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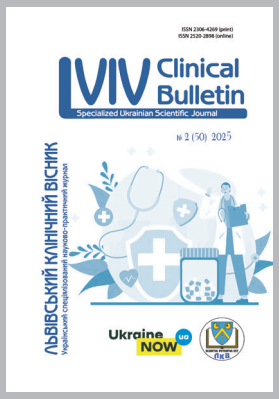

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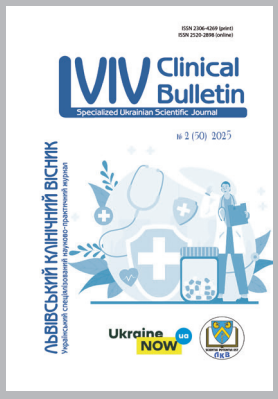

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Comprehensive Assessment of Cardiohemodynamics and Catestatin Parameters as a Possible Predictor of Cardiovascular Dysfunction in Patients with Arterial Hypertension without and with Comorbid Type 2 Diabetes Mellitus and Obesity

Introduction. Currently, arterial hypertension (AH), type 2 diabetes mellitus (T2DM) and obesity are not considered as isolated pathological conditions, but as interrelated components of a single cardio-reno-metabolic continuum. These diseases share common pathogenetic mechanisms, among which the insulin resistance, chronic subclinical inflammation, endothelial dysfunction, dysregulation of hormonally active adipose tissue, and activation of neurohumoral systems play a leading role. The combination of AH, T2DM, and obesity significantly worsens the prognosis, accelerates the formation of complications such as left ventricular myocardial hypertrophy, diastolic dysfunction, heart failure, chronic kidney disease, and is associated with high mortality from cardiovascular causes and nephrological events [2, 10, 14].

In this regard, the management of such comorbid patients requires a comprehensive pathogenetically based algorithm for diagnosis, monitoring and individualised treatment. A key aspect of this process is the search for reliable biomarkers that would allow not only the risk stratification but also the detection of early functional changes in the cardiovascular system before the onset of clinically significant symptoms [9, 15].

One of these promising biomarkers that is gaining increasing attention in modern science is catestatin (CST), a biologically active peptide formed by the proteolytic cleavage of chromogranin A. CST plays a key role in the regulation of neurohumoral activity: it inhibits the release of catecholamines from sympathetic nerve endings by acting through nicotinic acetylcholine receptors. Thus, CST acts as an endogenous limiter of sympathoadrenal activation, which is of particular importance in conditions of chronic stress, hypertension, metabolic syndrome, and diabetes mellitus [3].

In physiological conditions, CST controls vascular tone, lowers blood pressure, modulates cardiac contractility, has vasodilatory, anti-inflammatory effects, and has a positive effect on glucose metabolism and insulin sensitivity. Experimental and clinical studies have demonstrated that CST can improve metabolic parameters, reduce body weight, reduce insulin resistance, and affect leptin and pro-inflammatory cytokines [3, 4].

A decrease in CST level is observed in patients with AH, heart failure, coronary heart disease, metabolic syndrome and T2DM. CST deficiency is accompanied by excessive sympathoadrenal activation, which in turn contributes to myocardial hypertrophy, activation of the renin-angiotensin-aldosterone system, increased fibrosis, decreased ejection fraction, and increased severity of structural and functional changes in the heart [5-7, 12]. Thus, CST is considered as an informative biomarker of neurohumoral stress, which potentially allows assessing degree of cardiovascular dysfunction in patients with comorbidities [13].

It is especially relevant to study the relationship between CST and cardiohemodynamic parameters, such as left ventricular myocardial mass indices, ejection fraction, diastolic function, volume and pressure characteristics of the heart [1]. The study of such relationships allows for a deeper understanding of the mechanisms of cardiac remodelling under conditions of metabolic stress, as well as identifying CST as a potential target for personalised pharmacotherapy.

Thus, the study of CST in patients with AH, obesity, and T2DM is a promising area that has both theoretical significance for understanding the pathogenesis of comorbidities and practical value for improving the clinical management strategy of patients with high cardiovascular risk.

The aim of the study. To comprehensively evaluate cardiohemodynamics and catestatin parameters as a possible predictor of cardiovascular dysfunction in patients with hypertension without and with comorbid type 2 diabetes mellitus and obesity.

Materials and methods. The study was conducted in accordance with the fundamental ethical principles and regulatory documents, in particular, the Charter of the Ukrainian Association for Bioethics, the provisions of Good Clinical Practice (GCP, 1992), Good Laboratory Practice (GLP, 2002), the principles of the Declaration of Helsinki, and the Council of Europe Convention on Human Rights and Biomedicine. The Ethics Committee of Kharkiv National Medical University approved the study. The study was conducted on the basis of the consultative polyclinic of the State Institution "L.T. Malaya National Institute of Therapy of the National Academy of Medical Sciences of Ukraine". The study included 250 patients (117 women and 133 men, mean age - 55.26 ±8.00) with hypertension without and in combination with T2DM and obesity, who were randomly divided into 4 groups: group 1 included patients with isolated AH (n = 49; 26 women, 23 men, mean age - 54.35 ± 8.17 years); group 2 - patients with AH and obesity (n = 62; 27 women, 35 men, mean age - 53.52 ± 9.24 years), group 3 – patients with AH and comorbid T2DM (n = 77; 41 women, 36 men, mean age – 56.26 ± 7.48 years), and group 4 - patients with AH and comorbid T2DM and obesity (n = 62; 39 women, 23 men, mean age - 56.50 ± 6.83 years). The control group consisted of conditionally healthy individuals of the same sex and age without verified metabolic disorders (n = 20).

