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Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction In Patients With Resistant Hypertension and Type 2 Diabetes Mellitus

Aim	To study the incidence and clinical and pathophysiological features of diastolic dysfunction (DD) and chronic heart failure with preserved ejection fraction (HFpEF) in patients with resistant arterial hypertension (RAH) associated with type 2 diabetes mellitus (DM).
Material and methods	A cross-sectional study that included 36 patients with RAH associated with type 2 DM (mean age, 61.4±6.4 years; 14 men) was performed. Measurement of office and 24-h blood pressure (BP), standard echocardiography with assessment of diastolic function (DF) and ventricular-arterial coupling, doppler ultrasound imaging of renal blood flow, and laboratory tests (blood glucose, glycated hemoglobin, blood creatinine, tumor necrosis factor α (TNF-α), brain natriuretic peptide (BNP), type 2 and type 9 matrix metalloproteinases (MMP-2 and MMP-9), tissue inhibitor of MMP 1 (TIMP-1), 24-h urine protein test, and 24-h urine volume test were performed for all patients. HFpEF was diagnosed according to criteria of the American Society of Echocardiography and the European Society of Cardiology 2019, and the Russian Clinical Guidelines on Diagnosis and Treatment of CHF 2017 and 2020.
Results	All patients had DD. Incidence of HFpEF detection according to the Russian Guidelines 2017 was 100%; according to the Russian Guidelines 2020, that included a required increase in BNP, and according to the criteria of the European Guidelines 2019, this incidence was 89%. In 55.6% of patients, DD corresponded to grade 2 (pseudonormal type). According to the correlation analysis, the DF impairment was associated with increases in pulse BP, myocardial mass, arterial and left ventricular elastance (arterial wall and left ventricular elasticity), basal glycemia and DM duration, MMP-2 level, proteinuria, blood creatinine, renal vascular resistance, and also with decreases in 24-h urine volume, MMP-9, TIMP-1, and TIMP-1/MMP-2. Significance of the relations of mean E/e' ratio with nighttime pulse BP, MMP-9, and 24-h urine volume were confirmed by results of multiple linear regression analysis. Increased myocardial and vascular wall stiffness, concentrations of MMP-2 and TNF-α and reduced 24-h urine volume were associated with progressive impairment of DF.
Conclusion	The combination of RAH and DM-2 is characterized by an extremely high incidence of DD that determines a great prevalence of HFpEF. The development and progression of DD in such patients are closely related with a complex of metabolic, proinflammatory and profibrotic biomarkers, increased vascular wall stiffness, pronounced left ventricular hypertrophy, and with structural and functional alterations in kidneys.

Keywords	Diastolic dysfunction; heart failure with preserved left ventricular ejection fraction; type 2 diabetes mellitus; resistant arterial hypertension; biomarkers; inflammation
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Introduction

Chronic heart failure with preserved ejection fraction (HFpEF) is associated with high cardiovascular mortality and mainly caused by diastolic dysfunction (DD) [1]. According to the modern vision, the development of DD is accompanied by structural and functional changes in the myocardium due to disturbed intracellular metabolism, oxidative stress, reduced levels of nitric oxide and cyclic guanosine monophosphate, endothelial and microvascular dysfunction, cardiomyocyte hypertrophy, interstitial fibrosis, and chronic low-intensity inflammation [1, 2]. These processes result in impaired left ventricular (LV) relaxation, decreased compliance, and inability to adequately fill. Key components of metabolic syndrome, such as type 2 diabetes mellitus (T2DM), obesity, and hypertension (HTN), are expected to stimulate the development and further progression of asymptomatic DD.

The combination of HTN and T2DM accelerates myocardial damage, especially if HTN is not controlled [3]. At the same time, the pathophysiological and molecular mechanisms of the development and progression of DD, as the underlying cause of CHF, and its prevalence in patients with resistant HTN (RHTN) and T2DM, are not well understood. Despite the known unfavorable prognostic significance of the increased E/e` as indicator of DD [4, 5], it is little known about its relationship with clinical data in patients with DM and RHTN.

Objective

To study the frequency as well as clinical and pathophysiological aspects of DD and chronic HFpEF in patients with RHTN and T2DM.

Material and Methods

The study included 36 patients with RHTN and T2DM. Exclusion criteria were atrial fibrillation, mitral and aortic valve stenosis, left ventricular ejection fraction (LVEF) <50%. The baseline clinical and demographic characteristics of the subjects are presented in Table 1.

