ALDOSTERONE SYNTHASE GENE C-344T POLYMORPHISM AS A RISK FACTOR OF EARLY LEFT VENTRICULAR REMODELING IN YOUNG HYPERTENSIVE PATIENTS WITH OBESITY

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Nowadays, cardiovascular diseases (CVD) are the leading cause of disability and mortality, according to the World Health Organization (WHO). In the structure of cardiovascular morbidity one of the leading places is occupied by arterial hypertension (AH), with coronary heart disease (CHD) and cerebrovascular diseases. AH is one of the main risk factor for cardiovascular diseases and their complications, disability and mortality [28].

An important component of the unfavorable situation with cardiovascular diseases in Ukraine and in the world is the early development of arterial hypertension and its high prevalence in young people of working age [8,15]. The importance of the problem of early blood pressure increasing in young patients is primarily associated with earlier damage of target organs [30]. According to recent studies, among young hypertensive patients there is a low adherence to treatment, a high percentage of undiagnosed and untreated cases, which leads to early damage of target organs and complications [13].

No less actual in the modern world with total digitalization and hypodynamia is the problem of high prevalence of obesity and overweight in the young generation. It is known that obesity is one of the important risk factors for cardiovascular diseases, including arterial hypertension. The presence of concomitant obesity and overweight, according to some studies, increases the risk of AH developing in men by 5,5-12 times, in women - by 4,5-18 times [6,35].

International population researches show an increased incidence of obesity among children and adolescents in parallel with an increased prevalence of hypertension in the same age groups [19]. The phenomenon when hypertension in childhood and adolescence progresses into adulthood is known as "BP tracking" [34].

The heart and blood vessels are the target organs in arterial hypertension. Left ventricular hypertrophy (LVH) is its earliest complication and basic risk factor for heart failure, myocardial infarction, stroke and sudden cardiac death [32].

Obesity, both an isolated disease and in combination with AH, is an independent risk factor for cardioremodeling processes due to hemodynamic and non-hemodynamic (metabolic, humoral) changes. However, research data about the exact mechanism and type of myocardial hypertrophic processes in obesity are quite contradictory [17]. According to some studies, left ventricular hypertrophy in obesity develops by eccentric type [14], according to other studies - concentric cardioremodeling processes are dominant [31].

The modern view of left ventricular remodeling includes not only an enlargement of the cardiomyocytes cell size (hypertrophy), as an adaptive response to increased pressure on the left ventricular wall, but also the interstitial histopathological changes - fibrosis, vascular remodeling, apoptosis. There is evidence that increased apoptosis of cardiomyocytes is a limiting factor that compensatory suppresses excessive myocardial hypertrophy. Myocardial fibrosis is associated with increased collagen synthesis, decreased collagenase activity and loss of mutual regulation between profibrotic and antifibrotic processes. In addition, in obesity there is interstitial fatty infiltration, accumulation of triglycerides in the contractile elements of the myocardium. All these structural changes in the myocardium, primarily of the left ventricle, at appropriate stage lead to functional disorders (diastolic and systolic), the development of heart failure, atrial fibrillation and malignant arrhythmias [3].

The complex of pathophysiological changes of the myocardium occurs under the influence of hemodynamic, neurogenic, humoral and genetic factors. The activation of the renin-angiotensin-aldosterone system (RAAS) is the one of the important links in the pathogenesis of AH, formation of target organs changes (hypertrophy, fibrosis, apoptosis) and complications [3,27].

According to many researches, aldosterone, as the component of RAAS, plays an important role in myocardial remodeling in AH. And gene polymorphism, which encodes aldosterone synthesis (aldosterone synthase), is considered as genetic marker ("candidate gene") for the risk of devevelopment of AH and target organs lesions. Recently, many researches deeper study the pathophysiological effects of aldosterone and its activated synthesis in the pathogenesis of essential arterial hypertension [11].

According to some studies, up to 15% of patients with essential AH and 22% of patients with resistant AH have excess aldosterone [3,22]. According to the Framingham study, patients with aldosterone levels in the upper quartile had a more severe increasing of blood pressure within 5 years, compared with patients in the lower quartile on aldosterone levels [3,20].

In addition to the effect on water-electrolyte metabolism, it was found the potention of aldosterone to affect hypertrophic and fibrotic processes in the myocardium, cause endothelial dysfunction and pro-inflammatory processes in the vascular wall, myocardium and kidneys, which leads to myocardiosclerosis and nephrosclerosis. There is evidence that these processes occur due to the ability of aldosterone to increase the expression of cardiotropin-1 protein, prohypertrophic cytokine, IL-18, activate collagen synthesis, cause the infiltration of endothelium by macrophages and focal necrotic changes in the myocardium, blood vessels. Also, according to some studies, aldosterone can negatively affect metabolic processes, namely, the level of glucose, insulin, C-peptide and insulin resistance - the index HOMA [3,4,10].

It was found that obesity, both alone and in combination with arterial hypertension, is accompanied by the synthesis of various adipocytokines and components of local RAAS by visceral adipose tissue [2]. Activation of local and systemic RAAS in hypertension and obesity is addictive, leads to deeper lesions of target organs in this comorbid combination, namely, remodeling processes of the myocardium, blood vessels and the development of cardiovascular complications.

Aldosterone is synthesized by the mitochondrial enzyme - aldosterone synthase, which is encoded by the CYP11B2 gene (cytochrome P450, family 11, subfamily B, polypeptide 2). The CYP11B2 gene is located on the short arm ("p") of chromosome 8 at position 22 and encodes a key enzyme in the synthesis of aldosterone (18-hydroxylase) from deoxycorticosterone [4].

