

## STRUCTURAL AND FUNCTIONAL IMPAIRMENTS OF THE LEFT CARDIAC CAVITIES IN PATIENTS WITH GOUT AND ESSENTIAL HYPERTENSION

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**Abstract.** The study is devoted to the examination of features of the structural and functional state of left heart in patients with gout and essential hypertension (EH) compared with patients suffering from only gout or EH. The complex analysis of the predictors of left ventricular diastolic dysfunction (LVDD) development in patients with a combination of gout and EH was conducted. 140 patients were examined and divided into three groups of study: group 1 – patients with EH (40 persons); group 2 – patients with gout (20 persons); group 3 – patients with gout and EH (80 persons). Patients with gout and EH are significantly different in terms of the end-diastolic volume index (EVDi), which is higher by 18% and 16% in comparison with patients with EH or gout, respectively, and in terms of the value of the left ventricular myocardium mass index (LVMMI) by 11% and 18%, respectively. In the analysis of patients by types of left ventricular geometry (LV) it was found that in group 3 the most unfavorable type is predominant is 48.8% of cases – concentric hypertrophy of LV against 27.5% in group 1 and 5% in group 2. LVDD was found in group 3 in 82.5% of cases, against 65% among patients in group 1 and 60% in patients in group 2. The E/E value – the ratio of the early diastolic left ventricular filling velocity to the maximum velocity of mitral annulus was higher by 13% than in the comparison groups. The main predictors of LVDD are the duration of gout and LVMMI. The presence of EH in patients with gout results in disorder of the structure and function of the heart, which increases the cardiovascular risks for such patients.

**Key words:** gout, essential hypertension, left ventricular diastolic dysfunction

## СТРУКТУРНИ И ФУНКЦИОНАЛНИ НАРУШЕНИЯ НА ЛЯВОТО СЪРЦЕ ПРИ ПАЦИЕНТИ С ПОДАГРА С ХИПЕРТОНИЯ

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**Резюме.** Разглеждат се характеристиките на структурното и функционалното състояние на лявото сърце при пациенти с подагра и есенциална хипертония (ЕХ) в сравнение с пациенти, страдащи само от подагра или ЕХ. Бяха изследвани 140 пациенти, разделени на три групи: I – пациенти с ЕХ (40 лица); II – пациенти с подагра (20 души); III – пациенти с подагра и ЕХ (80 души). Пациентите с подагра и ЕХ се различават значително по отношение на индекса на крайния диастолен обем, който е по-висок съответно с 18% и 16% в сравнение с пациентите само с ЕХ или само с подагра, а по отношение на стойността на левия индекс на вентрикуларна миокардна маса съответно с 11% и 18%. При анализа на геометрията на лявата камера (ЛК) е установено, че при 48,8% от случаите в III група преобладава най-неблагоприятната – концентрична левокамерна хипертрофия, в сравнение с 27,5% в I група и 5% във II група. Диастолна дисфункция (ДД) на ЛК е намерена в III група при 82,5% от случаите, срещу 65% сред пациентите в група 1 и 60% при пациенти в група 2. Основните предиктори на ДД са продължителността на подаграта и левия вентрикуларен миокарден индекс. Наличието на хипертония при пациенти с подагра води до нарушение на структурата и функцията на сърцето, което увеличава сърдечно-съдовия риск.

**Ключови думи:** подагра, артериална хипертония, диастолна функция на лявата камера

## INTRODUCTION

Gout is a topical medical, social and economic problem of our times, which mainly affects the able-bodied population and is the cause of the development of many concomitant diseases, in particular cardiovascular ones (CVD). According to the recent epidemiological studies on gout, from 1 to 4% of the adult population in the world suffer from gout [8]. According to the US National Health and Nutrition Program, 74% of patients with gout have been diagnosed with EH, 14.4% of patients had myocardial infarction and 10.4% of patients had a stroke [7]. The overall risk of mortality from CVD increases by 15% with each increase in uric acid (UA) by 1 mg/dL [5]. There are controversial data on how the UA affects the CVD: on the one side, it is a powerful antioxidant that neutralizes up to 70% of free radicals in blood plasma [3] and increases the production of nitric oxide and thereby causes vasodilatation, and on the other side, in hydrophobic conditions it may act as a prooxidant inducing the intracellular oxidative stress [10], as well as the synthesis of proinflammatory cytokines [9].

