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Influence of Autonomic Dysfunction, Gln27Glu Polymorphism of β2-Adrenergic Receptor, and I/D Polymorphism of Angiotensin-Converting Enzyme Genes on Target Organs (Heart and Brain) in Kyrgyz Patients with Essential Hypertension

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Abstract

Background: Essential hypertension (EH) is traditionally associated with overactivity of sympathetic and renin-angiotensin systems and has multifactorial origin, arising from an interaction between susceptibility genes and environmental factors. **Objectives:** to examine the autonomic nervous system, polymorphism of the angiotensin-converting enzyme (ACE) and β2-adrenergic receptor (β2-AR) genes in hypertensive patients with complications (left ventricular hypertrophy and ischemic stroke). **Methods:** Heart rate variability (HRV) with active tilt-test, 24 h blood pressure monitoring (BP), echocardiography, Gln27Glu polymorphism of β2-AR, and I/D polymorphism of ACE genes were studied in 250 Kyrgyz EH patients with and without complications. **Results:** A significant reduction of HRV and decreased response of LF (low frequency) component to tilt-test in hypertensive patients were observed compared to control. Tilt-test in patients with complications of EH had shown inverse response of LF to orthostatic test. Patients with Gln27Gln genotype in comparison to other variants of Gln27Glu polymorphism of β2-AR were characterized by increasing meanings of BP and its morning raises, which possibly may cause increasing of left ventricular mass in these patients. In EH patients with ischemic stroke, DD genotype frequency was more than twofold greater than those with uncomplicated EH. Night hypertension, greater BP variability, and increased carotid intimal thickness are common features in patients with the DD genotype of the ACE gene. **Conclusion:** The inverse reaction of LF to orthostatic test can be regarded as an unfavorable prognostic sign, predisposing complications of EH. Our data support an association between I/D polymorphism of ACE gene and stroke in patients with EH. IJBM 2011; 1(2):59-65.

Key words: *essential hypertension, heart rate variability, stroke, genes.*

Introduction

Long-existing high blood pressure (BP) leads to the damage of target organs (heart, kidneys, blood vessels, and eyes), contributes to the development of myocardial infarction, stroke, and chronic heart and kidney failure [1].

The progression of EH may cause cardiac complications [2] in 70% of cases, a leading component of which is left ventricular hypertrophy (LVH). Numerous studies have demonstrated that LVH is an independent risk factor for heart failure, acute coronary syndrome, arrhythmias, and sudden death [3] and significantly worsens prognosis of the disease [4].

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Among numerous complications of arterial hypertension, brain stroke is the leading cause of morbidity and mortality. This problem is especially specific to the Kyrgyz Republic because hypertensive Kyrgyzs are more prone to ischemic stroke than Caucasians. According to a survey of the World Health Organization, Kyrgyzstan holds the first place in the Eurasian region with respect to mortality due to ischemic stroke (88.7 per 100000) [5].

Epidemiology studies involving twins, siblings, or families suggest that in addition to hemodynamic risk factors in the development of complications of EH, heredity and neurohumoral effects can play a significant role [6].

The role of heredity in development of LVH in large population studies was revealed. The most convincing data in this respect were obtained on twins [7] and suggest that the mass of the heart by 60% or more has a genetic predisposition.

The next important question is the role of hereditary factors in the development of ischemic stroke. In particular, the study of Bak S. et al. [8] using the twin analysis showed that concordance with mono- and dizygotic twins at risk for ischemic stroke was 19 and 8.5%, respectively.

As a possible candidate genes of LVH and ischemic stroke are considered genes of sympathoadrenal [9] and renin-angiotensin [10] systems.

The purpose of this study was to examine the autonomic nervous system (ANS), polymorphism of the angiotensin-converting enzyme (ACE), and β2-adrenergic receptor (β2-AR) genes in patients with essential hypertension with complications (LVH and ischemic stroke).

Methods

This study was approved by the Institutional Review Committee and patients volunteered informed consent. All participants (250 males with EH) were Kyrgyz by descent, between 40 and 65 years. Hypertension was diagnosed, if resting clinic blood pressure was >140/90mmHg on two occasions (WHO 1999). The control group included healthy age-matched Kyrgyz men with normal BP and drawn from the same local population (66 males).