For today the most common and studied polymorphism of the CYP11B2 aldosterone synthase gene is the change of cytosine (C) to thymine (T) in the regulatory region of the gene at the

-344 position and is signed as (C-344T) CYP11B2. According to the results of majority studies, it was revealed the association of the T-allele of the C-344T polymorphism of the aldosterone synthase gene with its enhanced expression, aldosterone hypersynthesis, the development of essential AH and target organ lesions, including hypertrophic and fibrotic processes of the myocardium [29, 38]. Furthermore, according to appropriate studies, it was found a correlation between the T-allele of the C-344T polymorphism of the aldosterone synthase gene and the development of resistant forms of AH, ischemic stroke, atrial fibrillation, hypertrophic cardiopathy, disorders of glucose homeostasis and others [5, 37].

A number of researches have been performed for study of the aldosterone synthase gene C-344T polymorphism in patients with abdominal obesity and metabolic syndrome, and their results were contradictory [9, 24]. There is evidence that the carrier of the T-allele increases the risk of hypertension on the background of existing abdominal obesity [2]. However, according to other studies, the opposite results were obtained, i.e. the association of the C-allele of the aldosterone synthase gene C-344T polymorphism with the development of AH and cardiovascular complications was found [36]. And according to other researches, there were no correlations of this polymorphism with AH and it were found no significant differences between hypertensive and non-hypertensive patients [25].

Contradictory results of many researches of the features of aldosterone synthase gene genetic expression have been demonstrated in different European and Asian countries, where significant ethnic and population differences have been revealed.

Today, despite the obvious genetic and pathophysiological links, there is no unequivocal statement about the pathological effect of aldosterone synthase gene C-344T polymorphism on the development of functional hyperaldosteronism and on the realisation of hypertensive phenotype, which requires further study of this link of AH pathogenesis with involvement of hypertensive patients of various population and age groups.

The purposes of the research were:

- to study the prevalence of C-344T polymorphism and the distribution of aldosterone synthase gene (CYP11B2) genotypes in young patients with arterial hypertension, depending on the presence or absence of concomitant obesity (or overweight)
- to analyze the association of aldosterone concentration with aldosterone synthase gene genotypes in young patients with arterial hypertension and concomitant obesity (or overweight)
- to study the features of left ventricular hypertrophy by echocardioscopy and to identify their association with different genotypes of the aldosterone synthase gene in young patients with arterial hypertension, depending on the presence or absence of concomitant obesity (or overweight)

Material and methods. Patients were examined in the cardiology department of the Multidisciplinary Medical Center of the Odessa National Medical University, Odessa, Ukraine.

The inclusion criteria for patients in the research were the presence of essential arterial hypertension (Guidelines ESC/ESH 2018), young age (according to the WHO) - from 18 to 44 years old.

The exclusion criteria were: no inclusion criteria; secondary hypertension; confirmed endocrine obesity; the presence of HF III-IV FC; chronic kidney diseases III-IV stages; manifest endocrine pathology; pregnancy and lactation; documented oncological pathology; mental disorders; patients who underwent cardiovascular events (MI, TIA, stroke) in less than 6 months before the start of the research; acute infectious diseases; asocial personalities; uncompensated kidney and liver diseases with severe renal and hepatic insufficiency, refusal to be observed by doctor or participate in the research program.

Agreement to participate in the research was documented by the bilateral signing of an informed agreement form. The research was conducted with following of safety measures for life and health, in compliance with human rights and moral-ethical standards, in accordance with the principles of the Helsinki Declaration of Human Rights and Order of the Ministry of Health of Ukraine № 693 from 01.10.2015, Council of Europe Convention on Human Rights and Biomedicine (ETS-164) from 04.04.1997.

123 young patients with essential arterial hypertension (18-44 years old) were examined, the average age was (32,83±0,58) years old, the male/female ratio was 72/51 respectively. For all patients the body mass index (BMI) was calculated using the Quetelet's formula: body weight/height^2 (kg/m^2). Depending on BMI, all patients were divided into 3 groups: group 1 (n=41) consisted of patients with normal body weight (NBW), BMI=18,5 to 24,9 kg/m2; group 2 (n=40) consisted of patients with overweight, BMI=25-29,9 kg/m2; group 3 (n=42) – patients with obesity – BMI≥30 kg/m2.

All patients were performed polymerase chain reaction (PCR) analysis of the C-344T polymorphism of the aldosterone synthase gene (CYP11B2). Venous whole blood samples were used as the test material. Blood sampling was performed in vacuum plastic test tubes, volume 3,0 ml, type Vacuette, with added ethylenediaminetetraacetic acid disodium salt (EDTA) as an anticoagulant at a final concentration of 2,0 mg/ml. Genomic DNA was isolated using the Blood Genomic DNA Extraction kit-50; 100 (LLC "PRODUCTION COMPANY SIMESTA", Ukraine). PCR analysis of the CYP11B2 gene was performed using a set of reagents "CARDIOGENETICS HYPERTENSION for the determination of genetic polymorphisms associated with the risk of arterial hypertension development, by real-time PCR ("DNA technology", RF) on an amplifier with a fluorescent signal detection system in the real-time CFX96 (Bio-Rad, USA). Based on the results of PCR, one of three possible genotypes of the aldosterone synthase gene C-344T polymorphism was identified: CC, CT, TT. For obtaining of more significant statistical results during comparing the frequency of genotypes occurrence, "pathological" genotypes (CT and TT) were combined into one group.

