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ALLELE STATUS OF ALDOSTERONE SYNTHASE (CYP11B2) GENE POLYMORPHISM AND CARDIAC REMODELING AFTER ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

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Aldosterone plays an important role in the development of reparative and reactive fibrosis and cardiac remodeling (CR) after myocardial infarction. The objective of the study is to investigate the structural and functional parameters of the myocardium, heart rate variability (HRV), exercise intolerance, levels of sST2 in association with polymorphism of CYP11B2 gene of aldosterone-synthase in ST-myocardial infarction (STEMI) patients during a 6-months follow-up period. 85 STEMI patients were enrolled: 68 (80 %) male and 17 (20 %) female, mean age was 58,94 ± 10,16 years. Examinations were performed twice: during 1–3 days after PCI with infarct-related artery stenting and included clinical assessment, ultrasound diagnostic, immunofermentative blood analyses (sST2), polymerase chain reaction in real time (polymorphism –T344C of the CYP11B2 gene). After 6-months of observation, 57 patients were reexamined – clinical assessment, ultrasound diagnostic, HRV were performed. CYP11B2 TT-genotype in 6 months after STEMI is associated with a maladaptive character of after infarction remodeling.

KEY WORDS: STEMI, CYP11B2 gene polymorphism, cardiac remodeling

АЛЕЛЬНИЙ СТАТУС ПОЛІМОРФІЗМУ ГЕНА CYP11B2 АЛЬДОСТЕРОН-СИНТАЗИ ТА СЕРЦЕВЕ РЕМОДЕЛЮВАННЯ ПІСЛЯ ІНФАРКТУ МІОКАРДА З ЕЛЕВАЦІЄЮ СЕГМЕНТА ST

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Альдостерон відіграє важливу роль в розвитку репаративного та реактивного фіброзу та кардіального ремоделювання після інфаркту міокарда. Метою роботи стало визначити асоціації морфофункціональних та біохімічних показників з різними генотипами поліморфних варіантів гена CYP11B2 альдостерон-синтази в динаміці спостереження протягом 6 місяців. В дослідження включено 85 пацієнтів з ГІМпST, з них 68 (80 %) чоловіків та 17 (20 %) жінок, в середньому віці 58,94 ± 10,16 років. Дослідження проводилось двічі: протягом 1–3 дня після стентування інфаркт-залежної артерії та включало клінічну оцінку, ультразвукову діагностику, імуноферментний аналіз sST2, полімеразну ланцюгову реакцію поліморфізма –T344C гена CYP11B2. Через 6 місяців спостереження до клініки звернулось 57 пацієнтів, яким було проведено клінічну оцінку, ультразвукову діагностику, дослідження варіабельності серцевого ритму. Поліморфний генотип TT гена CYP11B2 асоціюється з мальадаптивним характером ремоделювання після інфаркту міокарда.

КЛЮЧОВІ СЛОВА: ГІМпST, поліморфізм гена CYP11B2 альдостерон-синтази, ремоделювання серця

АЛЛЕЛЬНИЙ СТАТУС ПОЛИМОРФИЗМА ГЕНА CYP11B2 АЛЬДОСТЕРОН-СИНТАЗЫ И РЕМОДЕЛИРОВАНИЕ СЕРДЦА ПОСЛЕ ИНФАРКТА МИОКАРДА С ЭЛЕВАЦИЕЙ СЕГМЕНТА ST

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Альдостерон играет важную роль в развитии репатативного и реактивного фиброза и ремоделирования сердца после инфаркта миокарда. Целью работы явилось определить ассоциации

морфофункциональных и биохимических показателей с различными генотипами полиморфных вариантов гена CYP11B2 альдостерон-синтазы в динамике наблюдения в течение 6 месяце. В исследование включено 85 пациентов с ОИМпST, из них 68 (80 %) мужчин и 17 (20 %) женщин, в среднем возрасте 58,94 ± 10,16 лет. Исследование проводилось дважды: в течение 1–3 дня после стентирования инфаркт-зависимой артерии, что включало клиническую оценку, ультразвуковую диагностику, иммуноферментный анализ sST2, полимеразную цепную реакцию полиморфизма –T344C гена CYP11B2. Через 6 месяцев наблюдения в клинику обратилось 57 пациентов, которым была проведена клиническая оценка состояния, ультразвуковую диагностику, исследование вариабельности сердечного ритма. Полиморфный генотип TT гена CYP11B2 ассоциируется с мальадаптивным характером ремоделирования после инфаркта миокарда.

