ORIGINAL ARTICLE

THE RELATIONSHIPS OF IRS-1 POLYMORPHISM WITH HEMODYNAMIC DISORDERS IN HYPERTENSIVE PATIENTS DEPENDING ON BODY WEIGHT AND METABOLIC COMORBIDITY

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ABSTRACT

The aim: The aim was to study the relationships of IRS-1 gene polymorphism with indicators of the structural and functional state of the heart and blood vessels in patients with arterial hypertension under conditions of different metabolic comorbidity and body weight.

Materials and methods: We examined 340 patients with arterial hypertension with different body weight and different types of metabolic comorbidity and 30 healthy individuals aged 45-55. Anthropometric, Biochemical, Molecular genetic methods, Instrumental, Statistical methods were used.

Results: The presence of G/R + R/R genotypes in hypertensive patients with normal body weight was associated with an increase in intima-media thickness (CIMT), pulse wave velocity of carotid artery (cPWV) and lower endothelium-dependent vasodilatation (EDVD) compared with G/G genotype carriers. Hypertensive patients with obesity, carriers of G/R and R/R genotypes displayed more pronounced similar changes in vascular remodeling (higher CIMT, cPWV and lower EDVD) and as well as cardiac remodeling (larger sizes and left ventricular mass (LVM)) compared with G/G genotype carriers. Overweight carriers of the G/R + R/R genotypes were characterized by enlargement of LVM and its sizes, a higher CIMT indicator, but this effect was less than in the comorbidity of hypertension and obesity. In hypertensive patients with hypertension, obesity and type 2 diabetes mellitus, the presence of G/R + R/R genotypes was associated with an increase in left ventricular size, left ventricular mass index (LVMI) and CIMT.

Conclusions: The relationships of IRS-1 polymorphism with indicators of cardiovascular remodeling in hypertensive patients depending on body weight and the presence of various metabolic comorbidity have been established.

KEY WORDS: arterial hypertension, insulin receptor substrate-1 gene, metabolic comorbidity, genetic polymorphism

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INTRODUCTION

For many years hypertension concerned being a sort of an epidemic, having a leading position in terms of prevalence and overall mortality and is often associated with obesity (OB) and overweight [1, 2]. Genetic predisposition to hypertension is manifested under the influence of environmental factors - high-calorie diet, excessive fat intake and low physical activity [3, 4]. These environmental factors contribute to the development and progression of components of the metabolic syndrome in hypertension due to impaired expression of genes that control the signal of insulin, polymorphic lipid disorders, defects in enzymes of glucose metabolism [4, 5].

A number of studies have shown that gene polymorphism has a greater impact on the hypertension course and complications than on its development [6]. A significant number of studies are devoted to the study of genetic polymorphism of key components of RAAS [7, 8]. Some provisions regarding the expression and polymorphism of various AH genes and their relationship with blood pressure levels and the degree of hypertensively-associated organ lesions remain discussed and actively studied [6, 9].

According to most researchers, the most significant predictors of hypertension and obesity are hereditary risk factors. At the same time, despite significant advances in genetic research, there are conflicting views on the role of gene expression and genetic polymorphism in the development and course of disease in different patient populations, as well as their impact on the drug therapy effectiveness [4, 9, 10].

Hyperinsulinemia and IR largely determine the severity of cardiovascular complications in patients with hypertension and obesity. Recently published results of clinical and experimental studies indicate that IR causes a violation of the physiological mechanisms of vasodilation. The action of insulin on the endothelium is mediated by its own receptors and is realized through a multistage signaling system associated with increased synthesis of nitric oxide

Table I. Distribution of G / G and G / R + R / R genotypes of the IRS-1 gene in study groups

Genotype	Group 1	Group 2	Group 3	Group 4	Group 5
	AH + obesity	AH and normal body weight	AH and overweight	AH, obesity and type 2 diabetes	The test group
	n=200	n=50	n=50	n=40	n=30
G/G	110 (55%)[1-5]	32 (64%)[2-5]	22 (44%)[2-3, 3-5]	16 (40%)[2-4, 4-5]	25 (83,4%)
G/R+ R/R	90 (45%)[1-5]	18 (36%)	28 (56%)[3-5]	24(60%)[4-5]	5(16,6%)

Note. 1-5 – statistically significant differences between groups 1 and 5;2-3 – statistically significant differences between groups 2 and 3; 2-4 – statistically significant differences between groups 2 and 4; 2-5 – statistically significant differences between groups 2 and 5; 3-5 – statistically significant differences between groups 3 and 5;4-5 – statistically significant differences between groups 4 and 5.