Verification of AH, its stage and degree was performed according to current European guidelines (European Society of Hypertension - ESH, 2023), diagnosis of T2DM - according to the American Diabetes Association (ADA, 2021) recommendations, and obesity - according to the criteria of World Health Organization (WHO, 1997). All patients provided informed consent to participate in the study.

Exclusion criteria for the study were: type 1 diabetes mellitus, congenital heart and urinary tract defects, presence of an artificial pacemaker, presence of artificial heart valves, heart failure of stages II B and III, acute myocardial infarction, infectious and severe inflammatory processes, haematological diseases.

To determine the diastolic function of the heart, transthoracic echocardiography was performed using an ultrasound machine ULTIMA PA (Radmir, Ukraine) using a sector phased array transducer with a frequency range of 2.0-3.0 MHz according to the standard method according to the recommendations of of the American Echocardiographic Society, the following parameters were measured aortic size (Aorta), left atrium (LA), right atrium (RA), left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), right ventricle (RV), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular myocardial mass (LVMM), left ventricular myocardial mass index (LVMMI1) and LVMMI2, relative left ventricular wall thickness (RLVWT), left ventricular ejection fraction (LVEF), early diastolic filling velocity (VE), late diastolic mitral inflow velocity (VA), VE/VA ratio and isovolumic relaxation time (IVRT).

Indicators of CST, cardiotrophin-1 (CTF-1), leptin, cystatin C (Cys C), neutrophil gelatinase-associated lipocalin (NGAL), N-terminal pro-brain natriuretic peptide (NT-proBNP), 25-hydroxyvitamin D (25(OH)D), β_2-microglobulin, insulin were determined in blood serum by enzyme-linked immunosorbent assay (ELISA) using a Labline-90 analyser (Austria) and certified test systems manufactured by Fine Test, BT LAB, DBC, Elabscience, Monobind Inc., Orgentec in accordance with the manufacturers' instructions.

Biochemical parameters (creatinine, urea, lipid profile, glycated haemoglobin (HbA1c)) were studied using the same analyser. Urea was measured by the enzymatic method using urease and glutamate dehydrogenase (Liquick Cor-UREA 30 kits, Cormay, Poland), and creatinine was measured by the modified M. Jaffe method (Liquick Cor-CREATININ 30 kits). Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were determined by the enzymatic method (Human kits, Germany). The serum content of low-density lipoprotein cholesterol (LDL-C) was calculated by the formula of V.T. Friedewald: LDL-C = TC = (HDL-C + TG / 2.22); VLDL-C as TG / 2.22 (mmol/l).

Statistical processing of the results of the study was performed using Statistica 12.0 software (StatSoft Inc., USA), licence number STA999K347150-W and Microsoft Office Excel 2013. Quantitative data are presented as mean and margin of error (M ± m). To assess the reliability of differences between groups, parametric (Student's t-test, analysis of variance, ANOVA) and nonparametric (H. B. Mann-Whitney U-test) methods were used, depending on the nature of the distribution. To analyse the relationship between diastolic function (VE, VA, VE/VA, IVRT) and CST, K. Pearson's correlation analysis was used. Univariate and multivariate linear regression analysis was used to determine the factors that may affect CST. An error of less than 5.0 % ($p < 0.05$) was considered as significant.

Results and discussion. The results of the study of CST levels in the examined groups of patients are presented in Table 1.

Table 1

Indicators of catestatin in the examined groups of patients (parameters; n; M±δ; *p*)

Parameter	AH (n = 49)	AH+obesity (n = 62)	AH+ T2DM (n = 77)	AH+obesity +T2DM (n = 62)	*p*
	1 group	2 group	3 group	4 group	
CST	2.07±0.43	3.03±1.22	3.18±1.39	3.3±1.2	p_{1-2}= 0.0000001 p_{1-3}= 0.0000001 p_{1-4}= 0.0000001

The study found that significant differences in CST levels were observed only when comparing the results of patients with isolated AH and other groups - AH + obesity, AH + T2DM, AH + obesity + T2DM. No significant

differences were found between the groups with dual (AH and obesity or AH and T2DM) and triple (AH, obesity and T2DM) disease. Since CST has antihypertensive, metabolic, and anti-inflammatory effects, it has been determined that its level, like that of CTF-1, increases in response to cardiovascular stress, but its effectiveness as a biomarker of cardiovascular events in patients with AH remains insufficiently studied. Therefore, the results obtained (Table 1) indicate that CST is a more sensitive marker for assessing cardiometabolic risks in patients with isolated AH, whereas its prognostic value in patients with comorbidities requires further investigation. In the presence of comorbidities such as obesity and T2DM, the likely reason for the absence of differences is likely to be the rapid reaching of the maximum CST concentration, as well as its increase due to compensatory mechanisms in the case of additional metabolic disease.

