

Features of management of patients with chronic heart failure and diabetes mellitus

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Abstract: SCODIAC was a pilot study that revealed an increase in the use of SGLT2i in 123 outpatient patients with heart failure (HF) and type 2 diabetes mellitus. The SCODIAC-II study, the second phase of the program, was conducted on a larger group of patients in order to identify diagnostic and therapeutic pathways and check whether the use of innovative antidiabetic treatment methods can change echocardiographic parameters and methods of cardiovascular therapy. This retrospective study involved 406 patients with CH-diabetes referred to cardiologists and diabetologists from the relevant medical areas of the campaign, and were divided into group a, consisting of 136 patients with preserved ejection fraction (CH-pEF) (> 45%), and group b, consisting of 270 patients with reduced efficiency factor (HF-rEF) (POS. 45%). All patients periodically underwent clinical and echocardiographic examinations. Antidiabetic therapy was replaced after 1 year by the wider use of GLP1-AR, gliptins and SGLT2i. Cardiovascular therapy has also been modified due to the increased use of sacubitril/valsartan and a decrease in ACE and ARB levels in patients with HF reflux. During echocardiography, the E, Rate A, and E/e' ratio were significantly reduced in 25 patients with HF-pEF and 60 patients with HF-rEF treated with SGLT2i, both in relation to the entire sample of subjects at the beginning of the study, and in other patients with diabetes mellitus. The LAVi result decreased only in patients with hf-pEF, while EF increased only in patients with hf-rEF. The approach to patients with HF and diabetes mellitus should be carried out in medical institutions, be interdisciplinary and integrated. SGLT2i can improve left ventricular function in patients with refractory to HF and replace cardiovascular therapy in almost this category of patients. The test registration protocol was approved by the Ethics Committee of the Federico II University of Naples and registered ClinicalTrial.gov (CT04375943). The principles set out in the Helsinki Declaration have been observed.

Keywords: type 2 diabetes mellitus, diabetic cardiopathy, arterial hypertension

INTRODUCTION

It is proved that type 2 diabetes mellitus (DM), the incidence of which has been continuously increasing in recent years, is an independent risk factor for the development of coronary heart disease (CHD). The presence of DM in patients with

coronary heart disease significantly increases the likelihood of developing chronic heart failure (CHF), and is also a predictor of death in patients with CHF. At the same time, it was shown that 30-50% of DM patients with a transient decrease in local myocardial contractility do not have hemodynamically significant lesions of the coronary arteries, which indicates the presence of a specific myocardial conditions - diabetic cardiomyopathy. Its existence was confirmed by the Framingham study, which revealed a large thickness and mass of the left ventricular myocardium (LV) in patients with DM. It is believed that an increase in the diastolic stiffness of the myocardium is one of the characteristic features of diabetic cardiomyopathy, since disorders of LV diastolic function are its earliest manifestations. To date, numerous studies have proven the effectiveness of strict glycemic control in reducing risk development and progression of various complications of DM.

The aim of the study was to study the effect of glycemic control on the development of diastolic dysfunction and LV remodeling in DM patients with the absence or presence of concomitant arterial hypertension.

MATERIALS AND METHODS

133 patients with DM aged from 26 to 66 years (mean age 46.3 ± 8.4 years) were examined. In 75 (56.4%) patients arterial hypertension (AH) was detected with DM, among which there were 32 (42.7%) with grade 1 and 43 (57.3%) patients with grade 2 of the disease. The average duration of DM was less than 5 years in 67 (50.4%) patients, from 5 to 10 years - in 28 (21.1%), more than 10 years - in 1 (0.7%). In 8 (6%) patients, the length of DM could not be established, in 29 (21.8%) patients, DM was detected for the first time.

As a criterion for compensation of carbohydrate metabolism in patients with diabetes, according to the recommendations of the European Bureau The International Diabetes Federation and the European Bureau WHO, the glycosylated hemoglobin index (HbA1c) was used [5]. It was revealed that 61 (45.9%) patients with DM had a low risk of vascular complications ($HbA1c \leq 6,5\%$), 12 (9%) - risk of developing macroangiopathy ($HbA1c > 6,5\%$), 60 (45,1%) patients are at risk of developing microangiopathy ($HbA1c > 7.5\%$). There were no significant differences in the state of compensation depending on the presence of hypertension in patients with DM.