The subjects were divided in two groups. Group 1 – patients with uncomplicated EH (180 males). Group 2 – patients with EH complicated by ischemic stroke, confirmed by computerized tomography of the brain (70 males). Exclusion criteria were acute myocardial infarction, heart failure, atrial fibrillation, valvular heart disease, diabetes mellitus and secondary hypertension.

Ambulatory blood pressure

A 24-hour BP and heart rate monitoring were conducted with Tonoport IV device (Marquette Hellige, Freiburg, Germany) in 180 patients from Group 1. BP and heart rate were measured every 15 min from 06:00 to 24:00 hours, and every 30 min from 24:00 to 06:00 hours. The 24-hour average systolic and diastolic BP, time index (percentage of increase in BP at 24 hours), variability (standard deviation) of both systolic (SBP) and diastolic BP (DBP), daily index (percentage fall in the mean arterial pressure at night compared with daytime), morning rises of SBP and DBP were analyzed. Based on the variability and the fall in the mean nocturnal BP compared with the mean daytime BP, patients were classified as "dippers" (fall ≥10% to 20%), "extreme dippers" (≥20%), "non-dippers" (≥0% to <10%), and "night-peakers" (<0%).

Carotid ultrasound

Examination of the carotid arteries was performed in 51 EH patients (from Group 1) with Acuson Sequoia-256 (Siemens, Germany). The carotid arteries were identified by B- and Doppler-mode regimen. The image was synchronized with the R wave on the ECG and stored on sVHS videotapes. Vessel diameter, intima-media thickness, peak systolic velocity, end-diastolic velocity, the resistivity index and systolic to diastolic ratio (S/D) – were measured. Echocardiography was carried out with Sequoia-512 Echo machine (Acuson, USA) in M- and B-mode in 180 patients from Group 1. End-diastolic and end-systolic volumes, left ventricular posterior wall thickness, interventricular septum thickness, diameter of aorta, left atrial dimension, and ejection fraction were estimated. Myocardial mass were calculated by the formula of Devereux and Reichek (1977) [11]. Myocardial mass index (MMI) was determined by the relation of myocardial mass to body surface area.

Heart rate variability (HRV) and active tilt-test

ANS reactivity was assessed using analysis of HRV at rest and during active 90° head-up tilt in 82 untreated patients (66 patients without and 16 patients with stroke). Patients from Group 1 were divided into three subgroups according to their left ventricular mass index: Subgroup 1 was composed of 19 hypertensive patients with normal MMI (<94 g/m^2); Subgroup 2 – by 34 patients with intermediate MMI of 94–134 g/m^2; and in Subgroup 3 were included 13 patients with LVH (MMI>134 g/m^2). All subgroups did not differ by age, duration of disease, and body mass index (BMI). ECG recordings were further analyzed by spectral analysis of HRV (fast Fourier transformation) with specially developed software according with standard requirements for HRV processing (Memoport 2000, Marquette Hellige, Germany) and evaluation of short-term recordings [12]. Total power (TP, 0.0033-0.40 Hz) was divided into three frequency bands: the power of very low frequency (VLF, 0.033-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.40 Hz). They were expressed in absolute and relative value to total power.

Biochemical and molecular genetics methods

Levels of glucose, cholesterol were determined in all patients by standard methods on the automatic analyzer Beckman Synchron SX4 delta Clinical System (USA).

ACE and β2-AR genotyping was performed in 190 patients with EH including 120 patients without and 70 patients with stroke. DNA was extracted from venous blood samples using Nucleon BACC3 kits (Amersham Pharmacia Biotech, Sweden). The ACE I/D and β2-AR genotypes were determined by the polymerase chain reaction (PCR) method with the oligonucleotide primers:

5'-CTGGAGACCACTCCCATCCTT-3' and

5'-GTGGCCATCACATTCGTCAGAT-3',

based on previously described methods [13, 14].

Statistical analysis was carried out using STATISTICA software package and standard statistical

software. Clinical data were compared using unpaired and paired two-sample t-tests for assessment of normality data distribution; nonparametric tests (Mann–Whitney U-test and Wilcoxon test) were used for sample data that were not normally distributed. Allele and genotype distributions in groups were compared using contingency tables and nonparametric chi-square test, z-test. Stepwise multiple regression analysis was carried out in two models. The first model with MMI was analyzed incorporating age, BMI, Gln27Glu polymorphism of β2-AR gene, and the I/D polymorphism of the ACE gene, the most important parameters of 24-h BP monitoring (average meanings, time index, variability, daily index, and morning rises) and HRV (VLF%, LF%, and HF%) as independent variables. The second model, with the presence of ischemic stroke as dependent variable, was carried out using the following independent variables: age, BMI, smoking, glucose, total cholesterol, SBP, DBP, data of echocardiography (MMI, end-diastolic and end-systolic volume, wall thickness, left atrial dimension, ejection fraction), data of carotid ultrasound (intima-media thickness, the presence of atherosclerosis), and I/D polymorphism of the ACE gene. A *p* value less than 0.05 was considered statistically significant.

