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ASSESSMENT OF DIASTOLIC FUNCTION AND SERUM NGAL AND CYSTATIN C CONTENT IN ARTERIAL HYPERTENSION IN PATIENTS WITH STAGE 1 OBESITY

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The purpose of the study was to investigate changes in central hemodynamic parameters, left ventricular diastolic function, and markers of renal dysfunction in patients with arterial hypertension associated with obesity. A total of 53 patients (mean age 52.6 ± 2.5 years) with stage II, grade 2 arterial hypertension were examined and, according to their body mass index, were divided into two groups: group 1 – 25 patients with normal body weight, and group 2 – 28 patients with grade I obesity. The control group included 20 persons (mean age 52.1 ± 2.3 years) with cardiovascular risk factors and normal blood pressure. All participants underwent clinical and laboratory examinations, including 24-hour blood pressure monitoring, echocardiography with assessment of transmitral Doppler blood flow, and enzyme-linked immunoassay was used to determine serum cystatin C and neutrophil gelatinase-associated lipocalin levels. Statistical analysis of the results was performed using the Statistica 10.0 software. It has been established that in patients with arterial hypertension combined with obesity, there is an increased incidence of concentric and eccentric left ventricular hypertrophy and impaired left ventricular diastolic function. It has been determined that in patients with arterial hypertension associated with obesity, morphofunctional changes in the heart and kidneys occurring in parallel, including the progression of diastolic dysfunction, increasing left ventricular myocardial mass index and serum levels of cystatin C and neutrophil gelatinase-associated lipocalin, and reducing the estimated glomerular filtration rate.

Key words: arterial hypertension, obesity, left ventricular remodeling, diastolic function, neutrophil gelatinase-associated lipocalin, cystatin C.

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ОЦІНКА ДІАСТОЛІЧНОЇ ФУНКЦІЇ ТА СИРОВАТКОВОГО ВМІСТУ NGAL ТА ЦИСТАТИНУ С ПРИ АРТЕРІАЛЬНІЙ ГІПЕРТЕНЗІЇ У ПАЦІЄНТІВ З ОЖИРІННЯМ І СТУПЕНЯ

Метою дослідження було вивчити зміни показників центральної гемодинаміки, діастолічної функції лівого шлуночка та маркерів ренальної дисфункції у пацієнтів з артеріальною гіпертензією, асоційованою з ожирінням. Обстежено 53 пацієнтів (середній вік $52,6 \pm 2,5$ роки) з артеріальною гіпертензією II стадії 2 ступеня, які відповідно до індексу маси тіла були розділені на 2 групи: група 1 – 25 пацієнтів з нормальною масою тіла та група 2 – 28 пацієнтів з ожирінням I ступеня. Контрольну групу склали 20 осіб (середній вік $52,1 \pm 2,3$ роки), в яких встановлені серцево-судинні чинники ризику і нормальний артеріальний тиск. Усім обстеженим проведено клініко-лабораторне обстеження, у тому числі, добовий моніторинг артеріального тиску, ехокардіографію з оцінкою трансмітрального доплерівського кровотоку, методом імуноферментного аналізу визначали в сироватці крові вміст цистатину С та ліпокаліну, асоційованого з желатиназою нейтрофілів. Статистична обробка результатів проводилася з використанням статистичних програм Statistica 10.0. Встановлено, що у пацієнтів з артеріальною гіпертензією в асоціації з ожирінням зростає відсоток концентричної та ексцентричної гіпертрофії лівого шлуночка і порушення діастолічної функції лівого шлуночка. Визначено, що у пацієнтів з артеріальною гіпертензією в асоціації з ожирінням відбуваються паралельно морфофункціональні зміни серця і нирок, а саме прогресування діастолічної дисфункції, підвищення індексу маси міокарда лівого шлуночка і сироваткового вмісту цистатину С та ліпокаліну, асоційованого з желатиназою нейтрофілів та зниження розрахункової швидкості клубочкової фільтрації.

Ключові слова: артеріальна гіпертензія, ожиріння, ремоделювання лівого шлуночка, діастолічна функція, ліпокалін, асоційований з желатиназою нейтрофілів, цистатин С.

