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LIPID DISODERS IN HYPERTENSIVE PATIENTS WITH DIASTOLIC DYSFUNCTION AND ASYMPTOMATIC HYPERURICEMIA

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Abstract

Currently hyperuricemia is considered as a risk factor of complications and incresed mortality rate in patients with arterial hypertension and heart failure.

The aim of the study was to analyze the peculiarities of lipid spectrum and lipid peroxidation in patients with essential arterial hypertension (AH) with diastolic heart failure in normo- and hyperuricemia.

Material and methods. We examined 165 patients with essential AH stage II with left ventricular diastolic dysfunction. In addition to general clinical examinations, Echocardioscopy to determine left ventricular function, uric acid (UA) level, NT-pro BNP, as well as lipid spectrum and lipid peroxidation indexes were determined.

Results. In patients with AH with left ventricular diastolic dysfunction (LV DD) we have found the combination of lipid and purine metabolic disorders. In patients with AH with LV DD, a direct correlation was found between the level of atherogenic LDL cholesterol (LDL-C) and the degree of AH ($r = 0.44$, $p < 0.001$), as well as LDL-C and functional class (FC) of heart failure (HF) ($r = 0.53$, $p < 0.001$), which confirmes that disease progression with elevating of blood pressure and FC of HF is accompanied by an increase in the atherogenic cholesterol level. In addition, patients had a direct relationship between the level of LDL-C and UA ($r = 0.43$, $p < 0.001$), which confirms the simultaneous violation of both lipid and purine metabolism.

The development of LV DD was accompanied by changes in the atherogenicity of blood plasma and at the same time depended on the level of uric acid. On the one hand, an inverse corelations were found between the level of LDL-C and E' ($r = -0.45$, $p < 0.001$), and between the level of UA and E' ($r = -0.51$, $p < 0.001$), which indicates more pronounced intracardiac fibrous changes of the mitral ring in patients with elevated LDL-C, deterioration of relaxation processes and increased myocardial stiffness in hypercholesterolemia and disorders of purine metabolism. On the other hand, there is a direct correlation between hyperuricemia (HU) and increased lipoperoxidation, in particular malonic aldehyde and decreased activity of antioxidant enzymes, which confirms the excessive activation of lipid peroxidation in patients with arterial hypertension with asymptomatic HU.

Conclusions. Patients with essential hypertension and diastolic heart failure have more pronounced disorders of lipid metabolism and lipid peroxidation (LPO) processes in the presence of comorbid hyperuricemia compared with patients without hyperuricemia. The development of diastolic dysfunction is accompanied by an increase in NT-proBNP and changes in plasma atherogenicity and at the same time depends on the level of uric acid. Hyperuricemia in patients with essential hypertension is associated with a significantly higher incidence of LV diastolic dysfunction.

Keywords: *arterial hypertension, left ventricle diastolic dysfunction, asymptomatic hyperuricemia, lipids, lipid peroxidation*

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally. Arterial hypertension (AH) is well known to be a major risk factor for CVDs. Worldwide prevalence estimates for AH may be as much as one billion individuals, and approximately 7.1 million deaths per year may be due to AH (1). The number of hypertensive patients continue to grow, while it is predicted that as many as 1.5 billion individuals will be suffering from AH in 2025 (2-4). The global prevalence of AH in adults is about 30 to 45 % (2), in Ukraine, according to official statistics – 30,1% (5).

Comorbidity, as the pathogenetic combination of various pathological conditions, is a feature of modern chronic diseases, especially with age (6-8). Besides, the presence of comorbidities, in particular, AH is determined recently as one of the main burdening factors of the COVID-19 course and mortality (9). Among the patients with hypertension there is a significant proportion of people with heart failure caused mainly by diastolic disorders (10). In recent years, the relationship of AH with disorders of lipid and purine metabolism - gout and asymptomatic hyperuricemia (HU) was revealed (11-15). It turned out that the incidence of HU is much higher among patients with hypertension than in the general population and is, on average, from 25 to 50 %. The incidence of hypertension is also much higher among patients with gout - up to 50 %. It should be noted that HU is considered as an independent risk factor for complications and mortality in patients with hypertension and heart failure (11, 13, 15, 16).

The aim of present study was to study the features of lipid metabolic disorders in patients with AH with diastolic dysfunction of the left ventricle depending on the level of uric acid.

Materials and methods

The study included 165 hypertensive patients (97 women (58.8%) and 68 men (41.2%)) with AH stage II, of which 84 (main group) - with asymptomatic HU with UA >360 µmol/l (EULAR, 2006), and 81 - with normouricemia (comparison group). The age of the subjects (56.35 ± 0.62) years, with no significant difference between groups. The control group consisted of 30 relatively healthy individuals of the same age and sex.

