

**Indicators of left ventricle hypertrophy in patients with arterial hypertension combined with obesity and their interconnection with polymorphism of Lys198Asn gene of endothelin-1.**

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**Abstract.** One of the independent factors of development of cardio-vascular complications is in left ventricular hypertrophy. Each year more and more publication appear that prove this problem is genetically determined.

**Aim** of the study was to find dependence of left ventricular hypertrophy indexes to polymorphism of Les198Asn gene endothelin-1 and BMI.

**Materials and methods.** We took research in 160 patients with arterial hypertension, using ECG and polymerase chain reaction (PCR). Groups were divided additionally according to BMI (body mass index).

**Results.** It was found, that patients with obesity had their Left ventricular mass and hypertrophy left ventricular indexes higher, than in patients with normal and increased body weight. Carriers of Asn198Asn and Lys198Asn genotypes Left ventricular mass and hypertrophy left ventricular indexes are higher than in carriers of Lys198Lys genotype.

**Conclusions.** It was determined that in patients-carriers of Asn198Asn genotype, Left ventricular mass (LVMI) and hypertrophy left ventricular indexes (LVMMI) were higher compared to patients-carriers of Lys198Lys and Lys198Asn type, both in men and women. The dependence of LVMI and LVMMI are shown to be higher in patients with obesity than in people with normal and increased body mass.

**Key words:** left ventricular hypertrophy, genes` polymorphism, endothelin-1, Lys198Asn genotype.

**Introduction.** Left ventricular hypertrophy is pathological thickening of left ventricular myocardium, developed in response to constant stain on heart, usually caused by chronic hypertension [1]. In short-term prospective this structural change leads to heart compensate

high hemodynamic strain. However, in long-term prospective lasting left ventricular hypertrophy (LVH) is an independent risk factor of development for numerous vascular pathological states, such as cardiac failure, ischemic heart disease, stroke, arrhythmia, sudden cardiac death, cardio-vascular diseases and correspondent mortality [2].

LVH frequency in general population equals 3%, in case of arterial hypertension – 7 – 40% [9]. According to Kannel W.B. et al. LVH, diagnosed with ECG in patients with blood pressure more than 160/95 is met 10 more often than in normotensive patients [3]. Increasing of left ventricular mass index (LVM) is possible before hypertension develops. Douglas P. et al., (2012) writes that LVH risk can be hereditary and cause hypertension. It is proved that increasing of blood pressure alongside with other factors (high body mass, age, male gender, race, neurohumoral and growth) lead to development and progress LVH. One of the main risk factors of LVH development is presence of comorbid diseases: obesity, which provokes increasing of heart afterload, 2 type diabetes. Decreasing of blood pressure, body mass index lead to decreasing of hypertrophy, and in the case of their absence prevents its development [10].

Endothelin-1 (ET-1) is cardiotropic that is occurred as inotropic influence on myocardium, regulates preload and afterload, leads to increasing of myotic process in myocardium and development of LVH [5-8].

The purpose of this research was defining of indexes of intercardial and system hemodynamics in patients with arterial hypertension, according to polymorphism of Lys198Asn gene endothelin-1. Question of implement of current polymorphism factor on LVH level is relevant and requires further studying to improve treatment tactics.

**Aim.** Detection of LVH indexes dependence in patients with arterial hypertension from polymorphism Lys198Asn gene endothelin-1 and body mass index.

## Materials and methods

160 patients with vary arterial hypertension diagnoses of I, II phases 1, 2, 3 levels were examined during the study. Among examined patients were 83 women (51,9 %) and 77 men (48,1%) at the age of 33 – 87 years, median (interquartile range) – 67 (58–67) years. All patients were divided into 3 groups, depending of BMI. I group – BMI < 24,9 kg/m<sup>2</sup>; II group – BMI = 25,0 – 29,9 kg/m<sup>2</sup>; III group – BMI > 30,0 kg/m<sup>2</sup>. I group consisted of 75 patients, in which 41 women (54,7%) and 34 men (45,3 %). Age range of examined patients in I group equaled 68 (60–75) years. In II group were 48 patients, in which 20 women (58,3%) and 28 men (41,7%). Age range of examined persons in II group was 65 (54–76) years. In III group 37 patients were included, 22 women (59,5%) and 15 men (40,5%). Age range of examined patients of III group was 65 (60–77) years.