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Despite decades of improved guidelines, pharmacological innovations, and procedural advances, the overall prevalence of cardiovascular disease continues to increase, preexisting risk factors worsen, and healthcare costs increase [1, 2, 13]. Arterial hypertension (AH), one of the most common chronic diseases in the world, is a major risk factor for the development and progression of cardiovascular complications, such as coronary heart disease, chronic heart failure, life-threatening cardiac arrhythmias, cerebrovascular disease, stroke, sleep apnea syndrome, and others. It should be noted that AH rarely occurs in isolation and is often

accompanied by other common conditions, such as obesity and metabolic disorders, which synergistically increase cardiovascular risk [10].

Obesity is a pandemic, independent, and modifiable cardiovascular risk factor distinct from other well-known risk factors such as arterial hypertension, hypercholesterolemia, and diabetes mellitus [3]. Over the past four decades, the prevalence of obesity has quadrupled to a record high of 42 % among US adults [12].

Obesity-related hypertension is an urgent and significant public health problem that is constantly growing. Of particular note is the fact that the interaction between arterial hypertension and obesity increases the

risk of cardiovascular disease, and optimal treatment strategies remain an ever-changing issue.

Arterial hypertension is one of the key pathogenetic factors contributing to the progressive deterioration of renal function [7]. According to studies conducted in the United States, hypertension is the cause of approximately 30 % of cases of end-stage renal disease [7].

The purpose of the study was to examine changes in central hemodynamic parameters, left ventricular diastolic function, and markers of actual dysfunction in patients with obesity-associated hypertension.

Materials and methods. The study was conducted in accordance with the basic provisions of the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the Declaration of Helsinki of the World Medical Association on Ethical Principles of Scientific Medical Research Involving Human Subjects (1964, 2008 ed.) and the requirements of Good Clinical Practice (GCP) of 1996 and the Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009.

All subjects gave informed consent to participate in the investigation. Before the start of the study, patients did not regularly take antihypertensive drugs.

The study included 53 patients with stage II arterial hypertension of the 2nd degree aged 43–60 years (mean age 52.6 ± 2.5 years), of whom 15 (28.3 %) were men and 38 (71.7 %) were women, who were referred for examination to the Government Institution “L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine”, Kharkiv. Patients were divided into 2 groups according to body mass index (BMI): group 1 – 25 patients with arterial hypertension and normal body weight, and group 2 – 28 patients with obesity of the 1st degree.

The control group consisted of 20 people, 10 men and 10 women (mean age 52.1 ± 2.3 years), with established cardiovascular risk factors and normal blood pressure.

The exclusion criteria were: pregnant women, professional athletes with a history of regular use of antihypertensive drugs, secondary hypertension, long-term hypertension stage III, stage 3, the presence of coronary artery disease, angina pectoris, myocardial infarction, previous cerebral stroke, transient ischemic attack, chronic heart failure stage III and IV NYHA with heart rhythm and conduction disorders, inflammatory diseases, kidney pathology, severe chronic renal failure, autoimmune and endocrine diseases (including diabetes mellitus), severe concomitant diseases.

All patients underwent a general clinical examination, which included a questionnaire to identify risk factors for cardiovascular diseases, examination, anthropometric measurements to determine body mass index and waist circumference, a complete blood count and urine test (with determination of albuminuria, biochemical blood test to determine fasting glucose, total cholesterol (TC),

low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), creatinine (with calculation of glomerular filtration rate (GFR) according to the CKD-EPI formula), and a 12-lead ECG on an ECG600G device («Heaco Ltd», Great Britain).

Clinical BP measurements were performed using validated oscillometric devices 3 times with an interval of 1 minute, by the same doctor for 5 days in the morning hours from 9 to 11 a.m. in a sitting position after a 10-minute rest on the same arm. The arm for BP measurement was determined upon admission for higher BP when comparing measurements on the right and left arms.