(NO). In patients with hypertension in the conditions of IR significantly induced NO endothelium-dependent vasodilation (EDVD) [11].

Presence of two components: genetic (hereditary) and acquired is clearly traced in the IR development [12]. Despite the fact that IR has a clear genetic condition, the exact genetic disorders that underlie it have not yet been identified. That indicates its polygenic nature. One of the most recognized polymorphisms of the IRS-1 gene, which is associated with the development of IR in many populations, is G972R - polymorphism [13, 14].

The results of numerous studies of IRS-1 polymorphism have proved its association with the development of type 2 diabetes in different populations [13–17], but there are insufficient data on its influence on the formation of comorbidity of hypertension and obesity, in particular, at the stage of IR absence.

THE AIM

The aim was to study the relationships of IRS-1 gene polymorphism with indicators of the structural and functional state of the heart and blood vessels in patients with arterial hypertension under conditions of different metabolic comorbidity and body weight.

MATERIALS AND METHODS

Clinical - anamnestic with office measurement and home blood pressure monitoring in accordance with the 2018 ESC/ESH Guidelines for the management of AH [1] - to assess the clinical manifestations of AH and study the etiological factors of the disease. Anthropometric - to assess the degree of obesity and diagnose abdominal obesity height, body weight, body mass index, waist circumference, thigh volume, index «waist – thigh" were determined. The insulin concentration, fasting glycemia were determined for calculating the HOMA index. Molecular genetic methods using polymerase chain reaction - established the presence of genetic polymorphisms G972R gene IRS-1 (genotypes G/G, G/R and R/R). Instrumental - to assess the structural and functional state of the heart and blood vessels the ultrasound scanner "IMAGIC Agile" was used.

Left ventricular diastolic function was evaluated by pulmonary artery blood flow and transmitral diastolic blood flow in pulsed Doppler with the determination of the following parameters: maximum early LV filling rate in spectral mode (E), maximum late (atrial) filling speed (A), ratio of maximal rates of early and late filling of LV at spectral mode (E/A), time of isovolumic relaxation of LV (IVRT), time of deceleration early diastolic flow rate (DT), maximum early LV filling rate at tissue mode (e´), mean pulmonary artery pressure (AP) by Kitabatake, ratio of E and e´ (E/e´). For studying endothelial function, the degree of endothelium-dependent vasodilation (EDVD) in reactive hyperemia was determined in all patients according to the method of Celermajer D.S. in the modification of the method by Ivanova O.V. [18, 19]. We measured the intima media thickness (CIMT) of the carotid artery according to the generally accepted method. The pulse wave velocity (PWV) in the carotid artery (cPWV) was determined by the W-Track method; determination of the PWV in the abdominal aorta (aPWV) was performed using a phased sensor.

Difference between SBP and DBP evaluated as pulse BP.

Average BP was calculated by the formula:

Average BP = 0.42 × (SBP – DBP) + DBP

The volumes of left and right atria (LAV and RAV, respectively), end-systolic and end-diastolic diameters (LVESD and LVEDD, respectively) of the left ventricle (LV), diameters of LA and aorta (LAD and AD, respectively) were evaluated. The ejection fraction (EF) was calculated by the formula:

EF = (EDV – ESV) / EDV,

where ESV and EDV are the end-systolic and end-diastolic LV volumes, respectively.

The thickness of the posterior wall of the LV and the thickness of the interventricular septum in the systole (TPWs and TIVSs, respectively) and diastole (TPWd and TIVSd, respectively) were measured. The relative wall thickness of the LV (RWT) was calculated by the formula:

RWT = (TPWd + TIVSd) / LVEDD

The LV myocardial mass index (LVMI) was calculated as the ratio of the LV myocardial mass (LVM) to the surface area of the body (S):

LVMI = LVM / S

The statistical processing of the obtained data was carried out using the package of statistical software "SPSS 17" (IBM), Microsoft Office Exel-2003. The data are presented as mean values ± standard deviation. Significance was set at a p value of < 0.05 in all cases.

