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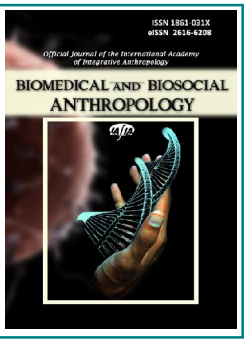

Associations of excess myocardial mass, echoreflectiveness and aldosterone synthase gene polymorphism in men with hypertension

Osovska N. Y., Lozinska M. S., Lozinsky S. E., Taran I. V., Mazur Y. V., Dovganiuk I. E., Gribenuk O. V., Kuzminova N.V.

National Pirogov Memorial Medical University, Vinnytsya, Ukraine

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CORRESPONDING AUTHOR

e-mail: lozserg1@gmail.com

Lozinsky S. E.

Hypertensive remodeling of the left ventricle (LV) is largely due to the influence of a number of control genes. In particular, the regulatory gene CYP11B2, which is responsible for the activity of aldosterone in blood plasma, affects the processes of cardiomyocyte hypertrophy, myocardial fibrosis and microcirculation. This study is devoted to the search for the effect of polymorphic aldosterone synthase carriers on the severity of the components of left ventricular hypertrophy in men with essential hypertension (EH) and representatives of the control group, residents of Podyllia region. The aim of the study was to determine associations between excess (inappropriate) myocardial mass, parameters of standard echocardiography and parameters of echoreflectivity in men with essential hypertension, carriers of different polymorphic variants of aldosteronesynthase gene. The study involved 150 men, aged 45-60 years, residents of the Podyllia region, who had no irreversible damage of target organs. Among them, 50 were in the control group, 58 - had EH of 1st stage and 42 men had EH of 2nd stage. All participants were measured for office blood pressure, performed a standard echocardiographic examination with the addition of standard EchoCG protocol by determination of the parameters of echoreflectivity and evaluation of appropriateness of left ventricular l mass (LVM) to hemodynamic load, according to the formula de Simone et al. and calculating the excessiveness ratio (ER) and determined the C-344T polymorphism of the CYP11B2 gene in venous blood samples by PCR. Statistical processing of the obtained results is performed using a specialized statistical application "Statistica 12.0". It was found that the prevalence of CC polymorphism of the CYP11B2 gene in men with inappropriate LVM was almost twice higher than in men with appropriate to hemodynamic load LVM ($p=0.015$ by criterion χ^2). At the same time, men with inappropriate LVM were characterized by higher values of echoreflectivity parameters BB and mCSV. In contrast to patients of the control group and patients with EH of 1st stage, patients with EH of 2nd stage, actual LVM (287.4 (53.9) g) significantly ($p<0.001$) exceeded the predicted values (189 (37.8) g). According to the results of Spearman's rank correlation analysis, it was found that the carrier of the CC genotype of aldosterone synthase gene is associated with higher values of the LVM ER. Thus, patients carrying the polymorphic CC variant of CYP11B2 gene are characterized by more pronounced cardiomyocyte hypertrophy, greater excess of LV mass relative to individual hemodynamic needs, more aggressive processes of myocardial fibrosis.

Keywords: *aldosteronesynthase, CYP11B2, aldosterone, hypertension, left ventricular hypertrophy, excessiveness ratio, inappropriate left ventricular mass.*

Introduction

Left ventricular hypertrophy (LVH) is an important risk factor for sudden death, heart failure, myocardial infarction or stroke [15, 17, 18, 23]. It is known that the most characteristic variant of myocardial remodeling in patients with HD is concentric LVH [24]. According to current data, LVH is not only a hypertrophy of cardiomyocytes, but also includes the processes of fibrosis and changes in the microcirculatory tract [2]. Assessing the severity of LV remodeling processes is an integral part of the standard echocardiogram protocol, as it largely determines the

patient's prognosis [11]. Attempts to improve the prognostic value of echocardiography for patients with HD de Simone and co-authors have proposed a method for assessing the compliance/inconsistency of LV mass with blood pressure (BP). It was noted that the presence of excess LV myocardial mass had an additional negative impact on the prognosis in this cohort of patients [4].