24-hour blood pressure monitoring was performed on the AVRМ-04 device (Meditech, Hungary). Recording was performed automatically at 15-minute intervals during the day (from 6 a.m. to 10 p.m.) and at 30-minute intervals at night (from 10 p.m. to 6 a.m.) for 24 hours. The study began at 9:00 a.m. and ended after 24 hours. Patients kept individual diaries, where they recorded their activity during the day, as well as the time of going to bed and getting up. The following were assessed: average values of systolic blood pressure, diastolic blood pressure, pulse pressure (PT), mean BP per day, day and night, variability of BP during the day and night, time index (TI) of hypertension – % of measurements of systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90 mm Hg during the period of alertness, and, respectively, ≥ 120 and ≥ 70 mm Hg. during sleep. The severity of the biphasic rhythm of blood pressure day-night was also assessed by the diurnal index (DI), which was calculated by the formula:

$$DI = 100 \% \times (BP_d - BP_n) / BP_d,$$

where BP_d – average BP during the period of wakefulness; BP_n – average BP during sleep.

According to the value of the DI, four groups of patients were distinguished:

- “dipper” (DI – 10–20 %) – optimal nightly decrease in BP;
- “non-dipper” (DI – 0–10 %) – insufficient nightly decrease in BP;
- “night-picker” (DI <0) – persistent increase in nightly BP;
- “over-dipper” (DI >20) – excessive nightly decrease in BP.

The assessment of structural and functional parameters of the heart was performed on a GE Medical Systems (Germany) device with a Doppler sensor that allows working in M- and B-modes, and also has an energy Doppler sensor that makes it possible to determine the diastolic function of the LV in the pulse-wave mode. To assess the diastolic function of the LV using the pulsed Doppler echocardiography method, transmitral blood flow indicators were determined: the E/A ratio (where E is the maximum flow velocity of the early filling period, and A is the maximum flow velocity of the late filling period), left atrial volume (LAV), indexed left atrial volume (iLAV), and the average value of the early diastolic motion velocity of the fibrous ring (e' mean) was also calculated. E/e' was

calculated – the ratio of the transmitral flow velocity to the average velocity of the fibrous ring of the mitral valve. This indicator indirectly reflected the LV filling pressure.

Chronic kidney disease (CKD) was defined according to the Clinical Practice Guideline for Evaluation and Management Chronic Kidney Disease (KGIGO, 2012). Renal function was assessed by glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.

Serum concentrations of markers of renal dysfunction, cystatin C (Bio Vendor, Czech Republic) and neutrophil gelatinase-associated lipocalin (NGAL, Hycult Biotech, Netherlands), were measured using enzyme-linked immunosorbent assay kits.

Statistical analysis of the study results was performed using the Statistica 10.0 program (StatSoft Inc., USA) and a package of application programs. The arithmetic means of the studied values, standard deviations, and representativeness errors were calculated. To identify the relationship between the studied values, Spearman correlation analysis was used. We evaluated differences in indicators between groups using the Mann-Whitney test and Student's t-test. The significance level p was taken to be less than 0.05.

Results of the study. According to clinical measurements and BPM, uncontrolled arterial hypertension was confirmed in patients of both groups. When studying the levels of office and daytime BP, it was found that the levels of systolic and diastolic BP did not differ significantly between the data of patients of both groups (Table 1).

Table 1

Blood pressure indicators according to office measurement and 24-hour blood pressure monitoring ($M \pm m$)

Parameters	Group 1 (n=25)	Group 2 (n=28)
Clinical BP		
SBP, mm Hg	161.0 $\pm$ 2.7	158.7 $\pm$ 2.3
DBP, mm Hg	94.5 $\pm$ 2.3	97.1 $\pm$ 2.1
24-hour blood pressure monitoring		
SBP (24), mm Hg	145.6 $\pm$ 2.5	147.0 $\pm$ 2.1
DBP (24), mm Hg	90.7 $\pm$ 2.4	90.6 $\pm$ 2.9
SBP day, mm Hg	150.0 $\pm$ 2.0	153.3 $\pm$ 2.5
DBP day, mm Hg	93.5 $\pm$ 2.1	94.0 $\pm$ 2.5
SBP night, mm Hg	136.1 $\pm$ 2.7	138.3 $\pm$ 2.6
DBP night, mm Hg	81.7 $\pm$ 2.8	82.5 $\pm$ 2.7
TI SBP day, %	60.7 $\pm$ 4.1	70.2 $\pm$ 4.8
TI DBP day, %	55.9 $\pm$ 4.6	59.2 $\pm$ 4.9
TI SBP night, %	69.7 $\pm$ 4.7	75.2 $\pm$ 4.9
TI DBP night, %	67.9 $\pm$ 5.3	69.0 $\pm$ 5.1

