revealed positive changes in LV hemodynamic parameters (Table II).

Table II shows that the mean kinetics of diastolic flow of the fibrous ring after treatment were significantly lower in the group of patients with HT and HT with compared with the control group. While the e`mean level in patients with HT and T2DM was significantly lower compared with patients with HT. After treatment, the myocardial diastolic relaxation rate was significantly accelerated in both groups (HT and HT with T2DM) compared with pre-treatment ($p<0.05$) (Table II).

Thus, the myocardial kinetic capabilities after treatment have significantly improved, indicating the possibility of reverse shifts in the functional state of cardiomyocytes at this stage of disease and the absence of significant fibrosing alterations, which are leveled by compensatory capabilities when hemodynamic and metabolic disorders of the myocardium are normalized.

It is worth noting that the absolute values of the E/e`mean ratio, (LAV), and (LAVI) after a three-month treatment with Eplerenone and Trimetazidine became lower compared to their pre-treatment values. Our findings are consistent with the results of other researchers [16-19].

Thus, a three-month treatment with Eplerenone and Trimetazidine contributed to the normalization of hemodynamics and metabolic processes, led to an improvement in myocardial functionality (increased myocardial diastolic relaxation rate), inhibition or termination of further development of adverse changes in cardiohemodynamics such as an increase in left ventricular filling pressure (E/e`mean) and impaired geometric parameters of the heart (LAV).

DISCUSSION

Analyzing the results for indexed left atrial volume (iLAV), it should be stated that the highest rates were in patients with HT and T2DM, somewhat lower at HT, and even lower in the control group, but the differences didn't reach a probable level. This suggests that functional changes in cardiomyocyte kinetics that occur in patients with comorbid pathology and are caused by metabolic and hemodynamic disorders, can progress relentlessly. Ultimately, these changes are transferred into diastolic and systolic dysfunction, and into further progression of heart failure.

One of the most significant criteria for evaluating the diastolic function of LV is the ratio of the maximum flow rate of the early filling period E to the mean value of the rate of early diastolic movement of the fibrous ring of the mitral valve e'mean (E/e'mean indirectly reflects the increase in pressure in the LV cavity).

As the results show, a significant increase in the ratio of E/e'mean occurs in the group of patients with HT and T2DM and HT (p). In this case, the probable difference in the ratio of E/e'mean between the HT and HT groups with DM Type 2 is not established. However, the highest indicators of this ratio (E/e`mean) were found in patients with HT and T2DM. As a result, an increase in the parameters that indicate an increase in pressure in the LV cavity can be changes in the volume indicators of the left atrium (LA). Therefore, the next important parameter in the analysis of the state of diastolic dysfunction, which may indicate the development of diastolic heart failure is an increase in left atrial volume (LAV). Thus, a significant increase in left atrial volume in both groups (HT and HT with T2DM) ($p<0.05$) was found compared to the control group, while this indicator probably didn't differ between groups.

The analysis of the kinetic capabilities of the myocardium after treatment indicates a significant improvement in them, which indicates the possibility of reverse shifts in the functional state of cardiomyocytes at this stage of the disease and the absence of significant fibrosing changes that level out the compensatory capabilities in the normalization of hemodynamic and metabolic disorders of the myocardium.

It is noteworthy that the absolute ratios of E/e'mean, (LAV) and (iLAV) after three months of treatment with eplerenone and trimetazidine were lower compared to their pre-treatment values. The data we obtained are consistent with the results of other researchers [16-19].

Thus, three-month treatment with eplerenone and trimetazidine contributed to the normalization of hemodynamics and metabolic processes, led to an improvement in myocardial functionality (an increase in the rate of myocardial relaxation in diastole), inhibition or cessation of further development of adverse changes in cardiohemodynamics in the form of an increase in the pressure of filling the left ventricle (E/e'mean) and a violation of the geometric parameters of the heart (LAV).

Therefore, the study of the parameters of the diastolic function of the left ventricle at the stage of functional myocardial damage is necessary in order to prevent or reverse the development of heart failure in patients with comorbid pathology (HT with T2DM), which is the key to improving cardiovascular prognosis.

CONCLUSIONS

1. In patients with hypertensive disease of the II stage and hypertensive disease with concomitant type 2 diabetes mellitus, the values of the kinetics of the diastolic movement of the fibrous ring of mitral valve were significantly lower compared to similar indicators of the control group, and these changes were more expressive in comorbid patients.
2. After a three-month course of treatment with Eplerenone and Trimetazidine, the rate of myocardial relaxation in diastole likely increased in both groups of those examined.
3. The prescribed treatment with Eplerenone and Trimetazidine has led to a decrease in the rate of progression of heart failure and a reduction in cardiovascular risks.

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