Dividing of groups according to BMI means anthropometric data varies with statistically significant range of BMI ( $p < 0,05$ , Kruskal-Wallis). Patients with obesity had following circumference of waist: in women 103 (96-115) cm, in men 108 (105–116) cm, that indicated abdominal type of obesity.

With ECG analysis, we studied left ventricular end-diastolic dimension (LVEDd), thickness of the interventricular septum (TIS), PWT in M-mode from parasternal access at the level of mitral valve chord along cardial long axis. Left ventricular myocardium mass (LVMM) was calculated by formula Penn Convention:  $LVMM = 1,06 \times \{ [EDD + DLVPWT + ISTD]^3 - EDD^3 \} - 13,6$  (g). To calculate LVMMI we used formula, recommended by ASE (American Society of Echocardiography) (2005):  $LVMMI = LVMM/height^2,7$ . To confirm the diagnosis of LVH we examined and compared ECG data: LVMM in women >162 g, in men >224 g; LVMMI in women >44 g/m<sup>2,7</sup>, in men >48 g/m<sup>2,7</sup> [13]. Polymorphism of Lys198Asn gene of endothelin-1 was identified with polymerase chain reaction with further analysis of restriction fragments. Data were statistically processed with non-parametric methods, as

division of LVMM (left ventricular myocardium mass) and HLVMM (hypertrophy left ventricular myocardium mass) indexes by Gauss were not equal to normal. For description of LVMM and HLMM we used median data and interquartile range (25th and 75th percentiles). To compare mentioned indexes we used rankings` analysis variation ANOVA by Kruskal-Wallis criteria. Using of this method we checked null hypothesis for absence of difference between groups. If  $p > 0,05$ , than null hypothesis about median difference absence in groups was proved, that means groups were not different. If  $p < 0,05$ , null hypothesis was not proved, and, correspondently, we got alternative hypothesis that proved median difference in groups. In the last case, we compared groups in pairs with non-parametric Mann-Whitney U-test and Bonferroni correction to evaluation of p-value.

Patients were enrolled in the study after informed consent obtained in accordance with the Helsinki Declaration of the World Medical Association on the Ethical Principles of Scientific and Medical Research. The study was approved by the Bioethics Committee for experimental and clinical studies at Sumy State University Medical Institute.

## **Results**

At the first stage we analyzed dependence of ECG data from polymorphism Lys198Asn gene of endothelin-1 (Table I).

Table I

**Median (interquartile range) of ECG indexes of left ventricular myocardium hypertrophy in patients with arterial hypertension, depending on polymorphism Lys198Asn in gene endothelin-1.**

Indicators Genotype	Mass of myocardium of left ventricle, g	Left ventricular myocardial mass index, g/m <sup>2</sup> , <sup>7</sup>
Lys198Lys (n=74)	243 ( 183 – 300)	73 (42 – 88)
Lys198Asn (n=73)	290 (201 – 332)	81 (47 – 90)
(n=13)	320 (285 – 360)	89 (84 – 94)
p (Kruskel-Wallis)	p < 0,003	p = 0,008

The results proved that data of LVMM and LVMMI in patents with arterial hypertension and different genotype polymorphism of Lys198Asn of gene endothelin-1 ( $p_1 = 0,003$ ;  $p_2 = 0,008$ , Kruskel-Wallis). Carriers of Asn198Asn genotype LVMM is 24% higher than in patients with Lys198Lys type ( $p = 0,001$ , Mann-Whitney). Patients with hypertension and Lys198Asn genotype LVMM was 9% higher to Lys198Lys type ( $p = 0,021$ , Mann-Whitney). The same tendency is observed among carriers of Lys198Asn and Asn198Asn types, though, it had not been statistically significant ( $p = 0,136$ , Mann-Whitney). LVMMI in patients with Asn198Asn genotype is higher compared to data of patients-carriers of Lys198Lys type for 17% ( $p = 0,007$ , Mann-Whitney) and 9% higher in Lys198Asn carriers compared to Lys198Lys ones ( $p = 0,028$ , Mann-Whitney). Between carriers of Lys198Asn and Asn198Asn genotypes difference was not statistically significant ( $p = 0,121$ , Mann-Whitney).