Univariate and multivariate linear regression analysis was performed to determine the factors associated with CST score, including a wide range of clinical, laboratory and biochemical parameters (Table 2).

Table 2

Factors affecting the catestatin value (χ^2; *p*; β-coefficient; OR; %; CI)

Parameters	Dependent component: CST (Y)							
	Univariate linear regression analysis (χ^2 = 31.69; *p* = 0.083)				Multivariate linear regression analysis (χ^2 = 29.72; *p* = 0.0018)			
	β-coefficient	OR	95.00% CI	P	β-coefficient	OR	95.00% CI	P
1	2	3	4	5	6	7	8	9
CTF-1, pg/ml	-0.003	0.996	0.99-1.00	0.087	-0.003	0.997	0.994-0.999	0.011
Cys C, ng/ml	-0.0006	0.999	0.99-1.01	0.917				
Atherogenicity coefficient (AC)	-1.277	0.279	0.07-1.08	0.064	-0.897	0.408	0.232-0.717	0.002
NGAL, ng/ml	-0.077	0.926	0.84-1.02	0.125	-0.073	0.929	0.849-1.016	0.108
NT-proBNP, pg/ml	-0.0005	0.999	0.99-1.00	0.758				
25(OH)D, ng/ml	-0.007	0.993	0.95-1.04	0.741				
β_2-microglobulin, μg/ml	-0.466	0.627	0.37-1.06	0.079	-0.459	0.632	0.393-1.017	0.059
HbA1c, %	0.911	2.486	1.03-5.99	0.043	0.872	2.393	1.289-4.442	0.006
Diastolic blood pressure (DBP), mmHg	-0.005	0.995	0.94-1.05	0.865				
TC, mmol/l	-5.973	0.003	0.00-193373.30	0.519				
Body mass index (BMI), kg/m^2	0.046	1.047	0.86-1.27	0.649				
Insulin, μU/ml	-0.0226	0.978	0.92-1.04	0.462				
Creatinine, μmol/l	-0.004	0.996	0.96-1.03	0.848				
Obesity, %	0.938	2.556	0.34-18.99	0.359	1.148	3.148	1.067-9.292	0.038
Systolic blood pressure (SBP), mmHg	0.024	1.024	0.98-1.07	0.255	0.026	1.026	0.988-1.066	0.178
T2DM, %	-0.039	0.961	0.11-8.72	0.972				
Urea, mmol/l	-0.177	0.838	0.65-1.09	0.185	-0.199	0.819	0.647-1.039	0.101
Gender, w/m, %	-0.853	0.426	0.15-1.23	0.114	-0.739	0.478	0.193-1.185	0.111

End of the Table 2

1	2	3	4	5	6	7	8	9
TG, mmol/l	1.741	5.700	0.00-46056.55	0.7045	0.403	1.497	0.963-2.596	0.151
HDL-C, mmol/l	4.674	107.138	0.00-4.09E+009	0.599				
VLDL-C, mmol/l	3.347	28.419	0.00-5.41E+009	0.731				
LDL-C, mmol/l	6.751	854.942	0.00-88.7E+009	0.474	0.457	1.579	0.936-2.666	0.087

Notes: OR = odds ratio; CI = confidence interval.

The univariate analysis ($\chi^2 = 31.69$; $p = 0.083$) revealed a tendency for CST to be associated with individual predictors, but the multivariate model ($\chi^2 = 29.72$; $p = 0.0018$) was more informative, demonstrating the presence of statistically significant relationships. This made it possible to build a regression equation:

Y=exp(0.252–0.003X1–0.897X2–0.073X3––0.459X4+0.872X5+1.148X6+0.026X7–0.197X8––0.739X9+0.403X10+0.457X11)/(1+exp(0.252––0.003X1–0.897X2–0.073X3–0.459X4+0.872X5++1.148X6+0.026X7–0.197X8–0.739X9++0.403X10+0.457X11)), where:

X1 (CTF-1), X2 (AC), X3 (NGAL), X4 (β_2-microglobulin), X5 (HbA1c), X6 (obesity), X7 (SBP), X8 (Urea), X9 (gender), w/m, X10 (TG), X11 (LDL-C)

According to the results of multivariate analysis, it was found that a decrease in CST was associated with an increase of serum CTF-1 (β = -0.003; 95.00% CI: 0.994-0.999; $p = 0.011$), AC (β = -0.897; 95.00% CI: 0.232-0.717; $p = 0.002$), and β_2- microglobulin concentration (β = -0.459; 95.00% CI: 0.393-1.017; $p = 0.059$). Instead, an increase of CST was statistically significantly correlated with HbA1c (β = 0.872; 95.00% CI: 1.289-4.442; $p = 0.006$) and percentage of obesity (β = 1.148; 95.00% CI: 1.067-9.292; $p = 0.038$). There was also a positive trend towards an association of CST with serum TG (β = 0.403; $p = 0.151$) and LDL-C (β = 0.457; $p = 0.087$), although these associations did not reach statistical significance. Other markers, including NGAL, NT-proBNP, 25(OH)D, Cys C, carbohydrate and lipid metabolism parameters, blood pressure, BMI, insulin, creatinine and urea, did not show a significant effect on CST levels in the multivariate model.