Results

Autonomic regulation in patients with EH and target organs damage

Both LF and HF bands were reduced in hypertensive patients compared to control so that total power was significantly reduced too. Besides this, patients with LVH (Subgroup 3) had lower values of HF power compared to patients with normal LV geometry. Analysis of relative values of spectral components in proportion to the total power in hypertensive patients with different types of cardiac remodeling had shown significant reduction of HF in subgroup with LVH compared to subgroup with normal and intermediate MMI. It was accompanied by growth of VLF that in general shows presence of ANS dysfunction in hypertensive patients with LVH (Table 1).

The study of HRV in patients with EH and ischemic stroke revealed significant reduction in power of all spectral components (TP, VLF, LF, HF) compared to control. Besides that, HRV in patients with EH and stroke was similar to those of patients from the subgroup with LVH (Table 1).

Autonomic nervous system reactivity was assessed using spectral analysis of HRV during tilt-test. As it was expected, healthy subjects had shown significant increasing of LF ($p<0.001$) and reduction of HF bands ($p<0.001$) to orthostatic test (Table 2). Hypertensive patients had demonstrated decreased response of sympathetic component to tilt-test. So, the power of LF component was changed on 28% in subgroup with normal MMI and on 15% in subgroup with intermediate MMI, which were significantly lower compared to dynamics of LF in control group (86%, $p<0.01$ and $p<0.001$, respectively).

Another response to tilt-test was observed in EH patients with complications. Thus, in patients with LVH (Subgroup 3) and patients with ischemic stroke (Group 2), the power of LF component during tilt-test did not increase, but it actually decreased (-27.3% in patients with LVH and -34% in patients with stroke).

The reaction of the parasympathetic component (HF) in patients with EH of all groups was comparable to that in healthy individuals, so sympathetic-parasympathetic index (LF/HF) was increased in all groups of patients.

Association between Gln27Glu gene polymorphism of β2-AR and the I/D polymorphism of ACE gene with target organs damage (heart and brain) in patients with EH

Our previous studies have demonstrated the association between Gln27Glu polymorphism of β2-AR and I/D polymorphism of the ACE gene with the presence of EH in Kyrgyz population [15, 16]. Therefore, we seemed interested in investigating the effect of these genetic factors on the development of EH complications.

For study the clinical features of EH according to Gln27Glu polymorphism, homozygote on Glu-allele were united to heterozygote because of dominant influence of Glu-allele in this polymorphism [16].

Results of 24-h BP monitoring in hypertensive patients with different variants of Gln27Glu polymorphism had shown increased meanings of both systolic (143.1±1.2 mmHg) and diastolic BP (95.3±1.4 mmHg) in Gln27-homozygote compared to carrying Glu-allele (135.2±2.1 mmHg for SBP, $p<0.01$ and 90.2±1.8 mmHg for DBP, $p<0.04$). Besides that, patients with Gln27Gln genotype had more rapid morning rises of SBP (15.5±1.3 mmHg/h versus 10.8±4.1 mmHg/h in patients with Glu-allele, $p<0.02$). That, as it known, may be an unfavorable factor increasing the risk of cardiac and cerebral complications of EH.

Results of echocardiography had revealed increased myocardial mass index in patients with Gln27Gln genotype: 103.0±2.6 g/m^2 versus 96.7±1.8 g/m^2 in patients with Glu-allele ($p<0.05$). During multiple regression analysis, also including in the model Gln27Glu polymorphism of β2-AR gene, it was revealed that independent risk factors increasing myocardial mass in patients with EH were SBP ($\beta=0.38$, $p<0.006$), body mass index ($\beta=0.26$, $p<0.008$), SBP variability ($\beta=0.15$, $p<0.02$), morning rises of SBP ($\beta=0.14$, $p<0.001$), and VLF% ($\beta=0.11$, $p<0.01$). Consequently, the influence of Gln27Glu polymorphism of β2-AR gene on the mass of myocardium was mediated by the action of hemodynamic factors.

