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CARDIAC REMODELING IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND HYPERTENSION

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ABSTRACT

Combination of type 2 diabetes mellitus with hypertension accelerates the development of diastolic heart dysfunction and myocardial remodeling. In turn, a change in the geometry of the heart is associated with the accelerated development of heart failure.

The aim of this study was to examine the parameters of remodeling and the diastolic function of the myocardium in patients suffering from type 2 diabetes mellitus with moderate hypertension.

Two groups of patients matched for sex and age were examined. Group I included 256 patients with type 2 diabetes mellitus and moderate hypertension; Group II consisted of 148 patients with grade II hypertension. To evaluate the remodeling of the myocardium and diastolic function, all patients underwent echocardiography using a Philips EPIQ machine in standard B-mode and M-modes.

As a result of the study, it was revealed that when type 2 diabetes mellitus is combined with moderate hypertension, 91% of patients develop left ventricular hypertrophy, and hypertrophic forms of left ventricular remodeling are observed in 83% of patients (hypertrophic and eccentric hypertrophy). The patients with moderate hypertension in combination with diabetes mellitus develop diastolic dysfunction in 88% of cases, its rigid type prevailing. The most sensitive method for detecting early signs of diastolic myocardial dysfunction in patients with diabetes mellitus and hypertension is tissue Doppler echocardiography.

KEYWORDS: *type 2 diabetes mellitus, hypertension, myocardial remodeling*

INTRODUCTION

Cardiovascular pathology is the leading cause of death in patients with type 2 diabetes mellitus (DM) [*Bell DS., 1995*]. Hypertension (HTN) is also known to be an independent risk factor for vascular catastrophes in type 2 diabetes, revealed in 80% of these patients. Hypertension greatly aggravates the course of diabetes, worsens the prognosis, makes it difficult to achieve glycemic control and, as a result, elevates the mortality rates of the patients by 5-7 times [*Wachter R. et al., 2007*]. Thus, type 2 diabetes and hypertension are two interrelated pathologies, the combination of which occupies a leading place in the structure of morbidity and mortality at the present time.

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For a long time, atherosclerotic lesion in the coronary arteries has been considered as the prevailing mechanism of myocardial damage and the development of chronic heart failure (CHF) in type 2 diabetes. However, the results of later studies allow us to identify peculiar variety of heart damage, diabetic cardiomyopathy, as the leading cause of CHF. Diabetic cardiomyopathy is a specific myocardial lesion in diabetes, manifested by diastolic dysfunction and myocardial remodeling and developed regardless of the presence of hypertension and/or myocardial ischemia [*Bell DS., 1995*]. In patients with type 2 diabetes, an elevated left ventricular mass is observed due to cardiomyocyte hypertrophy and an increase in the interstitial component caused by chronic hyperglycemia, hyperinsulinemia due to insulin resistance, activation of the renin-agiotensin system and numerous other metabolic disorders [*Russo C et al.*, 2010]. It has been established that left ventricular hypertrophy develops in 32% of normotensive patients with

type 2 diabetes [*Struthers AD, Morris AD., 2002*]. In addition, taking into account a very high prevalence of HTN in patients with type 2 diabetes, the hemodynamic factor is important in the development of myocardial remodeling. Hemodynamic overload is known to influence the development of left ventricular myocardial remodeling in HTN of any origin [*Lorell BH, Carabello BA., 2000*]. Thus, the combination of type 2 diabetes with HTN accelerates left ventricular hypertrophy (LVH). In turn, a change in the geometry of the heart is associated with disorders of rhythm and conduction, deterioration of coronary hemodynamics and accelerated development of CHF [*Palmieri V et al., 2001*]. Accordingly, the results of many studies confirm a significant effect of LVH on the prognosis for not only development of arrhythmias and development and progression of heart failure, but also for cardiovascular mortality in general [*Sapozhnikova IE et al., 2012*].