The criterion for exclusion from the study was the presence of Coronary heart disease, for the diagnosis of which electrocardiography (ECG), bicycle ergometry, Holter ECG monitoring, echocardiography were performed. Echocardiography was performed on an ultrasound scanner Philips "En Visor C" in accordance with the recommendations of the ASE Nomenclature and Standardization Committee. LV parameters were calculated using the disk method (modified Simpson algorithm). To assess the diastolic properties, the time of isovolumic relaxation (IVRT, ms), the

time of slowing down of early filling (DT, ms), the ratio peaks of the rates of early and late LV diastolic filling (E/A), the ratio of the maximum rates of systolic and diastolic antegrade blood flow in the pulmonary veins (S/D). Diastolic dysfunction was diagnosed according to the criteria of the working group of the European Society of Cardiology, depending on the age of patients: IVRT (less than 30 years) > 92 ms; IVRT (from 30 to 50 years) > 100 ms; IVRT (more than 50 years) > 105 ms; DT (less than 50 years) > 220 ms; DT (more than 50 years) > 280 ms; E/A (less than 50 years) < 1.0; E/A (more than 50 years) < 0.5; S/D (less than 50 years) > 1.5; S/D (more than 50 years) > 2.5. Three types of LV filling disorders were distinguished: with delayed relaxation, pseudonormal and restrictive, which correspond to a minor, moderate and severe degree of diastolic dysfunction. In order to diagnose LV remodeling, myocardial mass (MM) was determined according to the formula R.B. Devereux: $0.8 \times 1.04 \times (\text{final diastolic size} + \text{thickness of the interventricular septum} + \text{thickness of the posterior LV wall})^3 - \text{final diastolic dimension}^3) + 0.6$; myocardial mass index (iMM) - by dividing MM by body surface area; index of relative wall thickness (IOTs) of the left ventricle - the ratio of the sum of the thickness of the interventricular septum and posterior wall to the final diastolic size LV. To evaluate the geometric model of LV, the classification of G. Ganau et al. was used: normal geometry - $iMM \leq 125 \text{ g/m}^2$ for men and $\leq 110 \text{ g/m}^2$ for women, $IOTs < 0.45$; eccentric hypertrophy - an increase in iMM with normal IOTs; concentric remodeling - normal iMM, $IOTs \geq 0.45$; concentric hypertrophy - increase in iMM, $IOTs \geq 0.45$. The diagnosis of diabetic neuropathy was carried out on the basis of collecting anamnesis and identifying patient complaints, studying vibration, tactile and temperature sensitivity, determining the rate of propagation of excitation in various areas of the motor fibers of the nerves of the lower extremities on the Neuro-EMG-Micro apparatus. Three types of neuropathy were distinguished: mainly axonal, mainly demyelinating, mixed lesion of the nerve conductor. In total, it was revealed 70 (52.6%) DM patients with neuropathy, 57 of them (81.4%) with axonal, 8 (11.4%) with demyelinating and 5 (7.2%) of patients with mixed type. Statistical processing of the obtained results was carried out using the Statistica 8.0 statistical package ("StatSoft, Inc."). The research data are presented in the form of the number of cases with the presence of the studied trait, the percentage of their number in the group is indicated in parentheses. The comparison of discrete quantities was carried out using Pearson's criterion χ^2 . The differences between the groups were considered statistically significant at $p < 0.05$.

RESULTS and DISCUSSION

Diastolic dysfunction, among the types of which delayed LV relaxation prevailed - in 87.5% of cases. LV remodeling was observed in 63 (47.3%) patients with DM, of which eccentric hypertrophy prevailed - 58.7%. In 34.9% of patients

with DM, concentric LV hypertrophy was detected, which has a more unfavorable prognostic value compared to other variants of LV remodeling. Diastolic dysfunction (54.7% > 25.9%; $p=0.0001$) and LV remodeling (57.3% > 34.5%; $p=0.01$) were observed significantly more often in patients with DM and hypertension. Availability Hypertension was accompanied by a tendency to increase the development of the pseudonormal type (12.2% > 6.7%), the appearance of a restrictive type of diastolic dysfunction, as well as an increase in cases of detection of concentric hypertrophy (39.5% > 25%) LV.

