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Genetic Aspects of the Course and Prognosis of Chronic Heart Failure with Hypertension

Khokhlov AL* **and Rybachkova YV**

Department of Clinical Pharmacology, Yaroslavl State Medical University University, Russia

***Corresponding author:** Khokhlov AL, Department of Clinical Pharmacology, Yaroslavl State Medical University University, Russia, Tel: 8(4852)460935; E-mail: al460935@yandex.ru

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Abstract

Background: Advances in medical science and the introduction of a huge number of new drugs do not reduce the urgency of effective and safe pharmacotherapy. One of the prognostic criteria of high efficiency of pharmacotherapy in patients with chronic heart failure (CHF) is considered genetic features of the patient.

Materials and methods: Clinical and genetic studies conducted in 111 patients with CHF and arterial hypertension (AH). All patients underwent laboratory and instrumental methods of research. The median age was 63.5+11.6 years. The main cause of heart failure in 90 patients had coronary heart disease (CHD): exertional angina - 64 (57.6%), myocardial infarction (PICS) - 26 (23.4%), and violation of the type of atrial fibrillation of the heart rate - 36 (32.4%). The average duration to CHF 10.5+6.3 years. Polymorphisms of these genes were analyzed in serum: ADD1: 1378, AGT: 704, AGT: 521, AGTR1: 1166, AGTR2: 1675, CYP11B2: -344, GNB3: 825, NOS3: -786, NOS3: 894.

Results: Depending on staging CHF most significant changes were traced by polymorphisms of genes AGTR2: 1675, CYP11B2: -344 and NOS3: -786. In patients with CHF progression of the disease is associated with increased frequency of polymorphisms of genes AGTR2: 1675, CYP11B2: -344, NOS3: -786, AGT: 704, GNB3: 825. The success of pharmacotherapy in the outpatient phase is associated with an increase of 32.2% frequency of gene polymorphism AGTR2 1675 as a combination of mutation homozygotes and heterozygotes, 26.9% - polymorphism GNB3: 825 from heterozygotes. In patients with CHF and CHD is more common gene polymorphism AGTR2: 1675, and in the presence of PICS - a GNB3: 825.

Conclusion: Introduction into clinical practice of individual approach to the choice of drug and dosing regimen based on the factors affecting the pharmacological response will increase the effectiveness and safety of pharmacotherapy.

Keywords: Genetic testing; Chronic heart failure; Arterial hypertension; Personalized medicine; Gene polymorphism

Introduction

Advances in medical science and the introduction of a huge number of new drugs do not reduce the urgency of effective and safe pharmacotherapy. One of the major challenges facing practitioners is to increase the efficacy and safety of drug therapy conducted by individualizing treatment of the patient. This requires a complete representation of the features of both the drug (pharmacokinetics and pharmacodynamics) and the patient (patient's individual characteristics, including genetic).

As one of the most common cardiovascular disease, arterial hypertension (AH) is a major risk factor for various cardiovascular complications such as stroke, myocardial infarction (MI), chronic kidney disease and chronic heart failure (CHF) [1]. Reduced blood pressure (BP) in patients with varying degrees of hypertension reduces the risk of stroke and myocardial infarction and as the final stage of the cardiovascular continuum of chronic heart failure and thus significantly improves the quality of life of patients. However, despite the rather extensive range of drugs available in a doctor's arsenal, control of blood pressure levels in a number of cases it is still unsatisfactory and every year the number of people with uncontrolled blood pressure increased [2,3]. According to various authors, in 10-45% of patients the use of drugs is not effective [4-6].

Materials and Methods

Genetic studies were conducted in 111 patients with CHF on the background of hypertension. The average age was 63.5+11.6 years. Women in the study were 52 (46.8%), men 59 (53.2%). Inclusion criteria for a group of patients with CHF: patients without age restrictions. The diagnosis of CHF was based on the classification proposed by the Society of Heart Failure Specialists (OSSN) and approved by the Russian Congress of Cardiologists in 2003, which provides for the unification of the current classification of CHF stages and functional class (FC) according to the classification of the New York Association of Cardiology (NYHA, 1964). These moments were crucial for the inclusion of patients in this group. Criteria for exceptions for this group were patients with oncological pathology and heart defects. The diagnosis of hypertension was based on the criteria proposed by the Russian Medical Society for Arterial Hypertension and VNOK (fourth revision, 2010). This group of patients was selected

for examination at the time of admission to the cardiology department due to worsening of CHF flow, pharmacotherapy at the hospital stage, as well as outpatient stages for 1 year and 5 years prior to the present hospitalization according to outpatient charts was analyzed.