The most important stage of myocardial remodeling is the state of its diastolic function [*Ageev FT, Ovchinnikov FT 2002*]. In case of type 2 DM, left ventricular diastolic dysfunction is considered to be the earliest sign of heart damage [*Kazuomi KE, et al., 2005*]. LV diastolic function is estimated by the volume of transmitral diastolic blood flow and the early diastolic mitral annular velocity, which are the first markers of hemodynamic overload of the heart, leading subsequently to a change in the geometry of the left ventricle [*Nagueh S.F. et al., 2009*]. That is, diastolic dysfunction often precedes left ventricular hypertrophy, a decrease in its systolic function, and can occur in the absence of any symptoms of heart failure. Diastolic filling indices reflect the functional state of the myocardium and its reserve more accurately than systolic filling indices [*Karpov R, Purse O, 2007; Gul K et al., 2009*].

Despite a fairly extensive study of the problem of cardiac remodeling in modern cardiology, it remains insufficiently researched in patients with type 2 DM in combination with HTN. A more detailed analysis of aspects of myocardial remodeling in the above-mentioned patients will make it possible to predict a number of cardiovascular events, optimize treatment and, ultimately, improve the prognosis for this category of patients.

The aim of this study was to examine the parameters of remodeling and the diastolic function of the myocardium in patients suffering from type 2 diabetes mellitus with moderate hypertension.

Material and methods

To solve the task, two groups of patients were examined. Group I consisted of 256 patients with type 2 DM and moderate hypertension. The average age of patients was 48.5 ± 2.5 years, with male patients constituting 47% and female patients 53% of all the subjects. The average duration of diagnosed diabetes was 5.2 ± 1.8 years, HbA1c being equal to 7.9 ± 1.1%. Group II included 148 patients with grade II essential hypertension. The average age of patients in this group was 47.3 ± 3.6 years, 44% of them being male patients and 56% female patients. Most patients of group I were overweight or had grade 1 obesity; patients with normal body weight prevailed in Group II. So the body mass index was 31.4 ± 2.5 kg/m^2 in patients with type 2 diabetes and hypertension and 23.6 ± 2.8 kg/m^2 in patients without type 2 diabetes, p=0.0021. The two groups did not differ in the average duration of diagnosed HTN: 6.1 ± 1.9 and 6.2 ± 1.8 years, respectively. The control group consisted of 30 healthy individuals matched for age and sex (Group III).

The non-inclusion criteria for the study were: a history of myocardial infarction or an acute impairment of cerebral circulation, morbid obesity, pronounced disorders of the kidneys and respiratory organs, NYHA (1984) functional class III and IV chronic heart failure, hypertrophic cardiomyopathy, persistent atrial flutter or atrial fibrillation.

Structural and functional parameters of the heart were estimated by echocardiography using a Philips EPIQ machine in standard B-mode and M-mode [*Lang R.M. et al., 2005*]. The left ventricle end-diastolic diameter (LVED), interventricular septal thickness (IVST) and left ventricle posterior wall thickness (LVPWT) were assessed. The LV relative wall thickness (LVRWT) was calculated by the following formula: LVRWT = (IVST + LVPWT) / LVED. The left ventricular mass (LVM) was calculated according to the Devereux formula. The LVM index (LVMi) was calculated as the ratio of LVM to body surface area. LV myocardial hypertrophy was diagnosed if LVMi was greater than or equal to 125 g/m^2 in men and 110 g/m^2 in women.

Based on the values of LVMi and LVRWT, the fol-

lowing types of cardiac remodeling were identified:

1. LV normal geometry: LVMi within normal limits and LVRWT less than 0.45;
2. LV concentric remodeling: LVMi within normal limits and LVRWT more than 0.45;
3. Concentric LV hypertrophy: LVMi greater than normal and LVRWT more than 0.45;
4. Eccentric LV hypertrophy: LVMi greater than normal and LVRWT less than 0.45.

The LV diastolic function was estimated by the transmitral diastolic blood flow in a pulsed wave Doppler mode. The peak early diastolic flow velocity (peak E), the peak atrial systolic flow velocity (peak A), the E/A ratio and the time of slowing down of the blood flow velocity during the early diastole (the deceleration time is the time taken from the maximum E point to baseline) (DT) were calculated. Tissue Doppler echocardiography was also used to assess diastolic dysfunction. The ratio E/e was determined, where e is the early diastolic mitral annular velocity. This parameter is the most sensitive marker of the filling pressure of the left ventricle and closely correlates with cardiac catheterization data (E/e $\leq$ 8 being normal). The value of E/e > 15 is highly specific for increase in the filling pressure in the left ventricle. Additionally, the pulmonary capillary wedge pressure (PCWP) was estimated by the formula: 2 + 1/3 × E/e, which normally equals to 8-10 mm Hg and is a marker of the left ventricular relaxation [*Ommen S.R. et al., 2000; Mogelvang R. et al., 2009*].