The obtained logistic equation allows us to quantify the predicted changes in CST depending on a set of clinical and laboratory parameters. This indicates the feasibility of using CST as a potential marker of metabolic dysfunction, in particular in patients with obesity, insulin resistance and renal damage.

The next stage of our study was the assessment of cardiac structure and function (Table 3), which revealed the cumulative effect of obesity, T2DM and their combination on changes in instrumental markers in patients with AH. In particular, this was manifested by significantly higher LA, RA, LVEDD, $LVMMI_1$ and $LVMMI_2$ in patients with comorbidities ($p < 0.05$). It was found that the effect of T2DM was significantly greater than that of obesity, which was confirmed by significant differences between the groups of AH with obesity and AH with T2DM, while the combination of these diseases led to the worst results.

Table 3

Comparative characteristics of the results of cardiac ultrasound examination in the studied groups of patients (n; M±δ ; *p*)

Parameters	AH (n = 49)	AH + obesity (n = 62)	AH + T2DM (n = 77)	AH + obesity + T2DM (n = 62)	*p*
	1 group	2 group	3 group	4 group	
1	2	3	4	5	6
Aorta, cm	3.27 ± 0.22	3.34 ± 0.14	3.4±0.19	3.4±0.16	p_{1-2}=0.0385 p_{1-3}=0.0018 p_{1-4}=0.0009 p_{2-3}=0.0937 p_{2-4}=0.0536 p_{3-4}=0.9218
LA, cm	3.63±0.25	4.04±0.46	4.02±0.5	4.25±0.38	p_{1-2}=0.0001 p_{1-3}=0.00004 p_{1-4}=0.00001 p_{2-3}=0.7991 p_{2-4}=0.0109 p_{3-4}=0.0071

Contin of the Table 3

1	2	3	4	5	6
RA, cm	3.83±0.24	4±0.47	4.17±0.44	4.36±0.39	p_{1-2}=0.0328 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.0461 p_{2-4}=0.00003 p_{3-4}=0.0186
LVEDD, cm	4.59±0.40	5.05±0.56	4.87±0.47	5.52±0.47	p_{1-2}=0.00001 p_{1-3}=0.0012 p_{1-4}=0.00001 p_{2-3}=0.0693 p_{2-4}=0.00001 p_{3-4}=0.00001
LVESD, cm	3.32±0.44	3.46±0.35	3.87±0.35	3.88±0.50	p_{1-2}=0.0838 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.00001 p_{2-4}=0.00001 p_{3-4}=0.8617
RV, cm	1.73±0.08	1.96±0.22	2.09±0.24	2.09±0.21	p_{1-2}=0.00001 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.0036 p_{2-4}=0.0022 p_{3-4}=0.9824
IVST, cm	1.26±0.06	1.24±0.07	1.26±0.07	1.32±0.06	p_{1-2}=0.0575 p_{1-3}=0.8815 p_{1-4}=0.00004 p_{2-3}=0.0381 p_{2-4}=0.00001 p_{3-4}=0.00007
LVPWT, cm	1.25±0.030	1.32±0.18	1.32±0.2	1.33±0.03	p_{1-2}=0.0204 p_{1-3}=0.0246 p_{1-4}=0.00001 p_{2-3}=0.9305 p_{2-4}=0.5466 p_{3-4}=0.6574
LVMM, g	203.16±28.02	250.19±40.28	253.4±49.65	305.41±24.97	p_{1-2}=0.00001 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.7102 p_{2-4}=0.00001 p_{3-4}=0.00001
LVMMI1, g/m^2	120.58±15.78	118.16±18.51	161.11±14.54	145.76±15.73	p_{1-2}=0.4787 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.00001 p_{2-4}=0.00001 p_{3-4}=0.00001
LVMMI2, g/m$^{2.7}$	52.77±5.13	59.49±9.61	61.99±8.23	74.53±7.64	p_{1-2}=0.00003 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.1432 p_{2-4}=0.00001 p_{3-4}=0.00001
RLVWT	0.52±0.050	0.52±0.05	0.53±0.06	0.53±0.05	p_{1-2}=0.7553 p_{1-3}=0.6257 p_{1-4}=0.2723 p_{2-3}=0.4114 p_{2-4}=0.1374 p_{3-4}=0.5674

