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DIASTOLIC DYSFUNCTION OF THE LEFT VENTRICLE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction. The earliest clinical manifestation of diabetic cardiomyopathy is considered to be left ventricular diastolic dysfunction (LVD), which, with progression, can lead to the appearance of clinical symptoms of chronic heart failure. According to some data, the prevalence of LVD among patients with type 2 diabetes mellitus (DM) without clinical signs of heart disease reaches 75%.

The aim of the study was to evaluate LV diastolic function in patients with DM 2 and AH, as well as to assess the relationship of early disorders of LV diastolic function with pathogenetic factors of HF development and risk factors for CVD.

Materials and methods. The study included 60 patients with DM2 who received oral hypoglycemic drugs to compensate for diabetes, and with arterial hypertension of the 1st-2nd degree (Russian recommendations of the VNOK, 2004). Patients older than 65 years with a clinic of heart failure, coronary heart disease, myocardial infarction or acute cerebral circulation disorder (ONMC) less than 1 year before the start of the study, as well as patients with severe liver and kidney dysfunction, were not included in the study.

There were 27 men and 33 women under observation in age from 40 to 65 years (on average 56.0±6.8 years) with a duration of DM 2 from 0 to 15 years (on average 4.8±3.9 years) and arterial hypertension from 0.5 to 25 years (on average 10.0±6.6 years). All the patients included in the study were overweight, the average BMI was 34.3 ±6.7 kg/m^2.

Results. According to the results of standard EchoCG, a violation of the diastolic function of the left ventricle was detected in 52% of patients. When using a standard echocardiogram in combination with a Valsalva test, signs of DDL were detected in 68% of patients. Thus, patients with a more severe stage of LVD were identified, in whom it was not possible to detect a violation of LV diastolic function during examination using standard EchoCG. The most sensitive method was tissue Doppler imaging: the prevalence of LDL according to this research method reached 85% (51 people) among patients with DM 2 and hypertension.

Conclusions. Most patients with DM2 and AH have early preclinical LV dysfunction – LV diastolic dysfunction. The prevalence of LVL in this group of patients was 85%

according to the TDV data, of which 68% of patients had a violation of LV relaxation; 32 of patients had a stage of pseudonormalization. The severity of EchoCG signs of LVD depended on the duration of DM2 and the presence of microvascular complications, as well as on the level of blood pressure, MAU and LV hypertrophy. There was no relationship between the indicators of LV diastolic function and the duration of blood pressure or the level of glycated hemoglobin.

Keywords: diastolic dysfunction of the left ventricle, diabetes mellitus, arterial hypertension

INTRODUCTION

The earliest preclinical manifestation of diabetic cardiomyopathy is considered to be left ventricular diastolic dysfunction (LVD), which, with progression, can lead to the appearance of clinical symptoms of chronic heart failure. According to some data, the prevalence of LDL among patients with type 2 diabetes mellitus (DM) without clinical signs of heart disease reaches 75%. The combination of DM2 and arterial hypertension (AH) increases the risk of developing macro- and microvascular complications of DM, as well as increases the frequency of detection of signs of LDL in patients with DM2. The vast majority of patients with DM 2 have high blood pressure (BP), therefore, from a practical point of view, it is interesting to study the prevalence of disorders of LV diastolic function in this category of patients, as well as to study the relationships LDV with risk factors for the development of complications of cardiovascular diseases (CVD) and pathogenetic factors for the development of HF. It is known that microalbuminuria (MAU) is an independent risk factor for complications with SZ, and also, according to some data, it can serve as a marker of DDLJ. Therefore, it is of interest to study the effect of MAU on the severity of EchoCG signs of LDL in patients with DM 2 and AH.

The aim of the study was to evaluate LV diastolic function in patients with DM2 and AH, as well as to assess the relationship of early disorders of LV diastolic function with pathogenetic factors of HF development and risk factors for CVD.

MATERIALS AND METHODS

Patients who have received oral hypoglycemic drugs to compensate for diabetes, and with arterial hypertension of the 1st-2nd degree (Russian recommendations of the VNOK, 2004). Patients over 65 years of age with a clinic of heart failure, coronary heart disease, myocardial infarction or acute cerebrovascular accident

(ONMC) less than 1 year before the start of the study, as well as patients with severe liver and kidney dysfunction, were not included in the study. There were 27 men and 33 women under observation in age from 40 to 65 years (on average 56.0±6.8 years) with a duration of DM 2 from 0 to 15 years (on average 4.8±3.9 years) and arterial hypertension from 0.5 to 25 years (on average 10.0±6.6 years).