In patients with arterial hypertension and normal body weight, the following systolic BP profiles were determined: dipper – 11 (48.0 %), non-dipper – 9 (40.0 %), night-picker – 2 (8.0 %) and over-dipper – 1 (4.0 %) (Fig. 1.A).

In patients with arterial hypertension associated with stage I obesity, the daily profiles of SBP were distributed as follows: dipper – 10 (34.5 %), non-dipper – 13 (44.8 %), night-picker – 4 (13.8 %) and over-dipper – 2 (6.9 %) (Fig. 1.B). Analysis of the daily profile of DBP did not reveal statistically significant differences in both groups of patients (Fig. 1, B, D).

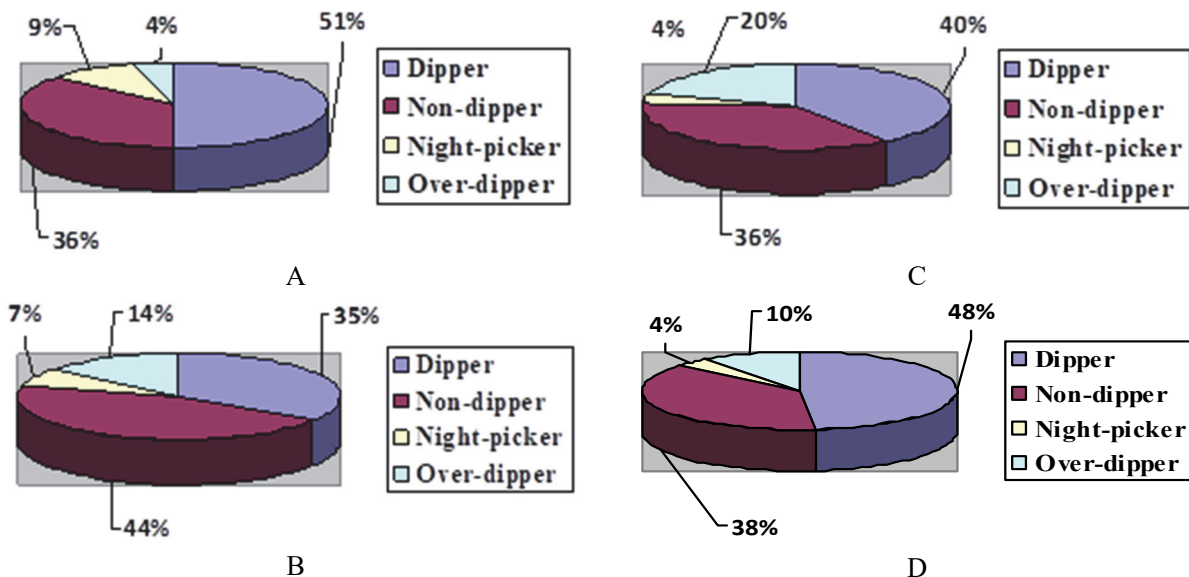


Fig. 1. Structure of daily SBP (A, B) and DBP (C, D) profiles in the examined patients: A, C – in patients with arterial hypertension with normal body weight; B, D – in patients with arterial hypertension in association with obesity of the I degree.

When analyzing the daily profiles of DBP, it was found that in patients with AH with normal body weight, the following DBP profiles were established: dipper – 10 (40.0 %), non-dipper – 9 (36.0 %), night-picker – 1 (4.0 %) and over-dipper – 5 (20.0 %). In the group with increased body weight or obesity of the I degree in patients with AH, the daily DBP profiles were: dipper – 14 (48.3 %), non-dipper – 11 (37.9 %), night-picker – 1 (3.5 %) and over-dipper – 3 (10.3 %).