Many questions about the association of gout and structural and functional changes of heart remain open. According to Jing-Chi Lin [6], the gout is directly associated with an increase in the size and volume of LV chambers, and 66.8% of patients with gout had been diagnosed with LVDD [1]. In case of combination of the gout with EH, the frequency of LVDD is 2,3 times greater than in patients with gout, with normal blood pressure (BP) [2]. According to other studies, the UA and the presence of gout do not have a significant effect on the structural and functional state of the cardiovascular system [4]. Features of the function and structure of LV in patients with gout with EH are still not fully studied.

## PURPOSE

To study the features of the disorder of structural and functional state of left ventricles in patients with gout with EH.

## MATERIALS AND METHODS

140 male patients were examined in the course of study and divided into 3 groups. The first group of the study included 40 men suffering from essential EH of II stage and 2nd degree. In the second group, there were 20 men with gout without EH. The third group of the study (main) included 80 persons with primary gout in combination with EH of II stage and

2nd degree. The diagnosis of gout was established in accordance with the recommendations of the European Antirheumatic League (EULAR, 2016), and EH – according to the recommendations of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) 2013.

The age of the studied patients from the first group on average was  $56.2 \pm 1.1$  years, in the second group –  $53.5 \pm 1.3$ , and in third group –  $56.8 \pm 0.9$  years. The average level of UA among the patients in the first group was  $357.8 \pm 16.8$   $\mu\text{mol/l}$ , second group –  $401.2 \pm 23.2$   $\mu\text{mol/l}$ , and third group –  $518.3 \pm 13.1$   $\mu\text{mol/l}$ . The average systolic blood pressure (SBP) among patients in the first group was  $139.9 \pm 2.2$  mm Hg, diastolic blood pressure (DBP) –  $91.9 \pm 1.6$  mm Hg. The patients from second group had the average indicators of SBP of  $126.3 \pm 2.1$  mm Hg, DBP –  $83.8 \pm 3.6$  mm Hg. Patients from the third group had the average values of SBP of  $131.1 \pm 2.1$  mm Hg, DBP –  $96.7 \pm 1.4$  mm Hg. The average duration of EH among patients from the first group was  $6.4 \pm 0.4$  years, among patients from the third group –  $7.3 \pm 0.4$  years. Duration of gout in the second and third groups on average is  $5.9 \pm 0.6$  and  $7.1 \pm 0.4$  years, respectively. The studied groups do not differ in terms of the age, duration of gout and EH.

The patients were examined by means of comprehensive clinical-anamnestic, laboratory, instrumental (echocardiography (Echo-CG) with the use of tissue Doppler imaging) studies. All patients included in the study passed Echo-CG implemented by "iE 33 Philips" ultrasound apparatus (USA) under the standard procedure in M- and B-modes, and location frequency of 7 MHz. The basic structural parameters were determined: the end-diastolic size (EDS, cm) and the end-systolic size (ESS, cm) of left ventricle, the size of the left atrium (LA, cm), the end-diastolic volume (EDV, ml) and the end-systolic volume (ESV, ml) of LV with the subsequent calculation of the corresponding indices (EDVi and ESVi, ml/m<sup>2</sup>). Imaging included apical two- and four-chamber views, from which LA volume was measured using the method of disks (Xcelera; Philips Medical Systems). This volume was used to calculate LA volume index (LAVi) to the body surface area (ml/m<sup>2</sup>) [11].

The ejection fraction (EF, %) of the LV was calculated by Simpson technique, the thickness of the interventricular septum (IVS, cm), and the left ventricle posterior wall (LVPW, cm).

The mass of the left ventricular myocardium (MLVM, g) was calculated according to the Devereux formula:  $\text{MLVM} = 1.04 \times (\text{EDS} + \text{IVS} + \text{LVPW})^3 - 1.04 \times \text{EDS}^3 - 13.6$ .

The index of LVMM (LVMMI), g/m<sup>2</sup>, was calculated as the ratio of MLVM to the area of the body surface area, the upper limit of the LVMMI for men was < 115 g/m<sup>2</sup>, and for women – 95 g/m<sup>2</sup>;

The type of LV geometry was calculated using the values of the relative thickness of walls of the LV (RThWLV) and LVMMI, where the relative thickness of walls was calculated by the formula:  $RThWLV = 2 \times LVPW/EDS$ .

In order to characterize the LVDD, the following indicators were used: E – the maximum early diastolic filling velocity, cm/s; A – maximum blood flow velocity during the atrial systole, cm / sec; IVRT – isovolumic relaxation time of LV, sec; DT – time of retardation of early diastolic filling, sec; E/A, ratio; E' – maximum velocity of mitral annulus, cm/s; E/E', ratio.