The frequencies of genotypes and allele's occurrence of the aldosterone synthase gene C-344T polymorphism in three groups of young hypertensive patients with normal BMI, overweight and obesity were analyzed.

In the examined groups, the level of aldosterone in blood was studied by the chemiluminescent method on an automatic chemiluminescent analyzer Mindray CL 900i ("Foramed", Ukraine). Blood sampling was performed from the cubital vein after a 30-minute rest in the prone position on an empty stomach in the morning for 2 hours after awakening (between 8:00 and 11:00). The reference values were the aldosterone level of 30-230 pg/ml.

For checking of the structural and functional condition of the heart and the type of myocardial remodeling, a transthoracic echocardiography in M- and two-dimensional modes was performed using a digital ultrasound apparatus of the latest generation Vivid E9 (General Electric, Healthcare Technologies, USA). Measurement was carried out according to the standard method of the American Society of Echocardiography recommendations [26].

The following echocardiographic parameters were assessed: left ventricular end-diastolic diameter (LVEDD, mm); interven-

tricular septal thickness (IVST, mm); left ventricular posterior wall thickness (LVPWT, mm).

Taking into account these indicators, the following parameters and indexes were calculated:

1) the relative wall thickness of the LV (LV RWT, units) by formula [26]:

$$RWT=2* LVPWT/LVEDD$$

2) LV myocardial mass (LVMM, g) according to the method of R.B. Devereux et al. [18]:

$$LVMM\ (g)=0.8\{1.04[([LVEDD + IVST + LVPWT]^3 - LVEDD^3)]\} + 0.6$$

Subsequently, LVMM was indexed to body surface area (LVMI, g/BSA m^2), and also to height ^{2,7} (LVMI, g/height m ^{2,7}).

The reference upper limits of the normal values of LVMI by linear measurement were 95 g/m^2 for female, 115 g/m^2 for male for the calculation using BSA; 44 and 48 g/m ^{2,7} in female and male respectively - on indexation of LVMM to height ^{2,7} [26].

LV myocardial mass indexation allows compare the patients with different body parameters. However, the question of whether to use height, weight, or BSA as the indexing term remains controversial. Some studies indicate that indexing to height raised to powers such as 1,7, 2,13 and 2,7 has advantages over indexing by BSA, especially in obese or overweight patients [12, 16]. There is evidence that the frequency of detection of hypertrophic processes of the LV in obesity is artificially underestimated using the traditional indexation of LVMM to BSA, therefore, it may be promising to index this parameter to height (height ^{2,7}) [23]. However, today there are no sufficient data to judge the additional diagnostic and prognostic value of this approach, and yet most studies use the traditional method of LVMM indexation to BSA [26].

Based on the LVMI and LV RWT values, the following types of left ventricular geometry (Fig.1) were identified in accordance with the principles of A. Ganau et al. [21]:

1) normal LV geometry with LVMI <115 g/m^2 in men, <95 g/m^2 in women, and LV RWT < 0,42;

2) concentric left ventricular hypertrophy (LVH) with LVMI ≥115 g/m^2 in men, ≥ 95 g/m^2 in women, and LV RWT ≥ 0,42;

3) eccentric LV hypertrophy with LVMI ≥115 g/m^2 in men, ≥ 95 g/m^2 in women, and LV RWT < 0,42;

4) concentric remodeling (CR) of LV with LVMI <115 g/m^2 in men, <95 g/m^2 in women, and LV RWT ≥ 0,42.

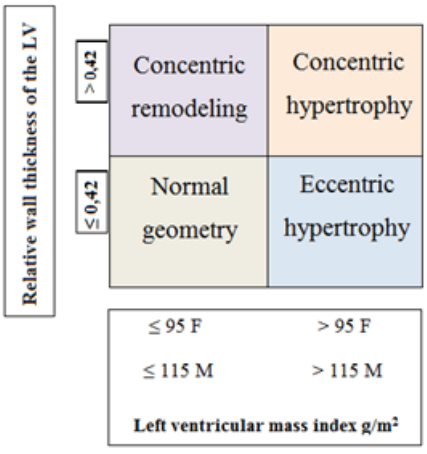

Fig. 1. Types of left ventricular geometry according to the principles of A. Ganau et al.

Statistical analysis of the obtained results was carried out by parametric and nonparametric methods using the statistical software programs Statgraphics Plus 5.0, Statistica 10.0. The frequencies of genotypes and alleles of the aldosterone synthase gene C-344T polymorphism were studied in the absolute and relative (%) values; the correspondence of the alleles and genotypes distribution to the Hardy–Weinberg principle was analyzed. Quantitative parameters were presented as average value (M), standard deviation and average error (m). A comparative analysis of the genotype and allele frequencies of the studied aldosterone synthase gene and types of left ventricular remodeling between the groups was performed using two-sided Fisher's exact test. To assess the significance of differences in quantitative parameters between two independent groups, we used the parametric Student's t-test and the nonparametric Mann–Whitney U-test. The results were considered statistically significant when p<0,05. The differences between groups 1 and 2 were designated as "p1", the differences between groups 1 and 3 - "p2", between groups 2 -3 - "p3".