КЛЮЧЕВЫЕ СЛОВА: ОИМпST, полиморфизм гена CYP11B2 альдостерон-синтазы, ремоделирование сердца

INTRODUCTION

Cardiac Remodeling (CR) is defined as a change in genes expression, molecules, cells, and interstitial which have a clinical manifestation in altering the size, shape and function of the heart after an injury [1]. Most of the geometric changes that have been formed during an early CR (less than 72 hours) were significantly limited by the area of the infarction and included stretching, spreading of the damaged zone and regional myocardial thinning. Whereas the late CR (more than 72 hours) involved myocardial stretching of the whole left ventricular (LV), including border zone infarcts, non-ischemic areas with subsequent hypertrophy, deformation of the LV shape and deterioration of systolic function [2].

Aldosterone plays an important role in the development of reparative and reactive fibrosis and CR in ST-segment elevation of myocardial infarction (STEMI) and after infarction cardiosclerosis [3–5]. There is convincing evidence about the local intracardiac formation of the hormone in acute myocardial infarction (AMI) and chronic heart failure (CHF) patients, along with the aldosterone synthesis activation by the adrenal glands and its flow into the bloodstream. Aldosterone is an inducer of inflammation in the vascular endothelium and perivascular zones of the myocardium. Aldosterone inhibits the release of NO, reduces expression of the vascular endothelial growth factor, causes proliferation of fibroblasts with the formation of collagen type I and type III and affects apoptosis that promotes interstitial myocardial fibrosis, its remodeling and dysfunction [4–6].

The relationship between aldosterone and sST2, which belongs to the IL-1 receptor family, was detected. sST2 blocks the cardioprotective effect of IL-33 and promotes the development of myocardial fibrosis [7–8].

The final stage of the aldosterone synthesis from desoxycorticosterone catalyzes the aldosterone synthase enzyme, whose primary structure is the CYP11B2 gene. In the literature association of the polymorphism of the promoter region of the aldosterone synthase gene CYP11B2 (–T344C) with cardiovascular risk is widely discussed.

The dynamics of morphofunctional changes in the myocardium in the acute period of STEMI and 6 months after the event, depending on the genotypes of polymorphous variants of the CYP11B2 gene TT, TC and CC have not been studied well [9]. One of the aldosterone properties is the ability to reduce baroreceptor's sensitivity, increase sympathetic and decrease parasympathetic activity [4]. The most informative method for a quantitative estimation of the cardiac autonomic regulation is the heart rate variability (HRV).

Decreased HRV as a background of significant increase in sympathetic and decrease of parasympathetic activities in AMI are important pathogenetic components of ventricular arrhythmias and arrhythmic death were shown in the North American groups' study [10].

In patients with after infarction cardiosclerosis, the deterioration of time and spectral analysis, sympathetic and parasympathetic imbalances became a prognostic factor in the risk of ventricular arrhythmias and sudden death [11–16]. Works devoted to the HRV study, depending on polymorphous variants TT, TC and CC of CYP11B2 gene were not found.

OBJECTIVE

To investigate the structural and functional parameters of the myocardium, HRV data, exercise intolerance, the different sST2 blood levels depending on the polymorphism of the aldosterone synthase gene CYP11B2 in STEMI patients during a 6-months follow-up period.

MATERIALS AND METHODS

In the Government institution «L. T. Malaya Therapy National Institute of the National Academy of Medical Science of Ukraine» 85 STEMI patients were enrolled in the first three days: 68 (80 %) male and 17 (20 %) female, mean age was 58, 94 ± 10, 16 years. The examination of all the patients with selective coronary angiography and stenting of the infarct-related artery were held in the Governmental institution of general and emergency surgery N.A. V. T. Zaitsev.