Comparative analysis of the alleles and genotypes frequency of Gln27Glu polymorphism of β2-AR gene did not revealed any differences between EH patients Group 2 with controls and Group 1.

The study of association of I/D polymorphism of the ACE gene with target organ damage in patients with EH had not shown significant differences between patients from analyzed groups according to echocardiography parameters (wall thickness, MMI) in EH patients with different genotypes (II, ID, and DD).

Of the 51 patients who underwent ultrasound examination of the carotid artery, patients with the DD genotype had a significantly greater carotid intima-media thickness compared to those with the II or ID genotypes, which suggest more pronounced remodeling. Intima-media thickness of the right carotid artery was 0.069±0.010 cm in DD patients compared to 0.057±0.012 cm in II homozygote ($p<0.01$), and to 0.056±0.010 cm in ID heterozygote patients ($p<0.02$). The corresponding figures for the left

Table 1

Power spectral components (M±m) of heart rate variability in hypertensive patients with and without complications and healthy subjects in rest

Parameters	Controls (n=16)	Group 1			Group 2 (n=16)	P Subgroups 1-2	P Subgroups 1-3	P Subgroups 2-3
		Subgroup 1 (n=19)	Subgroup 2 (n=34)	Subgroup 3 (n=13)				
TP, ms^2	2604.0±394.0	1815.7±278.9	1734.8±237.5**	1278.7±405.7**	976.2±81.2***†	ns	ns	ns
VLF, ms^2	1328.9±207.4	699.2±148.5**	838.9±112.3*	914.4±298.7	556.1±78.5***†	ns	ns	ns
LF, ms^2	697.5±113.2	460.8±69.4*	489.0±68.8**	274.4±86.8***	239.1±42.8***†	ns	ns	ns
HF, ms^2	422.9±75.8	323.5±60.9	211.8±27.1	119.1±43.8***	153.1±40.5***†	ns	<0.01	ns
LF/HF	2.34±0.36	2.16±0.37	2.57±0.34	3.77±1.17	3.72±1.30	ns	ns	ns
VLF%	49.6±2.7	44.4±3.4	52.1±2.5	58.2±5.26	56.7±7.2	ns	<0.05	ns
LF%	28.7±2.5	30.2±3.1	27.8±2.0	30.0±4.5	23.7±4.5	ns	ns	ns
HF%	15.6±2.0	17.5±2.1	17.1±1.8	7.6±1.4***	16.8±5.5	ns	<0.002	<0.001

Notes: *ns – non significant; * - p<0.05, ** - p<0.01, *** - p<0.001 – between hypertensive patients and control group;*
† - p<0.02 between hypertensive patients; Group 2 and Group 1 (Subgroup 1 and Subgroups 2).

Table 2

Power spectral components (M±m) of heart rate variability in hypertensive patients with and without complications and healthy subjects in rest and tilt-test

Groups		Test	LF, ms^2	LF-dynamic, %	HF, ms^2	LF/HF
Controls (n=16)		Rest	697.5±113.2	+86.1	422.9±75.8	2.34±0.36
		Tilt	1297.6±208.2***		191.2±35.6***	9.46±1.63***
Group 1	Subgroup 1 (n=19)	Rest	460.8±69.4	+27.7†	323.5±62.0	2.16±0.37
		Tilt	588.5±105.1		153.1±27.6***	5.45±1.36**
	Subgroup 2 (n=34)	Rest	489.0±68.8	+14.7†	211.8±27.1	2.57±0.34
		Tilt	561.3±97.5		89.7±13.3***	8.38±1.26***
	Subgroup 3 (n=13)	Rest	274.4±95.1	-27.3‡	119.1±43.8	3.77±1.17
		Tilt	199.2±66.4		33.7±11.0*	6.0±1.04*
Group 2 (n=13)		Rest	239.1±42.8	-34.0‡	153.1±40.5	3.72±1.30
		Tilt	159.0±30.1		52.5±16.7*	4.6±1.0

Notes: *** - p <0.01, *** - p <0.0001- between rest and tilt;*
† - p <0.01, ‡ - p <0.001 - between patients with EH (Subgroups 1-3 and Group 2) and control.

carotid artery were 0.062±0.003 cm, 0.056±0.008 cm, and 0.055±0.008 cm, respectively ($p<0.01$).