The aldosterone synthase gene (CYP11B2), which is the main regulator of aldosterone activity in plasma, according to previous studies, had a significant effect on blood pressure and the severity of structural and functional changes in the myocardium in patients with hypertension [6, 7, 16, 19]. Myocardial fibrosis is also an important sign of hypertensive heart, which is currently more difficult to detect than the actual LV hypertrophy [9, 22]. Changes in myocardial density resulting from fibrosis can be detected by echoreflective analysis [5]. This technique is one of the possible approaches for the quantitative assessment of myocardial fibrosis and indirectly reflects the state of myocardial diastolic function. The gold standard for assessing the severity of fibrosis is to determine the volume fraction of interstitial collagen [20]. Previous studies have shown that echoreflectiveness showed a strong correlation with the volume fraction of interstitial collagen [5]. Therefore, echoreflective analysis was chosen to assess the fibrous component in hypertensive LV remodeling.

The aim of the study was to determine whether there are associations between excess (inappropriate) myocardial mass, parameters of standard echocardiography and parameters of echoreflectiveness in men with essential hypertension when carrying polymorphic variants of the aldosterone synthase gene.

Materials and methods

The study involved 150 men, aged 40-60 years, residents of the Podillia region, who had no irreversible damage to target organs. Among them, 50 were in the control group (men without signs of cardiovascular pathology), 58 - had HD stage I and 42 men had HD stage II. All study participants were measured for office blood pressure, performed a standard echocardiographic examination with the addition of the examination protocol to determine echoreflective parameters and determine the C-344T polymorphism of the CYP11B2 gene in venous blood samples by PCR. The study was performed in compliance with the bioethical norms of the Declaration of Helsinki, the relevant provisions of the WHO and the laws of Ukraine. Each study participant signed an informed consent to participate in the study. Study participants did not receive antihypertensive therapy or at the time of the examination, the break in taking antihypertensive drugs was at least 1 month.

Studies of the structural and functional state of the heart were performed using echocardiography using equipment "Imagic Sigma 5000" (Kontron Medical) transthoracic method in the supine position in the left side in M- and B-modes, according to the recommendations of the American Association of Echocardiography (ASE), basic hemodynamic parameters.

To determine the type of LV remodeling, the relative wall thickness index (RWT) was calculated, taking the values of less than 0.42 and LVMMI as the normal RWT value.

The criterion for left ventricular hypertrophy was considered to be the index of LVMM, indexed to the patient's height. Given that only men participated in the study, the cut-off level was 50 g/m$^{2.7}$ [21].

According to the obtained echocardiographic parameters, the correspondence of the left ventricular myocardial mass to the blood pressure level was calculated according to the formula proposed by De Simone et al. [3]:

LVMp = 55.37 + 6.64 x height (m)$^{2.7}$ + 0.64 x W - 18.07 x sex,

where LVMp - appropriate LVMM, SW - Stroke Work (hemodynamic load, or "shock work"), calculated by the formula: SW=CAT x SV x 0.0144, sex - for men, this ratio is 1. In case of exceeding the predicted values of myocardial mass is considered inappropriate (inadequate) hemodynamic load.

Echoreflective analysis was performed according to the method described by Hiremath P. et al. [5]. Initially, a qualitative image of the left ventricle was obtained from the parasternal access in longitudinal section into the diastole phase. This image was stored in a database and subjected to spectral analysis using a special software package for

