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O.M. Bilovol, I.I. Kniazkova, V.M. Mishchenko[1], V.P. Starenky, N.V. Kuzminova[2], A.V. Krivoshapko, L.P. Abramova
Kharkiv National Medical University, Kharkiv; [1] Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine, State Institution, Kharkiv
[2] National Pirogov Memorial Medical University, Vinnytsya

CHANGES IN THE DIASTOLIC FUNCTION OF THE HEART AND TUMOR NECROSIS FACTOR-ALPHA IN PATIENTS WITH COMBINED PATHOLOGY: ARTERIAL HYPERTENSION WITH TYPE 2 DIABETES AND OBESITY

e-mail: sskripka72@gmail.com

The purpose of the work was to study the features of the diastolic function of the left ventricle and the tumor necrosis factor-α level in patients with combined pathology: arterial hypertension with type 2 diabetes and obesity. Disorders of the diastolic function of the left ventricle were established to be more often registered in patients with arterial hypertension with type 2 diabetes and obesity, compared to the group of patients with arterial hypertension and type 2 diabetes with normal body weight. A significant increase in the content of tumor necrosis factor-α was determined in the group of patients with arterial hypertension with type 2 diabetes and obesity compared to the group with arterial hypertension and type 2 diabetes with normal body weight.
Key words: arterial hypertension, type 2 diabetes, diastolic dysfunction, tumor necrosis factor-α.

О.М. Біловол, І.І. Князькова, В.М. Міщенко, В.П. Старенький, Н.В. Кузьмінова, О.В. Кривошапко, Л.П. Абрамова

ЗМІНИ ДІАСТОЛІЧНОЇ ФУНКЦІЇ СЕРЦЯ ТА ФАКТОРУ НЕКРОЗУ ПУХЛИНИ-АЛЬФА У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ, ПОЄДНАНОЮ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА ОЖИРІННЯМ

Метою. роботи було вивчення особливостей стану діастолічної функції лівого шлуночка та фактору некрозу пухлин-α у пацієнтів з поєднаною патологією артеріальна гіпертензія з цукровим діабетом 2 типу та ожирінням. Встановлено, що у пацієнтів з артеріальною гіпертензією з цукровим діабетом 2 типу та ожирінням порівняно з групою пацієнтів з артеріальною гіпертензією і цукровим діабетом 2 типу з нормальною масою тіла частіше реєстрували порушення діастолічної функції лівого шлуночка. Визначено достовірне підвищення вмісту фактору некрозу пухлин-α у групі пацієнтів з артеріальною гіпертензією з цукровим діабетом 2 типу та ожирінням у порівнянні з групою з артеріальною гіпертензією та цукровим діабетом 2 типу з нормальною масою тіла.
Ключові слова: діастолічна дисфункція, фактор некрозу пухлин – альфа, артеріальна гіпертензія, цукровий діабет 2 типу.

The work is a fragment of the research project "To determine the features of immunocytokine imbalance in comorbid patients with arterial hypertension and type 2 diabetes and cardiovascular and renal complications", state registration No. 0123U101711.

The trend today is to increase arterial hypertension (AH) in combination with type 2 diabetes mellitus (DM type 2) [5]. The combination of AH and DM type 2 leads to a mutual influence on the course of diseases, nature and severity of complications. Often such a combination complicates the diagnosis, and also determines the peculiarities of the choice of drug therapy. Thus, among patients with DM type 2, hypertension is found in 60–80 % [9]. On the other hand, DM type 2 is one of the risk factors for the development of cardiovascular diseases [14]. It has been demonstrated that the combination of

AH and DM type 2 is associated with earlier disability in this patients' cohort, increased risk of developing cardiovascular complications in them and a higher mortality rate compared to the general population [4].

Metabolic disorders caused by hyperglycemia lead to persistent structural and functional changes in internal organs, including the myocardium. A special form of heart damage in diabetes is diabetic cardiomyopathy, which is characterized by accelerated development and progression of chronic heart failure (CHF) [15]. But until now there are no clear diagnostic criteria for diabetic cardiomyopathy [2]. Diastolic dysfunction of the left ventricle (LV) is the earliest preclinical manifestation of diabetic myocardial damage [12].

