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The Role of Modifiable and Non-Modifiable Factors in the Development of Right and Left Ventricular Myocardial Dysfunction in High-Risk Patients

Aim	To study early manifestations of left ventricular (LV) and right ventricular (RV) myocardial remodeling in high-risk patients.
Material and Methods	Intracardiac hemodynamics was studied by equilibrium radionuclide ventriculography (ERVG) in 83 patients (mean age, 61.1±8.9 years) with preserved LV ejection fraction according to echocardiography data, a body weight index (BWI) >25 kg/m^2, obesity, and type 2 diabetes mellitus (DM2). Parameters of intracardiac hemodynamics were compared in patients with different degrees of obesity and DM2 durations in age groups of younger and older than 60 years.
Results	All patients had both LV and RV diastolic dysfunction. The diastolic dysfunction progressed with age and DM2 duration, primarily by the restrictive type. The increase in BWI, in contrast, was associated with increases in ventricular volumetric parameters. It was noted that specifically modifiable risk factors (obesity and DM2), but not the age, mostly facilitated the impairment of RV relaxation.
Conclusion	The strategy of normalizing the body weight and carbohydrate metabolism is priority in combatting the development and progression of chronic heart failure in high-risk group patients.

Keywords	Obesity; body weight index; age; type 2 diabetes mellitus; equilibrium radionuclide ventriculography
For citation	Podzolkov V.I., Vanina D.D., Pokrovskaya A.E., Dragomiretskaya N.A., Kozlov V.V. The Role of Modifiable and Non-Modifiable Factors in the Development of Right and Left Ventricular Myocardial Dysfunction in High-Risk Patients. Kardiologiia. 2022;62(11):26–32. [Russian: Подзолков В.И., Ванина Д.Д., Покровская А.Е., Драгомирецкая Н.А., Козлов В.В. Роль модифицируемых и немодифицируемых факторов в становлении дисфункции миокарда правого и левого желудочков у пациентов из группы высокого риска. Кардиология. 2022;62(11):26–32].

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Obesity and diabetes mellitus (DM) type 2 are currently regarded as the epidemics of the 21st century as well as chronic heart failure (CHF) and atrial fibrillation [1]. The problem of obesity and type 2 DM is becoming more urgent also due to the growing social relevance of these conditions known to be risk factors for many cardiovascular diseases (hypertensive heart disease (HHD), coronary artery disease (CAD), CHF, arrhythmias) and other diseases [2, 3].

Many studies on the relationship between obesity, type 2 DM, and CHF, mainly chronic heart failure with preserved ejection fraction (HFpEF), have been published to date [4, 5]. The results of most current studies of myocardial remodeling and the development of diastolic dysfunction (DD) describe the state of the LV myocardium. At the same time, obesity and related respiratory disorders are known potent risk factors for right ventricular failure, which in turn is a more significant predictor of an unfavorable outcome [6, 7].

According to available ideas of phenotypic clusters among patients with chronic HFpEF, overweight patients with type 2 DM and most severe signs of DD and patients with pulmonary hypertension and right ventricular (RV) dysfunction are at a higher risk of adverse clinical outcomes [8].

However, diagnosis of chronic HFpEF is intrinsically challenged by difficulties due to the complexity of applying the necessary instrumental techniques [9]. The diagnostic criteria for chronic HFpEF provided in the ESC guidelines include preserved LVEF (≥50%), echocardiographic signs of DD, and elevated levels of brain natriuretic peptide (BNP) as well as symptoms and signs of CHF [10, 11]. Examination of the right heart by conventional transthoracic echocardiography may be challenged in obese patients due to inadequate ultrasound window and anatomical particularities of RV. They also have reduced levels of the recommended biochemical markers of CHF, BNP and its N-terminal precursor (NT-proBNP) due to their increased degradation in adipose tissue [12–14].

Thus, the method of equilibrium radionuclide ventriculography (ERV) used by us in obese and overweight patients is essential as, unlike conventional echocardiography or MRI, it is highly reproducible, independent of specialist's skills, accurate, and allows for a more detailed study of the diastolic function of LV and RV. ERV can also be used to examine patients with intracardiac devices. It is helpful in the presence of arrhythmias, and there are no body weight restrictions [15].

ISSN 0022-9040. Kardiologiia. 2022;62(11). DOI: 10.18087/cardio.2022.11.n2154

Early diagnosis and management of diseases is the top priority of modern medicine. In this regard, it seems to be particularly relevant to identify the processes of pathological RV and LV remodeling at the stage of early preclinical manifestations of chronic HFpEF for timely initiation of treatment and monitoring of high-risk patients.