Next phase was checking difference existence of LVMM and LVMMI in men and women depending on genotype polymorphism of Lys198Asn of gene endothelin-1. It is determined that there is difference of LVMM and LVMMI in men depending of genotype ( $p_1 = 0,002$ ;  $p_2 = 0,010$ , Kruskel-Wallis). After comparison according to Mann-Whitney method, it was determined that in men-carriers of Asn198Asn genotype LVMM is 31% higher that in representatives of Lys198Lys type ( $p = 0,002$ , Mann-Whitney). In patients-men with

hypertension and Lys198Asn genotype LVMMI is 27% higher comparing to Lys198Lys ( $p = 0,005$ , Mann-Whitney). In carriers of Lys198Asn and Asn198Asn genotypes difference was not statistically significant ( $p = 0,394$ , Mann-Whitney). LVMMI analysis in men with different genotype polymorphism of Lys198Asn of gene endothelin-1 it was determined that in men-carriers of Asn198Asn type LVMMI is 50% higher than in patients with Lys198Lys ( $p = 0,010$ , Mann-Whitney). In carriers of Lys198Asn genotype LVMMI was higher compared to patients with Lys198Lys for 41% ( $p = 0,021$ , Mann-Whitney). In patients with arterial hypertension with genotypes Lys198Asn and Asn198Asn difference in LVMMI was not registered ( $p = 0,223$ , Mann-Whitney) (Fig. 1).

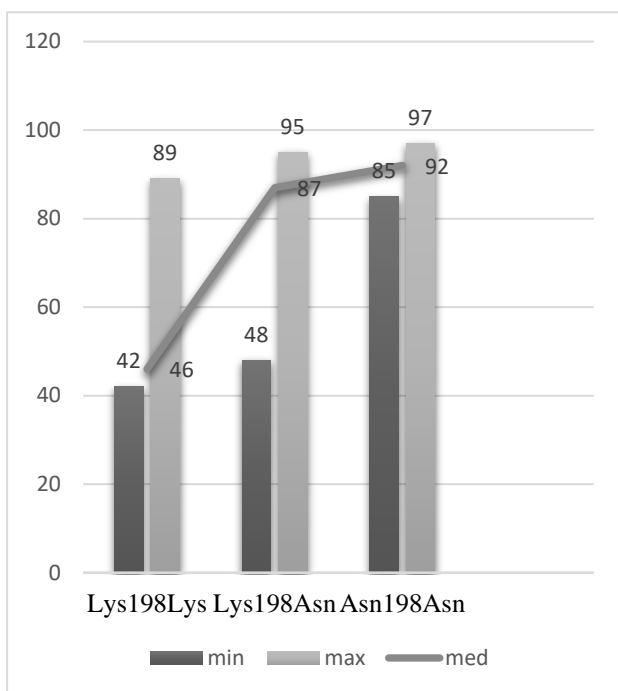
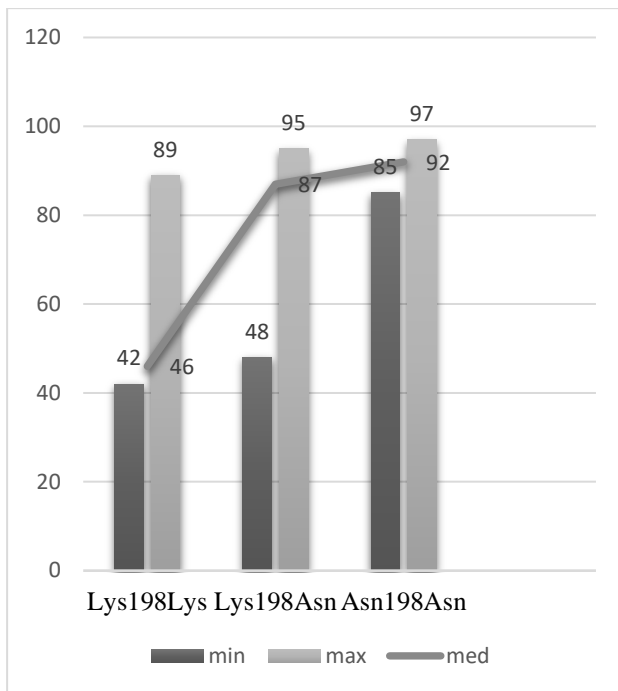


Fig. 1. Median (interquartile range) of ECG indexes in men depending on polymorphism of Lys198Asn in gene endothelin-1.