The purpose of the study was to establish the features of the diastolic function of the left ventricle and the level of tumor necrosis factor-α in patients with the combined pathology: arterial hypertension with type 2 diabetes and obesity.

Materials and methods. 50 patients were examined (28 men and 22 women, mean age – 50.7±3.9 years) with AH of the 2nd degree and DM type 2 of moderate severity, subcompensated. Of these individuals, 26 patients (15 men and 11 women, mean age – 50.9±3.3 years) obesity of the 1st degree was determined (group 1). 24 patients (13 men and 11 women, mean age – 51.1±3.5 years) were of normal body weight (group 2), and they did not receive permanent antihypertensive therapy.

The control group consisted of 20 practically healthy people (mean age 50.1±2.8 years).

All patients were examined according to the recommendations of the European Hypertension Society and the European Society of Cardiology (ESH/ESC, 2018), American Diabetes Association (ADA) 2019, and International Diabetes Federation (IDF) 2018, body weight was measured according to WHO recommendations.

All subjects signed an informed consent to participate in the study.

Patient groups were comparable in terms of age, gender, duration of hypertension, office systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), and body mass index (BMI). At the time of inclusion in the study, the level of glycated hemoglobin (HbA1c) in patients with AH and DM type 2 was <8.0 %, which was achieved with the help of diet and oral hypoglycemic agents, according to clinical recommendations.

In patients of group 1, the body mass index (BMI), the ratio of waist circumference/hip circumference (OT/OS) was determined, which indicated the abdominal type of obesity of the 1st degree (BMI 30.0–34.9 kg/m²).

All examined persons underwent a general clinical examination and anthropometric measurements., measurement of office blood pressure, heart rate (HR), determination of glucose concentration in fasting blood serum (FSC), glycosylated hemoglobin level (HbA1c) and insulin in whole blood, lipid profile indicators; insulin resistance was assessed according to the HOMA-IR index. Using enzyme immunoassay kits, the concentration of TNF-α (DRG, USA) was determined in the blood serum of patients.

To determine the diastolic function of the heart, transthoracic echocardiography was performed, which was carried out on the ultrasonic device ULTIMA PA (Radmir, Ukraine) using a sector-phased sensor with a frequency range of 2–3 MHz according to the standard method according to the recommendations of the American Society of Echocardiography (2016). To assess LV diastolic function, the parameters of transmitral blood flow were determined by the method of pulsed Doppler echocardiography: E/A ratio (where E is the maximum flow rate of the early filling period, and A is the maximum flow rate of the late filling period) [11]. In addition, the mean value of the speed of the early diastolic movement of the annulus fibrosus (e`mean) was calculated. Also, E/e' is the ratio of the speed of the transmitral flow to the average speed of the fibrous ring of the mitral valve; this indicator indirectly reflects the filling pressure of the left ventricle.

Statistical analysis of the data was performed using the statistical software package Statistica, 10.0 (Stat Soft Inc, USA). The Kolmogorov-Smirnov test was used to assess the nature of the distribution in the population based on sample data. Differences between groups of mean values and their errors (M±m) were evaluated using the Student-Fisher test. A probable error of less than 5 % ($p < 0.05$) was considered reliable.

Results of the study and their discussion. The clinical data of the patients permitted establishing the absence of statistical differences between the groups by age and gender. There were no significant differences between the groups of examined patients in terms of blood pressure levels, duration of AH, lipid metabolism disorders.

Data on the parameters characterizing the diastolic function of the myocardium in patients with AH and DM type 2, taking into account BMI, are presented in Table 1.

Table 1.