Most patients took diuretics, inhibitors of the sympathoadrenal and renin-angiotensin-aldosterone systems, and calcium channel blockers (Table. 2).

Office and 24 hour blood pressure (BP) was measured in all patients (automatic ambulatory oscillometric system ABPM-04, Meditech). Laboratory tests included estimation of basal plasma glucose level, renal function (24-hour albuminuria, 24-hour urine volume), serum creatinine, estimated glomerular filtration rate (eGFR) using the CKD-EPI formula, and glycated hemoglobin (HbA1c) (turbidimetric inhibition immunoassay in the Roche/Hitachi Cobas C501 system). Enzyme-linked immunosorbent assay (ELISA) using the Infinite F50 microplate reader and the Magellan Tracker software was applied to measure the levels of tumor necrosis factor alpha (TNF-α), brain natriuretic peptide (BNP) and markers of fibrosis: plasma levels of matrix metalloproteinases (MMPs): (MP-2 and MMP-9, tissue inhibitor of MMP-1 (TIMP-1), with the calculation of the TIMP 1/MMP-2 ratio. Echocardiography and ultrasound Doppler flowmetry were performed on the expert ultrasound system (Philips IE33) following the standard protocols.

Chronic HFpEF was diagnosed in accordance with the guidelines of the American Society of Echocardiography and the 2019 HFA/ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (based on a total score of major (2 points) and minor (1 point) functional, structural, and biomarker criteria [6]), and the Russian guidelines for the management of CHF of 2017 and 2020 [7, 8].

DD was diagnosed according to Russian clinical guidelines for the management of CHF [8]. Peak transmittal early filling velocity (E, cm/s) and peak atrial systolic velocity (A, cm/s) and their ratio (E/A) were measuerd. LV isovolumic relaxation time (IVRT) was calculated from the apical 5 chamber view. DD grade I (or delayed relaxation) was established with E/A ≤ 0.8 and E ≤ 50 cm/s. E/A >2 corresponded to DD grade III (restrictive type). In all other

Table 1. Clinical characteristics of patients with resistant hypertension and diabetes mellitus type 2

Parameter	Value
Age, years	61.4 ± 6.4
Male	14 (38.9 %)
LVEF, %	66.9 ± 5.38
Body mass index, kg/m^2	35.2 ± 5.4
Chronic kidney disease, Grade 3	11 (30.6 %)
Coronary artery disease	23 (63.9 %)
History of myocardial infarction	4 (11.1 %)
History of stroke	10 (27.8 %)
Peripheral atherosclerosis	34 (94.4 %)
Abdominal obesity	30 (83.3 %)
Isolated systolic HTN	(48.6 %)
Left ventricular hypertrophy	32 (88.9 %)
Office SBP/DBP, mm Hg	172.1 ± 17.3/89.8 ± 16.4
SBP/DBP 24h, mm Hg	158.6 ± 15.2/79.8 ± 12.7
Glycated hemoglobin, %	7.2 ± 1.2
Basal glucose level, mmol/L	8.6 ± 2.3
eGFR (CKD EPI), mL/min/1.73 m^2	70.8 ± 22.2

Table 2. Characteristics of antihypertensive, sugar-lowering, and lipid-lowering therapy in the examined patients

Parameter	Value
Antihypertensive therapy	
Number of antihypertensive agents per patient	4.5 ± 1
Beta-blockers	28 (77.8)
Angiotensin-converting enzyme inhibitors / angiotensin II receptor blockers	35 (97.2)
Diuretics	35 (97.2)
Calcium channel blockers	30 (83.3)
Other	16 (44.4)
Imidazoline receptor agonists	12 (33.3)
Alpha blockers	5 (13.9)
Antidiabetic therapy	
Insulin therapy + metformin	14 (38)
Metformin monotherapy	10 (27.8)
Metformin + sulfonylureas	7 (19.4)
Sulfonylurea monotherapy	7 (19.4)
Diet only	2 (5.6)
Statins	36 (100)

The data are presented as the mean and standard deviation (M ± SD) or the absolute and relative values (n (%)).

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cases, we used additional indicators: e` and E/e`, where e` is early diastolic lateral mitral annular velocity calculated in the pulse-wave tissue Doppler mode. Signs of DD were:

1) Mean ratio of septal E/e` and lateral E/e` > 14;

2) Left atrial volume index ≥ 34 mL/m^2;

3) Tricuspid regurgitation velocity > 2.8 m/s.