Results and discussion. Analyzing the obtained data, the following patterns were revealed. Table 1 shows the prevalence of genotypes and alleles of the C-344T polymorphism of the aldosterone synthase gene in hypertensive young patients with normal weight, overweight and obesity. Thus, in patients with AH and normal BMI (group 1), the "normal" genotype CC was found in 16 patients (39,02%), in AH and overweight (group 2) the genotype CC was found in 10 patients (25, 00%), in AH and concomitant obesity (group 3) - in 9 patients (21,43%). The frequency of "pathological" genotypes (CT+TT) of C-344T polymorphism in group 1 was 60,98% (25 patients), in group 2 – 75,00% (30 patients), in group 3 – 78,57% (33 patients). That is, in all examined groups of young hypertensive patients "pathological" genotypes (CT+TT) were more frequent, while in groups 2 and 3 – with high significance (P=0,000), in group 1 – non-significantly, p=0,08. Comparing the frequency of genotypes occurrence between groups, no significant differences were obtained (p1=0,24, p2=0,09, p3=0,80), i.e. the distribution of the genotypes frequencies of the studied polymorphism does not significantly influence on the body mass indices. The obtained results coincide with a plenty of larger population studies, where the role of the C-344T polymorphism of the aldosterone synthase gene was studied and the high prevalence of the CT and TT genotypes of this polymorphism in patients with arterial hypertension was shown [2,3,29,38].

Analyzing the occurrence of the -344C and -344T alleles of the C-344T polymorphism of the aldosterone synthase gene (Table 1) in young hypertensive patients, there were significant differences only between groups 1 and 3 (p2=0,04), i.e. in the group of hypertensive patients with obesity the "pathological" -344T-allele was significantly more frequent than in the group with normal BMI. Significant differences between other groups were not obtained (p1=0,34, p3=0,35). At the same time, the occurrence of the "normal" -344C-allele of the aldosterone synthase gene in groups 1 and 2 (P=0,01 and P=0,27 respectively) exceeded the frequency of the -344T-allele, in group 3 - the opposite situation, without a significant differences (P=0,64). The obtained result can be explained by the low incidence of "pathological" homozygotes (TT genotype) in the examined patients; in the structure of "pathological" genotypes, heterozygotes (CT genotype) predominated, that influenced on such frequency distribution of alleles.

Table 1. Distribution of genotypes and alleles of aldosterone synthase gene C-344T polymorphism in young patients with arterial hypertension, depending on the presence or absence of concomitant obesity (or overweight), abs ./%

Genotypes of aldosterone synthase gene	All young patients with AH (n=123)			p
	Group 1 AH with normal BMI (n=41)	Group 2 AH with overweight (n=40)	Group 3 AH with obesity (n=42)	
«Normal» genotype CC, abs./%	16 (39,02 %)	10 (25,00 %)	9 (21,43 %)	p1=0,24 p2=0,09 p3=0,80
«Pathological» genotypes CT+TT, abs./%	25 (60,98 %)	30 (75,00 %)	33 (78,57 %)	
	P=0,08	P=0,000	P=0,000	
Alleles				
-344C	52 (63,4%)	44 (55%)	40 (47,6%)	p1=0,34 p2=0,04 p3=0,35
-344T	30 (36,6%)	36 (45%)	44 (52,4%)	

note: P - significance of differences between the frequency of genotypes occurrence ("normal" and "pathological") within each group; p1 - significance of differences between 1st and 2nd groups; p2 - significance of differences between 1st and 3rd groups; p3 - significance of differences between 2nd and 3rd groups

Table 2. Aldosterone concentration in young patients with arterial hypertension, depending on the presence or absence of concomitant obesity (or overweight), M±m

Aldosterone blood concentration	All young patients with AH (n=123)			p
	Group 1 AH with normal BMI (n=41)	Group 2 AH with overweight (n=40)	Group 3 AH with obesity (n=42)	
Aldosterone, pg/ml	139,4±6,86	158,85±7,3	181,92±6,74	p1=0,055 p2=0,000 p3=0,023

note: p1 - significance of differences between 1st and 2nd groups; p2 - significance of differences between 1st and 3rd groups; p3 - significance of differences between 2nd and 3rd groups

According to the results of the study of the blood aldosterone concentration in three examined groups (Table 2), the average value of this parameter in all groups was within the normative limits: in group 1 – (139,4±6,86) pg/ml, in group 2 – (158,85±7,3) pg/ml, in group 3 – (181,92±6,74) pg/ml. Comparing the average aldosterone concentration between groups, significant differences were found only between hypertensive patients with normal BMI and with concomitant obesity (between groups 1 and 3, p2=0,000), as well as between overweight and obese patients (between groups 2 and 3, p3=0,023). There were no significant differences between groups 1 and 2 (p1=0,055). The presence of concomitant overweight and, to a greater extent, obesity significantly affects the blood aldosterone concentration, that is caused by activation of the local RAAS and increased secretion of aldosterone by visceral adipose tissue [1,2].

Analyzing the echocardiographic parameters of left ventricular hypertrophy in young hypertensive patients with different body weights (Table 3), significant differences were revealed in some indicators which characterize the geometry of the LV. The average value of LVMM in group 1 was (173,80±9,01) g, in group 2 – (206,18±7,91) g, and the maximum values reached in group 3 – (254,48±8,44) g, while the differences between the groups showed high significance (p1=0,010, p2=0,000, p3=0,000). After indexation of LVMM to body surface area (g/BSA m^2), the highest parameter was observed in young hypertensive patients with obesity (group 3) – (114,14±3,57) g/m^2, which significantly (p2=0,027) exceeded LVMI in hypertensive patients with normal BMI – (96,78±4,82) g/m^2. This parameter in overweight patients (group 2) was on intermediate position – (104,45±3,44) g/m^2, there were no significant differences with group 1 (p1=0,664), compared with group 3 – there was a significant difference (p3=0,033).