Parameters of heart diastolic function of patients with hypertension and type 2 diabetes depending on BMI (M±m)

Parameters	Group 1 (n = 26)	Group 2 (n = 24)	Control group (n=20)
E, sm/s	65.18±0.79*	69.29±1.01	78.21±1.27
A, sm/s	72.18±0.44*	76.35±1.17	65.18±1.29
E/A	0.90±0.02*	0.95±0.01	1.19±0.01
e`mean, sm/s	10.53±0.13*	11.79±0.15	14.56±0.21
E/e`mean	6.47±0.10	6.03±0.12	5.31±0.09

Note * – the difference in indicators is likely compared to the control group, p< 0,05.

The analysis of diastolic function parameters made it possible to establish reliable changes in the following parameters: E, A, E/A, the mean in the group of patients with AH and DM type 2 with obesity and in a group of patients with AH and DM type 2 with normal body weight.

Types of transmitral blood flow in patients of groups 1 and 2 were presented as follows: normal diastolic function – 7 (26.9 %) and 10 (41.7 %) (p< 0.05); relaxation disorders – 13 (50.0 %) and 13 (54.2 %); pseudonormal – 6 (23.1 %) and 1 (4.1 %) (p<0.05), respectively.

The content of the pro-inflammatory cytokine TNF-α in the blood of the examined patients is presented in Fig. 1.

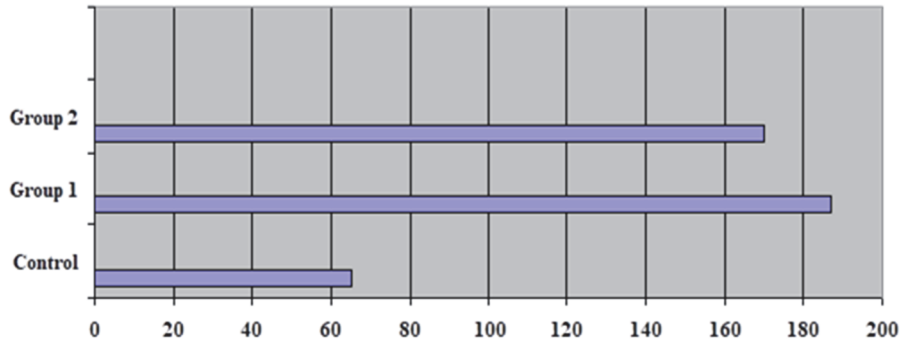

Fig. 1. The content of TNF-α in blood serum (pg/ml) in patients with a combination of AH and DM type 2 and obesity (group 1), patients with AH and DM type 2 with normal body weight (group 2), and the control group.

As shown in the figure, in patients with AH and DM type 2 with normal body weight (group 2), the TNF-α content in blood serum of 2.6 was significantly higher than the value in the group of healthy individuals (p<0.001).

The maximum levels of TNF-α in blood serum were noted in patients with type 2 diabetes in combination with AH and obesity, which were by 2.9 times higher than the values of healthy individuals (p<0.001). It was found that with the comorbidity of diabetes and AH and obesity, the TNF-α content in blood serum was by 10 % higher (p<0.05) compared to patients with AH and DM type 2 with normal body weight.

Prolonged AH contributes to heart remodeling due to increased pressure after exercise. LV or left atrial remodeling is usually accompanied by systolic and/or diastolic dysfunction [7]. Violation of LV relaxation, as a rule, is the initial manifestation of LV diastolic dysfunction [15], caused by uncontrolled AH or concomitant diseases, such as DM type 2, obesity or dyslipidemia. Therefore, in a particular patient, the cause of diastolic dysfunction is not always obvious. In addition, CHF with preserved LV ejection fraction is at least partially characterized by diastolic dysfunction. Left ventricular hypertrophy and diastolic dysfunction have been found to be associated with mortality and cardiovascular events [12].

There are two main mechanisms contributing to the development of LV dysfunction caused by AH [6]: the mechanism by which the pressure load due to AH induces LV hypertrophy and diastolic heart failure; the mechanism by which oxidative stress after activation of the renin-angiotensin-aldosterone system (RAAS) and increased secretion of pro-inflammatory cytokines causes LV dysfunction.