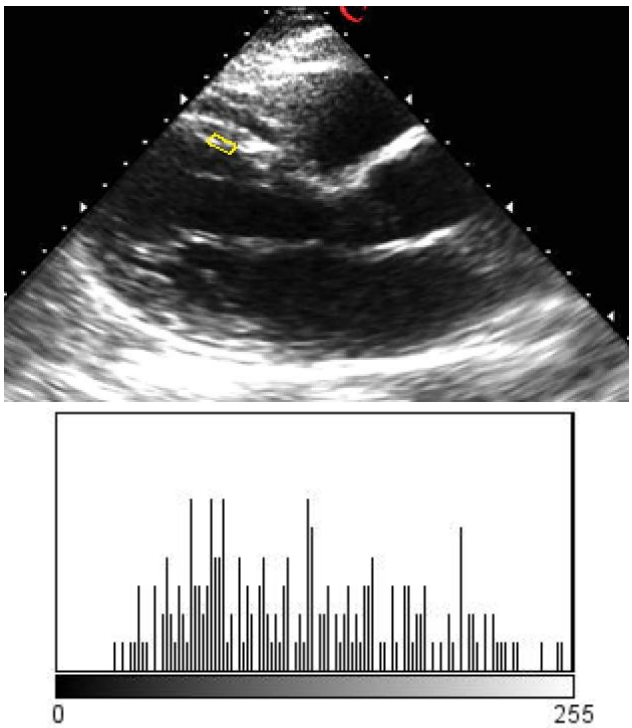

Fig. 1. Methods of echoreflectiveness analysis. On the left - the received image of a left ventricle. The area of interest (ROI) is highlighted in a yellow rectangle. On the right - the spectrum of the intensity of the gray scale within the ROI.

image analysis "ImageJ". The image of the interventricular septum highlighted an area of interest (ROI), measuring 20 x 10 mm, the boundaries of which were not in contact with the endocardium. Next, we analyzed the pixel intensity of the selected area on a gray scale, which consisted of 255 color gradations. Parameters such as Broad Band (BB) - bandwidth, Kurtosis (K) - slope steepness and Skewness (Sk) - slope steepness, mean color scale value (mCS) - average value of spectrum intensity were obtained. An example of the image and the obtained spectrum of the interventricular septum is presented in Figure 1.

CYP11B2 gene polymorphism was determined by PCR in venous blood samples collected on the day of the visit.

Statistical processing of the obtained results was performed using a specialized statistical application "Statistica 12.0". The obtained data were checked for belonging to the normal distribution law. In the case of compliance with the normal distribution, the results obtained were given as the mean and standard deviation. In case of discrepancy, the median was given, indicating 25-75 % of quartiles, including half of all parameter values. When comparing groups for one parameter or another in the normal distribution used Student's t test, and in the absence of a normal distribution - the Mann-Whitney test. For the convenience of graphical presentation and comparison of data, the display of 95 % confidence intervals was used.

Results

A total of 50 men without signs of cardiovascular pathology and 100 men with hypertension were examined. Among the last 58 participants had hypertension without any damage to target organs, and 42 patients had hypertension with LVH, established by values of LVMMI >50 g/m$^{2.7}$. The results of anthropometry and standard echocardiography for the examined groups are presented in table 1.

Analysis of anthropometric parameters revealed that the groups of subjects did not differ in age or height, but body weight increased significantly ($p<0.001$ test ANOVA) with the group number (Fig. 2).

The same trends were observed in the analysis of SBP and DBP ($p<0.001$) (Fig. 3).

In turn, the analysis of LVMM in the study groups found that LVMM indexed to the growth of patients in the control group and the group of men with HD stage I did not differ significantly, while in patients with HD stage II it was significantly higher than in the groups 1 and 2 (Fig. 4).

All patients examined by us were divided on the basis of determining the adequacy of left ventricular mass. As a result, 45 were classified as having adequate and 105 as patients with inadequate LVMM.

When calculating the appropriate values of LVMM for the groups we examined, we found that the values of PLVMM, calculated by the formula, increased relatively evenly (Fig. 5).

Table 1. Comparative characteristics of anthropometric and Echo-CG parameters in the groups of examined (M ± SD).