All patients underwent biochemical methods of research: lipid spectrum, creatinine level, fasting plasma glucose, total protein and its fractions, hepatic enzymes, C-reactive protein and electrolytes. Electrocardiographic study was conducted in 12 leads according to the standard method. Echocardiography (ECHO-CG) was used to evaluate the global and local contractility of the left ventricle (LV), the size of the heart chambers and the thickness of its walls. The following parameters were determined: the mass of the myocardium of the LV, the dimensions of the left ventricle in systole and diastole, the thickness of the interventricular septum, the thickness of the posterior wall of the LV, the terminal systolic and the end diastolic volume of LV, LV stroke volume, LV ejection fraction (LVEF), assessment of diastolic function of LV.

Genes encoding elements of the renin-angiotensin-aldosterone system were determined in the blood serum: angiotensinogen genes - AGT: 704, AGT: 521, angiotensin II receptor - AGTR1: 1166, AGTR2: 1675; aldosterone synthetase - CYP11B2: -344, genes regulating intracellular ion homeostasis - G-protein beta (3) - subunit of GNB3: 825, alpha adduct ADD1: 1378, as well as genes determining the structure of endothelial NO synthase (eNOS) - NOS3 : -786, NOS3: 894). A set of reagents was used to determine the genetic polymorphisms associated with the risk of developing hypertension, by polymerase chain reaction (PCR) in human DNA preparations obtained from peripheral blood. To estimate the amount of isolated DNA, a set of reagents for PCR amplification of human genomic DNA in real time produced by NPO DNA-Technology was used. The need for studying these gene polymorphisms, in our view, is due to the fact that they have prognostic value for the development of AH, coronary heart disease, including myocardial infarction and worsening of CHF flow [7,8].

The statistical processing of the results was carried out using STATISTICA 10. For intergroup comparisons, Student's t-test was used. Differences were considered reliable at $p < 0.05$ (p - achieved level of significance). Description of qualitative data was carried out by constructing conjugacy tables with indication of absolute and relative (%) frequencies of occurrence of symptoms. An assessment of the significance of the intergroup differences and the correspondence of the frequencies of the occurrence of genotypes in the observational sample was carried out according to the Hardy-Weinberg law. In addition, the Pierson chi-square test was used for statistical processing. If this criterion is not applicable (the presence of expected frequencies in the cells of the conjugacy table less than 5), a two-sided Fisher exact test was used. The mean value and the standard error of the mean value of the quantitative variables studied (M ± m) were determined. For the analysis of the correlation of features, the nonparametric Spearman method, Tau-Kendel, was used.

The main cause of CHF in 90 patients was CHD: stenocardia of tension - 64 (57.6%), basically there were 3 functional class 40 (62.5%); postinfarction cardiosclerosis (PICS) - 26 (23.4%), and heart rhythm disorder by type of atrial fibrillation - 36 (32,4%) in combination with AH. The structure of associated clinical conditions in patients with genetic studies is presented in Table 1.

Associated clinical conditions	**The group with CHF, n=111**
Stenocardia tension:	64 (57,6%)
1 FC	2 (3,1%)
2 FC	22 (34,4%)
3 FC	40 (62,5%)
4 FC	-
A history of myocardial infarction	26 (23,4%)
Heart rhythm disturbance:	
Atrial fibrillation:	36 (32,4%)
constant	21 (58,3%)
paroxysmal	15 (41,7%)
Diabetes mellitus type II	21 (18,9%)
Sharp disturbance of cerebral circulation in the anamnesis	9 (8,1%)

Table 1: Structure of associated clinical conditions in patients with CHF.

The mean duration of AH was 15.1+9.7 years. The mean duration of CHF was 10.5+6.3 years. Stage 1 of CHF was observed in 36%, 2A in 43.9% and 2B in 21.1% of patients. Depending on the functional classes (FC) 1 FC took place in 34%, 2 FC in 23.7% and 3-4 FC in 43.2% of cases.

The distribution of gravity and FC CHF are presented in Table 2.