We additionally checked difference presence of LVMM and LVMMI in women with hypertension depending of genotype polymorphism of Lys198Asn of gene endothelin-1. It was found, that difference is typical for women either ( $p_1 = 0,004$ ;  $p_2 = 0,010$ , Kruskal-Wallis). In women-carriers of Asn198Asn genotype LVMM is 44% higher than in patients with Lys198Lys ( $p = 0,046$ , Mann-Whitney). In women with arterial hypertension and Lys198Asn genotype LVMM was higher for 26% compared to Lys198Lys type ( $p = 0,002$ , Mann-Whitney). In carriers of Lys198Asn and Asn198Asn types difference had not been statistically significant ( $p = 0,547$ , Mann-Whitney). LVMMI in women with Asn198Asn genotype is for 54% higher than in representatives of Lys198Lys genotype ( $p = 0,004$ , Mann-Whitney). In patients-women with hypertension with Lys198Asn genotype LVMMI was higher compared to Lys198Lys genotype for 43 % ( $p = 0,005$ , Mann-Whitney). In women with hypertension and genotypes Lys198Asn and Asn198Asn difference in LVMMI was not registered ( $p = 0,460$ , Mann-Whitney) (Fig. 2).

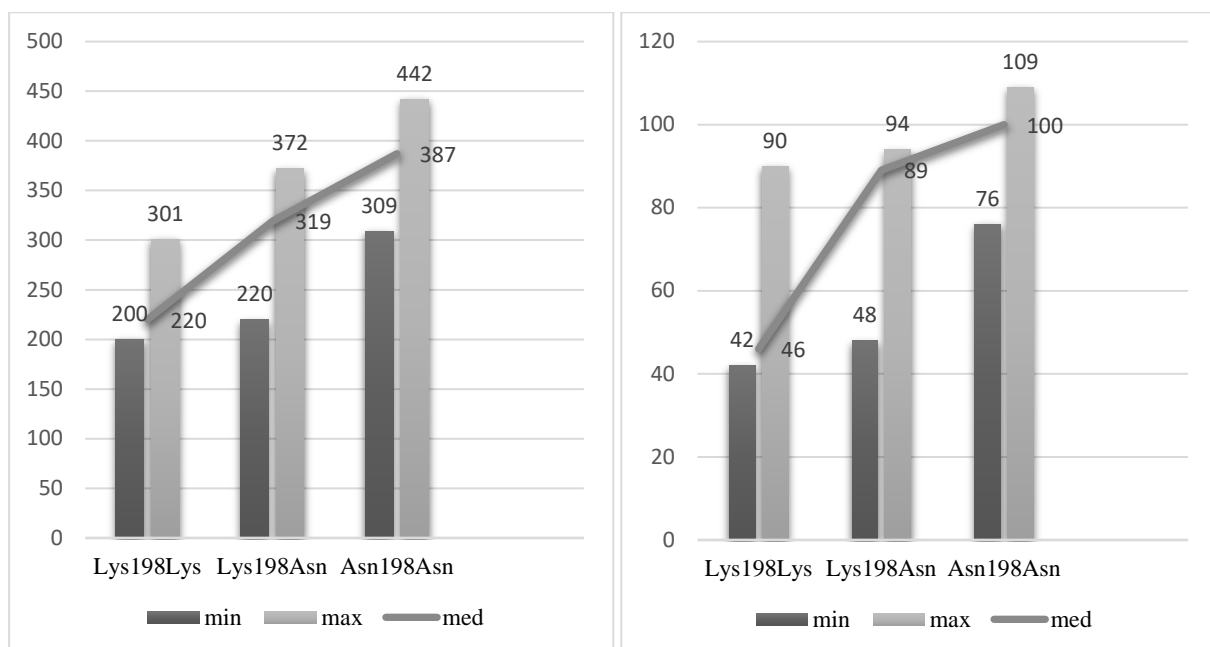


Fig. 2. Median (interquartile range) of ECG indexes in women depending on polymorphism of Lys198Asn in gene endothelin-1.