Table II. Comparative evaluation of hemodynamic parameters of obese hypertensive patients and obese hypertensive patients with type 2 diabetes depending on the genotypes G / G and G / R + R / R of the IRS-1 gene

Indicators	AH + obesity			AH + obesity + type 2 diabetes		
	G/G	G/R + R/R	p	G/G	G/R + R/R	p
	n = 110	n = 90		n = 16	n = 24	
Weight [kg]	97,15 ± 10,77	105,41 ± 9,08	0,000	103,25 ± 7,85	100,63±7,64	0,199
BMI [kg/m2]	33,36 ± 2,76	36,58 ± 1,49	0,000	34,49 ± 0,40	36,01 ± 1,05	0,003
Waist [cm]	106,70 ± 7,61	108,79 ± 7,30	0,051	107,56 ± 0,73	105,71 ±9,47	0,122
Hip [cm]	117,34 ± 8,84	114,14 ± 7,45	0,007	107,38 ± 6,62	110,58 ± 6,88	0,163
Waist-to-hip ratio	0,92 ± 0,11	0,96 ± 0,10	0,005	1,00 ± 0,11	0,96 ± 0,09	0,126
HOMA-IR	3,03 ± 1,15	3,87 ± 1,38	0,000	6,16 ± 0,97	9,04 ± 0,86	0,000
SBP [mm Hg]	172,74 ± 4,08	171,74 ± 4,75	0,102	166,38 ± 2,90	166,17 ± 2,79	0,772
DBP [mm Hg]	101,69 ± 3,16	101,17 ± 2,92	0,228	98,63 ± 1,86	99,33 ± 1,76	0,199
Heart rate [bpm]	71,65 ± 1,88	71,80 ± 1,95	0,571	72,56 ± 1,36	72,75 ± 1,45	0,825
Pulse BP [mm Hg]	71,05 ± 3,69	70,58 ± 4,32	0,110	67,75 ± 3,96	66,83 ± 3,61	0,334
Average BP [mm Hg]	131,53 ± 3,08	131,39 ± 3,14	0,511	127,08 ± 1,31	127,40 ± 1,38	0,709
CIMT [mm]	0,88 ± 0,08	0,95 ± 0,08	0,000	0,93 ± 0,09	0,98 ± 0,05	0,037
CIMT bifurcation [mm]	1,34 ± 0,16	1,38 ± 0,15	0,076	1,34 ± 0,13	1,37 ± 0,18	0,610
cPWV [m/s]	8,34 ± 1,01	8,85 ± 1,11	0,001	8,87 ± 0,94	9,03 ± 1,07	0,669
aPWV [m/s]	8,36 ± 0,97	8,63 ± 1,14	0,077	9,12 ± 1,23	8,94 ± 1,32	0,825
EDVD (%)	7,09 ± 1,24	6,69 ± 1,01	0,015	6,76 ± 0,60	6,51 ± 0,67	0,264
TIVSd [cm]	1,15 ± 0,12	1,20 ± 0,11	0,008	1,16 ± 0,06	1,20 ± 0,10	0,314
TIVSs [cm]	1,44 ± 0,16	1,50 ± 0,14	0,005	1,39 ± 0,09	1,48 ± 0,12	0,008
TPWd [cm]	1,17 ± 0,13	1,20 ± 0,15	0,176	1,16 ± 0,10	1,19 ± 0,15	0,508
TPWs [cm]	1,58 ± 0,32	1,64 ± 0,38	0,222	1,44 ± 0,18	1,57 ± 0,32	0,147
LVEDD[cm]	4,84 ± 0,33	4,95 ± 0,34	0,017	4,7 ± 0,16	4,96 ± 0,39	0,036
LVESD[cm]	3,17 ± 0,26	3,28 ± 0,27	0,006	3,09 ± 0,13	3,27 ± 0,34	0,126
EDV [mL]	110,34 ±18,31	116,54 ±19,54	0,022	103,20 ± 8,54	116,93 ±21,99	0,036
ESV [mL]	40,51 ± 8,53	43,81 ± 9,17	0,010	37,83 ± 3,85	43,99 ± 11,69	0,126
EF (%)	63,35 ± 3,64	62,55 ± 2,84	0,089	63,33 ± 2,34	62,76 ± 3,30	0,858
LVM [g]	254,43 ±64,97	276,17 ±68,38	0,023	240,34 ±29,25	274,81 ±67,58	0,090
LVMI [g/m^2]	122,22 ±30,37	128,79 ±32,23	0,140	113,68 ±13,71	130,27 ±31,53	0,038
RWT	0,48 ± 0,04	0,48 ± 0,05	0,716	0,49 ± 0,03	0,48 ± 0,04	0,517
LAD [mm]	38,44 ± 3,07	38,07 ± 3,40	0,419	38,01 ± 4,04	33,19 ± 1,44	0,270
AD [mm]	33,31 ± 1,83	32,92 ± 0,83	0,205	32,66 ± 0,81	17,18 ± 3,51	0,581
Mean pulmonary AP [mm Hg] by Kitabatake	16,12 ± 3,48	16,50 ± 2,87	0,400	17,30 ± 2,71	17,18 ± 3,51	0,923
RAV [mL]	40,13 ± 5,34	38,53 ± 3,86	0,018	37,44 ± 2,84	39,55 ± 5,02	0,362
LAV [mL]	52,51 ± 5,21	51,41 ± 4,57	0,121	50,56 ± 3,37	52,19 ± 3,60	0,544
e´[cm/s]	11,58 ± 2,34	11,38 ± 2,09	0,537	10,83 ± 2,68	10,96 ± 1,69	0,679
E [cm/s]	67,01 ± 12,30	66,95 ± 6,93	0,970	64,01 ± 7,33	68,49 ± 12,43	0,143
A [cm/s]	79,78 ± 11,84	77,32 ± 9,33	0,110	75,30 ± 8,95	72,42 ± 12,54	0,314
E/A	0,85 ± 0,18	0,87 ± 0,11	0,330	0,85 ± 0,08	0,97 ± 0,24	0,095
DT [s]	0,16 ± 0,11	0,15 ± 0,07	0,435	0,15 ± 0,04	0,15 ± 0,04	1,000
IVRT [s]	0,12 ± 0,02	0,12 ± 0,03	0,896	0,11 ± 0,02	0,10 ± 0,02	0,155
E/e´	5,91 ± 1,12	6,05 ± 1,13	0,374	6,26 ± 1,78	6,47 ± 1,78	0,517