FC of CHF	**1**	**2**	**3**
	1 stage n=40 (36%)	**2A stage n=47 (42,3%)**	**2B stage n=24 (21,6%)**
1 FC	37 (92,5%)*	1 (2,1%)	-
2 FC	3 (7,5%)	21 (44,7%)**	1 (4,2%)
3 FC	-	25 (53,2%)***	19 (79,2%)
4 FC	-	-	4 (16,7%)#
Note: * - p<0,001 when comparing 1 and 2, 1 and 3; ** - p<0.05 when comparing 2 and 1, 2 and 3; *** - p<0.001 when comparing 1 and 2 groups; # - p<0.05 when comparing 2 and 3.			

Table 2: Structure of chronic heart failure, n=111.

With regard to the distribution of hypertension, in 100% of cases, there were 3 stages, 1 degree was found in 34 (30.6%), 2 in 31 (28%) and 3 in 46 (41.4%).

Among comorbidity were impaired on the type of arrhythmia heart rhythm (27.9%), conduction abnormalities (15.3%), varicose veins of lower extremity disease (14.4%), cholelithiasis (12.6%). According to echocardiography (ECHO - CG) more significant changes for the worse can be traced from the end-systolic dimension (ESD), the size of the left atrium (LA), left ventricular ejection fraction (LVEF), interventricular septum thickness (IVST) and local contractility (E/A). This information is presented in Table 3.

ECHO-CG indicators	The group with CHF,
	n=111
EDD, мм	51,6+6,1
ESD, мм	37,25+6,7
LA, мм	42,6+5,8
TPWLV, мм	10,6+1,5
LVEF, %	50,3+5,5
IVST, мм	11,5+1,7
E/A	0,84+0,14

Table 3: ECHO-CG data in patients with CHF at the hospital stage.

With increasing severity of heart failure end-diastolic dimension (EDD) increased by 6%, the ESD - 16% LA - 21%, the thickness of the left ventricular posterior wall (TPWLV) - 4%, IVST - by 8% against the decrease LVEF 13.2% and the index of E/A of 13%.

The analysis of drug therapy was carried out personalized drug therapy, taking into account concomitant diseases and risk factors, as well as according to the national recommendations on the diagnosis and treatment of CHF (fourth revision).

The pharmacotherapy of CHF on the hospital stage and outpatient for 1 year and 5 years (Table 4) was analysed.

Preparations	Hospital stage, n=111	Outpatient stage for 1 year, n=96	Outpatient stage for 5 years, n=96
Inhibitors of angiotensin-converting enzyme	91 (82%)	83 (86,4%)	84 (87,5%)
Antagonists of the receptors for angiotensin II	20 (18%)	24 (25%)	5 (26%)
Beta-blockers	83 (74,8%)	75 (78,1%)	78 (81,2%)
Diuretics (thiazide and thiazide-like)	54 (48,6%)	70 (72,9%)	87 (90,6%)
Diuretics (loop)	37 (33,3%)	36 (37,5%)	37 (38,5%)
Antagonists of aldosterone	30 (27,02%)	23 (23,9%)	37 (38,5%)
(spironolactone)			
Cardiac glycosides (digoxin)	21 (18,9%)	14 (14,6%)	18 (18,7%)
Blockers of slow calcium channels	44 (39,6%)	32 (33,3%)	43 (44,8%)
Statins	63 (56,7%)	45 (46,9%)	50 (52,1%)
Antiaggregants	76 (68,5%)	77 (80,2%)	78 (81,2%)
Anticoagulants	35 (31,5%)	3 (3,1%)	9 (9,4%)
Nitrates	28 (25,2%)	17 (17,7%)	23 (23,9%)
Molsidomine	-	3 (17,6%)	3 (13%)
Antiarrhythmics of Class III	7 (6,3%)	6 (6,2%)	9 (9,4%)
Moxonidine	-	4 (4,2%)	6 (6,2%)
Trimetazidine	-	15 (15,6%)	19 (19,8%)
Ivabradin	-	1 (1%)	3 (3,1%)
Meldonium	-	-	2 (2,1%)
Absence of pharmacotherapy	-	15 (13,5%)	15 (13,5%)

Table 4: The frequency of prescribing drugs in patients with genetic studies.

Compliance with the standard of treatment of more than 80% at the outpatient stage for 1 year before entering the hospital was 75%, for 5 years - 86.4% ($p<0.05$) (Table 5).