If at least two criteria were positive, DD was estimated as grade II (or pseudonormalization). If there were no data on tricuspid regurgitation, and/or only one criterion was present, then DD stratification was carried out depending on the values of IVRT, E/A and deceleration time of early LV filling (DT E, ms). Criteria of grade I (abnormal relaxation) were IVRT > 100 ms, E/A < 1, and DT E > 240 ms, criteria of grade II (pseudo-normalization) were IVRT 70–100 ms, E/A > 1, and DT E 150–240 ms [9]. Effective arterial elastance (Ea) and left ventricular elastance (Ees), which characterize the elasticity of the arterial wall and LV, respectively, were additionally calculated [10].

The diagnosis of RHTN was confirmed according to the 2020 Russian clinical recommendations for the management of HTN [11]. Patient adherence to treatment was assessed using the interview.

The data were analyzed using Statistica 10.0 and SPSS 26. The normality of variable distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were presented as the mean and standard deviation (M ± SD), non-normally distributed variables were expressed as the median and interquartile range (Me [25th percentile; 75th percentile]). The categorical data were presented as the absolute and relative values (n(%)). The standard methods of descriptive statistics were applied; differences between continuous variables in the independent samples were detected using the Student's t-test and the Mann-Whitney U-test. Pearson's chi-squares test and Fisher's exact test were used to analyze categorical variables. Pearson correlation analysis and least squares multiple linear regression analysis were implemented to find possible correlations. The correlation of biomarkers with diastolic function (DF) pseudo-normalization was identified using a logistic regression model followed by an assessment of the model sensitivity and specificity using the ROC analysis. The critical significance value for all the statistical analysis procedures used was p = 0.05.

The study was approved the Biomedical Ethics Committee of the Research Institute for Cardiology (Protocol no.139 dated 18/11/2015). All patients signed the informed consent before being included in the study.

Results

DD was detected in all examined patients. The frequency of HFpEF was 89 % based on the criteria of the 2020 Russian clinical guidelines for the management of CHF, including elevated levels of BNP (> 35 pg/mL). HFpEF was diagnosed in the same proportion of patients (89 %) according to the 2019 HFA/ESC guidelines. HFpEF was determined in 100 % of patients in accordance with the 2017 Russian guidelines for the management CHF, which do not include mandatory increase of BNP.

The correlation analysis showed than mean E/e` was significantly correlated with hemodynamic parameters, structural changes in LV, the duration and severity of carbohydrate metabolic disorders, the structural and functional state of the kidneys, and markers of fibrosis (MMP-2, TIMP-1, TIMP-1/MMP-2, MMP-9)(see Figure 1).

DD grade I and grade II were detected in 44.4 % and 55.6% of patients, respectively. Patients with DD grade II differed from patients with DD grade I by higher pulse BP and its variability, LV elastance, TNF-α, MMP-2, and lower 24 hour urine volume (Table 3).

According to the multiple linear regression analysis, mean E/e` was significantly correlated with night pulse BP, MMP-9, and 24 hour urine (Table 4). Final model: R = 0.81, R^2 = 0.65, corrected R^2 = 0.61, standard error of estimation 2.56 (p = 0.00004). The distribution of model residuals was normal (p = 0.09).

A logistic regression model was constructed to confirm the correlation of DD pseudonormalization with subclinical inflammation and profibrotic state (Table 5).

The model was significant (p = 0.002) with the sensitivity of 77.8 % and the specificity of 84.6 %. The resulting area under the ROC curve was 0.89 for the whole model. The model's –2Log likelihood was 17.52, and the Nagelkerke R2 was 0.56.