After indexation of LVMM to height^{2,7} (g/height $m^{2,7}$), more significant differences were found between the groups, which justifies this approach to calculation of LVMI in patients with overweight and obesity. Thus, LVMI in group 1 was (40,52±2,01) g/$m^{2,7}$, in group 2 – (47,91±1,57) g/$m^{2,7}$, in group 3 – (59,54±2,03) g/$m^{2,7}$, wherein the differences between all three groups were more significant compared with the indexation to BSA (p1=0,012, p2=0,000, p3=0,000 versus p1=0,664, p2=0,027, p3=0,033 respectively). Analyzing the obtained data, it can be assumed that indexation of LVMM to height^{2,7} in overweight and obese patients with a higher probability helps to reveal an increased LVMM compared with traditional indexation to BSA. The received results have matched with some studies which had shown an advantage of indexation of LVMM to height raised to the power of 2,7 in obese or overweight patients compared with indexation to BSA. That is, on the traditional calculation of LVMI in overweight hypertensive patients, a certain proportion of cases of LV hypertrophy is "masked" or "lost", which leads to an inadequate assessment of the target organs condition and, accordingly, inadequate management of this category of patients [12,16]. LV RWT in the examined groups was: in group 1 – (0,41±0,02), in group 2 – (0,39±0,01), in group 3 – (0,40±0,02), while there were no significant differences between the groups (p1=0,347, p2=0,63, p3=0,687). Overweight or obesity in young with AH patients did not significantly affect the average value of LV RWT.

Table 3. Echocardiographic parameters of left ventricular hypertrophy in young patients with arterial hypertension, depending on the presence or absence of concomitant obesity (or overweight), M±m

Echocardiographic parameters	All young patients with AH (n=123)			p
	Group 1 AH with normal BMI (n=41)	Group 2 AH with overweight (n=40)	Group 3 AH with obesity (n=42)	
LVEDD, mm	48,90±0,98	53,15±1,06	57,02±1,04	p1=0,004 p2=0,000 p3=0,011
IVST, mm	9,59±0,29	10,08±0,24	10,71±0,29	p1=0,257 p2=0,013 p3=0,109
LVPWT, mm	9,83±0,34	10,13±0,24	11,05±0,32	p1=0,385 p2=0,008 p3=0,048
LVMM, g	173,80±9,01	206,18±7,91	254,48±8,44	p1=0,010 p2=0,000 p3=0,000
LVMI, g/BSA m^2	96,78±4,82	104,45±3,44	114,14±3,57	p1=0,664 p2=0,027 p3=0,033
LVMI, g/height $m^{2,7}$	40,52±2,01	47,91±1,57	59,54±2,03	p1=0,012 p2=0,000 p3=0,000
LV RWT, units	0,41±0,02	0,39±0,01	0,40±0,02	p1=0,347 p2=0,63 p3=0,687

note: p1 - significance of differences between 1st and 2nd groups; p2 - significance of differences between 1st and 3rd groups; p3 - significance of differences between 2nd and 3rd groups

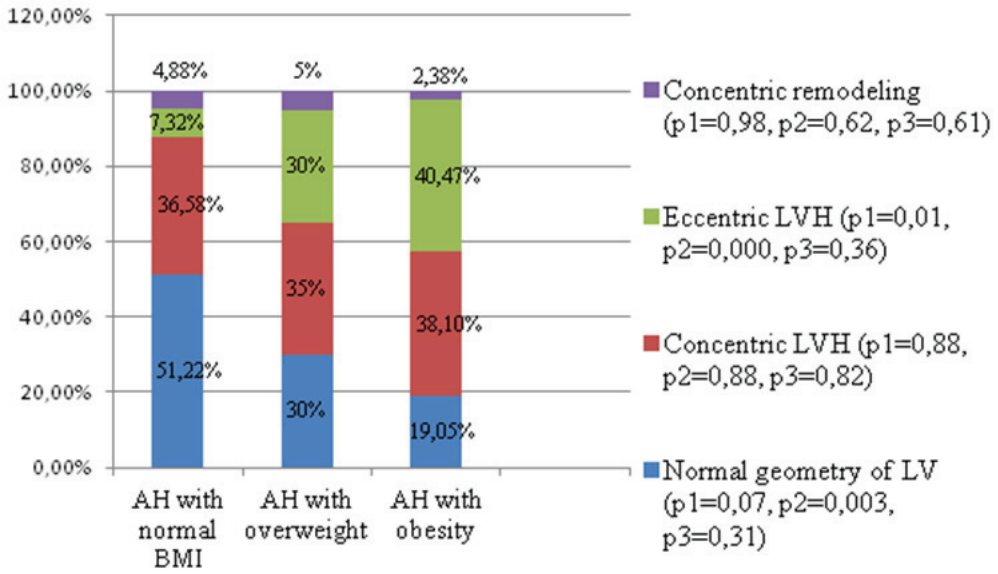

Fig. 2. Distribution of left ventricular geometry in young hypertensive patients with normal BMI, overweight and obesity, %. Note: p1 - significance of differences between 1st and 2nd groups; p2 - significance of differences between 1st and 3rd groups; p3 - significance of differences between 2nd and 3rd groups

On the basis of the obtained echocardiographic parameters, it was performed an analysis of the geometry type and features of LV remodeling in the examined young hypertensive patients (Fig. 2).