Twenty-four-hour average systolic and diastolic BP did not differ in hypertensive patients with different I/D genotypes. However, variability of systolic and diastolic BP was significantly greater in the DD genotype group compared to patients with other genotypes. Variability of systolic BP was 17.2±3.5 mmHg in DD patients compared to 14.7±3.6 mmHg in ID patients ($p<0.05$) and to 14.9±3.8 mmHg in II homozygote patients ($p<0.05$). Diastolic BP was 14.7±2.6 mmHg in DD patients, being significantly higher than ID heterozygote patients (12.7±3.0 mmHg, $p<0.03$) and II homozygote patients (12.7±3.4 mmHg, $p<0.05$).

Although there were no intergroup differences with regard to the average daily index of BP, qualitative analyses of BP profile revealed an abnormal daily BP rhythm in the form of non-dipping, night peaking, or extreme dipping in most of the patients with the DD genotype (83%).The prevalence of an abnormal BP profile was significantly lower in II and ID genotypes (44.2%, $p<0.01$; and 56.1%, $p<0.05$, respectively).

Analysis of the frequency of alleles and genotypes of the ACE gene in EH patients with or without a stroke showed no significant differences in I and D allele frequencies in comparable groups. However, the DD genotype frequency was more than twofold greater in EH patients with ischemic stroke than those with uncomplicated EH (0.23 versus 0.11, $p<0.02$) (Table 3). Multiple regression analysis revealed that one of independent risk factors for ischemic stroke in EH patients was the presence of DD genotype of ACE gene ($\beta=0.22$; $p=0.05$).

Table 3
Genotyping of ACE I/D polymorphism among hypertensive patients and healthy subjects

Genotypes and alleles	Group 1 (n=180)	Group 2 (n=70)	P
II	69 (38.3%)	24 (34.8%)	ns
ID	91 (50.6%)	29 (42.2%)	ns
DD	20 (11.1%)	16 (23.2%)	<0.02
I-allele	229 (63.6%)	61 (44.2%)	ns
D-allele	131 (36.4%)	77 (55.8%)	ns

***Notes**: ns – non significant*

Discussion

Recent studies of short-term recordings have shown the association between HRV and clinical manifestations of EH and its complications. Functional tests allow evaluation of reserve capacity of autonomic regulation of the cardiovascular system. One of those simple but at the same time highly informative test is the orthostatic test. The mechanism of compensatory response to the orthostatic effect is a change of baroreceptor activity in response to decreased BP, vagal inhibition, and increasing of sympathetic influences on heart and blood vessels.

Our study had shown decreasing of HRV with inhibition of parasympathetic modulation in patients with EH compared to control. This influence was more expressed in patients with left ventricular hypertrophy and ischemic stroke. In addition, relative increasing of very low frequency component (VLF, %) in these groups of patients indicated an increasing role of the neurohumoral factors on the regulation of cardiac rhythm in patients with cardiac and cerebral complications, i.e., that they have signs of autonomic dysfunction.

This observation was in agreement with previous reports that revealed decreasing of HRV (LF and HF component) in EH patients with LVH compared to healthy people [17, 18]. Besides that, HRV was negatively correlated with LV mass and did not depend on age, presence of coronary heart disease, and treatment with β-blockers. Similar results were obtained in the study of HRV in patients with stroke: decreasing HRV was found in ischemic stroke [19, 20].

Changes in the spectral parameters of heart rate during orthostatic test are still the subject of debate. For example, some authors noted a decreased response of sympathetic component to tilt-test in patients with EH, which is associated with reduction of sympathetic activity due to decreasing reverse neuronal capture of mediator [21]. Other researchers have not revealed specific patterns in response to the orthostatic test in EH patients [22].

Data analysis of tilt-test in our study showed significant reduction of HRV and decreased response of LF component to tilt-test in hypertensive patients. The letter depends from cardiac remodeling, and shows decline in reserve capacity of sympathetic regulation in these patients.

The most expressed changes were observed in EH patients with complications. In 70% of cases in this group, it was registered inverse response of LF to orthostatic test. It is known that LF modulation of HRV reflects the activity of baroreflex at rest and during orthostasis. Therefore, it was revealed that inverse reaction of LF component may be regarded as manifestation of baroreflex failure associated with cardiovascular remodeling. This is evidenced by peak power localization of LF trend in the range of 0.05–0.08 Hz that we identified in these patients at rest.