According to the European guidelines for the diagnostics and treatment of STEMI (2012) the diagnosis was established. The study protocol was confirmed by the Commission of Ethics and Deontology of the GI «L. T. Malaya Therapy National Institution of NAMS of Ukraine» in accordance with the thesis of the Helsinki Declaration, the study was performed. All patients had signed the informed consent.

The follow-up period was for 6 months and after that period 57 patients were examined again. All subjects have received standard therapy for 6 months. During the hospital period, 2,4 % patients died, after 6 months – 3,5 % patient.

End-diastolic (EDV), end-systolic (ESV) volume of left ventricle (LV), end-systolic (ESD) and end-diastolic (EDD) diameter of LV, LV myocardial mass (LV MM), LV ejection fraction (LV EF) (Simpson formula), and diastolic dysfunction has been determined as the maximal speed of early diastolic filling E (m/s), maximal velocity of atrial diastolic filling A (m/s), their E/A ratio were evaluated by ultrasound diagnostic.

With the Holter monitor «Cardio Sens «KhAI-Medica»» 6 months after the index event, HRV was investigated. The following data were evaluated: SDNN is the standard deviation of normal to normal R-R intervals, RMSSD the root mean square differences of successive R-R (heart beat) intervals, pNN50 is the proportion of NN50 divided by the total number of NN (R-R) intervals, TP is the total strength of the spectrum, ULF is an ultra-low-frequency component of HRV, VLF is the spectral strength in the very low-frequencies, LF is the power of low frequency oscillations, HF is the power of the spectrum of high-frequency oscillations, LF / HF – the ratio. To determine physical activity tolerance, all patients were given a six minute walk test.

Investigation of allele polymorphism –T344C of the CYP11B2 gene was performed by polymerase chain reaction in real time. The level of sST2 using the Presages ST2 Assay (Critical Diagnostics, USA) reagent enzyme immunoassay method was determined. The control group included 30 practically healthy persons; the average value of sST2 for those patients was 19.4 [15.9–29.1] ng/ml.

This work is the fragment of scientific research were done in the department of acute myocardial infarction of Government institution «L. T. Malaya Therapy National Institute of the National Academy of medical science of Ukraine»: «To investigate modern models of risk stratification and personification preventive measures of sudden cardiac death in patients after acute coronary syndrome», registration № 0114U001167, code: 02/14.

The study was planned as the only-case design. The statistical processing of the obtained data using the Statistica 8.0 software package (Statsoft Inc, USA), Microsoft Office Excel 2003 was performed. The data is presented as Median (Me), upper (UQ) and lower (LQ) quartile sampling. U-Criterion Mann Whitney to assess intergroup differences was used. A statistically significant difference was considered if P-value is lower than 0.05.

RESULTS AND DISCUSSION

The analysis of the alleles and genotypes distribution of the CYP11B2 aldosterone synthase gene shows the following frequencies of T and C alleles in patients with STEMI – 52 % and 48 %, the frequency of homozygous TT, heterozygous TC and homozygous CC – n = 22 (25,9 %), n = 46 (54,1 %) and n = 17 (20 %), respectively. The observed frequency of genotypes was in Hardy-Weinberg equilibrium ($X^2 = 0,63$; $p > 0,05$).

Characteristics of myocardial infarction depending on genotypes of polymorphic variants-T344C of the aldosterone synthase CYP11B2 gene are presented in Table 1.