Alongside with studying dependence of ECG data from Lys198Asn polymorphism, we took research on dependence of these data from BMI (Table II).

Table II.

Median (interquartile range) of ECG indexes of left ventricular myocardium hypertrophy in patients with arterial hypertension, depending on body mass index.

Indicators Group	Mass of myocardium of left ventricle, g	Left ventricular myocardial mass index, g/m <sup>2</sup> , <sup>7</sup>
I group (n=75)	264 ( 198 – 300)	76 (42 – 88)
II group (n=48)	267 (200 – 319)	79 (44 – 89)
III group (n=37)	320 (240 – 390)	86 (54 – 95)
p (Kruskel-Wallis)	p < 0,001	p = 0,002

Results` analysis showed presence of difference of LVMM and LVMMI data according to studied groups ( $p_1 < 0,001$ ;  $p_2 = 0,002$ , Kruskel-Wallis). In III group patients LVMM data were 18% and 16% higher than in patients of I and II groups correspondently ( $p_1 < 0,001$ ;  $p_2 = 0,004$ , Mann-Whitney). Difference between results of I and II groups were not statistically significant ( $p = 0,260$ , Mann-Whitney). LVMMI in patients of III group is 11% higher compared to results of I group ( $p < 0,001$ , Манна-Уїтні) and 8% compared to II ( $p = 0,026$ , Mann-Whitney). ). Difference between results of I and II groups were not statistically significant ( $p = 0,218$ , Mann-Whitney).

We also studied dependence of LVMM and LVMMI from BMI in men. It was proved that both indexes differ by the formed by BMI group for study ( $p_1 < 0,001$ ;  $p_2 = 0,001$ , Kruskel-Wallis). LVMM in III group is 45% higher compared to I ( $p < 0,001$ , Mann-Whitney), in II group index is 24% increased compared to the same group ( $p < 0,050$ , Mann-Whitney). In III group LVMM is 25% increased compared to LVMM in II ( $p = 0,003$ , Mann-Whitney). LVMMI in III group is higher for 53% and 16% correspondently compared to I and II groups ( $p_1 < 0,001$ ,  $p_2 = 0,004$ , Mann-Whitney), in II group current index is also increased compared to I, however, this difference is not statistically significant ( $p = 0,237$ , Mann-Whitney) (Fig. 3).