In the group of patients with normal body weight, normal LV geometry was predominant – it was in 21 patients, which was 51,22%, concentric LVH was found in 15 patients (36,58%), the most rare types – eccentric LVH and concentric remodeling

Table 4. Association of C-344T polymorphism genotypes of the aldosterone synthase gene with blood aldosterone concentration and echocardiographic parameters of left ventricular hypertrophy in young patients with arterial hypertension, M±m

Parameters	All young patients with AH (n=123)		p
	«Normal» genotype CC n=35	«Pathological» genotypes (CT+TT) n=88	
Aldosterone, pg/ml	122,95±6,25	175,26±4,57	p=0,000
LVMM, g	185,2±9,40	222,49±6,76	p=0,001
LVMI, g/BSA m^2	96±4,33	108,86±2,76	p=0,014
LVMI, g/height $m^{2,7}$	43,49±2,12	51,78±1,54	p=0,001
LV RWT, units	0,37±0,01	0,41±0,01	p=0,08

note: p - significance of the difference between groups with "normal" and "pathological" genotypes

– were observed in 3 (7,32%) and 2 patients (4,88%), respectively. In patients with AH and overweight, concentric LVH was non-significantly more frequent – in 14 patients (35%), eccentric LVH and normal LV geometry were equally often observed – in 30% of cases each type, the most rare type of LV geometry – concentric remodeling – was observed in 2 patients (5%). In the group of patients with AH and obesity the eccentric LVH predominated (17/40,47%). Concentric LVH was found in 16 patients (38,1%), normal LV geometry – in 8 patients (19,05%), CR – in 1 patient (2,38%). Comparing the obtained results between the groups, significant differences were obtained in regard to the incidence of eccentric LVH between patients with normal BMI and obesity (7,32% vs 40,47% respectively, p2=0,000), as well as compared with overweight patients (7,32% vs 30% respectively, p2=0,01). Therefore, the eccentric type of LVH in the presence of overweight and, especially, concomitant obesity in our study was observed significantly more often compared with patients with normal BMI, there were no significant differences between groups 2 and 3 (p3=0,36). The received result coincides with the results of other researches of cardioremodeling processes in obese patients, where eccentric LVEH was predominant [14, 33]. Also, significant differences between the groups were observed in regard to the normal LV geometry, which significantly prevailed in group 1 compared with group 3 (p2=0,003), compared with group 2 and between group 2 and 3 – the differences were non-significant (p1=0,07, p3=0,31). No significant differences were found between the groups in regard to concentric LVH (p1=0,88, p2=0,88, p3=0,82) and concentric remodeling (p1=0,98, p2=0,62, p3=0,61).

In the performed research it was studied the association of "normal" and "pathological" genotypes of C-344T polymorphism of the aldosterone synthase gene with plasma aldosterone concentration and echocardiographic parameters of myocardial remodeling in young hypertensive patients (Table 4).

Thus, the average value of aldosterone concentration was significantly higher (p=0,000) in patients with "pathological" genotypes (CT+TT) – (175,26±6,25) pg/ml against patients with "normal" CC genotype, where the average value of this parameter was (122,95±6,25) pg/ml. Analyzing the average values of echocardiographic indices, in carriers of genotypes (CT+TT) the LVMM was significantly higher than in carriers of the CC genotype – (222,49±6,76) g versus (185,2±9,40) g respectively (p=0,001). Also, significant differences were obtained in regard to the average value of LVMI, both in indexation to BSA and height^{2,7}. In carriers of genotypes (CT+TT) this parameter was (108,86±2,76) BSA m^2 and (51,78±1,54) height $m^{2,7}$, which significantly exceeded the average LVMI value in carriers of the CC genotype of the studied aldosterone synthase gene polymorphism, where this parameter was (96,00±4,33) BSA m^2 and (43,49±2,12) height $m^{2,7}$ (p=0,014 and p=0,001 respectively). Thus, the carriage of the -344T allele of the C-344T polymorphism of the aldosterone synthase gene is significantly associated with both increased aldosterone synthesis and higher values of LVMM and LVMI in patients with arterial hypertension, which coincides with the data of other studies [2,7].

Conclusions. In the examined young patients with arterial hypertension the "pathological" genotypes (CC+CT) of the aldosterone synthase gene C-344T polymorphism were significantly more frequent in patients as with normal body weight and with concomitant obesity or overweight.

The average blood aldosterone concentration in all groups of examined young hypertensive patients was within the normative values, however, in concomitant overweight and obesity this parameter was significantly higher, that confirms the presence of additional activation of aldosterone synthesis in such comorbid combination and requires further study of the exact mechanism of this type of hyperaldosteronism.

Concomitant overweight and, to a greater extent, concomitant obesity significantly influenced on the echocardiographic parameters characterizing left ventricular hypertrophic processes in young patients with arterial hypertension. In the structure of the geometry types of the left ventricle, as the weight parameters of young hypertensive patients increased, the proportion of eccentric left ventricular hypertrophy significantly increased and the proportion of normal LV geometry decreased.

"Pathological" genotypes (CT+TT) of the C-344T polymorphism of the aldosterone synthase gene are associated with a higher blood aldosterone concentration and more expressed left ventricular hypertrophic processes in young patients with arterial hypertension.