Table 1

Clinic-instrumental characteristic of myocardial infarction of researched patients depending on polymorphous variants -T344C of the CYP11B2 gene aldosterone synthase

Data	TT N 22 (25,9 %)	TC N 46 (54,1 %)	CC N 17 (20 %)	χ^2 P_{1-2}, P_{1-3}, P_{2-3}
Complicated STEMI	8 (36,4 %)	16 (37,8 %)	6 (35,3 %)	0,02 p = 0,89 0,07 p = 0,79 0,07 p = 0,79
Anamnesis of MI	1 (4,5 %)	4 (8,6 %)	3 (17,6 %)	0,43 p = 0,46 0,73 p = 0,20 0,30 p = 0,28
Anterior STEMI	15 (68,2 %)	26 (56,2 %)26	11 (64,7 %)11	0,85 p = 0,36 0,01 p = 0,91 0,34 p = 0,56
Posterior STEMI	7 (31,8 %)	20 (43,5 %)	6 (35,3 %)	0,43 p = 0,51 0,01 p = 0,91 0,09 p = 0,77
Data of selective coronaroangiography				
1 CA>50%	6 (27,3 %)	8 (17,4 %)	3 (17,6 %)	0,39 p = 0,53 0,11 p = 0,75 0,12 p = 0,73
2 CA>50%	2 (9,1 %)	7 (15,2 %)	5 (29,4 %)	0,10 p = 0,75 1,49 p = 0,22 0,83 p = 0,36
3 CA>50%	2 (9,1 %)	8 (17,4 %)	1 (5,9 %)	0,29 p = 0,59 0,05 p = 0,82 0,57 p = 0,45
Types of coronary flow				
Right	11 (50 %)	17(40 %)	9 (52,9 %)	1,05 p = 0,31 0,02 p = 0,89 0,73 p = 0,39
Left	1 (4,5 %)	4 (8,7 %)	3 (17,6 %)	0,01 p = 0,91 0,65 p = 0,42 0,30 p = 0,58
Balanced	1 (4,5 %)	1 (2,2 %)	2 (11,8 %)	0,05 p = 0,82 0,05 p = 0,82 0,85 p = 0,36

Regarding to table 1, all patients with STEMI were compatible above coronary atherosclerosis but significant differences had not observed.

The changes in the morphofunctional state of the LV, which occurred within 6 months after STEMI, depending on genotypes of polymorphic variants-T344C of the aldosterone synthase CYP11B2 gene, are presented in Table 2.

Table 2

Dynamics of morphofunctional myocardial changes 6 months after STEMI depending on polymorphous variants -T344C of the CYP11B2 gene aldosterone synthase

Parameters		TT	TC	CC
LV EDV, ml	1	124,00 [96,00-144,00]	118,00 [103,00-159,00]	118,00 [107,00-144,00]
	2	155,60 [133,00-182,00]	135,00 [96,00-182,00]	143,50 [120,00-176,00]
	P	0,030	0,668	0,074
LV ESV, ml	1	63,00 [44,00-67,00]	58,00 [45,00-92,00]	60,00 [50,00-79,00]
	2	61,00 [56,00-90,00]	55,00 [42,00-75,00]	58,00 [43,00-82,00]
	P	0,526	0,851	0,827
LV EDD, sm	1	5,00 [4,60-5,40]	5,16 [4,90-5,60]	5,15 [4,70-5,40]
	2	5,42 [5,02-5,70]	5,25 [4,65-6,00]	5,30 [5,10-5,90]
	P	0,033	0,645	0,120
LV ESD, sm	1	3,70 [3,30-4,00]	3,70 [3,23-4,05]	3,59 [3,20-4,22]
	2	3,80 [3,60-4,00]	3,60 [3,20-4,10]	3,80 [3,20-4,30]
	P	0,483	0,869	0,580
Left atrium, sm	1	3,98 [3,70-4,30]	4,27 [3,87-4,70]	4,30 [3,80-4,60]
	2	3,80 [3,60-4,20]	4,30 [3,80-4,70]	4,00 [3,70-4,20]
	P	0,479	0,762	0,193
EF, %	1	50,65 [46,00-55,00]	54,00 [47,00-58,00]	51,00 [48,00-54,00]
	2	53,50 [49,00-60,00]	56,50 [47,50-60,50]	57,00 [52,00-59,00]
	P	0,309	0,311	0,078
E/A	1	1,13 [0,66-1,20]	1,00 [0,75-1,40]	1,15 [0,50-1,40]
	2	0,85 [0,65-1,10]	1,20 [1,00-1,67]	1,00 [0,80-1,45]
	P	0,049	0,329	0,563
LV MM, g	1	242,50 [198,50-258,50]	258,50 [201,00-300,50]	246,00 [205,00-292,50]
	2	269,00 [234,00-305,00]	219,50 [160,00-265,50]	229,00 [170,30-231,00]
	P	0,046	0,095	0,089
Mitral valve regurgitation, stage 1–2	1	22,7%	8,7%	17,6%
	2	45,5%	4,3%	5,9%
sST2, ng/ml	1	40,73 [30,69-55,41]	51,47 [33,64-122,17]	44,93 [35,68-115,58]
	2	34,52 [25,86-35,49]	32,96 [24,78-42-58]	25,07 [21,37-40,20]
		0,11	0,004	0,052