End of the Table 3

1	2	3	4	5	6
LVEF, %	57.67±3.31	51.63±3.57	49.98±3.37	48.73±4.51	p_{1-2}=0.00001 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.0135 p_{2-4}=0.0004 p_{3-4}=0.1042
VE, cm/s	61.93±8.70	63.99±7.94	60.27±11.97	64.25±9.45	p_{1-2}=0.2102 p_{1-3}=0.4229 p_{1-4}=0.2033 p_{2-3}=0.0572 p_{2-4}=0.8785 p_{3-4}=0.0593
VA, cm/s	74.26±8.31	67.47±6.6	72.99±7.56	77.98±7.88	p_{1-2}=0.00001 p_{1-3}=0.4137 p_{1-4}=0.0237 p_{2-3}=0.00008 p_{2-4}=0.00001 p_{3-4}=0.0011
VE/VA	0.84±0.16	0.95±0.12	0.82±0.15	0.82±0.11	p_{1-2}=0.00017 p_{1-3}=0.4691 p_{1-4}=0.4906 p_{2-3}=0.00001 p_{2-4}=0.00001 p_{3-4}=0.9043
IVRT, ms	98.67±6.42	103.83±14.17	113.52±15.71	119.01±13.45	p_{1-2}=0.02129 p_{1-3}=0.00001 p_{1-4}=0.00001 p_{2-3}=0.00093 p_{2-4}=0.00001 p_{3-4}=0.05509

The presented results indicate that the mean values of LVESD, RV, IVRT were higher and LVEF was lower in patients with AH and obesity compared with patients with isolated AH, but the worst indicators were observed in patients with comorbid T2DM, and in the group with comorbid AH, T2DM and obesity, the additional presence of obesity did not have a statistically significant effect on cardiac functional parameters, indicating the dominant pathogenetic role of T2DM in the cardiac disorders severity increase.

Further analysis of the results showed that the aortic diameter and LVPWT were significantly higher only in patients with isolated AH and comorbidities, whereas no differences were observed between the groups with comorbidities. This suggests that these two markers may be early indicators of increased cardiovascular risk in patients with AH.

It was also found that the VE/VA ratio was significantly higher in patients with AH and comorbid obesity compared with other groups, due to a significantly lower rate of late VA filling ($p < 0.05$). The latter may indicate the initial manifestations of diastolic dysfunction in this group of patients, which requires further investigation for a more accurate understanding of these changes.

Thus, patients with comorbidities (AH, obesity, T2DM, and AH with T2DM) demonstrate more pronounced changes in the structure and function of the heart compared with groups of patients with AH and AH with comorbid obesity, indicating more severe course of the disease and greater vulnerability of the cardiovascular system.

In patients with AH and comorbid T2DM with obesity, significant differences were observed between the mean changes of IVRT, expressed in percentages, compared to the VE/VA index using analysis of covariance (ANCOVA) (Figures 1-4).

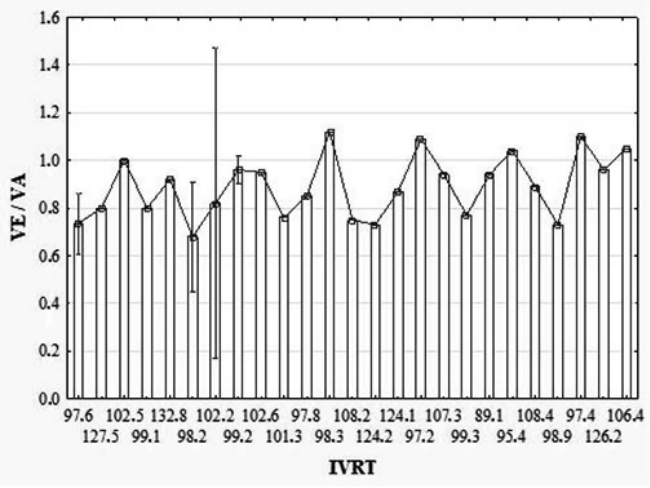

Fig. 1. Mean changes of isovolumetric relaxation time relative to the index of the ratio of early and late diastolic filling velocities in the group of patients with hypertension (sum of squares of deviations = sum of squares = 4.31; $p < 0.05$).

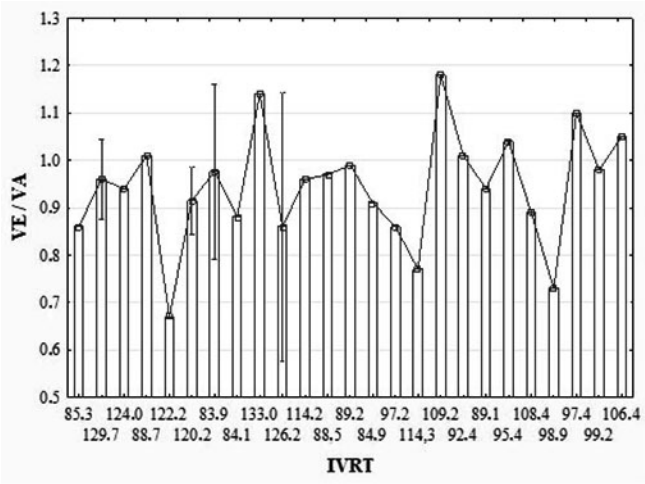

Fig. 2. Mean changes in isovolumetric relaxation time relative to the index of the ratio of early and late diastolic filling velocities in the group of obese patients with hypertension (sum of squares = 3.64; $p < 0.05$).