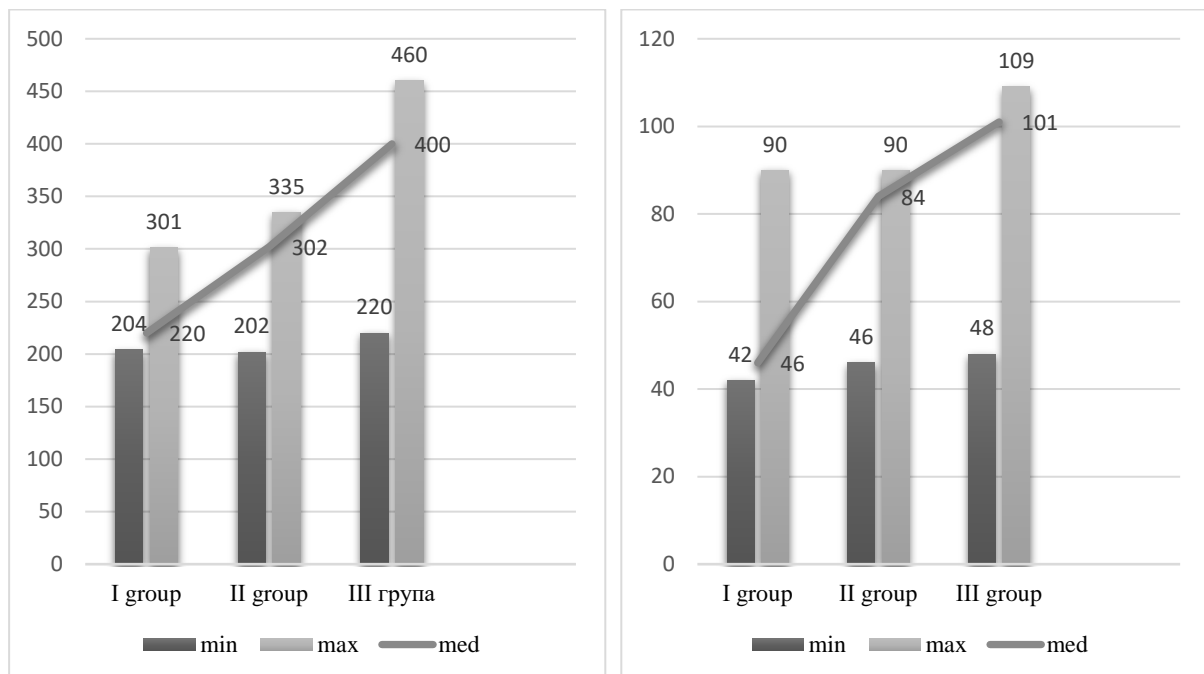


Fig. 3. Median (interquartile range) of ECG indexes of left ventricular myocardium hypertrophy in men with arterial hypertension, depending on BMI.

In women LVMM and LVMMI also differ dependently to BMI ( $p_1 < 0,008$ ;  $p_2 = 0,004$ , Kruskel-Wallis). LVMM in II group was 23% increased compared to I ( $p = 0,004$ , Mann-Whitney), in III group current index was 44% higher compared to the same group ( $p = 0,023$ , Mann-Whitney). In III group LVMM was higher compared to results of II group, however, this

difference is not statistically significant ( $p = 0,442$ , Mann-Whitney). LVMMI in III group was 53% increased compared to I group ( $p = 0,005$ , Mann-Whitney), in II group current index is increased compared to I for 41% ( $p = 0,014$ , Mann-Whitney). During comparison of results in II and III groups significant difference was not registered ( $p = 0,256$ , Mann-Whitney) (Fig. 4).

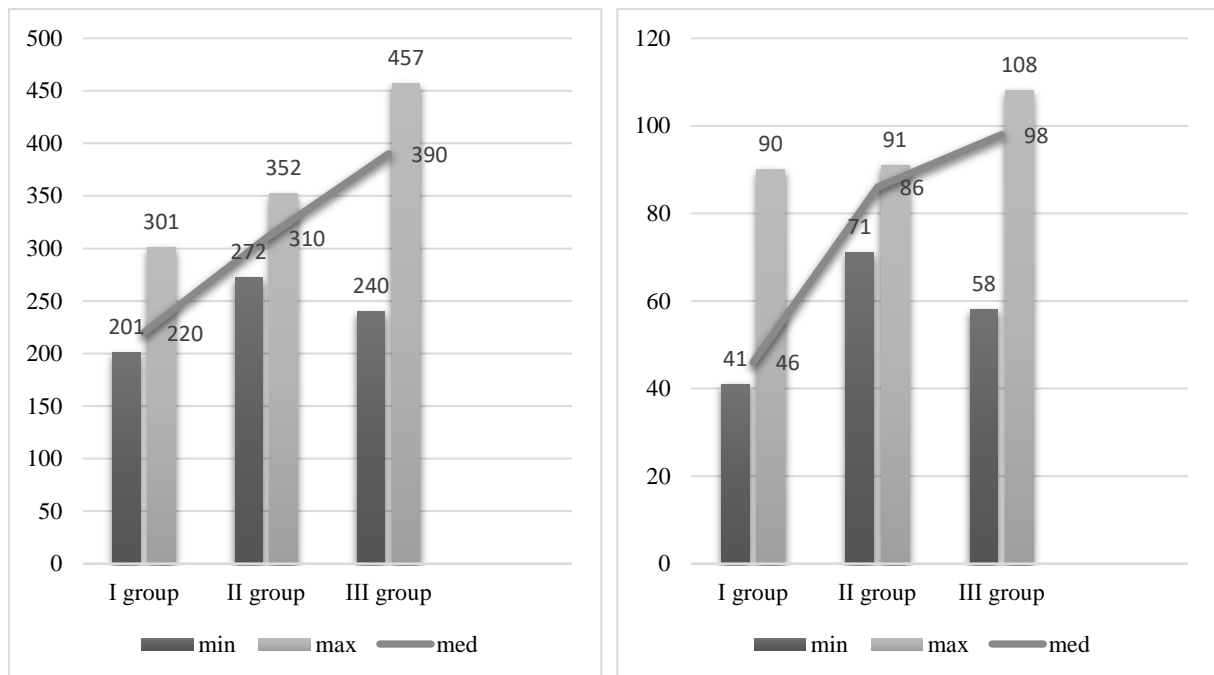


Fig. 4. Median (interquartile range) of ECG indexes of left ventricular myocardium hypertrophy in women with arterial hypertension, depending on BMI.