Note: 1 – hospital period of STEMI, 2 – 6 month after STEMI

Comparison of the cardiac hemodynamics parameters during the hospital period and 6 months after the event, depending on the polymorphous variants of the CYP11B2 (–T344C) gene, shows the following tendency of the course of LV CR: the

significant increase of LV EDV in patients with TT genotype in 6 months after STEMI (p = 0,030), a tendency for increase of LV EDV in CC homozygote (p = 0,074), for heterozygous TC there was no significant increase of the parameter (p = 0,668). A significant increase in LV EDD in the group with the genotype TT was observed (p = 0,033), the variance of TC and CC showed no significant changes. There was the statistical tendency to LV EF increase in patients with CC genotype (p = 0,078). In the groups of patients with heterozygote TC and homozygous TT, the level of LV EF increased nonsignificant.

The increase of the LV MM has occurred in the group with the TT genotype, unlike the variants of the TC and CC, there was a tendency to its reduction. The E/A ratio has been compared, its significant decrease in patients with polymorphous variant TT was observed (p = 0,049), in patients with TC and CC variants, E/A values remained within the normal limits. The number of patients with mitral valve deficiency whose genotype was TT has been increased twice, while in patients with variants of TC and CC genotypes frequency of occurrence of mitral regurgitation was rare. There are no significant changes in LV ESV, LV ESD, and LA diameter dynamic 6 months after STEMI.

The group of patients with the genotype TT had the lowest tolerance to physical activity and was 385,5 [312,0–482,5] m, in the group with TC – 480,0 [439,0–519] m, CC-495 [468,0–530,0] m (pTT-TC = 0,05, pTT-CC = 0,02, pTC-CC = 0,44). In the acute period of STEMI, increase in the level of sST2 was found in comparison with the control group regardless of the genotype (TT, TC and CC variants, p1 = 0,003, p2 = 0,002, p3 = 0,001, respectively). After 6 months, in patients with TT genotype the sST2 level decrease by 15,2 % (p = 0,11), in the TC group – 35,7 % (p = 0,004), in the CC – 44,2 % (p = 0,052), table 3.

Table 3

Data of cardiac rhythm variability depending on genotypes of polymorphous variants – TT, TC and CC of the aldosterone synthase CYP11B2 gene