BP - blood pressure; DBP - diastolic blood pressure; SBP - systolic blood pressure; A - maximum late (atrial) filling speed; AP - artery pressure; DT - time of deceleration early diastolic flow rate; E - filling rate in spectral mode; e - maximum early LV filling rate at tissue mode; E/A - ratio of maximal rates of early and late filling of LV at spectral mode; E/e - ratio of E and e; IVRT - time of isovolumic relaxation of LV; EDVD - endothelium-dependent vasodilatation; EF - ejection fraction; CA - carotid artery; IMT - intima-media thickness; LVM - left ventricular mass; LVMI - left ventricular mass index; PWV - pulse wave velocity (cPWV – carotid artery, aPWV - abdominal aorta); RAV - right atrial volume; LAV - left atrial volume; TIVSd - thickness of the interventricular septum (diastole); TIVSs - thickness of the interventricular septum (systole); TPWd - thickness of the posterior wall of the left ventricle in diastole; TPWs - the thickness of the posterior wall of the left ventricle in systole; LVEDD - end-diastolic diameters; LVESD - end-systolic diameters; EDV - end-diastolic volume; ESD - end-systolic volume; RWT - relative wall thickness; LAD - left atrial diameter; AD - aortic diameter.

Table III. Comparative evaluation of hemodynamic parameters of hypertensive patients with normal BMI and hypertensive overweight patients depending on the genotypes G / G and G / R + R / R of the IRS-1 gene

Indicators	AH + normal weight		p	AH + overweight		p
	G/G	G/R + R/R		G/G	G/R + R/R	
	n = 32	n = 18		n = 22	n = 28	
Weight [kg]	68,06 ± 5,20	70,39 ± 6,58	0,275	77,77 ± 7,31	85,39 ± 8,25	0,001
BMI [kg/m2]	23,76 ± 0,75	23,83 ± 0,78	0,824	27,02 ± 1,53	28,46 ± 1,59	0,002
Waist [cm]	79,22 ± 6,38	76,67 ± 4,79	0,192	80,18 ± 6,49	81,57 ± 6,81	0,564
Hip [cm]	95,44 ± 6,08	98,33 ± 5,51	0,075	98,00 ± 6,75	97,00 ± 5,20	0,755
Waist-to-hip ratio	0,83 ± 0,08	0,81 ± 0,06	0,061	0,82 ± 0,08	0,84 ± 0,06	0,385
HOMA-IR	1,98 ± 0,36	2,81 ± 0,22	0,000	2,09 ± 0,32	2,82 ± 0,42	0,000
SBP [mm Hg]	168,56 ± 5,24	170,56 ± 3,13	0,102	171,00 ± 4,78	172,61 ± 3,95	0,201
DBP [mm Hg]	101,41 ± 2,94	101,41 ± 2,17	0,132	100,77 ± 1,97	101,86 ± 2,89	0,287
Heart rate [bpm]	71,59 ± 2,14	71,59 ± 1,72	0,176	72,23 ± 1,85	71,64 ± 2,16	0,423