Statistical calculations were performed using the software packages Statistica 10 and Microsoft Office Excel. During the analysis, methods of descriptive statistics were used (n, the number of values in the analyzed data set, was calculated for quantitative variables; the arithmetic mean (M) and standard deviation (σ) were calculated for a normal distribution; the median (Me), and 25th and 75th percentile were used to describe signs that do not follow the normal distribution; and frequency and percentage were applied to describe categorical data). The Kruskal-Wallis test (H test) was used to assess differences between the samples according to the level of the parameter studied. The Spearman's rank correlation coefficient (Rs) was used in correlation analysis. In performing comparisons, we took the significance level (p) to be equal to 0.05.

RESULTS

As a result of the study, it was found that patients with type 2 DM who have moderate HTN develop LVH significantly more frequently and to a greater degree than patients with HTN but without carbohydrate metabolism disorders. There were no cases of LVH in the control group.

According to the results of the study, LVH was revealed in 91% (232 patients) in Group I and in 74% (109 patients) in Group II, p = 0.041. At that, LVM was equal to 292 (254; 318) g in group I and to 242 (198; 274) g in Group II, p = 0.036, and LVMI was 142 (128; 154) and 114 (106; 128), p = 0.033, correspondingly. Values of LVPWT and IVST were also significantly higher in the group of patients with type 2 DM in combination with HTN (Table 1).

When studying the types of LV remodeling in patients of the studied groups, we observed all four geometric models suggested by the classification.

So, in patients with HTN, left ventricular remodeling by the type of concentric hypertrophy was found in the largest number of patients, 78% (115 individuals). Eccentric hypertrophy was revealed in 8% (12 subjects), concentric myocardial remodeling in 12% (17 people) and the normal geometry of the left ventricle in 2% (4 people) of all the patients with HTN.

The patients with type 2 DM and HTN also demonstrate the largest number of cases of left ventricular remodeling by the type of concentric hypertrophy, 50% (128 people). At that, the frequency of eccentric hypertrophy, which is the most unfavorable form of left ventricular hypertrophy, was significantly higher and amounted to 43% (110 people), p = 0.032; concentric remodeling was revealed in 7% (18 people), and the normal geometry of the left ventricle was not determined in this group (Fig. 1).

Thus, when type 2 DM is combined with moderate hypertension, 91% of patients develop LVH, and hypertrophic forms of left ventricular remodeling are observed in 83% of patients (hypertrophic and eccentric hypertrophy). When studying the diastolic function in the patients evaluated patients, we obtained the following results (Table 2).

When assessing diastolic function using Doppler echocardiography, we revealed no significant differences between Groups I and II. When analyz-

ing the prevalence of various types of diastolic dysfunction of the left ventricular myocardium, a rigid (stiff) type was found most often in both groups, constituting 48% (123 patients) in Group I and 61% (91 individuals) in Group II, p = 0.051. The pseudo-normal pattern of diastolic dysfunction was determined in 41% (105 subjects) in Group I and in 34% (50 subjects) in Group II, p = 0.052. The restrictive type was the rarest in both groups: 11% (28 patients) in Group I and 5% (7 individuals) in Group II, p = 0.048 (Fig. 2).