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SUMMARY

ALDOSTERONE SYNTHASE GENE C-344T POLYMORPHISM AS A RISK FACTOR OF EARLY LEFT VENTRICULAR REMODELING IN YOUNG HYPERTENSIVE PATIENTS WITH OBESITY

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The purposes of the research were to study the prevalence of C-344T polymorphism and the distribution of aldosterone synthase gene (CYP11B2) genotypes, to analyze the association of aldosterone concentration with aldosterone synthase gene genotypes, to study the features of left ventricular hypertrophy (LVH) by echocardioscopy and identify their association with different genotypes of the aldosterone synthase gene in young patients with arterial hypertension (AH), depending on the presence or absence of concomitant obesity (or overweight). 123 young patients with essential AH (18-44 years old) were examined, the average age was (32,83±0,58) years old, the male/female ratio was 72/51 respectively. All patients were divided into 3 groups: group 1 (n=41) with normal body weight; group 2 (n=40) with overweight; group 3 (n=42) –with obesity. It was revealed that the "pathological" genotypes (CC+CT) of the aldosterone synthase gene C-344T polymorphism were significantly more frequent in patients as with normal body weight and with concomitant obesity or overweight. In concomitant overweight and obesity the average blood aldosterone concentration was significantly higher, that confirms the presence of additional activation of aldosterone synthesis in such comorbid combination and requires further study of the exact mechanism of this type of hyperaldosteronism. Concomitant overweight and obesity significantly influenced on the echocardiographic parameters characterizing LVH processes in young patients with AH with the significant increased proportion of eccentric LVH. "Pathological" genotypes (CT+TT) of the C-344T polymorphism of the aldosterone synthase gene are associated with a higher blood aldosterone concentration and more expressed LVH processes in young patients with AH.

Keywords: arterial hypertension, obesity, aldosterone, young age, aldosterone synthase gene, left ventricular hypertrophy, C-344T polymorphism.

РЕЗЮМЕ

ПОЛИМОРФИЗМ С-344Т ГЕНА АЛЬДОСТЕРОНСИНТАЗЫ КАК ФАКТОР РИСКА ГИПЕРТРОФИИ ЛЕВОГО ЖЕЛУДОЧКА У ПАЦИЕНТОВ МОЛОДОГО ВОЗРАСТА С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И СОПУТСТВУЮЩИМ ОЖИРЕНИЕМ

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Цель исследования - изучить распространенность полиморфизма С-344Т и распределение генотипов гена альдостерон-синтазы (CYP11B2), проанализировать связь концентрации альдостерона с генотипами гена альдостерон-синтазы, определить особенности гипертрофии левого желудочка и их связь с различными генотипами гена альдостерон-синтазы у молодых пациентов с артериальной гипертензией в зависимости от наличия или отсутствия сопутствующего ожирения или избыточной массы тела.

Обследовано 123 молодых пациента с эссенциальной артериальной гипертензией (АГ) в возрасте 18–44 года, средний возраст 32,83±0,58 года, соотношение мужчин/женщин - 72/51. Пациенты разделены на 3 группы: I группа (n=41) - с нормальной массой тела; II группа (n=40) - с избыточной массой тела; III группа (n=42) - с ожирением. Выявлено, что «патологические» генотипы (CC+CT) полиморфизма гена альдостерон-синтазы С-344Т достоверно чаще встречаются у пациентов как с нормальной массой тела, так и с сопутствующим ожирением или избыточной массой тела. При сопутствующем избыточном весе и ожирении средняя концентрация альдостерона в крови была достоверно выше, что подтверждает наличие дополнительной активации синтеза альдостерона в такой коморбидной комбинации и требует дальнейшего изучения точного механизма этого типа гиперальдостеронизма. Сопутствующие избыточная масса тела и ожирение существенно влияют на эхокардиографические параметры, характеризующие процессы гипертрофии левого желудочка (ГЛЖ) у молодых пациентов с АГ со значительным увеличением доли эксцентрической ГЛЖ. «Патологические» генотипы (CT+TT) полиморфизма С-344Т гена альдостерон-синтазы ассоциированы с более высокой концентрацией альдостерона и более выраженными процессами ГЛЖ у молодых пациентов с АГ.

რეზიუმე

ალდოსტერონსინთაზას გენი С-344Т-ის პოლიმორფიზმი, როგორც მარცხენა პარკუჭის ჰიპერტროფიის რისკის ფაქტორი ახალგაზრდა ასაკის პაციენტებში არტერიული ჰიპერტენზიით და თანმხლები სიმსუქნით

ე.იაკიმენკო, ე.ჩერნიშოვა, ვ.ბონდარი, ვ.კლოჩკო, ს.კოლომიეცი, ვ.თბილელი

ოდესის ეროვნული სამედიცინო უნივერსიტეტი, შინაგან დაავადებათა პროპედევტიკის და თერაპიის კათედრა, უკრაინა

კვლევის მიზანს წარმოადგენდა გენი С-344Т-ის პოლიმორფიზმის გავრცელების და ალდოსტერონსინთაზას გენის (CYP11B2) გენოტიპების გავრცელების შეფასება, ალდოსტერონის კონცენტრაციის კავშირის ანალიზი ალდოსტერონსინთაზას გენის გენოტიპებთან, მარცხენა პარკუჭის ჰიპერტროფიის თავისებურე-

ბების და მათი კავშირის გამოვლენა ალდოსტერონ-სინთაზას სხვადასხვა გენოტიპთან ახალგაზრდა პაციენტებში არტერიული ჰიპერტენზიით თანმხლები სიმსუქნის ან სხეულის ჭარბი მასის არსებობის ან არარსებობის პირობებში.