According to C.P. Appleton, depending on the transmitral flow parameters, the types of LV diastolic function are identified: normal LD diastolic function, type with disordered relaxation (type I), pseudonormal (type II) and restrictive (type III).

Statistical processing of the study results was carried out using STATISTICA 8.0 and Microsoft Excel 2007 programs. The regression and dispersion analyzes were used in order to determine the dependence of the signs.

## RESULTS

The analysis of the heart contractile function found that all three studied groups had a preserved systolic function and were not significantly different in terms of EF level. The morphological structure of LV among the examined patients was analyzed. The patients with isolated EH and with a combination of EH and gout had significantly higher levels of IVS, LVPW, MLVM and LVMMI than those who were only suffering from gout. All these parameters exceeded the relevant reference values among patients in the first and third groups. Thus, comparing the average values of the thickness of the IVS among patients in the main (third) group and the second group, a significant predominance of this parameter was found in patients with a combination of gout and EH by 18% ( $p = 0,02$ ), and compared with the first group – by 9% ( $p > 0,05$ ). The values of the thickness of the LVPW were significantly higher among patients in the third group compared with the second group by 9% ( $p = 0,01$ ). The presence of EH also negatively affects the level of MLVM. When comparing, the third group had larger values by 18% than the second one ( $p = 0,04$ ) and only by 3% against the first group ( $p > 0,05$ ). The difference of MLVM values between the first and second groups was 16% with

predominance for patients with EH ( $p = 0,05$ ). However, the value of the MLVM was significantly higher in the third group. The difference between the third and second groups at its level is 18% ( $p = 0,01$ ) and between the first group – 11% ( $p = 0,04$ ). Describing the size of the LA, it was found that its mean values were also the highest among the patients in the main group, but this indicator was significantly higher only when compared with the second group – by 11% ( $p = 0,03$ ), and with the first group only by 5% ( $p > 0,05$ ). The value of LA in all three groups was at the upper threshold level of normal LA size, which may be compensatory consequences as a result of an increase in LV size and a direct threat of atrial fibrillation. Also, LAVI is a powerful independent predictor of LV diastolic dysfunction and his mean values were also the highest among the patients in the main group, (compared with the second group – by 22% ( $p = 0,04$ ), and with the first group only by 8% ( $p > 0,05$ ).

When analyzing the LV volumes, the significant difference between the groups was found in terms of EDVi parameter. In the main (third) group, the EPV value exceeds the average level by 18% compared with the first group ( $p = 0,02$ ) and by 16% compared with the second group ( $p = 0,03$ ). Characteristics of structural and functional parameters of the left heart are shown in Table 1.

In the analysis of patients by types of LV geometry, it was found that in group 3 the most unfavorable type is predominant is 39 cases (48.8%) – concentric hypertrophy of LV against 11 (27.5%) cases in group 1 and 1 (5%) case in group 2. This demonstrates an increased load on the left ventricle myocardium, and in the future – an increased risk of developing the myocardial infarction or acute cerebrovascular accident. According to other types of LV geometry, the following results were obtained: the normal LV geometry was in the second group – 7 (35%) persons and absent in patients of other groups; the concentric remodeling of LV was in the first group with 16 (40.0%) examined patients, in the second group – 8 (40%) persons, in the third group – 19 (23.8%) persons, but the eccentric LV hypertrophy in the first group was in 16 (40.0%) persons; in the second group – in 4 (20%) patients, and in the third group – in 22 (27.5%) persons.

The total number of persons among the examined patients who had LVDD was 96 (68.6%) persons. Among the patients of the first group, LVDD was found in 26 (65.0%) examined persons, among them 17 (42.5%) patients had I type, II type – 9 (22.5%) persons, III type was not detected at all. Among patients of the second group, LVDD was

found in 12 (60%) patients, among them 9 (45%) persons had I type, type II – 3 (15%) persons and type III was absent. LVDD in patients of third group occurred in 66 (82.5%) persons, while in structure I type was detected in 30 (37.5%) examined persons, type II – in 34 (42.5%) persons, and type III – in 2 (2.5%) persons.