Pulse BP [mm Hg]	67,16 ± 4,29	69,16 ± 4,58	0,069	69,23 ± 5,00	70,75 ± 2,96	0,209
Average BP [mm Hg]	128,45 ± 3,47	127,65 ± 1,32	0,107	130,01 ± 2,40	131,57 ± 3,04	0,204
CIMT [mm]	0,81 ± 0,10	0,81 ± 0,12	0,002	0,82 ± 0,09	0,91 ± 0,08	0,000
CIMT bifurcation [mm]	1,12 ± 0,19	1,12 ± 0,23	0,002	1,23 ± 0,18	1,26 ± 0,13	0,605
cPWV [m/s]	7,40 ± 0,67	7,40 ± 1,48	0,013	7,75 ± 0,90	7,86 ± 0,72	0,682
aPWV [m/s]	8,04 ± 0,83	8,04 ± 1,23	0,176	8,39 ± 0,75	8,17 ± 0,61	0,319
EDVD (%)	9,03 ± 1,08	9,03 ± 1,70	0,004	8,46 ± 1,12	8,46 ± 0,92	0,815
TIVSd [cm]	1,10 ± 0,11	1,11 ± 0,10	0,856	1,10 ± 0,09	1,15 ± 0,07	0,033
TIVSs [cm]	1,50 ± 0,16	1,48 ± 0,16	0,754	1,47 ± 0,12	1,46 ± 0,12	0,907
TPWd [cm]	1,11 ± 0,09	1,15 ± 0,08	0,102	1,09 ± 0,11	1,15 ± 0,11	0,077
TPWs [cm]	1,65 ± 0,30	1,59 ± 0,23	0,592	1,51 ± 0,28	1,53 ± 0,22	0,653
LVEDD[cm]	4,78 ± 0,22	4,83 ± 0,24	0,379	4,78 ± 0,26	4,97 ± 0,26	0,007
LVESD[cm]	3,09 ± 0,16	3,14 ± 0,21	0,621	3,13 ± 0,19	3,22 ± 0,20	0,109
EDV [mL]	106,54 ±12,21	109,32 ±13,32	0,379	107,10 ±14,17	116,94 ±14,31	0,007
ESV [mL]	37,75 ± 4,82	39,31 ± 6,78	0,621	39,10 ± 5,75	41,83 ± 6,17	0,109
EF (%)	64,57 ± 2,19	64,16 ± 2,35	0,880	63,45 ± 3,20	64,26 ± 2,61	0,482
LVM [g]	227,64 ±33,55	239,65 ±29,96	0,157	227,93 ±35,61	259,80 ±40,32	0,007
LVMI [g/m^2]	128,11 ±19,57	131,42 ±15,89	0,518	120,69 ±16,83	130,21 ±17,85	0,068
RWT	0,47 ± 0,03	0,47 ± 0,04	0,671	0,46 ± 0,03	0,46 ± 0,03	0,274
LAD [mm]	34,02 ± 2,55	32,28 ± 7,62	0,092	37,99 ± 3,29	37,10 ± 1,95	0,637
AD [mm]	33,10 ± 0,92	32,91 ± 0,79	0,223	32,75 ± 1,96	13,97 ± 1,40	0,056
Mean pulmonary AP [mm Hg] by Kitabatake	13,18 ± 2,41	13,77 ± 3,42	0,701	14,50 ± 2,45	13,97 ± 1,40	0,274
RAV [mL]	39,16 ± 3,21	38,61 ± 2,82	0,223	37,36 ± 5,34	40,09 ± 5,07	0,097
LAV [mL]	46,29 ± 4,18	44,82 ± 3,94	0,115	46,06 ± 5,06	48,05 ± 2,88	0,237
e´[cm/s]	12,16 ± 2,34	12,40 ± 2,74	0,770	12,36 ± 2,60	12,88 ± 3,15	0,674
E [cm/s]	66,36 ± 8,10	66,37 ± 11,13	0,679	70,67 ± 11,97	65,78 ± 11,20	0,305
A [cm/s]	76,51 ± 11,73	83,11 ± 8,01	0,054	71,27 ± 9,10	80,62 ± 12,03	0,004
E/A	0,89 ± 0,18	0,80 ± 0,12	0,056	1,00 ± 0,16	0,82 ± 0,13	0,001
DT [s]	0,26 ± 0,36	0,19 ± 0,18	0,524	0,15 ± 0,03	0,14 ± 0,03	0,324
IVRT [s]	0,11 ± 0,02	0,11 ± 0,02	0,701	0,11 ± 0,01	0,10 ± 0,02	0,229
E/e´	5,64 ± 1,18	5,58 ± 1,44	0,808	5,72 ± 1,38	5,75 ± 1,76	0,422