LV diastolic dysfunction is the earliest preclinical manifestation of diabetic myocardial damage [12]. Among the pathogenetic mechanisms of heart damage in diabetes, it should be noted the contribution of metabolic changes caused primarily by insulin resistance, diabetic microangiopathy, as well as an abnormality in the formation of some cellular structures, in particular mitochondria, activation of the renin-angiotensin-aldosterone system (RAAS), cardiac autonomic neuropathy, increased free fatty acids, immune disorders, etc. [1]. On the other hand, oxidative stress and abnormal transport of calcium ions into cardiomyocytes is interconnected with the activation of proinflammatory cytokines, which induce insulin resistance through activation of nuclear factor Kappa (NF-kB) and phosphorylation of insulin receptor type 1 substrate [4].

Obesity has been shown to be a risk factor for CHF in numerous studies. CHF In this regard, the AHA/ACC/HFSA heart failure guidelines published in 2022 list obesity as a major risk factor for the development of CHF [4].

TNF-α is a soluble cytokine produced mostly by cells of the immune system, mainly monocytes and macrophages and has the ability to interact with other cytokines and stimulate the secretion of interleukins (IL-1, IL-6, etc.), interferon-γ, chemokines; during infections activates leukocytes, increases the production of other cytokines [10]. It is shown that the hyperproduction of TNF-α leads to insulin resistance, obesity, hyperleptinemia and, as a result, to DM type 2 [1].

Of great interest is the relatively little-studied aspect of the participation of pro-inflammatory cytokines in the development of myocardial fibrosis, which manifests itself in the detection of diastolic dysfunction in patients with AH in combination with DM type 2 and obesity. Recently, inflammatory and regulatory mechanisms involved in the occurrence and progression of diastolic function disorders in AH in combination with DM type 2 and obesity have been actively studied. At the same time, there is not enough information that would reveal the pathogenesis of diastolic dysfunction from the point of view of the influence of inflammatory cytokines in AH with DM type 2 and obesity. Our research was aimed at evaluating the contribution of the pro-inflammatory cytokine TNF-α to the development of diastolic dysfunction in patients with AH in combination with DM type 2 depending on BMI.

The most common parameters used in clinical practice to assess diastolic function are the ratio between early and late transmitral velocity (E/A), early diastolic velocity of the mitral annular displacement (e`mean) and the ratio E/ e`mean. In addition, left atrial enlargement and signs of pulmonary hypertension are used as auxiliary signs of increased left heart filling pressure [12].

We found that transmitral blood flow disorders in patients with AH and DM type 2 are more pronounced in comorbidity with obesity of the 1st degree. Analysis of the types of transmitral blood flow in patients with AH and DM type 2 with normal body weight and obese patients showed that that in the presence of obesity, a decrease in the percentage of patients with normal transmitral blood flow was observed and the progression of diastolic dysfunction in the form of a pseudo-normal type of blood flow was revealed.

It was established that adipocytes secrete TNF-α and IL-6 [3, 13]. In addition, adipose tissue is rich in macrophages, monocytes, and other immune cells that overproduce TNF-α and other cytokines [8]. The results of previous research testify the involvement of inflammatory mechanisms in the pathogenesis of heart failure, diabetes, coronary heart disease, violations of the geometry of the heart and vascular changes [4].

In our research a significant increase in TNF-α content was noted in patients with AH and DM type 2 and obesity compared to patients with AH and DM type 2 with normal body weight.

The obtained results can be explained by the fact that increased levels of TNF-α can lead to LV diastolic dysfunction by promoting myocyte hypertrophy due to the production of reactive oxygen intermediates in cardiac myocytes and inducing ventricular remodeling by promoting extracellular matrix protein production.

Conclusions.

1. In patients with AH and DM type 2 and obesity, compared to the group of patients with AH and DM type 2 with normal body weight, disorders of diastolic function of the left ventricle were more often registered.

2. A significant increase in the levels of TNF-α was established in the group of patients with AH and DM type 2 with obesity compared to the group with AH and DM type 2 with normal body weight.