Indices	Control group (Group 1), n=50	HD I stage (Group 2), n=58	HD II stage (Group 3), n=42	p
Average age, years	49.41±5.00	49.64±5.82	49.22±5.81	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Height, cm	175.1±11.4	176.5±6.8	178.4±5.5	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
Body weight, kg	81.00±14.00	94.72±19.23	103.6±16.8	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
SBP, mm Hg	124.5±16.4	151.4±18.2	160.1±23.0	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
DBP, mm Hg	76.12±9.94	92.33±12.0	96.11±13.83	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
FDS, mm	48.62±5.21	48.91±5.22	52.1±5.61	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
FSS, mm	32.72±4.13	33.31±4.53	34.32±5.61	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
EF, %	61.21±7.72	59.93±7.72	59.72±10.61	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
LVMM	160.4±36,4	172.9±34,9	287.4±36,1	$p_{1-2}>0.05$ **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
LVMMI, g/m$^{2.7}$	36.42±14.54	37.31±7.00	60.31±12.00	$p_{1-2}>0.05$ **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
RLVW, mm	9.421±1.311	9.932±1.512	12.51±4.74	$p_{1-2}>0.05$ **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
IVW, mm	9.120±1.110	9.831±1.622	13.51±2.13	$p_{1-2}>0.05$ **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
RWT	0.392±0.063	0.411±0.072	0.524±0.112	$p_{1-2}>0.05$ **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**
E	0.781±0.141	0.710±0.140	0.662±0.142	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** $p_{2-3}>0.05$
A	0.610±0.110	0.612±0,161	0.571±0.143	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
E'	0.161±0.041	0.082±0.034	0.061±0.032	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** $p_{2-3}>0.05$
E/A	1.311±0.271	1.253±0.474	1.221±0.373	$p_{1-2}>0.05$ $p_{1-3}>0.05$ $p_{2-3}>0.05$
E/E'	5.123±1.324	9.912±3.791	13.14±4.35	**$p_{1-2}\leq0.05$** **$p_{1-3}\leq0.05$** **$p_{2-3}\leq0.05$**

Continuation of table 1.

Indexes	Control group (Group 1), n=50	HD I stage (Group 2), n=58	HD II stage (Group 3), n=42	p
LA volume index, ml/m^2	19.52±2.76	30.31±4.98	34.91±3.10	**$p_{1-2}\leq0.05$ $p_{1-3}\leq0.05$ $p_{2-3}\leq0.05$**

Note: p - the significance of the difference according to the Mann-Whitney test.

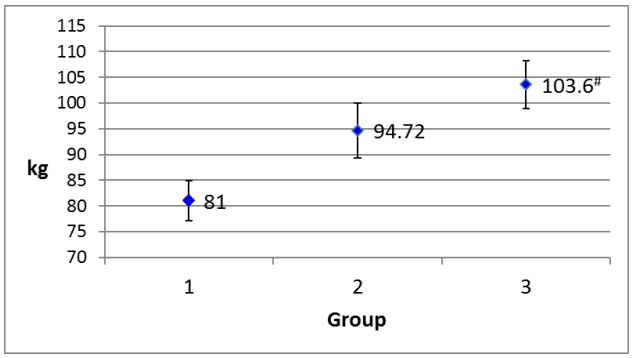

Fig. 2. Body weight at 95 % confidence interval (CI) in the groups of examined patients.
Notes: 1 - control group; 2 - group of patients with HD stage I; 3 - group of patients with HD stage II; dashes indicate 95 % of CI; * - the significance of the difference from the control group p≤0.05; # - significance of the difference from the group of patients with stage I HD and the control group p≤0.05.