Parameters	TT (1)	TC (2)	CC (3)	P
SDNN, msec	50,0 [41,0-57,0]	53,5 [45,25-57-50]	52,50 [49,50-70,00]	P_{1-2} = 0,088 P_{1-3} = 0,049 P_{2-3} = 0,290
RMSSD, msec	17,0 [11,5-24,5]	25,5 [18,75-31,50]	22,0 [14,50-39,50]	P_{1-2} = 0,001 P_{1-3} = 0,07 P_{2-3} = 0,442
pNN50, msec	0,9 [0,35-5,10]	4,15 [1,48-9,93]	2,8 [1,20-5,70]	P_{1-2} = 0,004 P_{1-3} = 0,034 P_{2-3} = 0,406
TP, $msec^2$	2343,5 [1676,0-3197,0]	2815,0 [2024,0-3467,5]	2598,5 [1854,0-3941,5]	P_{1-2} = 0,230 P_{1-3} = 0,211 P_{2-3} = 0,762
ULF, $msec^2$	566,5 [347,0-815,0]	511,5 [341,5-725,5]	489,5 [375,00-1046,00]	P_{1-2} = 0,706 P_{1-3} = 0,254 P_{2-3} = 0,190
VLF, $msec^2$	1125,0 [827,0-1664,0]	1365,0 [1074,5-1788,0]	1569,0 [1036,0-2475,0]	P_{1-2} = 0,169 P_{1-3} = 0,050 P_{2-3} = 0,158
LF, $msec^2$	532,0 [463,0-1198,0]	545,0 [346,5-894,5]	432,0 [202,0-625,0]	P_{1-2} = 0,650 P_{1-3} = 0,039 P_{2-3} = 0,081
HF, $msec^2$	107,5 [67,5-241,5]	250,0 [113,0-423,0]	123,0 [51,0-251,0]	P_{1-2} = 0,038 P_{1-3} = 0,044 P_{2-3} = 0,019
LF/HF	4,20 [3,20-4,60]	2,40 [1,76-3,65]	3,20 [2,03-3,60]	P_{1-2} = 0,001 P_{1-3} = 0,041 P_{2-3} = 0,266

The analysis of HRV data revealed a decrease in the time and frequency in all three groups of patients in comparison with the normal [10]. However, when the group of patients with the genotype of TT was compared, the lowest values of time domain data – SDNN (p1-2 = 0,088, p1-3 = 0,049), RMSSD (p1-2 = 0,001, p1-3 = 0,07), pNN50 (p1-2 = 0,04, p1-3 = 0,034), and frequencies - VLF (p1-3 = 0,050, p2-3 = 0,081), HF (p1-2 = 0,038, p1-3 = 0,044, p2-3 = 0,019) were observed. Spectral analysis revealed a significant difference between the LF components and the ratio of LF/HF in the TT genotype group compared to other groups (p1-3 = 0,089, p2-3 = 0,081) and (p1-2 = 0,001, p1-3 = 0,041) respectively. There was no significant difference between indicators TP and ULF.

Aldosterone synthase (CYP11B2) catalyzes the final stage of the aldosterone formation from a desoxycorticosterone. Beyond the adrenal gland expression of the CYP11B2 gene in smooth myocytes of blood vessels and cardiomyocytes, the existence of tissue-specific activation of myocardial aldosterone synthase in MI was shown. A significant increase in the expression of CYP11B2 mRNA in the myocardium in patients with chronic heart failure, and its positive correlation with the fraction of collagen in the myocardium, the severity of LV dysfunction was found [17–18]. Therefore, the gene aldosterone-synthase is considered as a candidate genome, which depends not only on the synthesis of aldosterone, but also on the course of CR. Regarding to the association of the polymorphism of the CYP11B2-T344C gene with the risk of MI, its following remodeling, and clinical course, the literature data are ambiguous: thus, Hengstenberg C. et al., 2000, according to the results of a 5-year follow up for patients with MI, did not find associations between the alleles of the CYP11B2 gene, the severity of myocardial dysfunction and CP indices [19].

Hautanen A. et al., 1999, showed that in male carriers of 344C-alleles, in those who are smoking and have dyslipidemia, the risk of MI increases compared to carriers of 344T-alleles [20]. According to Korneva V.A., 2011, the presence of the genotype of T-alleles in the homozygous state almost increased the risk of cardiovascular disease by 2 times [21]. In a study by Lobach L.E. et al., 2017, patients with TP + CT polymorphism of the CYP11B2 gene had an increased risk of MI [22]. In patients with ischemic genesis CHF, including a post-myocardial infarction cardiosclerosis, allele T, and the genotype TT of the polymorphic locus-T344C of the CYP11B2 gene were associated with the severe clinical manifestation of CHF, and the genotypes ST and allele T were more commonly recorded in patients with an unfavorable course of the disease [23].