All the patients included in the study were overweight, the average BMI was 34.3 ±6.7 kg/m^2. Glucose concentration in capillary blood was determined by glucose oxidase method, the level of glycated hemoglobin was determined on an automatic analyzer Diastat ("Bio-Rad", USA). The content of total cholesterol and triglycerides was determined in fasting blood serum by Metrolab2300 analyzer (France). The concentration of low-density lipoproteins was determined by the calculation method according to the W. Friedwald formula. The level of fasting glycemia was 7.3±1.2 mmol/l, glycosylated hemoglobin (HbA1c) – 7.2± 1.7%, total cholesterol (OH) – 6.2± 1.5 mol/L, triglycerides (TG) – 2.7±1.8 mol/L, which indicates unsatisfactory compensation for diabetes (European Diabetes Policy Group, 1999). All patients received therapy with oral hypoglycemic agents: 13% were on monotherapy with sulfonylureas, 16% took metformin, 63% received combination therapy, 5% of patients received drugs from the thiazolidinedione group.

Blood pressure was determined as the average of three blood pressure measurements with a mercury sphygmomanometer on both hands in a sitting position. Initial average office systolic Blood pressure was 153.5±11.5 mm Hg, diastolic blood pressure – 94.7±5.5 mm Hg, heart rate – 75.0± 8.5 per minute. 64% of patients received hypotensive therapy, 26% of them took diuretics, 21% – Ca2+ channel antagonists, the same number of patients took beta-blockers intermittently, 44% of patients occasionally took ACE inhibitors.

All patients underwent echocardiographic examination, Valsalva test and Doppler imaging of tissues. Echocardiographic examination was carried out on an Aspen device (Acuson, USA) with a 3.25 MHz sensor in M-modal and two-dimensional modes in standard echographic positions using pulsed and constant-wave dopplerography and color Doppler mapping. The assessment of the transmittal blood flow was carried out in the pulse Doppler mode from the apical four-chamber position. To assess the diastolic function, the following speed and time indicators were measured: the maximum blood flow rate of early diastolic filling (E), the maximum blood flow rate during atrial systole (A), the time of slowing down the blood flow of early diastolic filling of the left ventricle (DT), the time of isovolumetric relaxation (IVRT) and the E/A ratio. Diastolic dysfunction was established with an increase in IVRT >160 ms, an increase in DT >220 ms, decreasing the E/A ratio <1. For the

differential diagnosis of pseudonormalization of transmittal blood flow and normal diastolic function, a Valsalva test was performed. The sample was considered positive when the E/A ratio decreased by more than 40% and the E/A was restored<1.

To increase the accuracy of the assessment of diastolic function, Doppler imaging of tissues was used. The study was performed on an ultrasound scanner (Toshiba, Japan), with a 7.5 MHz sensor in the tissue pulse doppler mode from the apical four-chamber position parallel to the blood flow. The movement of the lateral and septum walls of the fibrous ring of the mitral valve (MC) at the beginning of diastole was evaluated. The peak rate of early diastolic filling (e) and the peak rate of atrial diastolic filling were determined (a) and their ratio (e/a). Diastolic dysfunction was diagnosed with the following values of the main indicators: the ratio of peaks E/A < 1; a decrease in the ratio E/A by at least 40% when performing the Valsalva test; the velocity of the septum part of the mitral valve ring (peak e) <8 cm/s; the velocity of the lateral part of the mitral valve ring (peak e) <11 cm/s. To determine microalbuminuria (MAU), Micral-test test strips ("Roche", Germany) were used. The morning portion of urine was examined three times, a test for MAU was considered positive in the presence of albumin in two portions. To exclude false positive results on the day of urine collection, patients were recommended to exclude a high-protein diet and avoid heavy physical exertion. Statistical processing of the results of the study was carried out using a package of application programs Statistika 6. To assess the reliability of the differences, the Student's t-test was used for series with a normal distribution of variables. The differences were considered significant at $p<0.05$. The dependence of the indicators was estimated by Spearman's method with the calculation of the correlation coefficient. The results are presented in the form of M ±SD, where M is the arithmetic mean, SD is the standard deviation.