When comparing the indicators of the structural and geometric state of the LV in the examined

patients with AH, it was found that the parameters of the LV DSR and DDR did not significantly differ in the groups with normal body weight and in individuals with obesity of grade 1. In patients with AH associated with obesity of grade 1, a significant thickening of the posterior wall of the LV (by 4.4 %; $p < 0.05$) and the interventricular septum (by 8.7 %; $p < 0.05$), an increase in the LV IMMI (by 13.4 %; $p < 0.05$) was detected in comparison with the group with normal body weight (Table 2).

Table 2

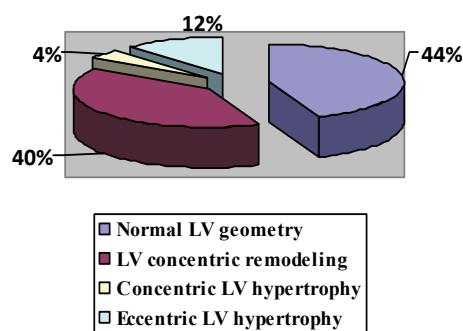
Results of echocardiographic research of examined patients (M $\pm$ m)

Parameters	Group 1 (n=25)	Group 2 (n=28)
LV end-diastolic dimension, cm	4.9 $\pm$ 0.15	5.2 $\pm$ 0.12
LV end-systolic dimension, cm	3.3 $\pm$ 0.11	3.4 $\pm$ 0.10
Ejection fraction, %	59.7 $\pm$ 1.3	59.9 $\pm$ 1.3
LV interventricular septal wall thickness, cm	1.09 $\pm$ 0.02	1.2 $\pm$ 0.05*
LV posterior wall thickness, cm	1.10 $\pm$ 0.02	1.21 $\pm$ 0.02*
LV myocardial mass index, g/m ²	103.8 $\pm$ 5.3	119.9 $\pm$ 5.1*

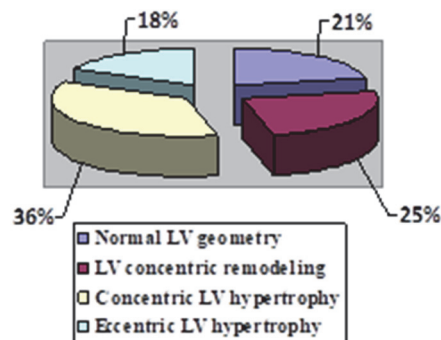
Notes: 1* – probability of differences between groups of examined patients $p < 0.05$.

According to echocardiographic data, structural and geometric remodeling of the LV was detected in

the examined patients. The types of LV remodeling in the examined patients are presented in Fig. 2 A, B.



A

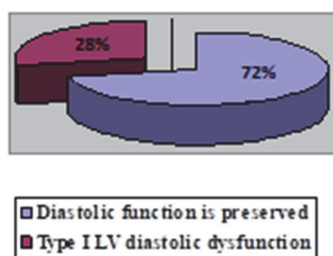


B

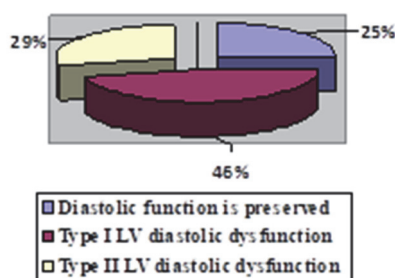
Fig. 2. Types of LV remodeling in patients with hypertension with normal body weight (A) and with grade 1 obesity (B).

Thus, in patients with hypertension, concentric LV remodeling was identified in 38.1 % of individuals with normal body weight and in 25 % of the group with grade 1 obesity; concentric LV hypertrophy – in 4.8 % and 35.7 %; eccentric LV hypertrophy – in 14.3 % and 17.9 %, respectively.

According to echocardiographic data, in 18 (72.0 %) patients with hypertension and normal body weight, no LV diastolic dysfunction was detected. At the same time, type I LV diastolic dysfunction was registered in 7 (28.0 %) patients of this group (Fig. 3.A).



A



B

Fig. 3. Analysis of LV diastolic function in patients with hypertension and normal body weight (A) and patients with hypertension in association with grade 1 obesity (B).