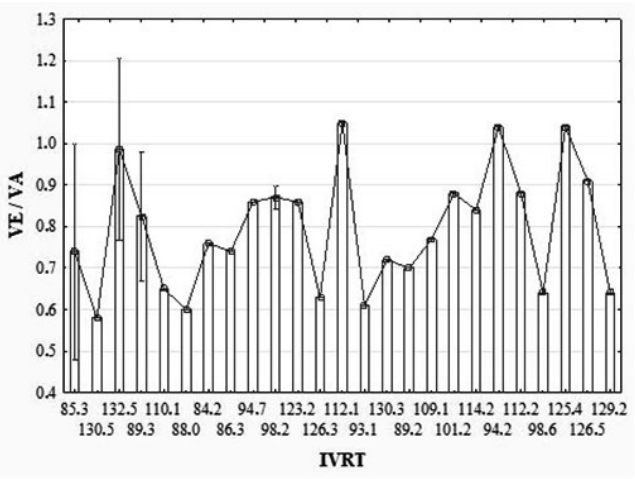

Fig. 3. Mean changes in isovolumetric relaxation time relative to the index of the ratio of early and late diastolic filling velocities in the group of patients with hypertension with type 2 diabetes mellitus (sum of squares = 5.36; $p < 0.05$).

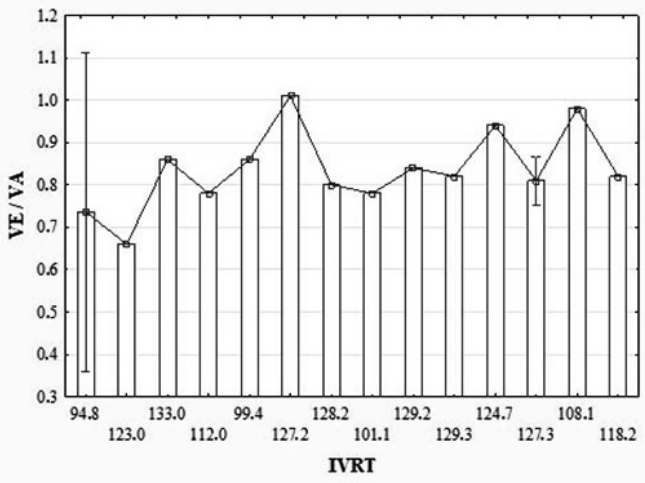

Fig. 4. Mean changes in isovolumetric relaxation time relative to the index of the ratio of early and late diastolic filling velocities in the group of patients with hypertension with concomitant type 2 diabetes mellitus and obesity (sum of squares = 3.74; $p < 0.05$).

In all groups of patients with AH – both isolated and in combination with comorbidities – there is a marked variability in the isovolumic relaxation time and the index of the ratio of early and late diastolic filling velocities. Given that isovolumetric relaxation time is an important marker of diastolic function, its changes in relation to the VE/VA index may reflect different degrees of diastolic dysfunction. The VE/VA index is a key criterion for assessing diastolic filling disorders, and the observed peaks and decreases of its values in different clinical groups indicate heterogeneity of diastolic function among the examined patients. In patients with isolated AH, VE/VA values fluctuate in the range of 0.6-1.0, which may indicate moderate diastolic filling disorders. Sharp fluctuations are observed, but without significant peak deviations. This is consistent with the information that AH is an independent risk factor for diastolic dysfunction, even without concomitant diseases. Patients with combined AH and obesity had more pronounced fluctuations in VE/VA parameters, which may indicate a more significant impairment of diastolic relaxation. Obesity is also associated with hypervolemia, increased preload, and impaired myocardial insulin sensitivity, which may contribute to a decrease in myocardial elasticity and impaired relaxation. The value of sum of squares (SS) = 3.64 and $p < 0.05$ indicate statistically significant differences from those in the control group, which confirms the negative impact of obesity on cardiac function. In patients with AH and T2DM, VE/VA showed even greater fluctuations and pronounced peaks. T2DM is associated with hyperglycaemia, myocardial protein glycation, and endothelial dysfunction, which contributes to impaired diastolic relaxation. SS = 5.36 and $p < 0.05$ indicate the significant differences compared with those in the control group, i. e. T2DM is a significant risk factor for diastolic dysfunction. The most pronounced VE/VA disorders were observed in the group of patients with a combination of AH, T2DM and obesity. VE/VA often decreases below 0.7, which may indicate a pronounced impairment of diastolic filling. The combination of AH, T2DM, and obesity has a powerful negative effect on cardiac function, as each of these factors mutually exacerbates diastolic dysfunction. SS = 3.74 and $p < 0.05$ confirm statistically significant differences from those in the control group. Such changes are typical for patients at high risk of heart failure with preserved ejection fraction, which requires early preclinical detection (screening).

Thus, the results of the echocardiographic study indicate that AH is a key risk factor for the development of diastolic dysfunction, even in the absence of comorbidities. Obesity further worsens diastolic function, as evidenced by an increase in the variability of the VE/VA index and a decrease in its mean values. T2DM has an even more pronounced negative effect due to metabolic disorders that contribute to increased myocardial stiffness and reduced myocardial relaxation.