RESULTS

Patients with DM2 and AH without clinical signs of circulatory insufficiency were characterized by normal systolic myocardial function (all patients had an ejection fraction of more than 50%) and normal intracardiac hemodynamics. The structural and functional parameters of the myocardium also corresponded to normal values. The results of echocardiological (Echo-KG) examination of patients are presented in Table 1. According to the results of standard echocardiography, a violation of the diastolic function of the left ventricle was detected in 52% of patients. When using a standard echocardiogram in combination with a sample Valsalva signs of LDL were detected in 68% of patients. Thus, patients with a more severe stage of LVD were identified, in whom it was not possible to detect a violation of LV diastolic function

during examination using standard EchoCG. The most sensitive method was tissue Doppler imaging: the prevalence of LDL according to this research method reached 85% (51 people) among patients with DM 2 and hypertension. Depending on the degree of violation of diastolic The functions of patients were distributed as follows: 68% of patients had a violation of LV relaxation, 32% of patients had a stage of pseudonormalization. The stage of relaxation disturbance was established at the following values of the transmittal spectrum indicators: IVRT > 100 ms, DT > 220 ms, E/A ratio < 1. Also, patients with impaired LV relaxation were included in the group of patients in whom signs of diastolic dysfunction were detected only with the help of tissue Doppler imaging (TDV). The pseudonormalization stage was established at values of IVRT < 100 ms, DT < 220 ms, E/A ratio > 1 and an increase in the E/A ratio by more than 40% from the initial value when performing the Valsalva test. The restriction stage (IVRT < 70 ms, DT < 160 ms, E/A ratio > 2) was not detected in any of the patients. Patients with signs of LDL were distinguished by a longer duration of DM2. As shown, in the subgroup of patients with impaired diastolic function, the average duration of DM2 was 5.2±3.9 years, in a subgroup of patients with normal diastolic function – 2.3± 2.2 years, $p<0.05$. The revealed relationship is confirmed by the result of correlation analysis, where the dependence of LV diastolic function indicators on the duration of DM was observed. The length of the SD correlated with the velocity

of the lateral part of the MK ring ($r=-0.291$, $p=0.1$) and the E/A ratio ($r=-0.401$, $p=0.012$). The duration of hypertension did not differ statistically significantly between the subgroups of patients with the presence and absence of LDL: 9.8±6.5 years and 12.0±7.6 years accordingly, $p>0.05$. Preclinical disorders of LV diastolic function in patients with type 2 diabetes are detected at the time of diagnosis of diabetes. The prevalence of LDL among people with newly diagnosed DM2 is 50%, while the frequency of detection of signs of LV diastolic dysfunction increased with increasing duration of DM. The level of glycosylated hemoglobin and fasting glycemia did not statistically significantly differ between subgroups of patients with normal and impaired LV diastolic function. Fasting blood glucose concentration It was 7.4±1.7 mmol/l in patients with LVDD and 7.2±1.6 mmol/l in patients with normal diastolic function, HbA1c - 7.3±1.0% and 8.1±1.7%, respectively, $p>0.05$ for all comparisons. No correlations were found between the parameters of LV diastolic function and indicators of carbohydrate metabolism compensation. There were no correlations between the signs LDL and lipid metabolism indicators, – total cholesterol, triglycerides and LDL. Thus, we found that in patients with impaired LV diastolic function significantly microvascular complications of DM were more often detected.

The prevalence of retinopathy and nephropathy was 86% in this category of patients and 29% in patients with normal diastolic function, p<0.05. There was a weak dependence of the rate of the septum part of the MK ring (peak e) on the presence of microvascular complications of DM: r=-0.283, p=0.227. The prevalence of MAU among patients with signs of LVD reached 70%, the average level of albumin excretion was 30 mg/l, while in patients with normal diastolic function MAU was not determined. The dependence of the signs of LDL in patients with DM 2 on the level of The MAU is confirmed by the correlation relationship: a statistically significant inverse correlation of the velocity of the septum part of the ring MK (peak e) from the level was noted MAU: r=-0.381, p=0.041. The blood pressure level was statistically significantly higher in the subgroup of patients with LVD – 156.4±11.8/95.4±5.6 mmHg. in comparison with the subgroup of patients with normal diastolic function – 145.0±7.6/91.4±6.9 mmHg. The correlation analysis noted the relationship of indicators LV diastolic function and blood pressure level: SAD correlated with the velocity of the lateral part of the ring MK (r=-0.345, p=0.042) and the E/A ratio (r=-0.245, p=0.109).