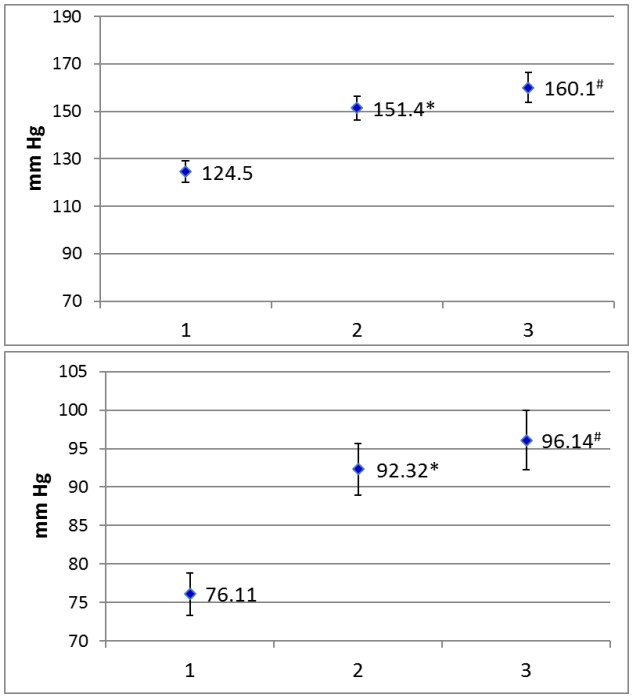

Fig. 3. Mean values and 95 % CI SBP (right panel) and DBP (left panel) in the groups of examined patients.
Notes: 1 - control group; 2 - group of patients with HD stage I; 3 - group of patients with HD stage II; dashes indicate 95 % of CI; * - the significance of the differences between the group of patients with HD stage I from the control group p≤0.05; # - the significance of the differences between the group of patients with stage II HD from the control group p≤0.05.

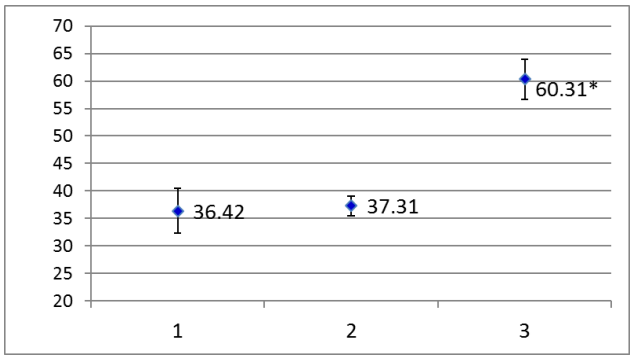

Fig. 4. Characteristics of LVMMI in groups of examined (g/m$^{2.7}$).
Notes: 1 - control group; 2 - group of patients with HD stage I; 3 - group of patients with HD stage II; dashes indicate 95 % of CI; * - the significance of the difference between the group of patients with stage II HD from the group of patients with stage II HD and the control group p≤0.05.

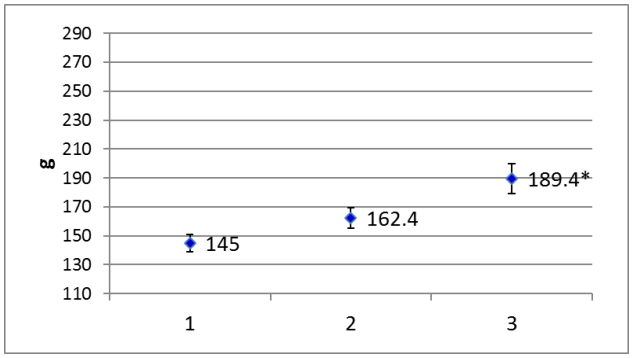

Fig. 5. Values and 95 % confidence interval for proper LVMM in groups of subjects.
Notes: 1 - control group; 2 - HD stage I; 3 - HD stage II; * - the significance of the difference between the group of patients with HD 2 from the control group (p<0.05 according to the Mann Whitney test).

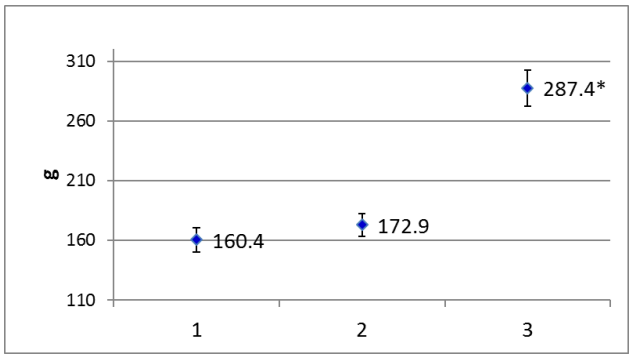

Fig. 6. Values and 95 % confidence interval for the actual values of LVMM in the groups of subjects.
Notes: 1 - control group; 2 - HD stage I; 3 - HD stage II; * - the significance of the difference between the group of patients with stage II HD from the control group and the group of patients with stage I HD (p<0.05 according to the Mann Whitney test).