Discussion

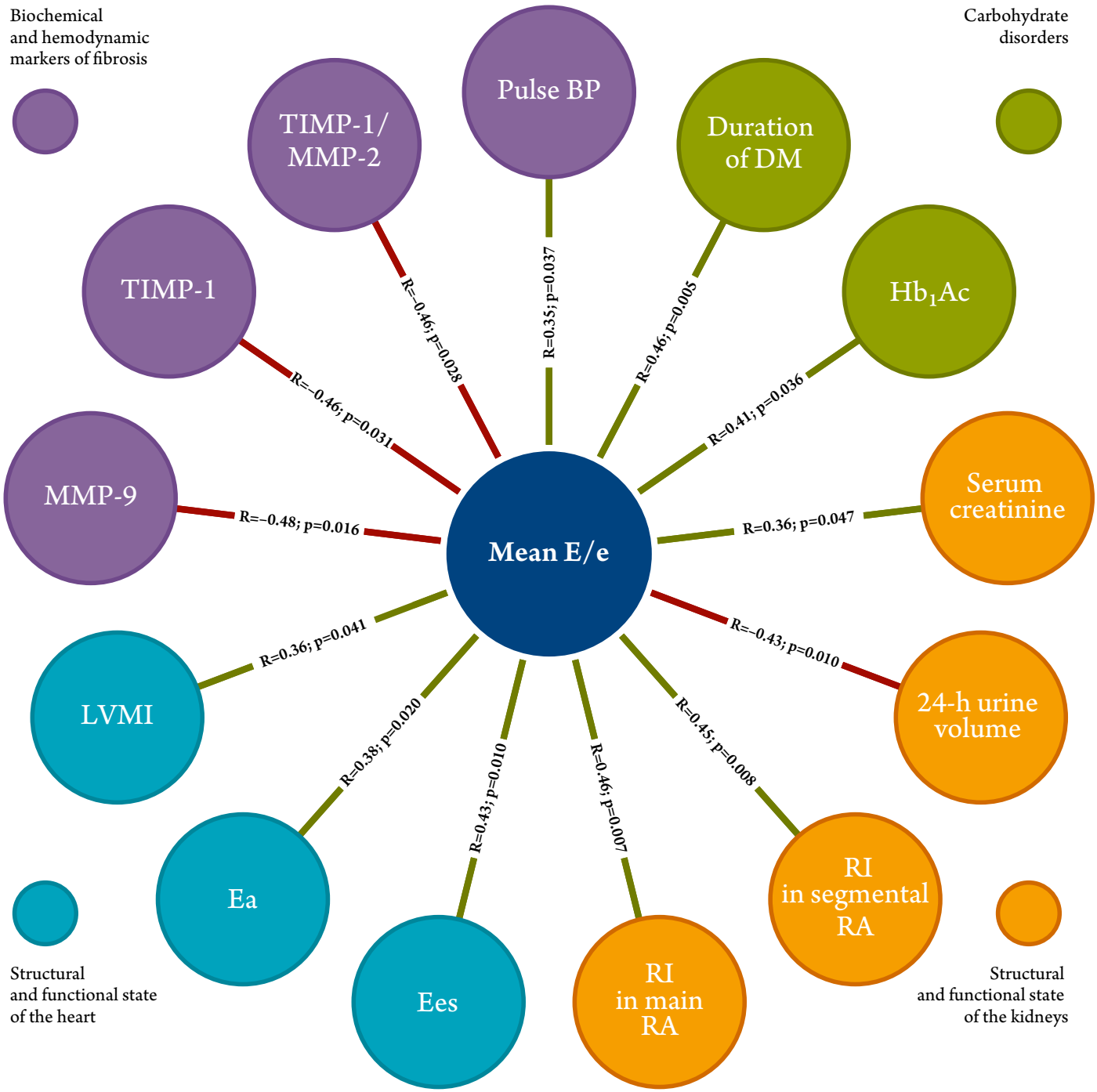
The present study showed for the first time the frequency of detecting DD in a selective group of patients with RHTN and T2DM.. According to the literature, the prevalence of DD reaches 50 % in T2DM and 84 % in HTN with LV hypertrophy [12, 13]. According to our findings, all examined patients with RHTN and T2DM had DD, which may reflect the synergy of the negative effect of DM and uncontrolled HTN on myocardial damage.

There are very few publications on the frequency of HFpEF for patients with RHTN, and there are no published data on for the combination of RHTN and T2DM. For example, in the study by Jin et al. [14], the prevalence of HFpEF in patients with RHTN was 65%, and only 50% of whom had DM. In our study, the frequency of HFpEF according to the 2020 Russian guidelines for the CHF and the 2019 HFA/ESC guidelines was similar and amounted to 89 %. At the same time, the frequency reached 100% when the 2017 Russian guidelines, which do not include

BNP, were used. The issue of using BNP for the diagnosis of chronic HFpEF remains a subject of scientific debate [15]. This is due to the findings, according to which BNP was not elevated in patients with invasively documented signs of high left atrial pressure [16, 17]. Moreover, the catabolism of BNP is significantly dependent on the volume of adipose tissue which contains receptors for this peptide, and thus, the levels of BNP can be within normal limits in obese patients [18].