LV myocardial mass index was higher in the subgroup of patients with LVD, however, the difference, contrary to expectations, did not reach the level of statistical significance (120.6±24.9 vs. 108.1±45.7). During the correlation analysis, the relationship of LV diastolic function indicators (according to TDV data) with the thickness of the posterior wall of the left ventricle (r=-0.332, p=0.037), the thickness of the interventricular septum (LV) (r=-0.259, p=0.107), the mass of the LV myocardium (r=-0.289, p=0.071) and mass index LV myocardium (r=-0.252, p=0.138). In addition, the thickness ZSLJ correlated with the time of isovolumetric relaxation (r=0.409, p=0.015) and with the E/A ratio (r=-0.282, p=0.078) according to standard echocardiography. Patients with impaired LV relaxation and pseudonormalization of transmittal blood flow differed statistically insignificantly in duration of DM2 and AH, blood pressure, glycosylated hemoglobin, fasting glycemia and MAU, as well as by the MMLF index and the presence of microvascular complications.

DISCUSSION

Diabetic cardiomyopathy is considered by many authors as an independent nosological unit. The first sign of cardiac dysfunction in this condition is considered to be diastolic dysfunction. The prevalence of LV diastolic dysfunction among patients with DM 2 without coronary artery disease, hypertension or other heart diseases reaches, according to various authors, from 50 to 75%. In a study by Poirier et al. to

assess the LV diastolic function in patients with DM 2, in addition to the standard EchoCG study, a sample was used Valsalva in order to identify patients with pseudonormalization of the transmittal spectrum. This made it possible to detect a higher prevalence of LDL than previously thought: more than 50% of patients patients with DM2 without any signs of heart disease had impaired LV diastolic function. Another similar study demonstrated an even higher frequency of detection of LDL in patients DM 2 without cardiovascular diseases, which reached 60%. Recently, with the advent of modern EchoCG examination techniques, the results which are relatively independent of the conditions of pre- and post-loading of the ventricles (such as tissue dopplervisualization) significantly increased the accuracy of the assessment of diastolic function. In a study by Boyer et al. the prevalence of LDL among patients with DM2 and normal blood pressure without signs of heart disease was 75%. According to the results of our study, the frequency of detection signs of LVD at rest in patients with DM2 and AH without clinical signs of circulatory insufficiency reached 85%. Concomitant arterial hypertension, which is known to make a significant contribution to the development of diastolic disorders, contributed to the high prevalence of LDL in the study group of patients. In all previous studies, an increase in blood pressure was an exclusion criterion. The overall goal of these studies was to prove the presence of disorders of diastolic function and demonstrate them widespread in patients with diabetes mellitus without any signs of cardiovascular pathology. Currently, the involvement of metabolic disorders inherent in DM in the development of LDL is not in doubt. The practical application of the obtained results is interesting. In daily practice, doctors rarely encounter isolated DM without concomitant cardiovascular pathology. As it is known, 70-80% of patients with DM have elevated blood pressure; in addition, early development of coronary heart disease is characteristic of patients with DM 2. The data obtained in this study reflect the prevalence of LDL in a non-selective sample of DM2 patients with concomitant hypertension. The question of the dependence of the parameters of LV diastolic function on the duration of DM is discussed in the literature. There are studies that show that there is no relationship between LDL and the duration of diabetes. It should be noted that in this study participated patients with both DM 2 and DM 1. As shown by many authors, preclinical signs of LVD are more pronounced and occur more often with DM 2 than with DM 1 [10]. In this study, the relationship between the prevalence of LDL and the duration of DM has been established: the duration of DM correlated with the E/A ratio ($r=-0.401$, $p=0.012$). In addition, there was a statistically significant difference in the duration of DM2 between the groups of patients with the presence and absence of LDL – 5.2 g and 2.3 g, respectively, $p=0.045$. The duration

of hypertension did not affect the prevalence DDLJ in patients with DM. However, an inverse correlation was revealed between the level of systolic blood pressure and the velocity of the lateral part of the MK ring (r=-0.345, p=0.042) and systolic blood pressure and the E/A ratio (r=-0.245, p=0.109). The relationship between the parameters of LV diastolic function and blood pressure level has been confirmed by other studies, which also revealed the dependence of LVL on the level of diastolic blood pressure. One of the problems of type 2 diabetes mellitus is the presence of its complications already at the time of diagnosis: 30-50% of patients with newly diagnosed diabetes have signs microanginopathies. Based on these data, the question was raised how early preclinical signs of LV diastolic dysfunction appear in patients with DM 2 and AH. In this study, it was shown that among people with newly diagnosed DM2, the prevalence of DDLJ was 50%, the frequency of detection of DDLJ among patients with a duration of DM2 for 1 year was 67%, and by the age of 4, the prevalence of DDLJ reached its maximum level of 87%.