Unlike the proper ones, the actual values of LVMM varied unevenly. The differences between the groups of patients with stage II HD and stage I HD were much more noticeable and significant compared with the differences between the group of patients with stage I HD and the control group

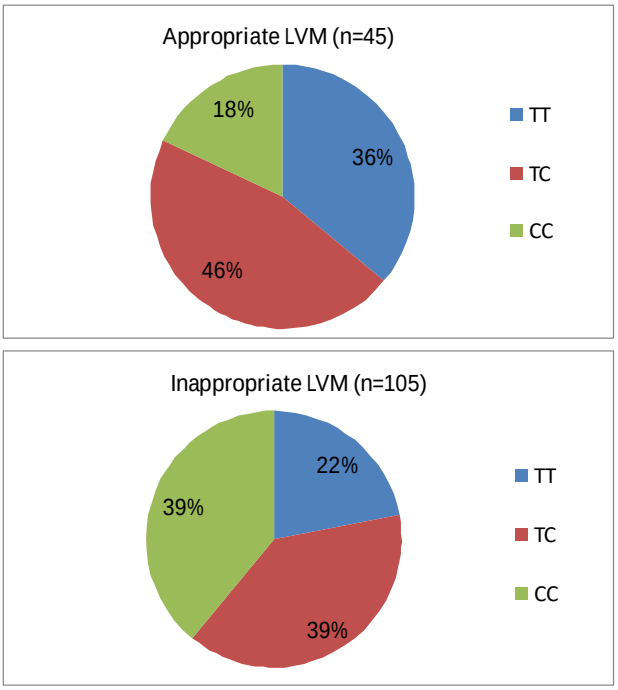

Fig. 7. Frequency (%) of CYP11B2 gene polymorphism in patients with corresponding left ventricular mass (right panel) and inappropriate left ventricular mass (left panel).

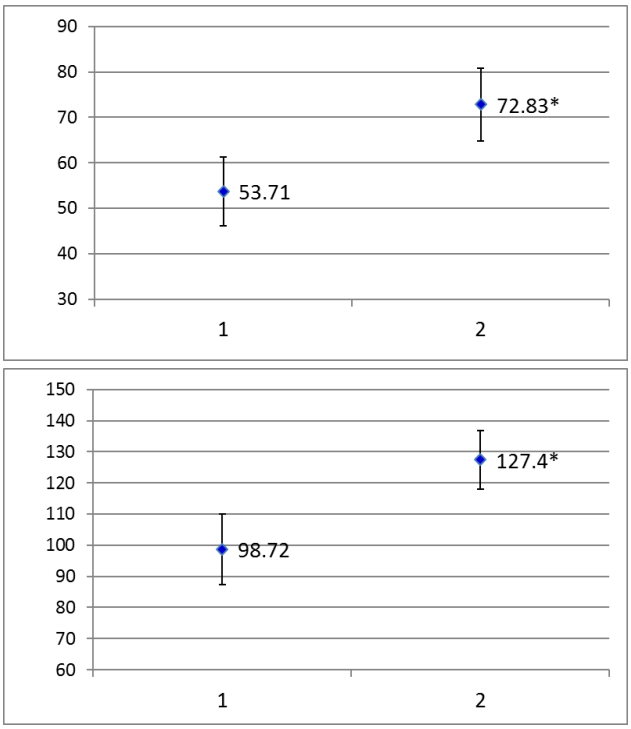

Fig. 8. Average values and 95 % confidence interval for the spectrum bandwidth of the reflected explosive signal BB (right panel); and the average intensity of the reflected ultrasound signal mCSV (left panel) in a group of patients with adequate and inadequate left ventricular myocardial mass.
Notes: 1 - group of patients with adequate LVMM; 2 - group of patients with inadequate LVMM; * - the significance of the difference according to the Mann-Whitney test $p<0.05$.