Objective

Study early manifestations of LV and RV remodeling in high-risk patients.

Material and Methods

The study included 83 overweight and obese patients with type 2 DM from 43 to 84 years old. Diagnoses were established following the WHO criteria. Inclusion criteria were body mass index (BMI) ≥ 25 kg/m^2, type 2 DM, sinus rhythm, LVEF (≥ 50%) according to echocardiographic findings. Exclusion criteria were symptomatic arterial hypertension (AH), clinical manifestations of CAD including myocardial infarction, hemodynamically significant valvular heart disease, inflammatory conditions of any origin, storage diseases, bronchial obstruction diseases, chronic cor pulmonale, CHF FC III–IV, blood diseases, severe liver pathology, severe kidney pathology, cancer.

In order to compare changes in intracardiac LV and RV hemodynamics depending on the age and duration of type 2 DM, all patients were divided into two subgroups: Subgroup 1 with patients younger than 60 years (n=35) and Subgroup 2 with patients older than 60 years (n=48).

To study the effects of obesity on intracardiac hemodynamics, all patients were additionally divided into three subgroups (A, B, C) depending on overweight or grade of obesity determined by BMI following the WHO guidelines [1]: Group A (n=31) – overweight patients (BMI 25.0–29.9 kg/m^2), Group B (n=32) – patients with obesity grade I (BMI 30.0–34.9 kg/m^2), and Group C (n=20) – patients with obesity grade II (BMI 35.0–39.9 kg/m^2).

The study was approved by the local ethics committee. All patients signed the informed voluntary consent.

Hemodynamics of both ventricles of the heart was studied by ERV. The examination was conducted using 99mTc-HSA 1–2 mL. The information was recorded using the SIEMENS Basicam gamma camera and the Gold Rada+ system for data analysis. A comprehensive assessment of systolic function was performed using the indicators of LV and RV ejection fraction, peak ejection velocity (Vpe), ejection at ⅓ systole, end-systolic volume (ESV), stroke volume (SV). Diastolic function was assessed by peak filling velocity (Vpf), filling at ⅓ diastole, end-diastolic volume (EDV) of both ventricles of the heart.

The data obtained were statistically processed using SPSS Statistics 22.0. Normally distributed numeric data are presented as the arithmetic means (M) and standard deviations (σ), and non-normally distributed data are expressed using the medians and interquartile ranges (Me [Q1; Q3]). Mann-Whitney test was used to identify intergroup differences. The Pearson and Spearman tests were applied for the correlation analysis. The differences were statistically significant with $p<0.05$.

Results

Clinical and demographic characteristics of subjects are provided in Table 1. In Subgroup 2, patients were significantly older and had a longer duration of type 2 DM. There were no significant differences in the severity of obesity, prevalence of HHD, or levels of glycated hemoglobin (HbA1c).

The analysis of the presented clinical and anthropometric data suggests that a typical patient in our study is a 60-year-old woman with grade I obesity, HHD and a 10-year history of type 2 DM, who has not achieved the target individual level of HbA1c, i.e., the administered sugar-lowering therapy is inadequate.

The ERV findings obtained during the examination are presented in Table 2.

All patients had preserved LVEF and no signs of cardiac chamber dilatation. At the same time, all LV indicators, except for ESV, were higher than for RV, which is the physiological norm. The main manifestation of DD was a decrease in filling at ⅓ diastole of both ventricles, the normal value of which is 50% of EF the corresponding ventricle [16]. Thus, diastolic disorders of LV and, to a greater extent, RV were detected in all patients examined.

The ratio of male and female patients under 60 years was comparable, and female patients predominated in the group of patients above 60 years, which reflects the general demographic situation in the Russian Federation. The study groups were comparable in terms of BMI, HbA1c, and HR.

The comparative analysis of ERV indicators of Subgroup 1 and Subgroup 2 showed no significant differences in LVEF and RVEF (Table 2). At the same time, LVEDV and LVESV were significantly lower in the group of older patients with a longer history of type 2 DM.

Patients in Subgroups A, B, C selected based on BMI (Table 3) were comparable in age, duration of type 2 DM, HbA1c, HR ($p>0.05$).

Significantly increased volumetric indicators of LV (LVEDV, LVESV, LVSV) were noted in the absence of differences in LVEF, when the parameters of intracardiac

hemodynamics were compared between the groups of patients with overweight and grade I obesity. A similar trend was observed for the respective parameters of RV (Table 4).