Given that DD is crucial in term of HFpEF, we analyzed the features of DD and its correlation with the data of laboratory tests and clinical examinations. The E/e` ratio is one of the most important indicators of DD. In studies including patients with HTN and T2DM, increased E/e` was an independent risk factor for the development of cardiovascular complications [4, 5]. The identified correlation of this indicator with myocardial mass

Figure 1. Correlations of mean E/e' with clinical examination and laboratory test data in patients with RHTN and T2DM



RHTN, resistant hypertension; BP, blood pressure; HbA1c, glycated hemoglobin; Ea, arterial elastance; Ees, ventricular elastance; RI, resistive index; RA, renal arteries; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; V, volume; 24h, 24-hour; LVMI, left ventricular mass index .

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Table 3. Differences in clinical examination and laboratory test parameters depending on the type of diastolic dysfunction

Parameter	DD grade I (n=16)	DD grade II (n=20)	P
PBP24h, mm Hg	74.1 ± 13.5	83.2 ± 11.1	0.034
PBP variability, mm Hg	12 ± 2.9	14.3 ± 3.4	0.041
Night-time PBP, mm Hg	74.1 ± 13.5	83.2 ± 11.1	0.034
Left ventricular elastance (Ees)	3.9 ± 1.1	4.8 ± 1.1	0.032
TNF-α, pg/mL	3.6 ± 3.4	6.9 ± 2.4	0.015
MMP-2, ng/mL	210.8 ± 48.9	318.3 ± 90.1	0.002
TIMP-1/MMP-2	3.1 ± 1.4	1.8 ± 0.8	0.009
24-hour urine volume	1,843.8 ± 445.3	1,447.4 ± 543.3	0.026

PBP, pulse blood pressure; TNF, tumor necrosis factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase.

Table 4. Parameters of multiple linear regression analysis reflecting the correlation with mean E/e` (n=36)

Variable	β	Standard error	p	95% CI	
				Lower limit	Upper limit
Constant	11.299	4.005	0.010	2.970	19.627
Pulse BP	0.129	0.040	0.004	0.045	0.213
24-hour urine volume	-0.004	0.001	0.002	-0.006	-0.002
MMP-9	-0.005	0.001	0.002	-0.008	-0.002

MMP, matrix metalloproteinase.

Table 5. Parameters of the multivariate logistic regression model of the correlation of DD grade II with MMP-2 and TNF-α (n=36)

Variable	B	RMS error	Wald	p	Exp (B)	95% CI for Exp (B)	
						Lower limit	Upper limit
TNF-α	0.277	0.190	2.117	0.146	1.319	0.908	1.915
MMP-2	0.024	0.012	3.831	0.050	1.024	1.000	1.049
Constant	-7.080	3.305	4.588	0.032	—	—	—

DD, diastolic dysfunction; TNF, tumor necrosis factor; CI, confidence interval; MMP, matrix metalloproteinase.

correspond to modern view on the LVDD pathophysiology, i.e., its inability to adequately fill due to impaired relaxation and decreased compliance, as both are characteristic of LV hypertrophy [13]. Relaxation is known to be an energy-dependent process, which is why factors affecting the removal of calcium from the cytosol and the separation of the actin-myosin interaction disrupt the physiology of myocardial relaxation.

As expected, the increase in mean E/e` correlated with the duration and severity of carbohydrate metabolism disorders. Hyperglycemia, hyperinsulinemia, and glycation products independently stimulate the collagen formation in the myocardial and blood vessel walls [19], which significantly restricts their compliance. The microcirculation disorders inherent to DM and the lack of myocardial energy supply compromise the relaxation processes.

It has been established that increased stiffness of the arterial wall, the generally accepted indicator of which is pulse BP, has a significant role in LVDF. According to our data, the increase in pulse BP and its variability was accompanied by the progression of DD, which could result from high load on LV during early reflection of the pulse wave.

Arterial wall elasticity (Ea) is an integral sign of arterial stiffness, and Ees is an indicator of LV wall motion and stiffness. According to our findings, the deterioration of DF in patients with RHTN and T2DM was associated with the increase in arterial and left ventricular elastance. Increased stiffness of the myocardium and vascular walls is likely to provide effective cardiac function by maintaining a normal arterial-ventricular coupling (Ea/Ees) ratio. At the same time, increased Ea and Ees may indicate an excessive stress of this adaptation mechanism, which is typical of patients with chronic HFpEF.