BP - blood pressure; DBP - diastolic blood pressure; SBP - systolic blood pressure; A - maximum late (atrial) filling speed; AP - artery pressure; DT - time of deceleration early diastolic flow rate; E - filling rate in spectral mode; e - maximum early LV filling rate at tissue mode; E/A - ratio of maximal rates of early and late filling of LV at spectral mode; E/e - ratio of E and e; IVRT - time of isovolumic relaxation of LV; EDVD - endothelium-dependent vasodilatation; EF - ejection fraction; CA - carotid artery; IMT - intima-media thickness; LVM - left ventricular mass; LVMI - left ventricular mass index; PWV - pulse wave velocity (cPWV – carotid artery, aPWV - abdominal aorta); RAV - right atrial volume; LAV - left atrial volume; TIVSd - thickness of the interventricular septum (diastole); TIVSs - thickness of the interventricular septum (systole); TPWd - thickness of the posterior wall of the left ventricle in diastole; TPWs - the thickness of the posterior wall of the left ventricle in systole; LVEDD - end-diastolic diameters; LVESD - end-systolic diameters; EDV - end-diastolic volume; ESD - end-systolic volume; RWT - relative wall thickness; LAD - left atrial diameter; AD - aortic diameter.

The study protocol was approved by the Ethics Committee. All participants were informed about the aim of the study and signed a written consent form.

RESULTS

According to the objectives of the study, 340 patients aged 45-55 were surveyed. Group 1 included 200 patients with AH with class I - II obesity, group 2 - 50 patients with AH and normal body weight, group 3 - 50 patients with AH and overweight, group 4 - 40 patients with AH, obesity and type 2 diabetes. The test group consisted of 30 healthy individuals without AH and obesity, according to the clinical-instrumental study data. Groups were formed by age and gender.

The prevalence of genotypes G/R and R/R in the polymorphism G972R of the IRS-1 gene in obese hypertensive patients is 45 %, that is 2.7 times higher than in the healthy group, 1.3 times higher than in the group with normal body weight and, accordingly, less 1.2 times and 1.3 times than in the group with excess body weight and triple comorbidity (AH, obesity and type 2 diabetes). The prevalence of G/G genotype in the G972R polymorphism of the IRS-1 gene in patients with AH with obesity is, respectively, 1.2 times and 1.5 times less than in patients with normal body weight and a group of healthy people, but 1. 4 times more than with triple comorbidity. (Tab. I).