When using tissue Doppler echocardiography, more severe diastolic dysfunction was revealed in patients with type 2 DM and HTN. It was found that the

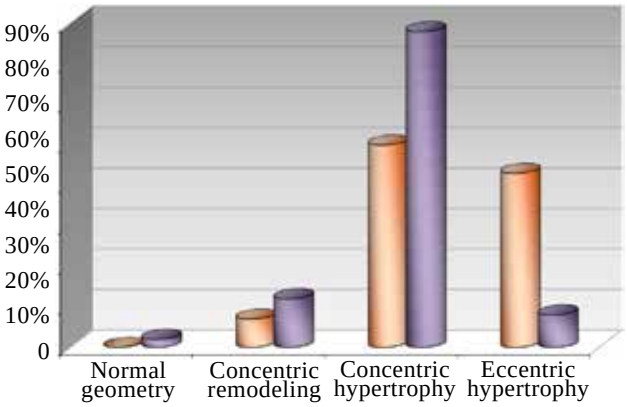

Figure 1. *Types of left ventricular geometry in patients with Tipe 2 diabetes mellitus (left columns) and hypertension (right columns)*

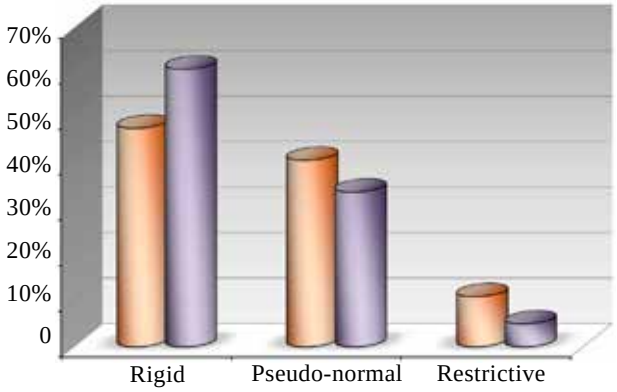

Figure 2. *Types of diastolic dysfunction in patients with Type 2 diabetes (left columns) and hypertension (right columns)*

Table 1.

Echocardiographic parameters characterizing left ventricular hypertrophy in patients with Type 2 diabetes mellitus and moderate hypertension

Parameters	Group I (n=256)	Group II (n=148)	Group III (n=30)	Significance
Posterior wall thickness (PWT), (*cm*)	1.2 (1.0; 1.4)	1.1 (0.9; 1.3)	0.8 (0.7; 0.9)	p_{1-2}=0.048, p_{2-3}=0.046, p_{1-3}=0.042
Interventicular septum (IVST), (*cm*)	1.2 (1.1; 1.4)	1.1 (1.0; 1.3)	0.8 (0.7; 0.9)	p_{1-2}=0.048, p_{2-3}=0.046, $p_{1-3=}$0.042
Mass, (*g*)	292 (254; 318)	242 (198; 274)	220 (216; 228)	p_{1-2}=0.036, p_{2-3}=0.041, p_{1-3}=0.033
Mass index, (g/m^2)	142 (128; 154)	114 (106; 128)	102 (98; 108)	p_{1-2}=0.033, p_{2-3}=0.037, p_{1-3}=0.031
Relative wall thickness	0.48 (0.42; 0.52)	0.54 (0.44; 0.58)	0.36 (0.34; 0.38)	p_{1-2}=0.046, p_{2-3}=0.041, p_{1-3}=0.044

Table 2.

Morphological and functional parameters of left ventricular diastolic function

Parameters	Group I (n=256)	Group II (n=148)	Group III (n=30)	Significance
Peak E, *m/s*	0.6 (0.58; 0.62)	0.51 (0.47; 0.59)	0.75 (0.72; 0.79)	p_{1-2}=0.051; p_{2-3}=0.044, p_{1-3}=0.046
Peak A, *m/s*	0.72 (0.65; 0.74)	0.68 (0.64; 0.72)	0.52 (0.5; 0.54)	p_{1-2}=0.053; p_{2-3}=0.046; p_{1-3}=0.043
Ratio E/A	0.83 (0.82; 0.84)	0.75 (0.73; 0.82)	1.45 (1.4; 1.47)	p_{1-2}=0.052, p_{2-3}=0.037, p_{1-3}=0.031
Ratio E/e	14 (12; 16)	9 (8; 11)	6 (5; 7)	p_{1-2}=0.043, p_{2-3}=0.049, p_{1-3}=0.032
PCWP	15 (14; 16)	11 (9; 13)	9 (8; 10)	p_{1-2}=0.044, p_{2-3}=0.051, p_{1-3}=0.039