The presented work was conducted to patients with myocardial infarction. In our study, the structural and functional parameters of the myocardial condition were obtained during the period of hospitalization (acute phase of the disease), and their changes within six-months of follow-up. Primary indicators of hemodynamics in STEMI patients with homozygote TT and CC, and heterozygote TC weren't significantly different. In the post-infarction period, the TT genotype carriers had a significant increase in the size and extent of LV (EDD, EDV), the degree of its hypertrophy (LVMM). These changes were accompanied by diastolic dysfunction with a significant slowing of the filling of the LV (reduction in E/A), an increase in the number of patients with regurgitation at the mitral valve, indicating an unfavorable maladaptive heart remodeling. Unlike patients with TT genotype, in patients with CC-genotype there was a tendency to increase inotropic function of the left ventricle, a significant decrease in the hypertrophy formation, a lack of significant changes in the parameters of LV dilatation, diastolic function and decrease the number of patients with mitral valve regurgitation, hence, indicating a favorable flow of structural and functional changes in the LV after the MI after 6 months. In patients carrying heterozygotes TC there was a tendency to decrease LVMM, and other hemodynamic parameters did not differ statistically.

Differences in cardiac remodeling after STEMI were reflected in the functional reserve of the cardiovascular system – in TT carriers compared to CC, the results of the 6-minute walk test revealed a significantly lower physical activity tolerance.

In all polymorphic variants of the CYP11B2 (-T344C) gene, there was a decrease in parasympathetic tone (SDNN, RMSSD, PNN50, HF), an increase in sympathetic activity (LF), a sympatho-parasympathetic index (LF/HF), but the most significant changes components of HRV in patients with the genotype of TT in comparison to the CC genotype were observed.

Excessive activation of the sympathetic component of the spectrum (LF) and reduction of the activity of the parasympathetic regulation mechanisms (HF) is the basis for the development of the maladaptation reaction and indication of an unbalanced function of the autonomic nervous system. The high LF/HF index characterizes the decrease in the sympathetic and parasympathetic balance in favor of the prevalence of the sympathetic VNS. Reducing the level of the very low-frequency spectrum (VLF) indicates the energy-deficient state of the autonomic nervous system, the strength of VLF-oscillations is a sensitive indicator of the metabolic processes management in a myocardium with disturbed geometry and metabolism and fibrotic changes. Changes in HRV in the patients after MI are associated with the development of the general adaptive syndrome and with significant structural and functional reorganization of the myocardium [11–12]. In our study, patients with the TT genotype were associated with an inadequate HR course with more pronounced changes in the time and frequency parameters of HRV, which suggests that this variant is unfavorable for the subsequent course of the after infarction period.

Interest in determining the sST2 level arose due to the following reasons: we diagnosed MI by the increased level of the specific biomarkers, which is associated with the degree of myocardial damage, HR, the risk of progression of CHF and the risk of sudden death [7]. Weir R.A.P et al., 2010, found the relationship between sST2, the evolution of MI, HR, aldosterone levels, and the efficacy of eplerenone in patients with high levels of sST2 [5]. Analysis of the relationship between the concentration of aldosterone and –T344C polymorphism of the CYP11B2 gene showed that T-allele associated with higher levels of hormone [24]. In our study, patients with the TT genotype compared with the TC and CC variants revealed a lower degree of reduction of sST2 after STEMI which connected to the adverse prognosis for those patients, and also demonstrated the possible relationship between elevated aldosterone, sST2 and pathological myocardial remodeling.

CONCLUSIONS

1. Patients with STEMI - carriers of homozygotes TT of the CYP11B2 gene in 6 months after the index event are associated with the occurrence of hypertrophy and left ventricular dilatation, diastolic dysfunction with violation of LV relaxation, and decreased tolerance to physical activity that indicates a maladaptive character of after infarction remodeling.

2. After the HRV data were compared in patients after STEMI. A decrease in the parasympathetic tone component, an increase in sympathetic activity, and sympathetic parasympathetic index in carriers of the TT genotype of the CYP11B2 gene indicated more pronounced autonomic imbalance than that in CC-genotype carriers.

PROSPECTS FOR FUTURE STUDIES

Prospects for future studies are to observe investigated patients to 1–3 years to do more reliable conclusions.

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