The diagnosis of AH was established according to the Unified clinical protocol of primary, emergency and secondary (specialized) medical care "Arterial hypertension" of Ministry of health of Ukraine (17) and to the 2018 ESC/ESH Guidelines for the management of arterial hypertension (18).

The criteria for inclusion of patients in the study were the presence of AH stage II, chronic HF I or II A stages (according to the classification of MD Strazhesko and VH Vasylenko) and I or II NYHA. Additional mandatory criteria for inclusion of patients in the main group were the presence of elevated UA in the blood more than 360 µmol/l, preserved LV systolic function.

Exclusion criteria were secondary hypertension, HF II B and III stages (Strazhesko, Vasylenko), III and IV FC HF according to NYHA, complicated hypertensive crises, myocardial infarction, acute HF, TIA / acute stroke, acute and chronic renal failure, complex arrhythmias, defects heart disease, COPD and other clinically significant comorbidities, as well as the use of uricodepressants during the last 4 weeks.

Informed written consent was provided by all participants. Ethical approval was obtained from I. Horbachevsky Ternopil National Medical University Ethics Committee (No 35 08/V, 2020).

Among the 165 patients with AH included in the study, HU was detected in half (50.9 %) of patients, and LV DD in 81.2 %. The presence of concomitant HU in patients with AH is accompanied by an increase in LV DD up to 96.4 % (p <0,001). The main group consisted of 81 patients with AH with comorbid HU (out of 84 patients) and existing LV DD, for comparison used data from 54 patients with normouricemia and LV DD and 27 patients with normal UA values and without LV dysfunction (comparison group).

In addition to the generally accepted clinical and laboratory methods of examination recommended by current clinical protocols, an assessment of the clinical course of AH and LV diastolic function in normo- and hyperuricemia was performed; laboratory tests: UA, NT-proBNP, lipid profile,

intensity of lipid peroxidation (LPO) and activity of enzymes of the antioxidant system (AOS); instrumental examinations: ECG and Echocardiography (Philips HD11XE device).

Lipid spectrum studying (the levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)), calculation of plasma atherogenic index (AI), LPO status evaluation, in particular malonic aldehyde (MA), and AOS studying (sulfhydryl groups (SH groups) level), superoxide dismutase (SOD) and catalase (CAT)) activities were determined.

The results obtained after entering into the electronic database "Microsoft Excel" (10.0) were processed by the method of variation statistics with the calculation of average levels of indicators and assessment of their variability: arithmetic mean (M), standard deviation (σ), mean error (m), with the accepted level statistical significance not less than 95% (p<0,05). Parametric indicators were evaluated according to Student's criteria, and non-parametric - according to Mann-Whitney criteria. Analysis of the relationships between the indices was determined by Pearson's linear correlation (r) and Spearman's rank correlation (rs). Statistical processing of the obtained data was performed using software packages "Statistica. Version 10.0» (Statsoft, Inc, USA) and SPSS Statistica (Version 21).

Results

It was established that the frequency of HU increased with intensifing severity of AH. Thus, 80.3 % of patients with the 3 degree of AH had elevated UA level. The UA level in patents of this group was higher than in patients with 1 and 2 degrees of hypertension in both HU and normouricemia. There was a direct correlation between the level of UA with the degree of AH in patients with HU (r = 0.52, p <0.001) and in patients with normouricemia (r = 0.28, p = 0.010), which indicates the relationship between hypertension and purine disorders. The main group was significantly dominated by patients with higher FC of HF. Thus, among patients with AH and HU there were 34.5 % of patients with I FC HF, 65.5 % - with II FC HF, while among patients with AH without concomitant HU - 87.6 % and 12.4 % respectively. There is a direct correlation between the level of UA and FC HF (r = 0.61, p <0.001). Thus, the comorbidity of hypertension with HU is associated with more pronounced functional disorders of the myocardium and the progression of HF.

LV DD was diagnosed in 96.4 % patients in the main group with HU against 66.7 % in the group of patients without elevated UA level (p <0,001). This indicates that HU is associated with a significantly higher frequency of LV DD (p <0.001). In patients of the main group, the level of UA was directly correlated with end-diastolic size of LV (r = 0.50, p = 0.002), which confirms the influence of purine metabolism disorders on myocardial remodeling and progression of HF. Close correlations were established between NT-proBNP with some indicators of LV DD, which confirmed the usefullness of its detection in patients with AH for early diagnosis. The rate of movement of the fibrous ring of the mitral valve E' was lowest in patients with AH with HU with pseudonormal type of LV DD (p <0.001). An inverse correlation between the level of UA and E' (r = -0.52, p <0.001) was found in patients with AH followed by HU but a direct correlation between UA and the ratio of the rate of early diastolic filling E to E' (E/E') (r = 0.56, p <0.001). Thus, HU is one of the important factors that cause increased stiffness of the myocardium and arterial wall, which initiate the development and progression of diastolic heart failure. In patients with AH with normouricemia, a correlation between the level of UA and such indicators as E 'and E/E', respectively, r = -0.51 (p <0.001) and r = 0.45 (p <0.001) were also found. Thus, even within normal values, the UA level has an effect on myocardial stiffness and progression of LV DD.