Notes: *Peak E - peak early diastolic flow velocity, peak A - peak atrial systolic flow velocity, E/A ratio and the time of slowing down of the blood flow velocity during the early diastole, The ratio E/e was determined, where e is the early diastolic mitral annular velocity, PCWC - pulmonary capillary wedge pressure*

early diastolic mitral annular velocity in patients with type 2 DM with HTN is lower than in patients with isolated HTN. The early diastolic mitral annular velocity is a more sensitive marker of impaired relaxation of the left ventricle than the transmitral E/A ratio. In both groups, the mean values of E/e and PCWP were higher than normal, the patients with type 2 DM and HTN developing more severe impairments of diastolic function (Table 2).

DISCUSSION

Comorbidity of type 2 DM and hypertension is known to be associated with a high risk of cardiovascular complications that affect significantly the disability and mortality of patients. The main target for attack in this combination of diseases is the heart [*Williams B. et al., 2018*]. What we mean is, first of all, development of left ventricular remodeling and diastolic dysfunction, which in turn lead to the accelerated atherosclerotic processes in the aorta and coronary vessels, heart rhythm disturbances and, as a result, heart failure. Thus, according to the results of our study, a greater frequency and severity of LVH was established in patients with type 2 DM who have moderate HTN than in patients with HTN without carbohydrate metabolism disorders. LVH was revealed in 91% in Group I and in 74% in Group II. At that, LVM and LVMi were also significantly higher in patients of Group I that Group II.

Certain peculiarities of myocardial remodeling are described for patients with type 2 DM and HTN in comparison with patients without carbohydrate metabolism disorders, such as more frequent development of hypertrophic types of left ventricular remodeling in general and of an eccentric pattern of hypertrophy in particular. Thus, 83% of patients with type 2 DM developed hypertrophic forms of left ventricular remodeling (hypertrophic and eccentric hypertrophy), with the eccentric pattern being observed in 43% of these patients, in contrast to 8% of such cases in the group of individuals without diabetes. Probably one of the leading causes of the development of eccentric hypertrophy is prevalence of obesity among patients with type 2 DM. Excessive accumulation of adipose tissue in type 2 DM is a trigger mechanism that causes a whole cascade of hormonal, neurohumoral and metabolic processes underlying the early and mainly hypertrophic myocardial remodeling in these patients. At that, hypertrophic and proliferative processes, leading to rapid hypertrophic remodeling of the heart, are complemented by processes of cardiac overload due to concomitant HTN, which leads to frequent development of an eccentric type of myocardial remodeling [*Demikhova N. et al., 2018*].

During tissue Doppler echocardiography, a very severe diastolic dysfunction was revealed in patients with type 2 DM and HTN, in contrast to traditional echocardiographic markers of myocardial diastolic function, which did not show significant differences in the groups under study. So, it was found that the early diastolic mitral annular velocity in patients with type 2 DM with HTN is lower than in those with isolated HTN. The early diastolic mitral annular velocity is a more sensitive marker of impaired relaxation of the left ventricle than the transmitral E/A ratio. At that, the average values of E/e and PCWP were higher than normal in both groups, but there were more severe disorders of diastolic function in type 2 DM in combination with HTN. Thus, tissue Doppler echocardiography makes it possible to reliably detect the development of myocardial dysfunction, especially at its early stages, preceding changes in the geometry of the left ventricle.

The revealed peculiarities of myocardial remodeling in patients with type 2 DM in combination with HTN have prognostically unfavorable significance and require the earliest and most effective correction of pathogenesis and clinical manifestations of this condition using the whole range of modern antihypertensive, hypoglycemic, antihyperlipidemic and antiplatelet agents.

CONCLUSION

When type 2 diabetes mellitus is combined with moderate hypertension, 91% of patients develop left ventricular hypertrophy, 83% of them having hypertrophic patterns of left ventricular remodeling (hypertrophic and eccentric hypertrophy).

In patients with moderate hypertension in combination with diabetes mellitus, the frequency of diastolic dysfunction was 88%, with the rigid type being the most prevalent.

The most sensitive method for detecting early signs of diastolic myocardial dysfunction in patients with diabetes mellitus and hypertension is tissue Doppler echocardiography.

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