There were found the correlations between the mean E/e` and the structural and functional state of the kidneys, which demonstrates the implementation of cardiorenal interactions, attract the attention. In accordance with the concept of these interactions, the load on the heart depends on the regulation of the water-salt balance by

the kidneys, and the blood flow created by the heart are very important for the kidneys. Thus, we have found an association of the increased mean E/e` ratio with elevated blood levels of creatinine and increased vascular resistance in the kidneys from ultrasound Doppler flowmetry. However, Tedesco et al. [20] described the relationship between renal resistive indices with DF in patients with HTN, but we did not find similar data for patients with RHTN and T2DM. Renal resistive index reflects microcirculatory impedance and can be a reliable indicator of increased vascular stiffness and systemic atherosclerosis, which allows predicting the outcomes of cardiovascular complications as well as kidney damage [21].

One of the clinically significant results of our study was the identification of correlations between DD indicators and fibrosis markers, which play essential roles in maintaining the structure and geometry of the heart chambers. For example, the deterioration of DD indicators was associated with an elevation of MMP-2 and a decrease in plasma MMP-9 and TIMP-1 and the TIMP-1/MMP-2 ratio. In a study by Ahmed et al. [22], multidirectional correlations of MMP-2 and MMP-9 gelatinase levels with the severity of LV hypertrophy and DD were also observed in patients with HTN and HFpEF. Experiments on mice are particularly interesting; it was shown, using the gene knockout method, that MMP-2 contributes to the development of atherosclerosis [23] and MMP-9, on the contrary, plays a protective role [24]. Moreover, Chavey et al. [25] showed that high levels of MMP-2 and low levels of MMP-9 were observed in genetically obese rats. It should be noted that the significance of the correlations between mean E/e` and night- pulse BP, MMP-9 and 24-hour urine volume was confirmed in our study by the results of multiple linear regression analysis.

The incidence of DD grade I and II was similar in our study (44.4 % and 55.6 %, respectively). At the same time, patients with DF pseudonormalization differed from the group with impaired relaxation by more severe changes in biochemical and hemodynamic markers of fibrosis (MMP-2, TIMP-1/MMP-2, pulse BP) and higher rates of left ventricular elastance. Moreover, patients with DD grade II had lower 24-hour urine volume and higher levels of TNF-α. Dunlay et al. [26] found that mortality in patients with heart failure is directly related to elevated levels of TNF-α and does not dependent on LVEF. The pathogenetic role of TNF-α in the progression of DD is attributable to its ability to cause apoptosis of cardiomyocytes and increase myocardial stiffness [27], and to disturb the balance between MMPs and their inhibitors by stimulating the degradation of the extracellular matrix [28]. The dependence of DD grade II on TNF-α and MMP-2 is supported by the results of the ROC analysis.

The practical significance of this study is determined by the recognition of the need for an integrated approach to the treatment of patients with RHTN and T2DM in order to reduce the risk of cardiovascular complications, which includes acting not only on BP and hyperglycemia, but also on pro-inflammatory and profibrotic conditions. Moreover, chronic low-intensity inflammation is currently regarded as a new risk factor for cardiovascular complications and a promising therapeutic target [29]. The possibilities of pharmacological correction of profibrotic changes are still very limited [30], and the findings that the antibiotic doxycycline can inhibit MMP-2 have not been clinically implemented [31].

Conclusion

Thus, the combination of resistant hypertension and type 2 diabetes mellitus is associated with a very high frequency of diastolic dysfunction, which determines the high prevalence of heart failure with preserved ejection fraction. The onset and progression of diastolic dysfunction in these patients are strongly associated with a complex of metabolic, pro-inflammatory, and profibrotic biomarkers, increased vascular wall stiffness, the severity of left ventricular hypertrophy, and structural and functional changes in the kidneys.

The study of resistant hypertension in patients with type 2 diabetes mellitus requires investigating left ventricular global longitudinal deformation. This is a more sensitive and reproducible indicator than left ventricular ejection fraction. In future, the studies may also estimate the efficacy of anti-inflammatory and anti-fibrotic agents for the treatment of patients with chronic heart failure with preserved ejection fraction, and renal denervation of the kidneys, given the significant role of sympathoadrenal hyperactivation in the development of chronic heart failure and the anti-inflammatory effects of this procedure [32].

Limitations

The study was limited to the number of patients and estimation of adherence to treatment by the interview.

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