Patients with combined pathology = AH, obesity and T2DM – have the worst diastolic function. This may indicate the presence of early preclinical manifestations of heart failure with preserved ejection fraction and

potentially be a predictor of its progression. The values of the SS and significance levels ($p < 0.05$) obtained in all groups confirm the presence of statistically significant differences between the comorbid groups and the control sample.

Thus, the results obtained emphasise the need for a comprehensive examination of patients with AH, especially in the case of its combination with T2DM and obesity. They are consistent with the data of previous studies by other authors [8, 11]. The combined assessment of cardiohemodynamic parameters, myocardial structural changes, and catestatin levels as a marker of neurohumoral activation allows for more accurate detection of early signs of cardiac dysfunction and stratification of the risk of heart failure. Further research should be aimed at a deeper understanding of the relationships between biomarkers and cardiac function in order to improve personalised approaches to diagnosis and treatment.

Conclusions. In patients with arterial hypertension in combination with type 2 diabetes mellitus and obesity, the most pronounced structural and functional changes in the heart were found. In particular, a significant increase of the left ventricular myocardial mass index (74.53 ± 7.64 g/m$^{2.7}$), a decrease of ejection fraction (48.73 ± 4.51 %), prolongation of isovolumic relaxation time (119.01 ± 13.45 ms) and a decrease in the ratio of early and late diastolic filling velocities (0.82 ± 0.11) were recorded, indicating the development of diastolic dysfunction.

The content of catestatin was significantly increased in patients with combined metabolic disorders = in the group with arterial hypertension, type 2 diabetes mellitus and obesity, it was 3.3 ± 1.2 ng/ml compared with 2.07 ± 0.43 ng/ml in patients with isolated arterial hypertension ($p < 0.001$). In multivariate regression analysis, significant associations were found with the levels of glycated hemoglobin (β = 0.872; p = 0.006), cardiotrophin-1 (β = -0.003; p = 0.011), atherogenicity coefficient (β = -0.897; p = 0.002), β_2-microglobulin (β = -0.459; p = 0.059) and percentage of adipose tissue (β = 1.148; p = 0.038).

The pronounced variability of the ratio of early and late diastolic filling velocities and isovolumic relaxation time in patients with different clinical forms of hypertension indicates a high sensitivity of these parameters to neurohumoral and metabolic load, which confirms their diagnostic value for the early detection of subclinical cardiac dysfunction.

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Conflict of interests
The authors declare no conflict of interests.

Comprehensive Assessment of Cardiohemodynamics and Catestatin Parameters as a Possible Predictor of Cardiovascular Dysfunction in Patients with Arterial Hypertension without and with Comorbid Type 2 Diabetes Mellitus and Obesity

I. Dunaieva

Introduction. Arterial hypertension (AH), type 2 diabetes mellitus (T2DM), and obesity form a cardiometabolic continuum with a high risk of cardiovascular dysfunction. Catestatin (CST) is a promising biomarker of neurohumoral activation and may reflect early cardiac functional abnormalities, especially diastolic dysfunction.

The aim of the study. To comprehensively evaluate cardiohemodynamics and catestatin parameters as a possible predictor of cardiovascular dysfunction in patients with hypertension without and with comorbid type 2 diabetes mellitus and obesity**.**

Materials and methods. A total of 250 patients with AH were divided into four groups: isolated AH, AH+obesity, AH+T2DM, and AH+T2DM+obesity; the control group consisted of 20 healthy individuals. Echocardiographic assessment of systolic and diastolic function was performed. Biomarkers including CST, cardiotrophin-1 (CTF-1), β2-microglobulin, glycated hemoglobin (HbA1c), neutrophil gelatinase-associated lipocalin (NGAL), 25-hydroxyvitamin D (25(OH)D), insulin, and leptin were measured. Statistical analysis included univariate and multivariate regression.

Results. The most pronounced cardiac remodelling (left ventricular hypertrophy, reduced ejection fraction, impaired filling = early diastolic filling velocity (VE)/late diastolic mitral inflow velocity (VA)<0.7) was observed in the AH+T2DM+obesity group. Elevated CST significantly correlated with HbA1c, CTF-1, β2-microglobulin, and body mass index (BMI) (p<0.05). A logistic regression model was developed to predict CST levels. VE/VA and isovolumic relaxation time (IVRT) showed the significant prognostic value.

Conclusions. Catestatin levels correlate with diastolic dysfunction and metabolic disorders in patients with arterial hypertension, type 2 diabetes mellitus, and obesity. Combined catestatin level and echocardiographic assessment improves the early detection and risk stratification of heart failure.