Hypertensive patients with obesity (Group 1), carriers of G/R and R/R genotypes displayed more severe vascular remodeling (higher CIMT (p = 0,000), cPWV (p = 0,001) and lower EDVD (p = 0,015)) and cardiac remodeling (larger sizes: TIVSd (p = 0,008), TIVSs (p = 0,005), LVEDD (p = 0,017), LVESD (p=0,006), EDV(p = 0,022), ESV (p = 0,010) and LVM (p = 0,023) compared with G/G genotype carriers. (Tab. II).

The presence of G/R + R/R genotypes in hypertensive patients with normal body weight (Group 2) was associated with an increase in CIMT (p = 0.002), cPWV (p = 0.002) and lower EDVD (p = 0.004) compared with G/G genotype carriers. (Tab. III).

Overweight (Group 3) carriers of the G/R + R/R genotypes were characterized by enlargement of LVM (p = 0.007) and its sizes (LVEDD, EDV (p = 0.007 for both indicators)), a higher CIMT indicator (p = 0.000), but this effect was less than in the comorbidity of hypertension and obesity. (Tab. III).

In hypertensive patients with triple comorbidity, the presence of G/R + R/R genotypes was associated with an increase in left ventricular sizes, LVMI (p = 0.038) and CIMT (p = 0.037). (Tab. II).

DISCUSSION

Arterial hypertension (AH) is referred to as "regulatory disease" in which the activity and interaction of neurohumoral factors of blood pressure are disrupted, leading to structural changes in the heart and blood vessels. A feature of hypertensive heart in patients with metabolic syndrome (MS) is left ventricular hypertrophy (LVH), inadequate blood pressure, as metabolic disorders themselves lead to structural and functional changes in the myocardium, myocardial microcirculation disorders and can provoke relaxation and myocardial infarction. This, in turn, contributes to the formation of left ventricular (LV) diastolic dysfunction and diastolic heart failure (HF) [20, 21].

Detection of marker gene polymorphisms associated with both CVD risk and overweight is due to the need to further study the contribution of the hereditary component to the pathogenesis of cardiovascular remodeling and the reasonable need to develop new methods for early diagnosis and treatment of non-resistant and resistant hypertension [22].

According to the results of the presented part of the scientific work in all studied groups, regardless of body weight and metabolic comorbidity, the IRS-1 polymorphism is more associated with the progression of the vascular remodeling than the cardiac one.

This proves the need for genetic screening of IRS-1 in patients with hypertension to detect G/R + R/R genotypes in order to strengthen control over the state of neurohumoral factors associated with the progression of cardiovascular remodeling in these groups of patients.

CONCLUSIONS

The relationships of IRS-1 polymorphism with indicators of cardiovascular remodeling in hypertensive patients depending on body weight and the presence of various metabolic comorbidity have been established.

REFERENCES

1. Williams B., Mancia G., Spiering W. et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36(10):1953-2041.
2. Whelton P.K., Carey R.M., Aronow W.S. et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13-115.
3. Conen D., Cheng S., Steiner L.L. et al. Association of 77 polymorphisms in 52 candidate genes with blood pressure progression and incident hypertension: the Women's Genome Health Study. J Hypertens. 2009;27(3):476-83.
4. Baranov V.S., Baranova E.V. Genom cheloveka, epigenetika mnogofaktornyih bolezney i personifitsirovannaya meditsina [Human genome, epigenetics of complex diseases, and personalized medicine]. Biosphere. 2012;4(1):76-85. (in Russian).
5. Puzyirev V.P. Meditsinskaya patogenetika [Medical pathogenetics]. Vavilov Journal of Genetics and Breeding. 2014;18(1): 7-21. (in Russian).
6. Delles C., Padmanabhan S. Genetics and Hypertension: Is It Time to Change My Practice? Canadian Journal of Cardiology. 2012;28:296–304.