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T.V. Bohdan, V.V. Bogdan, V.O. Sobol, I.V. Biliachenko, Yu.O. Moshkovska, Yu.V. Tyravska
Bogomolets National Medical University, Kyiv

RELATIONSHIP BETWEEN IMMUNOLOGICAL STATUS AND ISCHEMIA, ECTOPIC MYOCARDIAL ACTIVITY IN PATIENTS WITH ANGINA PECTORIS

e-mail: vik.o.sobol@gmail.com

The purpose of the study was to improve the diagnosis of stable angina and unstable angina by determining the correlations between the development of myocardial ischemia and cardiac arrhythmias with disorders of cellular and humoral immunity in patients with coronary artery disease. Using the obtained results, further optimize the treatment of patients with stable and unstable angina pectoris. It was determined that in the stable angina pectoris the development of painful myocardial ischemia depends on the level of CD4+ subpopulation (T-helpers) and circulating immune complexes, the development of painless myocardial ischemia depends on the level of CD4+ and CD8+ subpopulations (T-suppressors). Coronary artery disease destabilization and group ventricular extrasystoles are associated with elevated CD4+ subpopulations, CD8+ subpopulations and circulating immune complexes levels. Pathogenetic links between coronary circulatory disorders and ectopic myocardial activity with the development of imbalance of cellular and humoral immunity in patients with stable and unstable angina pectoris confirm the theory of immune inflammation as one of the pathogenetic links in the development of coronary artery disease and encourage studies and development of new drugs in antianginal therapy algorithms.

Key words: stable angina pectoris, unstable angina pectoris, painful ischemia, painless ischemia, extrasystole, immunity.

Т.В. Богдан, В.В. Богдан, В.О. Соболь, І.В. Біляченко,
Ю.О. Мошковська, Ю.В. Тиравська

ЗВ'ЯЗОК ІМУНОЛОГІЧНОГО СТАТУСУ З ІШЕМІЄЮ ТА ЕКТОПІЧНОЮ АКТИВНІСТЮ МІОКАРДА У ХВОРИХ НА СТЕНОКАРДІЮ

Метою роботи було удосконалити діагностику стабільної стенокардії та нестабільної стенокардії на підставі визначення кореляційних зв'язків між розвитком ішемії міокарда і порушень серцевого ритму з порушеннями клітинного і гуморального імунітету у хворих на ішемічну хворобу серця. Визначено, що при стабільному перебігу ішемічної хвороби серця розвиток больової ішемії міокарда залежить від рівня субпопуляції CD4+ (Т-хелпери) та циркулюючих імунних комплексів, розвиток безьольової ішемії міокарда – від рівня субпопуляції CD4+ та CD8+ (Т-супресори). Дестабілізація коронарного кровообігу та виникнення групової шлуночкової екстрасистолії пов'язані з підвищеним рівнем субпопуляції CD4+, субпопуляції CD8+ та рівнем імунних комплексів. Патогенетичні зв'язки порушення коронарного кровообігу і ектопічної активності міокарда з розвитком дисбалансу клітинного та гуморального імунітету у хворих на стабільну та нестабільну стенокардію підтверджують теорію імунного запалення, як однієї з патогенетичних ланок розвитку ішемічної хвороби серця і спонукають до пошуку та розробки нових лікарських засобів, які б входили у алгоритми антиангінальної терапії.

Ключові слова: стабільна стенокардія, нестабільна стенокардія, больова ішемія, безбольова ішемія, екстрасистолія, імунітет.

The study is a fragment of the research project "Changes in protein, carbohydrate, lipid metabolism in patients with coronary heart disease and arterial hypertension with heart rhythm disorders, possibilities of drug correction", state registration No. 0121U108875.

Coronary artery disease (CAD), manifested by severe clinical course, high disability and mortality among the population, has become widespread over the last decade [4]. This creates important medical and social problems and encourages clinicians to further study the causes, pathogenetic mechanisms, improve diagnosis, implementation of effective treatment algorithms and prevention of this disease [13]. Moreover,