With BMI > 35 kg/m², there was only a trend towards increased RVEDV and RVSV, and the LV parameters did not significantly differ in patients with grade I and II obesity (p>0.05), and there were no changes in filling at ⅓ diastole (Table 4).

A correlation analysis was carried out for all patients to assess the significance of the effects of factors such as age, obesity, and duration of type 2 DM history on the LV and RV ERV findings (Table 5).

The correlation analysis revealed no statistically significant relationships between the indicators of intracardiac LV hemodynamics and the risk factors of interest for chronic HFpEF – obesity, duration of type 2 DM, and age. However, a reliable correlation of RVEDV and RVSV with obesity was revealed, such as an increase in these parameters as BMI increased, which is clearly shown in Figure 1. There was a negative correlation between RVEDV and RVSV with duration of type 2 DM (Figure 2).

Discussion

ERV showed reduced filling at ⅓ diastole, of both ventricles in the patients examined with type 2 DM and overweight or grade I–II obesity, and normal LVEF, which we regard as a manifestation of DD against chronic HFpEF. The latter is based on impaired myocardial relaxation, which leads to reduced diastolic filling of the cardiac chambers and decreased cardiac output explained by the Frank-Starling mechanism [17].

The revealed decrease in LV volumetric parameters reflects with age the progression of DD, which naturally results from cardiomyocyte death and accumulation of collagen. Collagen deposits in the myocardium almost double in the course of a lifetime regardless of the presence of a pathology [18]. Similar results were demonstrated by Tromp et al., namely smaller LV dimensions in older individuals [19].

Reduced LVEDV and LVESV correspond to restrictive phenotype of diabetic cardiomyopathy [20]. Long-term hyperglycemia (our patients had a history of type 2 DM pf 10.0 [4; 19] years, HbA1c 8.9 [7.4; 9.8] %) and hyperinsulinemia, lipotoxicity result in coronary endothelial dysfunction, reduced

Table 1. Age-specific clinical characteristics of patients

Parameter	Whole group	Subgroup 1 (under 60 years)	Subgroup 2 (above 60 years)
Number of patients	83	35	48
Mean age, years	61.1 ± 8.9	53 ± 4.9	67 ± 5.5*
Male/female, n (%)	25 (30)/58 (70)	17 (48.5)/18 (51.5)	8 (16.6)/40 (83.4)*
Median BMI, kg/m²	33.2 [28.2; 36.3]	33.2 [30.6; 35.6]	32.8 [27.8; 36.4]
Overweight (BMI 25–30 kg/m²), n (%)	31 (37.3)	10 (28.6)	21 (43.7)
Obesity (BMI ≥ 30 kg/m²), n (%)	52 (62.7)	25 (71.4)	27 (56.3)
Duration of type 2 DM, years	10.0 [4; 19]	6 [4; 12]	13 [8; 20]*
HbA1c, %	8.9 [7.4; 9.8]	9.2 [7.8; 11.2]	8.3 [7.3; 9.4]
Hypertensive heart disease, n (%)	62 (74.6)	23 (65.7)	33 (68.75)
HR, bpm	80 [69; 95]	85 [73; 98]	80 [68; 92]

* p<0.05 versus Subgroup 1. BMI, body mass index; HbA1c, glycated hemoglobin.

Table 2. Intracardiac hemodynamics according ERV data of all patients, including the patient groups under 60 years and above 60 years

ERV parameter	Whole group	Subgroup 1 (under 60 years)	Subgroup 2 (above 60 years)	Whole group	Subgroup 1 (under 60 years)	Subgroup 2 (above 60 years)
	LV			RV		
LVEF, %	63 [56; 69]	61 [55; 66]	64 [58; 69]	52 [45; 59]	51 [46; 56]	52 [43; 61]
Filling at ⅓ diastole, %	20 [15; 26]	20 [15; 27]	20 [14; 25]	15 [11; 18]	14 [11; 18]	15 [12; 19]
Ejection at ⅓ systole, %	18 [13; 27]	16 [12; 24]	20 [15; 27]	15 [10; 22]	14 [9; 21]	16 [11; 23]
Vpe, %/s	326 [277; 382]	326 [297; 382]	320 [266; 381]	293 [240; 343]	299 [259; 338]	290 [223; 354]
Vpf, %/s	255 [206; 308]	254 [202; 343]	265 [206; 307]	202 [161; 238]	203 [172; 238]	200 [156; 239]
EDV, mL	117 [97; 139]	126 [104; 145]	115 [90; 127]*	121 [95; 149]	128 [103; 154]	116 [85; 136]
ESV, mL	42 [33; 56]	49 [37; 63]	37 [31; 53]*	55 [41; 70]	59 [45; 78]	50 [39; 66]
SV, mL	72 [58; 89]	76 [62; 91]	72 [58; 88]	61 [49; 80]	63 [49; 83]	60 [47; 73]