(Fig. 6).

Despite the very similar values of blood pressure in groups 2 and 3, the group of patients with stage II HD had significantly higher values of LVMM. Moreover, the difference between the actual values of LVMM and proper values of LVMM (PLVMM) in the group of patients with stage I HD was insignificant (172.9±34.9 g vs. 162.4±25.7 g; $p>0.05$), whereas in the group of patients with stage II HD LVMM values were significantly higher than PLVMM (287.4±53.9 g vs. 189.4±37.8 g, $p<0.001$ according to the paired Wilcoxon test). This is plausible evidence of an internal, possibly genetic, difference between patients with and without LVH. Therefore, some additional markers need to be studied to more accurately predict the corresponding LVMM values in these patients.

Therefore, the frequencies of aldosterone synthetase gene polymorphism were further determined based on the division of the examined patients into groups on the basis of LVMM compliance/non-compliance. Among patients with the corresponding LVMM, 8 men were carriers of the TT genotype, 16 had the CC genotype and almost half of the patients in this group (21 people) had the TC genotype. The vast majority of the patients we examined had an inadequate hemodynamic load of LVMM. Among them, 23 subjects were carriers of the TT genotype, and the frequency of TC and CC genotypes was the same and amounted to 41 people, respectively (Fig. 7).

As shown in the diagrams, the prevalence of CC polymorphism of the CYP11B2 gene in men with inappropriate LVMM was almost twice as high as among those with a corresponding hemodynamic load of LVMM. These differences were statistically significant by the criterion χ^2 ($p=0.015$).

Analysis of echoreflective parameters in groups reclassified by LV mass adequacy showed that patients with inadequate hemodynamic load LV mass were characterized by higher values of the spectrum of the reflected ultrasound signal (BB) and higher values of the average intensity of the reflected ultrasound signal, (mCSV), as shown in Figure 8.

Numerous studies have shown that the emergence of different types of myocardial remodeling is associated not only with hemodynamic load, but also with the impact on the heart of neurohumoral factors, the degree of activity of which is genetically determined. It is unknown at this time whether there are associations between left ventricular overweight and carriers of polymorphic variants of the CYP11B2 gene, which is an important component of RAAS that regulates plasma aldosterone activity. To clarify this question, Spearman's rank correlation was performed between LV excess mass ratio redundancy ratio (RR), which quantitatively reflects the degree of LV excess in relation to individual hemodynamic parameters and the frequencies of individual types of polymorphic variants of the aldosterone synthase gene. To do this, all respondents were ranked according to their redundancy ratio. All patients were

Table 2. Frequency distribution of CYP11B2 polymorphism among subjects ranked by adequacy ratio.

RR	TT	TC	CC
0.742	1	8	1
0.882	4	6	0
0.953	5	4	1
1.011	2	8	0
1.051	4	3	3
1.114	2	6	2
1.142	4	4	2
1.181	2	6	2
1.221	4	3	3
1.263	3	5	2
1.352	4	6	0
1.441	3	4	3
1.544	1	6	3
1.752	1	5	4
2.081	2	3	5

Table 3. Frequency distribution of CYP11B2 polymorphism among subjects ranked by left ventricular myocardial mass index.

LVMMI (g/m^2)	CC	TC	TT
52.83	0	6	4
65	2	4	4
74.12	3	4	3
79	3	4	3
81.91	2	5	3
85	1	8	1
89	2	6	2
94.54	4	3	3
99.12	4	3	3
103	1	6	3
109.8	2	6	2
118.4	2	7	1
127.6	3	3	4
138.4	2	6	2
165.7	0	6	4

divided into dozens, resulting in the formation of 15 groups of patients. In each of the 15 groups, the mean value of RR and the carrier frequency of each of the CYP11B2 gene polymorphisms were determined. The result was a data matrix presented in table 2.

The analysis revealed a moderate direct (r=0.70), significant (p<0.05) correlation between RR and the frequency of the CC genotype. Correlations with TC and TT genotypes were insignificant (r= -0.30 and r= -0.36; p<0.05). Thus, the frequency of the C allele increased significantly with increasing RR.