7. Muzhenya D.V., Tuguz A.R., Lyisenkov S.P. et al. Rol polimorfizma genov komponentov renin-angiotenzinovoy sistemyi v razvitii serdechno-sosudistyih zabolevaniy, izbyitochnoy massyi tela i ozhireniya u zhiteley Respubliki Adyigeya [Role of gene polymorphism of the renin-angiotensin system components in development of cardiovascular diseases, excess body weight and obesity in inhabitants of the Adyghea Republic]. Vestnik of Saint Petersburg University. Ser.: Medicine. 2018;13(4):344-54. (in Russian).
8. Watkins W.S., Hunt S.C., Williams G.H. et al. Genotype-phenotype analysis of angiotensinogen polymorphisms and essential hypertension: the importance of haplotypes. J Hypertens. 2010;28(1):65-75.
9. Acelajado M.C., Hughes Z.H., Oparil S., Calhoun D.A. Treatmtnt of resistant and refractory hypertension. Circ Res. 2019;124(7):1061-70. DOI:10.1161/CIRCRESAHA.118.312156.
10. Puzyrev V.P., Makeeva O.F., Freidin M.B. Syntropy, genetic testing and personalized medicine. Personalized Medicine. 2010; 7(4): 399-405.
11. Matsuda M., Shimomura I. Roles of oxidative stress, adiponectin, and nuclear hormone receptors in obesity-associated insulin resistance and cardiovascular risk. Horm Mol Biol Clin Investig. 2014;19(2):75-88.
12. Guo X., Cheng S., Taylor K.D. et al. Hypertention genes are genetic markers for insulin sensitivity and resistance. Hypertention. 2005;45(4):799-803.
13. Burguete-Garcia A.I., Cruz-Lopez M., Madrid-Marina V. et al. Association of Gly972Arg polymorphism of IRS-1 gene with type 2 diabetes mellitus in lean participants of a national health survey in Mexico: a candidate gene study. Metabolism. 2010;59(1): 38-45.
14. Bodhini D., Radha V., Mohan V. Association Study of IRS1 Gene Polymorphisms with Type 2 Diabetes in South Indians. Diabetes technology & therapeutics. 2011;13(7):767-72.
15. Ahluwalia T.S., Allin K.H., Sandholt C.H. et al. Discovery of coding genetic variants influencing diabetes-related serum biomarkers and their impact on risk of type 2 diabetes. Journal of Clinical Endocrinology and Metabolism. 2015;100(4):E664-71.
16. Shalimova A., Fadieienko G., Kolesnikova O. et al. The role of genetic polymorphism in the formation of arterial hypertension, type 2 diabetes and their comorbidity. J Current Pharmaceutical Design (USA). 2019;25:218-27.
17. Ahluwalia T.S., Allin K.H., Sandholt C.H. et al. Discovery of coding genetic variants influencing diabetes-related serum biomarkers and their impact on risk of type 2 diabetes. Journal of Clinical Endocrinology and Metabolism. 2015;100(4):E664-71.
18. Celermajer D.S., Sorensen K.E., Cooh V.M. et al. Noninvasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340: 1111–1115.
19. Ivanova O.V., Rogoza A.N., Balahonova T.V. et al. Opredelenie chuvstvitelnosti plechevoy arterii k napryazheniyu sdviga na endoteliy, kak metod otsenki sostoyaniya endoteliy zavisimoy vazodilatatsii s pomoschyu ultrazvuka vyisokogo razresheniya u bolnyih s arterialnoy gipertoniey [Sensitivity of endothelium of the brachial artery to shear stress-method to evaluate endothelial function in patients with hypertension]. Cardiology. 1998; 3:37– 42 (in Russian).
20. Nishida K., Otsu K. Inflammation and metabolic cardiomyopathy. Cardiovasc Res. 2017; 113 (4): 389-98. doi: 10.1093/cvr/cvx012.
21. Alpert M.A., Omran J., Bostick B.P. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Curr Obes Rep. 2016;5(4):424-34.
22. Psarova V. Molekuliarno-henetychni i neirohumoralni mekhanizmy sertsevo-sudynnoho remodeliuvannia ta yikh korektsiia u khvorykh na esentsialnu arterialnu hipertenziiu iz suputnim ozhyrinniam [Molecular genetic and neurohumoral mechanisms of cardiovascular remodeling and their correction in patients with essential hypertension with concomitant obesity] [dissertation manuscript]. Kharkiv. 2020, 393 p.

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