* p < 0.05 versus Subgroup 1. ERV, equilibrium radionuclide ventriculography; Vpe, peak ejection velocity; Vpf, peak filling velocity; SV, stroke volume.

ISSN 0022-9040. Kardiologiia. 2022;62(11). DOI: 10.18087/cardio.2022.11.n2154

Table 3. BMI-specific clinical characteristics of patients BMI-specific

Parameter	Group A (BMI 25.0–29.9 kg/m²)	Group B (BMI 30.0–34.9 kg/m²)	Group C (BMI 35.0–39.9 kg/m²)
Patients, n	31	32	20
Mean age, years	65 ± 7.6	63 ± 5.9	62 ± 4.5
Male/female, n (%)	7 (22.6)/24 (77.4)	13 (40.6)/19 (59.4)	5 (25)/15 (75)
Median BMI, kg/m²	26.9 [25.5; 27.9]	32.4 [30.8; 33.2]	36.5 [35.6; 37.8]
Duration of type 2 DM, years	14 [8; 18]	12.5 [5.5; 15]	13.1 [6; 16.7]
HbA1c, %	8.1 [7.4; 9.2]	9.2 [6.8; 11.1]	8.9 [7.6; 9.8]
HHD, n (%)	12 (57.1)	15 (51.7)	23 (63.6)

HbA1c, glycated hemoglobin.

Table 4. Intracardiac hemodynamics in patients with overweight or grade I and II obesity

ERV parameter	Group A (BMI 25.0–29.9 kg/m²), n = 31	Group B (BMI 30.0–34.9 kg/m²), n = 32	Group C (BMI 35.0–39.9 kg/m²), n = 20	Group A (BMI 25.0–29.9 kg/m²), n = 31	Group B (BMI 30.0–34.9 kg/m²), n = 32	Group C (BMI 35.0–39.9 kg/m²), n = 20
	LV			RV		
LVEF, %	62.5 [57; 72]	63 [54; 67]	64 [60; 69]	47.5 [43.5; 55.5]	48 [46; 53]	55.5 [50; 63]#
Filling at ⅓ diastole, %	22.5 [15; 26]	19 [15; 21]	21.5 [15; 27]	17 [14; 19.5]	13 [11; 17]*	15.5 [12; 18]
Ejection at ⅓ systole, %	17 [15.5; 27]	21 [12; 30]	18 [11; 24]	16 [11.5; 25]	14 [10; 21]	15.5 [9; 22]
Vpe, %/s	332.5 [276.5; 382.5]	308 [273; 375]	341.5 [304; 379]	300.5 [205.5; 353]	274.5 [236; 316]	307.5 [265; 365]
Vpf, %/s	242.5 [213.5; 270]	249.5 [202; 343]	260.5 [228; 297]	179.5 [151.5; 224.5]	192 [150; 220]	205 [172; 264]
EDV, mL	89 [83.5; 103.5]	127 [108; 142]*	119 [103; 139]*	99.5 [81; 119]	126 [98; 143]	131.5 [113; 160]*
ESV, mL	33 [24; 44]	48 [34; 63]*	40.5 [33; 55]*	42 [36.5; 64]	58.5 [48; 78]*	58.5 [43; 78]
SV, mL	55 [49; 73]	75 [61; 90]*	81 [66; 89]*	49.5 [43; 60]	59.5 [48; 71]	71.5 [54; 94]*#

* p<0.05 compared to Group A; # p<0.05 compared to Group B. ERV, equilibrium radionuclide ventriculography; Vpe, peak ejection velocity; Vpf, peak filling velocity; SV, stroke volume.