Using the technique described above, a correlation analysis was performed between the frequencies of the polymorphism and the LVMM index (Table 3).

It showed no significant correlation for any of the polymorphism variants. For the CC genotype r= -0.04, for the TC - r=0.16; TT - r= -0.36 (p>0.05 for all coefficients).

Discussion

The presence of an inappropriate level of hemodynamic load of LVMM in patients with uncomplicated HD is associated with a higher risk of cardiovascular events [8]. Studies have shown that the higher LVMM does not meet the appropriate values, the more pronounced is the degree of diastolic dysfunction and this may be a predictor of heart failure in patients with HD [14]. We found that PLVMM was associated with higher values of echoreflective parameters of mCSV and BB, which indirectly indicate the severity of DD. Additionally, we calculated a redundancy ratio that quantifies the difference between the appropriate and actual LVMM values for each individual patient. In our opinion, RR has additional prognostic value along with the standard assessment of LVH according to the Ganau criteria, because it is personalized and can be used not only in patients with HD, but also in healthy individuals. RR can also be informative for the assessment of changes in LVMM in the dynamics of patients receiving antihypertensive drugs that can affect the processes of myocardial remodeling. Thus, in a study by Gian Paolo Rossi, Maurizio Cesari, et al. evaluated the compliance of LVMM with treatment in patients with primary aldosteronism and found that in patients who received adequate treatment for 36 months, LVMM approached the appropriate values [12].

It is known that aldosterone, by acting on mineralocorticoid receptors, activates the MR-p38 MAPK-dependent pathway, which leads to increased expression of cardiotropin-1 protein, prohypertrophic cytokine, IL-18 and causes cardiomyocyte hypertrophy [10, 13]. Depending on the level of aldosterone activity, the parameters of compliance/non-compliance of LVMM with the level of hemodynamic load also change [10]. It was found that PLVMM significantly χ^2 (p=0.015 by criterion χ^2) correlated with the frequency of carrier of the CC genotype of the aldosterone synthase gene, and the frequency of carrier of the C allele of the CYP11B2 gene significantly increased with increasing RR. This association is confirmed by the results of large-scale meta-analyzes, where the carrier of the CC genotype CYP11B2 was associated with higher values of LVMM, LVMMI, FSS and FDS, compared with homozygotes for the T allele, and the carrier of TT polymorphism was associated with greater LV wall thickness [25].

According to Spearman's correlation analysis, a significant (p<0.05) correlation was found between RR and the frequency of the CC genotype, while no similar

associations were found with LVMMI. The obtained results suggest that the presence of the C allele in the CYP11B2 gene is associated not so much with the myocardial mass itself, but with its excess (non-compliance with individual hemodynamic needs). Thus, determining the carrier of this genotype may be useful to improve the quality of individual prognosis not only in individuals who already have hypertensive myocardial remodeling, but also in patients who do not yet have structural changes in the heart. In turn, the assessment of LVMM compliance allows not only to judge the absence or presence of LVH according to the generally accepted algorithm, but also to calculate the adequacy of the functional reserves of the patient's heart in relation to its hemodynamics. In addition, early diagnosis of LVMM excess can lead to the prevention of left ventricular diastolic dysfunction and associated morbidity and mortality.

The prospect of further research may be related to assessing the compliance of LVMM and calculating the excess rate in other cardiovascular diseases accompanied by myocardial remodeling, as well as the search for associations with biomarkers of fibrosis and myocardial hypertrophy and tracking the dynamics of excess LVMM in patients receiving treatment.

Conclusion

1. Patients with inadequate hemodynamic load LV mass are characterized by more pronounced hypertrophy and myocardial fibrosis, as indicated by significant differences in RR and echoreflectiveness.

2. Carriers of the C allele and the CC genotype of the aldosterone synthase gene are associated with higher values of the LV myocardial overweight factor, which can be considered as an unfavorable prognostic factor given the above associations.

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