When analyzing the Doppler echocardiographic parameters reflecting the state of the LV diastolic function, it was found that the most pronounced changes between the three groups occurred only for the indicator obtained by tissue Doppler imaging – E/E', the value of which was 13% higher than the first and second groups. The values of other indices (E, A, E / A, DT, IVRT) do not significantly vary between the groups. They fall within the limits of reference values, which may be due to the specific features of the LVDD structure. The summarized results of diastolic function parameters are presented in Table 2.

In order to determine the dependence of E/E' in patients of the third group on the studied factors, a stepwise regression model was formed which explains 50.6% (R<sup>2</sup> = 0.51) of variability of the indicator:

$$E/E' = 2.57 + 0.31 \times \text{duration of gout (years)} + 0.45 \times \text{MLVM (years)}.$$

Thus, the predictors of LV DD are MLVM (r = 0.56; p < 0,01) and duration of gout (r = 0.45; p < 0,001).

## CONCLUSIONS

The development of EH in patients suffering from gout is characterized by a significant increase in the size and volume of the left heart with the most frequent development of concentric hypertrophy of the LV in 48.8% of cases.

**Table 1. Structural and geometric indices and intracardiac hemodynamics indices in the studied groups (M ± m)**

Indicator	Group 1 (n = 40)	Group 2 (n = 20)	Group 3 (n = 80)	P1-2	P1-3	P2-3	Standard
EDS, cm	5.2 ± 0.1	4.5 ± 0.1	5.1 ± 0.1	0.10	0.89	0.21	40-55
ESS, cm	3.3 ± 0.1	3.0 ± 0.1	3.8 ± 0.5	0.97	0.73	0.74	20-40
EDV, ml	121.3 ± 4.2	117.4 ± 6.1	138.4 ± 2.9	0.08	0.05	0.02	70-155
ESV, ml	45.2 ± 2.3	48.6 ± 3.1	51.3 ± 1.5	0.68	0.09	0.79	45-75
EDVi, ml/m <sup>2</sup>	64.3 ± 4.2	67.4 ± 6.09	74.4 ± 2.9	0.03	0.02	0.12	55-73
ESVi, ml/m <sup>2</sup>	30.2 ± 2.3	32.6 ± 3.1	32.3 ± 1.5	0.68	0.09	0.79	23-38
EF, %	59.9 ± 0.5	58.4 ± 0.9	59.5 ± 0.4	0.41	0.92	0.58	55-65
LA, cm	3.8 ± 0.1	3.6 ± 0.1	4.0 ± 0.1	0.64	0.57	0.03	< 3.99
LAVI, ml/m <sup>2</sup>	38.9 ± 0.2	34.4 ± 0.3	42.2 ± 0.2	0.41	0.24	0.04	> 41
IVS, cm	1.2 ± 0.03	1.1 ± 0.02	1.3 ± 0.01	0.45	0.11	0.02	< 1.12
LVPW, cm	1.1 ± 0.02	1.0 ± 0.12	1.2 ± 0.01	0.05	0.30	0.01	< 1.0
MLVM, g	215.3 ± 7.6	186.3 ± 6.9	219.5 ± 5.1	0.05	0.89	0.04	< 200
LVMMI, g/m <sup>2</sup>	107.4 ± 3.1	97.4 ± 4.0	115.1 ± 2.5	0.03	0.14	0.01	< 110

**Table 2. Diastolic function indices of examined patients (M ± m)**

Indicator	Group 1 (n = 40)	Group 2 (n = 20)	Group 3 (n = 80)	P1-2	P1-3	P2-3	Standard
E, cm/s	0.7 ± 0.02	0.7 ± 0.03	0.7 ± 0.02	0.47	0.91	0.66	0.6 – 1.3
A, cm/s	0.6 ± 0.03	0.6 ± 0.04	0.7 ± 0.02	0.17	0.95	0.11	0.3 – 0.6
E/A	1.05 ± 0.03	1.2 ± 0.06	1.12 ± 0.04	0.15	0.62	0.44	1 – 1.6
IVRT, s	91.2 ± 2.1	82.2 ± 3.6	91.7 ± 1.8	0.13	0.98	0.09	< 99
DT, s	213.3 ± 8.13	173.8 ± 7.5	214.8 ± 5.5	0.02	0.99	0.01	160 – 240
E/E'	7.9 ± 0.4	7.8 ± 0.2	8.8 ± 0.2	0.88	0.03	0.03	< 7.9

Frequent (82.5%) disorder of LV diastolic function (with predominance of II type in 42.5% of cases) is typical for patients with gout in combination with EH, the predictors of which are LVMMI and duration of gout.

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