Table 5. Correlation coefficients for ERV indicators and main clinical and demographic parameters in patients with chronic HFpEF

Parameter	Obesity	Age	Duration of type 2 DM	Obesity	Age	Duration of type 2 DM
	LV			RV		
EF	0.071	0.150	-0.044	0.241*	0.130	-0.093
Filling at ⅓ diastole	0.022	-0.090	-0.098	-0.087	0.056	-0.011
Ejection at ⅓ systole	-0.225	0.217*	0.079	-0.128	0.177	0.071
Vpe	0.156	-0.082	-0.147	0.139	-0.112	-0.045
Vpf	0.079	-0.150	0.060	0.180	-0.037	-0.016
EDV	0.256*	-0.262*	-0.261	0.325*	-0.217*	-0.337*
ESV	0.104	-0.266*	-0.064	0.163	-0.163	-0.195
SV	0.263*	-0.175	-0.275*	0.340*	-0.176	-0.363*

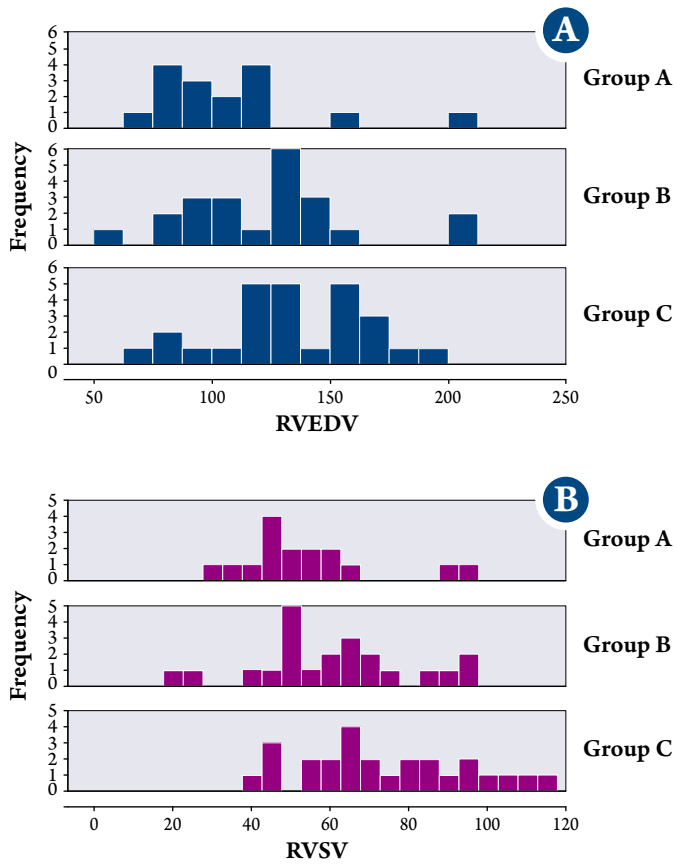
* Significant correlation at p<0.05. HFpEF, heart failure with preserved ejection fraction; ERV, equilibrium radionuclide ventriculography; Vpe, peak ejection velocity; Vfv, peak filling velocity.

NO synthesis, activation of cardiomyocyte hypertrophy, and interstitial fibrosis [21]. Jensen et al. [22] also showed using MRI imaging that volumetric parameters of both ventricles of the heart decreased with longer history of type 2 DM.

When studying the isolated effects of obesity on the parameters of intracardiac hemodynamics, a trend to increased EDV of both ventricles with higher BMI was shown, which was statistically significant only in RV. Dilated cardiac chambers can be regarded as a dilated phenotype of diabetic cardiomyopathy [20]. Adipose tissue is intensively supplied with blood, which why the volume of circulating blood increases with it accumulates, and the myocardial pre-load and post-load increases [23, 24]. Increased volumes of both ventricles is a natural results of the hemodynamic overload in obesity, and a reason for decreased exercise tolerance [25].

The possibility of a detailed study of RV function using ERV is an advantage of our study. The statistically more significant correlation of obesity and the duration of type 2 DM with changes in the RV parameters may

Figure 1. Frequency distribution of RVEDV (**A**) and RVSV (**B**) in the study subgroups