## Discussion

In clinical research of polymorphic types of gene EDN-1 that influence increasing of cardio-vascular diseases risk, we found that polymorphism of Lys198Asn gene of endothelin-1 is met more often. It is located in chromosome 6p24-p23 and includes 5 exons and 4 introns. Replacing of guanine to thymine in position 594 of nucleotide sequence (594G > T) leads to replacing of amino-acid lysine (Lys) to asparagine (Asn) in codon of 198 polypeptide (Lys198Asn), and changes protein structure and activity [11, 12]. Studying of polymorphic types of Lys198Asn gene of EDN-1 was carried in cases of arterial hypertension, coronary heart disease (CHD), chronic heart failure (CHF), blood-strokes, myocardial infarction.

Current study was aimed to determine interconnection of gene's difference with heart diseases' frequency, influence on disease mechanism, complications, progress, medical prognosis. Numerous previous studies proved dependence of genotype Asn198Asn, allele Asn and increased indexes of ET-1 in blood, and lead us to believe that contingent of patients-carriers of allele Asn is a group of high cardio-vascular diseases risk [13, 14, 15, 16].

There are not much researches and studies of influence of polymorphism Lys198Asn of gene endothelin-1 in development of left ventricular myocardium hypertrophy, changes of heart sizes and cavity volume, in other words, process of myocardium remodeling, presented. Palagnyuk GO, Zhebel' VM (2016) studied how carriage of allele Asn in patients with non-complicated hypertonia and complicated CHF was associated with negative changes of indexes of myocardium hypertrophy, left ventricular volume, LVEF, total peripheral resistance, diastolic function, systolic blood pressure, diastolic blood pressure, that increased correspondently to hypertension complication. Authors consider that patients with arterial hypertension, and carriers of allele Asn of gene endothelin-1 have negative prognosis of cardio disease and risk of CHF development [16]. Petyunina OV, Kopytsya MP (2018) studied clinical-genetic aspects of association of polymorphism of Lys198Asn of gene endothelin-1 with development of early and late myocardium remodeling after suffering acute myocardial infraction with elevation of ST (AMIeST). In acuity of AMIeST structural and functional indexes of myocardium depending on Lys198Asn polymorphism of gene endothelin-1 were not changed. In 6 months carriers of genotypes Lys198Asn + Asn198Asn compared to ones with genotype Lys198Lys had increasing of size and left ventricular volume, LVMM, diameter of left auricle, thus, predisposition of progressive myocardium remodeling and CHF development were evidenced [17]. M.Colombo et al. (2006) studied dependence of Lys198Asn polymorphism of gene endothelin-1 and H323H of gene ET-A receptors with development of CHF in patients with LVEF  $\leq$  40%. CHF risk was increasing in carriers of genotype Asn198Asn

compared to allele Lys (OR = 3,2; p = 0,03). In combination of carriage of homozygote Asn198Asn polymorphism of gene endothelin-1 and TT of gene ET-A CHF risk was highly increased (OR = 8,6; p = 0,005), that led to decreasing of FVC and increasing of EDD compared to patients-carriers of homozygotes Lys and C of correspondent genes [18]. Correlation of allele Asn of gene endothelin-1 with left ventricular hypertrophy and arterial hypertension was also found in other studies [19, 20, 21].

### **Conclusions**

Analysis of dependence of ECG indexes from polymorphism of Lys198Asn of gene endothelin-1 allowed to determine that in patients-carriers of genotype Asn198Asn, LFMMI and LVMM are higher than in carriers of genotype Lys198Lys and Lys198Asn both in men and women. Analysis result of dependence of LVMMI and LVMM from BMI demonstrated that in patients with obesity these indexes are higher compared to patients with increased and normal body mass. Prospective of further research is determination of influence of mentioned polymorphism types on effectiveness of anti-hypertension therapy and decreasing of LVH level.

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