The absence of DM compensation increased the incidence of diastolic dysfunction and LV remodeling. In patients with DM without hypertension and HbA1c level > 7.5%, compared with compensated patients, LV diastolic dysfunction was significantly more often detected (40% > 11.1%; $p=0.03$), and its more severe degree (pseudonormal type) was also observed. More frequent development of diastolic dysfunction during decompensation of DM without hypertension was accompanied by an increase in cases of concentric LV myocardial hypertrophy in patients with HbA1c > 6.5% (100% > 11.1%; $p=0.04$) and HbA1c level > 7.5% (30% > 11.1%). The increase in cases of diastolic dysfunction and cardiac remodeling in patients with diabetes mellitus and hypertension with decompensation was less obvious due to the contribution of hypertension to their development. However, even in these patients with HbA1c levels > 6.5% and 7.5%, compared with compensated patients, pseudonormal type of diastolic dysfunction (20% and 14.3% > 6.7%) and concentric LV myocardial hypertrophy (40% and 47.4% > 31.6%) were more often detected. Thus, in patients DM without hypertension, diastolic dysfunction and LV remodeling are often detected, which suggests the development of diabetic cardiopathy. The presence of hypertension in patients with diabetes exacerbates the course of cardiopathy, which leads to more severe remodeling of the heart. Decompensation of diabetes, both in the presence and absence of concomitant hypertension, is accompanied by weighting degrees of diastolic dysfunction and LV remodeling. The data accumulated in recent years indicate that DM contributes to an increase in the risk of developing CHF, caused, among other things, by diastolic dysfunction, which can be observed in the absence of hypertension and/or LV myocardial hypertrophy. In the pathogenesis of LV diastolic dysfunction in DM is assumed to involve various mechanisms - a decrease in the activity of sarcoplasmic Ca^{2+} -ATPASE, which leads to a slowdown in the extradition of Ca^{2+} ions from the cytoplasm during diastole, as well as activation of kinase C, provoking development of myocardial hypertrophy. The main role in the appearance of LV diastolic dysfunction is probably played by metabolic disorders in DM - glucose deficiency as an energy substrate and the transition of intracellular metabolism in the heart muscle to the oxidation of free fatty acids, leading to a decrease in ATP content and the

accumulation of undesirable metabolites in the cardiomyocyte. It was found that an increase in HbA1c levels is associated with an increased risk of heart failure regardless of the presence of diabetes. The absence of DM compensation is also associated with the risk of cardiovascular autonomic neuropathy, which is manifested by a decrease in the density of adrenergic innervation of the heart. A violation of the capture of metaiod-benzylguanidine (an analogue of norepinephrine) by postganglionic sympathetic fibers in DM was found. In turn, a violation of sympathetic innervation of the myocardium correlates with a decrease in LV contractility reserve in DM. Thus, cardiovascular autonomic neuropathy, the development of which depends mainly on the compensation and duration of DM, is associated with the occurrence of LV diastolic dysfunction. In this study, an increase in the development of diastolic dysfunction and LV remodeling in patients with decompensated DM was accompanied by more frequent detection of demyelinating neuropathy. It is known that hypertension often accompanies diabetes, which is accompanied by a decrease in life expectancy and an increase in the risk of premature death. There is an opinion that cardiac remodeling is a universal mechanism for the progression of all heart diseases, including hypertension, without exception. It is believed that under the influence of various stimuli (increased hemodynamic stress, effectors of hemodynamic systems), active relaxation of cardiomyocytes is disrupted and myocardial stiffness increases.

This study shows that the frequency of detection and severity of diastolic dysfunction and remodeling LV in patients with DM depends not only on the presence of concomitant AH, but to a greater extent from diabetes compensation.

CONCLUSION

The lack of glycemic control (HbA1c level > 7.5%) in patients with type 2 diabetes mellitus, regardless of the presence of concomitant arterial hypertension, leads to aggravation of diastolic dysfunction and LV remodeling against the background of increased development of demyelinating diabetic nephropathy.

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