	Ambulatory stage	
Indicators of the standard,%	1 year	5 years
80-100%	72 (75%)	83 (86,4%)*
50-79%	19 (19,8%)	11 (11,4%)
25-49%	5 (5,2%)	2 (2,1%)
<25%	-	-
Note: * - p<0,05 when comparing outpatient stages		

Table 5: Indicators of the standard for the prescription of medicinal products at CHF on an out-patient stage for 1 year and for 5 years before hospitalization (n=96).

Results and Discussion

Polymorphisms of these genes were analyzed in serum: ADD1: 1378, AGT: 704, AGT: 521, AGTR1: 1166, AGTR2: 1675, CYP11B2: -344, GNB3: 825, NOS3: -786, NOS3: 894.

The frequency of gene polymorphisms with managed and unmanaged risk factors (RF) are different. Certainly, among the uncontrolled risk factors of most importance, in our view, it has a family history. This RF was associated with AGT gene polymorphism: 521 as heterozygotes in 42.1% of cases. With regard to the different gender, the men showed increased incidence of gene polymorphism of CYP11B2: -344, among women - ADD1: 1378, AGT: 521, AGTR1: 1166 and CYP11B2: -344. Age has no significant differences in the frequency of occurrence of polymorphisms of genes and cannot be used as a predictor of adverse outcome. Increasing the frequency of occurrence of gene polymorphisms ADD1: 1378, AGT: 521 and CYP11B2: -344 noted for obesity, and polymorphisms of genes ADD1: 1378 and CYP11B2: -344 - when smoking. The increase in total cholesterol and low density lipoprotein cholesterol was associated with a high frequency of the gene polymorphism of CYP11B2: -344 and triglycerides in the blood with polymorphisms of genes ADD1: 1378 and CYP11B2: -344. Increased frequency of gene polymorphism GNB3 825 has been associated with impaired glucose tolerance. In the analysis of the relationship of genetic factors on the risk factors in this group of patients received the changes do not play a significant role in heart failure, and act, apparently, as predictors of hypertension. We can assume that the CHF and its current value is a set of genetic polymorphisms with external factors, as well as the simultaneous combination of a combination of polymorphisms of genes.

In the analysis of genetic markers for CHF among the polymorphisms of genes dominate NOS3: -786, AGT: 704 and CYP11B2: -344. Further investigations revealed that the frequency of occurrence of gene polymorphisms varies depending on the staging of CHF. The most significant changes can be traced by the polymorphisms of genes AGTR2: 1675, CYP11B2: -344 and NOS3: -786. The frequency of occurrence of gene polymorphism AGTR2 1675 at the most significant stage 2A (21.3%) compared to one-stage CHF. The revealed changes were associated with changes in the frequency of heterozygotes. When comparing the frequency of occurrence of gene polymorphisms with 1 stage and 2B, the results showed a high frequency of polymorphisms of genes AGTR2: 1675 (37.5%) and CYP11B2: -344 (62,5%) with severe chronic heart failure stage. We can assume that these gene polymorphisms responsible for a more unfavorable course of CHF. In addition, when the stage 2B increases the frequency of polymorphisms of genes AGTR2: 1675 by 16.2% and NOS3: -786 28.5% compared to the 2A-stage heart failure ($p < 0.05$). Thus, with an increase incidence of CHF severity gene polymorphisms increases and reaches a maximum at step 2B. This applies, above all, gene polymorphism NOS3: -786, which is significantly more common in more severe manifestations of heart failure.

Effect of gene polymorphism AGTR2 1675 on clinically significant heart failure indicators presented in Figure 1.

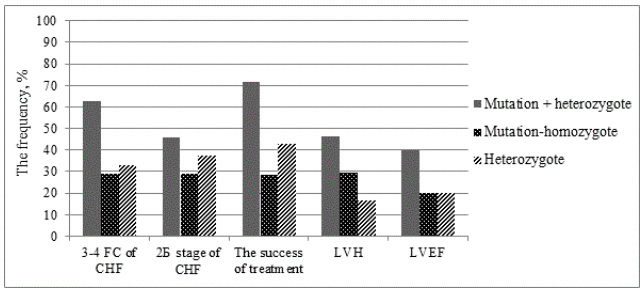

Figure 1: The frequency of the gene polymorphism AGTR2: 1675 at different rates of the CHF.

Depending on the FC of the CHF revealed changes manifested themselves in the form of increasing the frequency of polymorphisms of AGT: 704, AGTR2: 1675, CYP11B2: -344 and GNB3: 825. The frequency of occurrence was determined FC of the CHF and was the most significant at FC 3-4. Depending on the level of blood pressure and the incidence of gene polymorphisms, more severe hypertension may be associated with a polymorphism of AGT gene 704 and the AH easy flow - with GNB3: 825.