We have previously shown that decreasing of LF power modulation during active tilt-test in patients with EH without cardiac and cerebral complications associated with significant risk factors for cardiovascular disease (level and daily profile of BP, age) [23]. Taking that into account, we can assume that observed rigid or inverse reaction LF component during orthostasis may be considered as unfavorable prognostic sign of complications in patients with EH.

Recent studies evidenced that hereditary factor has significant role in target organs damage of EH. Great attention is paid to genes of two neurohumoral systems: the sympathoadrenal and renin–angiotensin systems [24, 25].
β2-adrenergic receptor contributes to BP regulation by mediating peripheral vasodilation [26]. In particular, it is shown that the presence of Gln27 allele is associated with more pronounced desensitization of the receptors and “in vivo” is manifested by lowering of basal blood flow and reduced vasodilator response to isoproterenol [27]. Indirect confirmation of this position is reflected in our study. Thus, patients with Gln27Gln genotype had significantly higher meanings both of systolic and diastolic BP in comparison to carrying of Glu-allele. Besides that, patients with Gln27Gln

genotype had more rapid morning rises of SBP, as it known, which may be explained by overactivity of sympathetic nervous system and therefore may cause increase of risk for cardio and cerebral complications of EH.

Our study showed that patients with Gln27Gln genotype had higher myocardial mass index and intima-media thickness in comparison with those carrying Glu-allele. However, there is a doubtful question: is increasing of myocardial mass in patients with Gln27Gln genotype caused by only hemodynamic factors? Or β2-adrenergic may cause direct hypertrophic effects on myocardium, which has been demonstrated "in vitro" [28]. Multiple regression analysis that was carried out showed that polymorphism of β2-AR gene does not play an independent role in increasing of myocardial mass. So, revealed association is probably mediated by hemodynamic factors.

In addition, we have not found association of polymorphic variants of β2-AR gene with ischemic stroke that is corresponding to the results of the study by Heckberg et al. [29].

It is shown that the activity of another neurohumoral system – the renin–angiotensin system, is genetically determined and can be associated with I/D polymorphism of the ACE gene. In our study, higher activity of ACE in DD homozygotes was associated with impaired daily profile of BP and increased of its variability. In addition, our work shows hypertrophic effects of renin–angiotensin system. Thus, ultrasound examination of the carotid artery revealed that patients with the DD genotype had a significantly greater carotid intima-media thickness compared to those with the II or ID genotypes, suggesting a more pronounced remodeling. The results of our study are in agreement with research results ELSA [30], which showed the association of D allele and DD genotype with the intimal thickness of carotid arteries. It is known that thickening of carotid intima-media is considered as the initial stage of atherosclerotic vascular damage. So, identified changes may reflect the high susceptibility to cerebral atherosclerosis and, consequently, to the development of stroke in DD patients.

Statistical analysis confirmed this hypothesis. Thus, in EH patients with ischemic stroke, the DD genotype frequency was more than twofold greater than those with uncomplicated EH. Moreover, data of multiple regression analysis evidenced that the presence of DD genotype was independent of BP and BMI predictor of ischemic stroke in patients with EH.

At the same time, we have not found association between I/D polymorphism of the ACE gene with the development of LVH and myocardial mass. It is in agreement with data from other studies [31, 32].

Conclusions

1. A significant reduction of HRV and decreased response of LF component to tilt-test in hypertensive patients were observed, compared to control, which indicates a decline reserve capacity of sympathetic regulation. Tilt-test in patients with complications of EH (LVH and ischemic stroke) had shown inverse response of LF: the power of LF component did not increase, but it actually decreased. The inverse reaction of LF in orthostatic test can be regarded as an unfavorable prognostic sign, predisposing cardiac and cerebral complications in patients with EH.
2. Patients with Gln27Gln genotype in comparison to other variants of Gln27Glu polymorphism of β2-AR were characterized by increasing meanings of BP and its morning raises, which possibly may cause increasing of left ventricular mass in these patients.
3. Our data support an association between I/D polymorphism and stroke in patients with EH. Presence of DD genotype may be considered as independent from daily profile of BP and intima-media thickness predictor of ischemic stroke in patients with EH, and allow selecting patients at high risk of stroke for adequate preventive interventions.

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