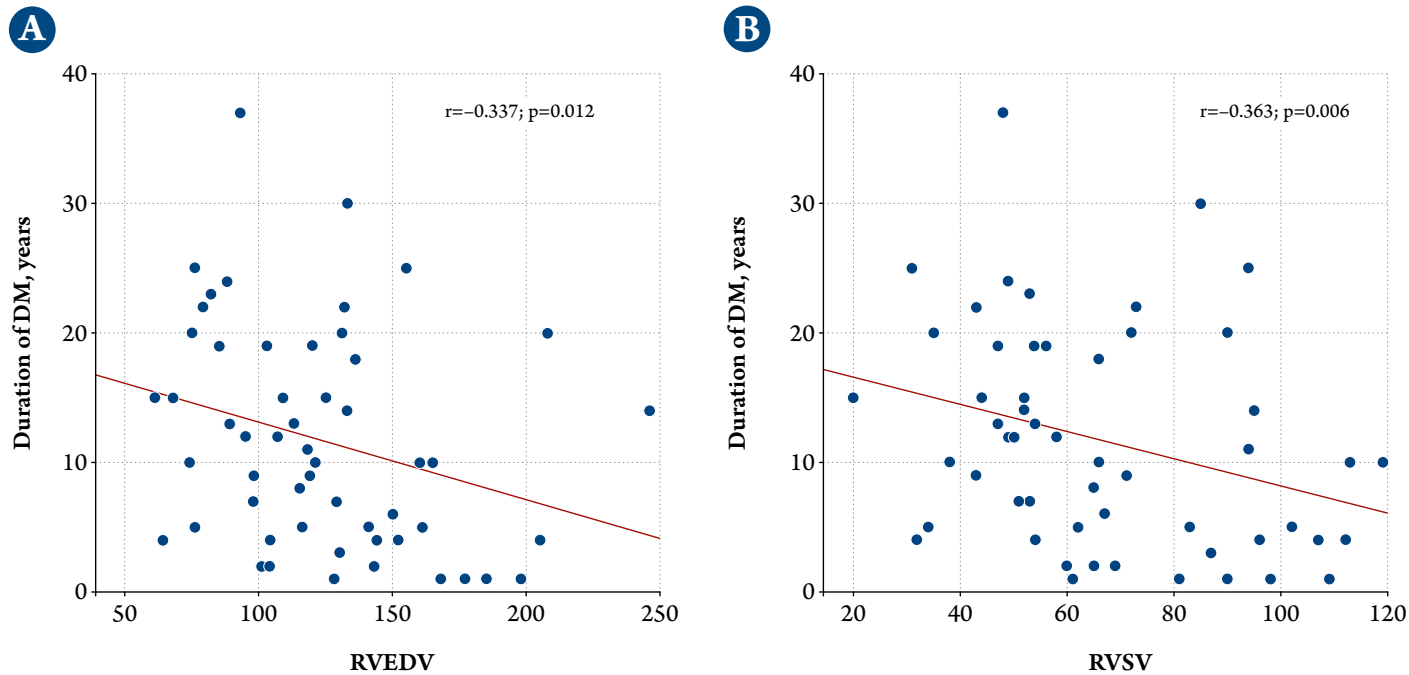
be indicative of its greater susceptibility to maladaptive remodeling, that is weaker compensatory capabilities. The comparison of the strength of correlations of RVEDV with obesity, duration of type 2 DM, and age showed a greater role of obesity and duration of type 2 DM in the development of RV remodeling than that of the age. Given that these conditions are potentially modifiable risk factors for chronic HFpEF, lifestyle modification strategy, namely normalization of body weight and carbohydrate metabolism, is a priority in stopping the progression of chronic HFpEF.

The limitations of this study can be a small sample size, heterogeneous sex composition, the impossibility of reliable exclusion of painless and low-symptomatic forms of CAD, the small strength of the correlations obtained, which is why we can see only the trend toward the identified patterns. We can suggest that the examination of these patients over time, taking into consideration the compliance with the recommendations for lifestyle modification and drug treatment, would be interesting, as well as the inclusion of AH risk as a risk factors of interest, which leaves room for future research.

Conclusion

Diastolic dysfunction progresses with age in patients with obesity and type 2 diabetes mellitus due to pathological remodeling of the heart and blood vessels. It is significant that changes in intracardiac hemodynamics shown by equilibrium radionuclide ventriculography corresponded in older patients to signs of a restrictive phenotype, and increased body mass index resulted in dilation predominantly of the right ventricle, which necessitates targeted study of its function in patients with metabolic disorders. Careful

Figure 2. Correlation between duration of type 2 DM and RVEDV (**A**) and RVSV (**B**)



ISSN 0022-9040. Kardiologiia. 2022;62(11). DOI: 10.18087/cardio.2022.11.n2154

correction of overweight, obesity, and type 2 diabetes mellitus is required as these are more significant factors (compared to age) in the development of pathological right ventricular remodeling, which are potentially modifiable.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 30/04/2022

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ISSN 0022-9040. Kardiologiia. 2022;62(11). DOI: 10.18087/cardio.2022.11.n2154