Analysis of LV diastolic function parameters in patients with hypertension associated with grade 1 obesity showed the following data: in 7 (25 %) patients, no diastolic function disorders were detected; in 13 (46.4 %) type I LV diastolic

dysfunction was registered, and in 8 (28.6 %) – type II LV diastolic dysfunction (Fig. 3.B).

Assessment of renal function using glomerular filtration rate (CKD-EPI) is presented in Fig. 4A.

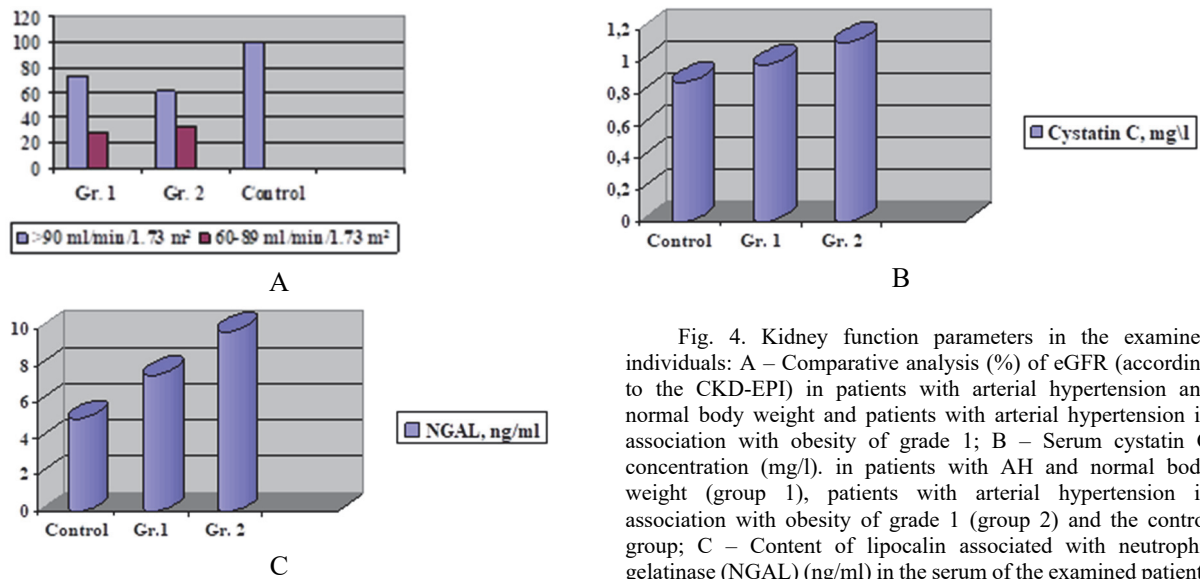


Fig. 4. Kidney function parameters in the examined individuals: A – Comparative analysis (%) of eGFR (according to the CKD-EPI) in patients with arterial hypertension and normal body weight and patients with arterial hypertension in association with obesity of grade 1; B – Serum cystatin C concentration (mg/l). in patients with AH and normal body weight (group 1), patients with arterial hypertension in association with obesity of grade 1 (group 2) and the control group; C – Content of lipocalin associated with neutrophil gelatinase (NGAL) (ng/ml) in the serum of the examined patients and the control group.

In a comparative analysis of eGFR (according to the CKD-EPI formula), it was found that in group 1 in 18 (72 %) patients this indicator was >90 ml/min/1.73 m² and in 7 (28 %) – 60-89 ml/min/1.73 m²; in group 2 in 17 (60.7 %) and 11 (39.3 %) respectively. It should also be noted that albuminuria more than 30 mg/ml was determined in 4 (16 %) patients with hypertension and in 9 (32.1 %) patients with hypertension associated with obesity.

Analysis of serum cystatin C (Fig. 4.B) showed that in patients with hypertension this indicator was 0.98 [0.72; 1.0] mg/l, which was 12.6 % ($p < 0.05$) higher compared to the control group (0.87 [0.71; 0.90] mg/l). A significant increase in this indicator was noted in patients with obesity-associated hypertension by 28.7 % ($p < 0.05$) – 1.12 [0.76; 1.39] mg/l compared to the control group and by 14.3 % ($p < 0.05$) compared to patients with hypertension and normal body weight.