გამოკვლეულია 18-44 წლის ასაკის (საშუალო ასაკი - 32,83±0,58 წელი) 123 ახალგაზრდა პაციენტი ესენციური არტერიული ჰიპერტენზიით, მამაკაცების და ქალების თანაფარდობა – 72/51. პაციენტები დაიყო სამ ჯგუფად: I ჯგუფი (n=41) – სხეულის ნორმალური მასით, II ჯგუფი (n=40) – სხეულის ჭარბი მასით, III ჯგუფი (n=42) – სიმსუქნით. გამოვლინდა, რომ ალდოსტერონსინთაზას გენი C-344T-ის პოლიმორფიზმის "პათოლოგიური" გენოტიპები (CC+CT) სარწმუნოდ უფრო ხშირია როგორც პაციენტებში სხეულის ნორმალური მასით, ასევე, პაციენტებში სიმსუქნით ან სხეულის ჭარბი მასით. სიმსუქნის ან თანმხლები სხეულის ჭარბი მასის შემთხვევაში ალდოსტერონის კონცენტრაცია სისხლში სარწმუნოდ უფრო მაღალია, რაც ადასტურებს ალდოსტერონის სინთეზის დამატებით აქტივაციას ამგვარ კომორბიდულ კომბინაციაში და მოითხოვს ასეთი ტიპის ჰიპერალდოსტერონიზმის ზუსტი მექანიზმის შემდგომ გამოკვლევას. თანხლები სიმსუქნე ან სხეულის ჭარბი მასა არსებითად მოქმედებს მარცხენა პარკუჭის ჰიპერტროფიისათვის დამახასიათებელ ექოკარდიოგრაფიულ პარამეტრებზე ახალგაზრდა პაციენტებში არტერიული ჰიპერტენზიით და მარცხენა პარკუჭის ექსცენტრული ჰიპერტროფიის წილის მნიშვნელოვანი მომატებით. ალდოსტერონსინთაზას გენი C-344T-ის პოლიმორფიზმის "პათოლოგიური" გენოტიპები (CC+CT) ასოცირებულია ალდოსტერონის უფრო მაღალ კონცენტრაციასთან და მარცხენა პარკუჭის ჰიპერტროფიის მეტად გამოხატულ პროცესებთან ახალგაზრდა პაციენტებში არტერიული ჰიპერტენზიით.

FEATURES OF THE CORONARY ARTERIES ANATOMICAL LESIONS IN NSTEMI PATIENTS DEPENDING ON THE ASSOCIATION WITH THE INITIAL CLINICAL CHARACTERISTICS

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Patients who suffered from Non-ST-Segment Elevation myocardial infarction (NSTEMI) remain one of the most difficult categories of invasive treatment, which requires systematization of experience and the development of a specific algorithm for the management of such patients. Data on the nature of coronary heart disease in patients with NSTEMI show that 10-20% of patients have intact coronary vessels, in 30-35% of cases lesions of one, in 25-30% - 2 vessels and in 5-10% - lesions trunk of the left coronary artery of different nature [8]. On the other hand, a number of studies show less significant anatomical changes in the coronary artery in women compared to men in various forms of acute coronary syndrome in all age groups [8,16,17].

The aim of the study is to determine the nature of the anatomical lesion of the coronary arteries in NSTEMI depending on different clinical characteristics.

Material and methods. All studies conform to the principles of the Declaration of Helsinki of the World Medical Association. The study protocol, the form of informed consent of patients and other documents related to the study were approved at the meeting of the Academic Council of the National Pirogov Memorial Medical University, Vinnytsya (excerpt from the protocol No. 2 from 27.02.2020). Informed consent to participate in the study was discussed and signed by all study participants.

We examined 156 patients with INSTEMI aged 38 to 80 (mean 62.0 ± 0.71, median – 62 and interquartile range – 55 and 70) years, who were urgently hospitalized in the Vinnytsya Regional Clinical Center of Cardiovascular Pathology.

The main criteria for inclusion of patients in the study were: NSTEMI, which emerged for the first time; age of patients up to 80 years and the patient's informed consent to participate in the study. The diagnosis of NSTEMI was established according to the recommendations of ESC, 2020. The criteria for exclusion from the study were: 1) STEMI, transferred in the past and recurrent acute myocardial infarction; 2) age of patients 80 years and older; 3) the presence of sinoatrial or atrioventricular block II-III degree, implanted or the need for implantation of an artificial pacemaker; 4) chronic heart failure NYHA-III, IV before the incident of acute myocardial infarction; 5) diseases of the respiratory system, kidneys and liver, which were accompanied by signs of pulmonary, renal and hepatic failure; anemic conditions with a hemoglobin level below 110 g/L; 6) the presence of rheumatic and congenital heart defects, idiopathic and inflammatory myocardial lesions and 7) malignancies, severe neuropsychiatric disorders, alcohol abuse. All patients underwent GRACE risk stratification according to the current protocol [3,4,9].

Results and discussion. The nature of the anatomical lesion of the coronary arteries in patients with NSTEMI is shown in Table 1. It was observed that in 22 of 156 (14.1%) examined during coronary angiography (CAG) were not found hemodynamically significant stenosis (HSS) of the coronary arteries (CA). In 88 of 156 (56.4%) subjects, single vascular lesions were registered (in the case of only HSS CA), in 27 (17.3%) – 2 vascular lesions and in 19 (12.2%) – 3 vascular lesions of main CA.

Analysis of the features of the anatomical changes of the CA along the main arteries showed that intact vessels (absence of any plaques) in the right coronary artery (RCA) were found in 101 (64.7%), in the anterior interventricular branch or left anterior descending (LAD) – in 38 (24.4%) and in the left circumflex artery (LCx) - in 94 (60.3%) subjects. Accordingly, HSS in the pool of RCA are registered in 40 (25.6%), in the pool of LAD – in 110 (64.7%) and in the pool of LCx – in 49 (31.4%) patients. In turn, to assess the severity of damage of main arteries, we calculated the conditional score of the CA, where 0 points – the absence of any plaques in the CA (intact artery), 1 point – the