In patients with AH an increased level of TC was revealed in 73.3 % of patents. The indicators of the lipid profile in patients with AH were significantly affected by disorders of purine metabolism.

Significantly higher levels of TC by 8.4 % (p = 0.009), LDL-C by 16.5 % (p = 0.001) were found in patients with asymptomatic HU, atherogenic index (AI) - by 28.6 % (p = 0.002), respectively, compared to those with normal UA values. An inverse correlation was found between the level of HDL-C and UA (r = -0.24, p = 0.029) and a direct correlation - between AI and UA (r = 0.29, p = 0.007), which

confirms the synergism in disorders of lipid and UA metabolism.

Increased atherogenicity of blood lipids was statistically associated with deterioration of LV diastolic function. In particular, an inverse correlation was found between LDL-C and E ' (r = -0.56, p = 0.004), and a direct correlation - with time of deceleration of early diastolic flow (T dec) (r = 0.53, p = 0.003). In general, an increase in TC was found in 77.3 % of patients with AH and LV DD with HU, with a direct correlation between the level of TC and FC HF (r = 0.35, p <0.001), as well as between the level of LDL-C and FC HF (r = 0.54, p <0.001).

As a result of comparing the indices of LPO and AOS, it was found that the content of malonic aldehyde (MA) in patients with AH and HU exceeded this index in patients with normouricemia by 8.1 % (p = 0.012), and was 2.3 times (p <0.001) higher, than in the control group (Table 2). The activity of catalase (CT) and superoxide dismutase (SOD) in the main group of patients was 13.3 % (p = 0.03) and 11.7 % (p = 0.002) lower, respectively, than in patients with normouricemia, and 63.2 % (p <0.001) and 41.1 % (p <0.001) lower compared to control values. There is a direct correlation between an increase in UA and an increase in MA content (r = 0.35, p = 0.007), which indicates the relationship between excessive activation of lipoperoxidation processes and an increase in UA content in the blood.

In patients with AH with LV DD, severe FC HF was associated with excessive intensification of LPO processes and weakening of AOS activity, which is confirmed by the revealed correlation between MA and FC HF (r = 0.42, p = 0.002). An inverse correlation between MA and E '(r = -0.39, p <0.001) and a direct correlation between CT and E' (r = 0.34, p = 0.002) was revealed in patients of the main group with asymptomatic HU, which indicates the relationship between excessive LPO of blood plasma and increased myocardial stiffness in patients with comorbid HU. Thus, increased myocardial stiffness, impaired relaxation of the heart muscle and, consequently, the progression of diastolic HF is accompanied by excessive lipid peroxidation and decreased antioxidant potential.

Discussion

More pronounced hemodynamic changes were found in examined patients with AH and LV DD followed by HU rather than by normouricemia. It should be noted that in patients with HU we have examined, the NT-proBNP index was significantly higher than in patients with normouricemia. The obtained data coincide with the results of other authors who found an association of BNP or NT-proBNP with the severity of both systolic and diastolic heart dysfunction (10, 14, 19).

In our study, a direct correlation was found between NT-proBNP and UA levels in patients with HU (r = 0.714, p = 0.047). Some authors found that the increase in the concentration of NT-proBNP and UA in the serum of patients is closely correlated with the course of acute HF, and convinced that the combination of UA and NT-proBNP levels appears to be more useful than either marker alone as an independent predictor for short-term outcomes in patients with acute HF (20). Our data, as well as the results of a number of other studies confirm the importance of determining NT-proBNP as a marker for early diagnosis of diastolic HF, which can be used for timely correction of therapy and prevention of HF progression, especially in HU.

In patients with AH with LV DD, an inverse correlation was found between LDL cholesterol and echocardioscopic index E '(r = -0.56, p = 0.004), as well as a direct correlation with Tdec (r = 0.528, p = 0.003), which is evidence of deterioration of LV diastolic function with a simultaneous increase in atherogenicity of blood lipids. These changes in the lipid spectrum confirm a more pronounced atherogenic dyslipidemia in patients with AH as diastolic HF progresses. At the same time at pseudonormal type of LV DD the direct correlation between TC and NT-proBNP was revealed (r = 0,424, p <0,001), that also confirms atherogenic changes in blood at HF progression. There are data that atherogenic changes in the blood lipid spectrum were found in patients with chronic HF (21-24).