Depending on the availability of clinical conditions associated with chronic heart failure gene polymorphism varies quite significantly. In coronary artery disease (angina) revealed increased frequency of gene polymorphism AGTR2 1675 as heterozygotes in 25% of cases. In the post-infarction cardiosclerosis noted a significant increase in the incidence of gene polymorphism GNB3: 825 as heterozygotes in 57.7% and a tendency to increase the frequency of gene polymorphism NOS3: -786 in 96.2% of cases.

Effect of gene polymorphism of AGT: 704 clinically significant heart failure indicators presented in Figure 2.

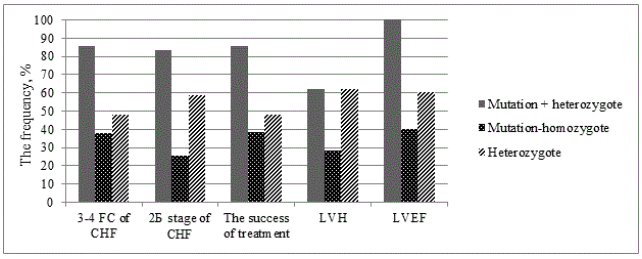

Figure 2: The frequency of AGT gene polymorphism: 704 at different rates of the CHF

For in-depth evaluation of the significance of genetic changes their analysis with favorable and unfavorable course of CHF. It has been established that the presence of hospitalization was associated with an increase in the incidence of gene polymorphism AGTR2: 1675 as a combination of mutation homozygotes and heterozygotes by 32.2% and separately for heterozygotes by 31.1% ($p < 0.05$). A similar direction was traced by the heterozygous gene polymorphism GNB3: 825 26.9%. These results give reason to believe that the identified genetic alterations are associated with the lack of success of pharmacotherapy.

The frequency of polymorphisms of genes also varied depending on the parameters of intracardiac hemodynamics. Under unfavorable terms echocardiography most frequently observed polymorphisms of genes AGT: 704, NOS3: -786 and GNB3: 825. These gene polymorphisms have been associated with decreased left ventricular ejection fraction, left ventricular hypertrophy (LVH), increase in EDD and ESD of the heart, TPWLV and IVST. Decreased left ventricular ejection fraction was associated with polymorphisms of genes AGT: 704 and GNB3: 825, increasing IVST with gene polymorphisms ADD1: 1378 and AGT: 521 ($p<0.05$).

Conclusion

Thus, one of the ways to improve the efficacy and safety of drug therapy is the introduction into clinical practice of individual approach to the choice of drug and dosing regimen based on the factors affecting the pharmacological response, which are available for the individual patient [9]. Identification of the genetic characteristics of patients - the basis of personalized medicine, because it allows you to predict the pharmacological response to drugs, and thus improve the effectiveness and safety of drugs, since the identification of the allelic variant, which leads to changes in the pharmacokinetics and/or pharmacodynamics in patients requiring therapy correction - dose drugs, the multiplicity of its application, the route of administration, the need for replacement by another drug and other technologies so-called personalized medicine [10]. That is, the use of this approach in clinical practice allows individualized pharmacotherapy.

According to the analysis, the progression of CHF is associated with an increase in the frequency of occurrence of AGTR2 gene polymorphisms: 1675, CYP11B2: -344, NOS3: -786, AGT: 704, GNB3: 825 and their heterozygotes. The degree of pharmacotherapy success at the outpatient stage is associated with a 32.2% increase in the AGTR2 gene polymorphism frequency: 1675 as a combination of homozygote and heterozygote mutation, and 26.9% with heterozygote polymorphism GNB3: 825. In patients with CHF and CHD: angina is

more often observed polymorphism of the gene AGTR2: 1675, and in the presence of a heart attack - with GNB3: 825. Indices of intracardiac hemodynamics in patients with CHF in the form of a reduced LVEF, increased CRD and CSF of the heart, LVS and TMZHP are associated With AGT: 704, NOS3: -786, GNB3: 825, ADD1: 1378 and AGT: 521 gene polymorphisms. As the size of the LP increased, the frequency of AGT gene polymorphism: 521 increased by 16%. LVH is associated with an increased incidence of polymorphisms of AGT: 704 and CYP11B2: -344 genes as heterozygotes.

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