Keywords: arterial hypertension, type 2 diabetes mellitus, obesity, catestatin, diastolic dysfunction, cardiohemodynamics

Комплексна оцінка кардіогемодинаміки й показників катестатину як можливого предиктора серцево-судинної дисфункції у пацієнтів із артеріяльною гіпертензією без і з коморбідним цукровим діябетом другого типу та ожирінням

І. П. Дунаєва

Вступ. Артеріяльна гіпертензія (АГ), цукровий діябет 2-го типу (ЦД2) та ожиріння є провідними компонентами кардіометаболічного континууму з високим ризиком серцево-судинних (СС) ускладнень. Катестатин (Catestatin - CST) – ендогенний пептид, що обмежує симпатоадреналову активацію, розглядається як потенційний маркер ранніх змін серцевої функції.

Мета. Комплексно оцінити кардіогемодинамічні показники та рівень катестатину як можливого предиктора серцево-судинної дисфункції у пацієнтів із артеріяльною гіпертензією і з коморбідним цукровим діябетом 2-го типу та ожирінням.

Матеріяли й методи. Обстежено 250 пацієнтів (117 жінок, 133 чоловіки; середній вік – 55.26 ± 8 років) з АГ: ізольовано (n = 49), у поєднанні з ОЖ (n = 62), з ЦД2 (n = 77), з ЦД2 + ОЖ (n = 62); контрольна група – 20 умовно здорових осіб. Визначали вміст CST, кардіотрофіну-1 (Cardiotrophin-1 − CTF-1), лептину, цистатину С (Cystatin C, Cys C), ліпокаліну, асоційованого з желатиназою нейтрофілів (Neutrophil gelatinase-associated lipocalin - NGAL), N-кінцевий фрагмент мозкового натрійуретичного пептиду (N-terminal pro-brain natriuretic peptide - NT-proBNP), 25-гідроксивітамін D (25-hydroxyvitamin D - 25(OH)D), β_2-мікроглобулін, інсулін, а також біохімічні показники − креатинін, сечовину, ліпідний профіль, глікований гемоглобін (Glycated hemoglobin - HbA1c). Ехокардіографічно оцінювали: розмір аорти, ліве передсердя (ЛП), праве передсердя (ПП), кінцевий діастолічний розмір лівого шлуночка (КДР ЛШ), кінцевий систолічний розмір лівого шлуночка (КСР ЛШ), правий шлуночок (ПШ), товщину міжшлуночкової перетинки (ТМШП), товщину задньої стінки лівого шлуночка (ТЗС ЛШ), масу міокарда лівого шлуночка (ММ ЛШ), індекс маси міокарда лівого шлуночка (ІММ ЛШ) та ІММ ЛШ2, відносну товщину стінки лівого шлуночка (ВТС ЛШ), фракцію викиду лівого шлуночка (ФВ ЛШ), швидкість раннього діастолічного наповнення (Early diastolic filling velocity - VE), швидкість пізнього діастолічного наповнення (late diastolic mitral inflow velocity - VA), співвідношення VE/VA і час ізоволюмічного розслаблення лівого шлуночка (Isovolumic relaxation time - IVRT). Для статистичного опрацювання застосовували програмне забезпечення Statistica 12.0 та Excel 2013. Дані подано як середнє значення ± стандартна похибка. Для міжгрупового порівняння використано t-критерій Стьюдента, дисперсійний аналіз ANOVA, U-критерій Х. Б. Манна – Д. Р. Вітні, для оцінювання взаємозв'язків – кореляційний аналіз К. Пірсона. Чинники впливу на CST визначали за допомогою уніваріянтного і мультиваріянтного лінійного регресійного аналізу. Результати вважали достовірними за $p < 0.05$.

Результати. Найгірші функційні показники виявлено у пацієнтів із АГ + ЦД2+ожиріння: ІММ ЛШ2 – 74,53 ± 7,64 г/м², ФВ ЛШ – 48,73 ± 4,51 %, IVRT – 119,01 ± 13,45 мс, VE/VA – 0,82 ± 0,11. Показник CST достовірно вищий у коморбідних групах, найвищий – 3,3 ± 1,2 нг/мл (проти 2,07 ± 0,43 нг/мл у разі ізольованої АГ; $p < 0,001$). У мультиваріянтному аналізі CST позитивно корелював із HbA1c ($\beta = 0,872$; $p = 0,006$) та відсотком жирової тканини ($\beta = 1,148$; $p = 0,038$), негативно — зі CTF-1 ($\beta = –0.,003$; $p = 0,011$), коефіцієнтом атерогенности ($\beta = –0,897$; $p = 0,002$) і β_2-мікроглобуліном ($\beta = –0,45$; $p = 0,059$). VE/VA та IVRT продемонстрували високу діягностичну чутливість до нейрогуморального і метаболічного навантаження.

Висновки. Поєднання артеріяльної гіпертензії, цукрового діябету 2-го типу та ожиріння супроводжується найгіршими показниками діастолічної функції і найвищим показником кетастатину. Його визначення разом зі співвідношенням швидкости раннього та пізнього діастологічного наповнення і часу ізоволемічного розслаблення лівого шлуночка є перспективним для ранньої діягностики серцевої недостатности зі збереженою фракцією викиду.

Ключові слова: артеріяльна гіпертензія, цукровий діябет 2-го типу, ожиріння, катестатин, діастолічна дисфункція, кардіогемодинаміка.

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