In our patients with AH with LV DD, more severe hypertension and FC of HF were associated with more pronounced pathological changes in the processes of LPO and a weakening of the activity of antioxidant enzymes. This is confirmed by the detected direct correlation between MA and FC of HF (r = 0.424, p = 0.002), as well as the inverse

correlation between SOD and systolic AP (SAP) (r = -0.577, p = 0.001) in patients with AH with LV DD. Similar data were obtained in our previous studies (21-23) and in the studies of Lankin V.Z. et al., who studied the indicators of LPO and AOS and pointed to the important role of oxidative stress and reduced AOS activity in the pathogenesis of CVDs (25).

In patients with AH with comorbid HU, a direct correlation between MA and of the aorta stiffness index was found (r=0.361, p=0.001), which confirms the relationship between excessive lipoperoxidation in the blood and increased arterial stiffness.

HU have been linked to dyslipidemia, insulin resistance (IR), and AH (26-28). IR is a key feature of metabolic syndrome, linking obesity, impaired glucose intolerance, dyslipidemia, and AH (29, 30). Lu W. et al. reported a significant relationship between HU and lipid metabolic disturbances in a rat model of hyperuricemia (31); moreover, recent studies revealed that high serum uric acid levels correlate with an increased TG to HDL-C ratio in patients (32). There are data that TG is an independent risk factor for HU (33).

Our results indicate that the increased concentration of UA in blood plasma may be associated with increased LDL oxidation, excessive accumulation of lipoperoxidation products and, thus, contribute to endothelial dysfunction and the development of atherogenesis in the vascular wall. Vascular damage, which results from lipid deposition and oxidative stress to the vessel wall, triggers an inflammatory reaction, and the release of chemoattractants and cytokines worsens the IR and endothelial dysfunction (34).

Conclusions

1. The correlation between the level of uric acid and the degree of hypertension (r = 0.52, p <0.001) and between the level of uric acid and the functional class of heart failure (r = 0.61, p <0.001) indicates the aggravating effect of hyperuricemia on the course of hypertension and heart failure.

2. Comorbidity of hypertension with hyperuricemia is accompanied by the development of diastolic dysfunction of the left ventricle in 96.4%, against 66.7% (p <0.001) in the group of patients with normouricemia. In hyperuricemia, a decrease in the maximum velocity of the mitral valve ring in the phase of early filling of the left ventricle E '(p = 0.04) and an increase in the ratio E/E' (p = 0.02) indicates greater myocardial stiffness in comorbidity of hypertension with hyperuricemia.

3. The parallelism between hemodynamic and metabolic disorders in patients with hypertension was revealed. The development of diastolic dysfunction is accompanied by changes in plasma atherogenicity and at the same time depends on the level of uric acid, which is confirmed by the correlation, on the one hand, between the value of low-density lipoprotein cholesterol and the maximum velocity of the mitral valve ring in the phase of early filling of the left ventricle E '(p = 0,004), and on the other - between hyperuricemia and an increase in total cholesterol (r = 0,39, p <0,001), the atherogenic index of plasma (r = 0,35, p <0,001) and the malonic aldehyde level (r = 0.39, p = 0.007).

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Table 1. Indices of blood lipid spectrum in patients with AH with normo- and hyperuricemia (M±m)

Index	Patients with AH with normouricemia (n=81)	Patients with AH with hyperuricemia (n=84)	p
TC, mmol/L	5,12±0,12	5,55±0,09	p=0,009
HDL-C, mmol/ L	1,07±0,03	1,01±0,02	p=0,140
LDL-C, mmol/ L	2,85±0,06	3,32±0,11	p=0,001
TG, mmol/ L	1,71±0,05	2,04±0,08	p=0,040
AI, standard units	3,57±0,09	4,59±0,12	p=0,002
Note: p – significant difference as compared to the normouricemia patients			

Table 2. Indices of LPO-AOS in patients with AH with normo- and hyperuricemia (M±m)

Index	Control group, (n=30)	Patients with AH with normouricemia (n=81)	Patients with AH with hyperuricemia (n=84)	p
MA, umol/ L	2,79±0,01	6,05±0,12*	6,54±0,11*	p=0,012
CP, mg/L	189,55±2,14	177,28±8,46*	160,46±8,07*	p=0,250
SH- groups, umol/ L	52,34±1,22	45,83±1,51*	42,57±0,57*	p=0,020
CT, %	17,12±0,38	12,27±0,32*	10,83±0,35*	p=0,030
SOD, units	64,20±0,42	42,82±0,77*	37,83±0,64*	p=0,002
Notes: 1.* – significant difference as compared to control group; 2. p – significant difference as compared to the normouricemia patients.				