It was found that the concentration of NGAL in the blood serum (Fig. 4.C) of patients with hypertension with normal body weight (group 1) increased by 32 % ($p < 0.05$) compared to the data of the group of healthy individuals. In patients with hypertension associated with obesity, a more significant increase in the level of NGAL in the blood serum by 48.5 % ($p < 0.05$) and 24.2 % ($p < 0.05$) was noted compared to the group of healthy individuals and patients with hypertension and normal body weight.

Discussion. The pathophysiology of hypertension in obesity is complex and multifactorial, involving numerous neurohormonal mechanisms, such as dysregulation of the renin-angiotensin-aldosterone system and cortisol regulation, activation of the sympathetic nervous system, renovascular disease, hypothalamic biology, and adipose tissue metabolism itself [9]. Studying the features of changes in central geodynamics, damage to target organs (heart and kidneys) in patients with obesity-

associated hypertension will contribute to improving the diagnostic algorithm and defining a personalized management strategy for such patients.

Currently, obesity is a major risk factor for heart failure worldwide, which is associated with left ventricular (LV) diastolic dysfunction [5]. Clinical evidence suggests that obesity may contribute to the development of heart failure with preserved ejection fraction (HFpEF), which includes cellular hypertrophy, left ventricular diastolic dysfunction, and increased extracellular collagen deposition [5]. It has been experimentally demonstrated that in obesity, excessive collagen deposition in the extracellular matrix (ECM) leads to increased myocardial stiffness and can impair diastolic cardiac function and contribute to heart failure with preserved ejection fraction [8].

Clinical studies have shown that the dynamics of weight gain are associated with the onset or exacerbation of a phenotype involving concentric LV remodeling, with an increase in its mass relative to the size of the cavity in large cohorts of obese individuals [6].

Impaired renal function and chronic kidney disease (CKD) are associated with an increased risk of all-cause and cardiovascular mortality. Obesity is a major risk factor for renal dysfunction, with cellular senescence and activation of the senescence-associated secretory phenotype (SASP) contributing to early renal damage. Obesity-related renal damage begins with reversible glomerular hyperfiltration and proteinuria, but can progress to glomerular, tubular, and interstitial damage, leading to fibrosis and irreversible renal failure [14]. A clinical research [15] using ultrasound-emitting devices (UEV) in obese individuals with normal renal function found that obesity induces podocyte senescence.

In current clinical practice, serum creatinine and urine output remain standard indicators of renal dysfunction, but both have well-known limitations,

including low sensitivity and delayed response to injury [11].

Cystatin C has been shown to be a more accurate indicator of GFR than creatinine, and its serum concentration is independent of muscle mass, age, or sex [14]. Serum cystatin C has been shown to be a strong and independent predictor of long-term all-cause and cardiovascular mortality in the general US population [7].

Our investigation found that the concentration of cystatin C in serum – a biomarker of renal dysfunction and cardiovascular complications – significantly increased in the association of hypertension and obesity.

In order to detect kidney damage at early stages, biomarkers are used, among which the most informative are neutrophil gelatinase-associated lipocalin (NGAL) in urine and serum, tissue inhibitors of metalloproteinases (TIMP) and insulin-like growth factor-binding protein-7 (IGFBP-7) [4]. The results of our study established an increase in serum NGAL levels in patients with hypertension in association with obesity. In a previous clinical study by Singh A. et al. [11], it was shown that serum NGAL levels are significantly increased in groups with higher degrees of obesity and positively correlated with various indicators of obesity.

Conclusions

1. In patients with hypertension associated with obesity, the percentage of concentric and eccentric hypertrophy, as well as impaired diastolic function of the left ventricle, increases.
2. It has been established that in patients with hypertension associated with obesity, morphofunctional changes in the heart and kidneys occur in parallel, namely, progression of diastolic dysfunction, increase in LV myocardial mass index and serum levels of cystatin C and NGAL against the background of decreased GFR.

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