The question of the involvement of microangiopathy in the development of LV diastolic function disorders in patients with DM is still remains debatable. There is no definitive opinion on the relationship between the parameters of diastolic function LV and microvascular complications of DM. There are studies that have established the relationship of LDL with retinopathy, but this relationship has not been confirmed by other authors. In our study, 86% of patients with DM2 with signs of LDL had microvascular complications of DM. Only 29% of patients with microvascular complications of diabetes mellitus were registered among patients with DM2 and AH without DPLJ. There is no unambiguous opinion about the relationship in the literature a number of indicators of carbohydrate metabolism (glycated hemoglobin and fasting glycemia) and parameters of LDL. Epidemiological studies have shown that poor glycemic control is associated with an increased risk of heart failure in patients with DM. A decrease in HbA1c reduces the risk of heart failure (HF) by 1.56 times, and an increase in HbA1c by 1% is associated with an increase in the risk of HF by 8%. The results of other studies confirm a decrease in the risk of HF in patients with DM against the background of good glycemic control. There is evidence that high hyperglycemia can provoke the development of DDLJ. However, not all clinical studies demonstrate a relationship between HbA1c and parameters DDLJ in persons with diabetes. Some authors find a correlation of glycemic control with LDL, as well as an improvement in heart function after adequate hypoglycemic therapy. In other works, such a relationship has not been revealed. In this study, there was also no correlation between the level of glycated hemoglobin and fasting glycemia with the parameters of LV diastolic function. According to some authors, the dependence of

the parameters of LV diastolic function is detected only with sufficiently poor glycemic control. In a study by Sanchez-Barriga et al. an association of HbA1c and DDL was found when achieving HbA1c level of 8%. In another study, a correlation was obtained at a concentration of glycated hemoglobin of 9.2%.

The relationship between LV diastolic function and MAU is more fully covered in the literature. An increase in urinary albumin excretion is associated with an increased risk of cardiovascular complications in both people without diabetes and in diabetic patients. This association is partly explained by the relationship between MAU and the parameters of LV diastolic function. As shown in the study by Liu et al. in patients with DM2 with MAU, there was a decrease in the E/A ratio and an increase in the time of slowing down the E peak. A proportional deterioration in LV diastolic function was revealed with an increase in MAU. The relationship of MAU with LDL in patients with DM2 was determined regardless of age, gender, BMI, duration of DM, blood pressure level, coronary heart disease and LV myocardial mass. Another study demonstrated a significantly higher the level of MAU among patients with DM and DDLJ is higher than in patients without signs of DDLJ. In our study, the prevalence of MAU among patients with DM2 with LDL was 70%, the average level was 30 mg/l, in patients without DDLZH MAU was not determined. An inverse correlation was also obtained between the velocity of the septum part of the MK ring (peak e) and the MAU level (r=-0.381, p=0.041). Another powerful predictor of cardiovascular mortality, especially among patients with hypertension, is left ventricular hypertrophy (LVH). LVH in combination with UIA indicates an unfavorable prognosis for patients with hypertension. A close relationship between LVH and MAU in patients with hypertension has been proven: in a study by Tsioufis et al. LVH occurs in 32% of cases among patients with MAU and 5% – among people with normoalbuminuria. There was a correlation between LVH and MAU in patients with DM2 and AH: an increase in MAU was associated with an increase in LV myocardial mass and, which once again confirms the above, with a deterioration in LV diastolic function. The relationship between LDL and LVH was studied in more detail in the work of Zabal-goitia et al., where the association was revealed LVL and LV myocardial mass in patients with DM 2: increase MMLF was registered in 62% of patients with signs of LDL, while among patients with normal diastolic function, MML was within the normal range. In our study, there was a correlation of LV diastolic function indicators (according to TDV data) with LVL thickness (r=-0.332, p=0.037), LVL thickness (r=-0.259, p=0.107), LV myocardial mass (r=-0.289, p=0.071) and LV myocardial mass index (r=-0.252, p=0.138). Thus, on the prevalence of LDL in patients with DM2 and AH may be

influenced by the duration of DM2, the presence of microvascular complications, the level of MU, the level of blood pressure and LVH.

CONCLUSION

Most patients with DM2 and AH have early preclinical LV dysfunction – LV diastolic dysfunction. The prevalence of LVL in this group of patients was 85% according to the TDV data, of which 68% of patients had a violation of LV relaxation; 32% of patients had a stage of pseudonormalization. The severity of EchoCG signs of LVD depended on the duration of DM2 and the presence of microvascular complications, as well as on the level of blood pressure, MAU and LV hypertrophy. Not marked any relationship between the indicators of LV diastolic function and the duration of blood pressure or the level of glycated hemoglobin.

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