DOI: https://doi.org/10.17816/PAVLOVJ65126

Полиморфизм гена изофермента CYP3A4 у пациентов с хронической ревматической болезнью сердца

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Цель. Выявление ассоциаций полиморфизма гена изофермента CYP3A4 с показателями эхокардиографии (ЭхоКГ), спирометрии и эндотелиальной функции у пациентов с хронической ревматической болезнью сердца (ХРБС).

Материалы и методы. Обследовано 128 пациентов с ХРБС (15,6% мужчин и 84,4% женщин). Генотипирование по полиморфным маркерам A392A, A392G, G392G выполнено методом ПЦР с электрофоретической схемой детекции результата «SNP-ЭКСПРЕСС» (НПФ Литех, Россия) после выделения ДНК из лейкоцитов венозной крови. ЭхоКГ выполнялась на аппарате Affinity 50 (Philips, Нидерланды), оценка эндотелиальной функции — на аппарате АнгиоСкан01 (АнгиоСкан-Электроникс, Россия), оценка функции внешнего дыхания — на спирометре SpiroLab II (MIR Medical, Италия).

Результаты. Дистанция теста 6-минутной ходьбы в группах значимо не различалась: A392A — 327,47 ± 6,71 м, A392G — 303,63 ± 26,19 м, G392G — 338,87 ± 20,12 м (p = 0,505), — как и площадь митрального отверстия: A392A — 1,74 (1,67;1,81) см^2, A392G — 1,68 (1,45;1,92) см^2, G392G — 1,65 (1,67;1,81) см^2 (p = 0,214). По показателям ЭхоКГ в группе гомозигот G392G выявлены наименьшие значения линейных размеров левого желудочка (конечный диастолический размер — 4,83 (4,72;4,95) см, конечный систолический размер — 2,97 (2,79;3,14) см), правого желудочка (2,45 (2,32;2,58) см), правого предсердия (4,09 (3,56;4,62) см) и критериев гипертрофии левого желудочка (толщина межжелудочковой перегородки — 0,88 (0,81;0,95) см, задней стенки — 0,88 (0,81;0,95) см). Статистически значимых различий по индексу окклюзии по амплитуде в группах получено не было, т.е. не выявлено влияния единичных нуклеотидных замен CYP3A4 на систему мелких резистивных артерий, тогда как значения сдвига фаз между каналами (отражают состояние крупных проводящих артерий) значимо различались. Полиморфизм G392G отличался наихудшими показателями: минимальные изменения отмечались в группе A392A. Результаты контурного анализа демонстрировали наибольшие значения индекса аугментации в группе G392G, отражая максимальную сосудистую жесткость. Влияния на показатели функции внешнего дыхания полиморфизма CYP3A4 в изучаемой когорте пациентов не выявлено. По показателям спирометрии значения обструктивных и рестриктивных показателей не достигали статистической значимости, хотя у гомозигот форсированная жизненная емкость легких (76,5 (71,1;82,0) %) и объем формированного выдоха за 1 с (84,6 (79,0;90,3) %) были наибольшими, с максимальными значениями жизненной емкости легких у гомозигот A392A (85,6 (82,3;88,8) %).

Заключение. У пациентов с ХРБС, гомозиготных по G392G, выявлены минимальные показатели гипертрофии и размеров полости левого желудочка и наименьшие значения полостей правых отделов сердца. Влияния на показатели функции внешнего дыхания полиморфизма CYP3A4 у исследуемых пациентов с ХРБС не получено.

Ключевые слова: *хроническая ревматическая болезнь сердца; митральный стеноз; полиморфизм изофермента CYP3A4*

Как цитировать:
Петров В.С., Никифоров А.А., Смирнова Е.А. Полиморфизм гена изофермента CYP3A4 у пациентов с хронической ревматической болезнью сердца // Российский медико-биологический вестник имени академика И.П. Павлова. 2021. Т. 29. № 2. С. 239–244. DOI: https://doi.org/10.17816/PAVLOVJ65126

Рукопись получена: 15.04.2021 **Рукопись одобрена:** 11.06.2021 **Опубликована:** 30.06.2021

ЭКО•ВЕКТОР

DOI: https://doi.org/10.17816/PAVLOVJ65126

Polymorphism of CYP3A4 isoenzyme gene in patients with chronic rheumatic heart disease

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AIM: This study aimed to identify the associations of CYP3A4 isoenzyme gene polymorphism with the parameters of echocardiography (EchoCG), spirometry, and endothelial function of patients with chronic rheumatic heart disease (CRHD).

MATERIALS AND METHODS: A total of 128 patients with CRHD (15.6% men and 84.4% women) were examined. A392A, A392G, and G392G polymorphic markers were genotyped through polymerase chain reaction (PCR) with an SNP-EXPRESS electrophoretic scheme (NPF Litekh, Russia) to detect results after DNA was isolated from leukocytes in venous blood. EchoCG was implemented on an Affinity 50 apparatus (Philips, the Netherlands), endothelial function was assessed with an AngioScan01 apparatus (AngioScan-Electronics, Russia), and respiratory function was examined using a SpiroLab II spirometer (MIR Medical, Italy).

RESULTS: The distance in a 6 min walk test did not show any significant differences among the groups: A392A – 327.47 ± 6.71 m, A392G – 303.63 ± 26.19 m, G392G – 338.87 ± 20.12 m (p=0.505). The area of the mitral opening was as follows: A392A – 1.74 (1.67; 1.81) cm2, A392G – 1.68 (1.45; 1.92) cm2, and G392G – 1.65 (1.67; 1.81) cm2 (p = 0.214). As for the EchoCG parameters, the group of G392G homozygotes had the lowest linear dimensions of the left ventricle (the end diastolic dimension – 4.83 (4.72; 4.95) cm, the end systolic dimension – 2.97 (2.79; 3.14) cm, the right ventricle (2.45 [2.32; 2.58] cm), of the right atrium (4.09 [3.56; 4.62] cm), and the criteria of left ventricular hypertrophy (thickness of the interventricular septum 0.88 [0.81; 0.95] cm, and the posterior wall – 0.88 (0.81; 0.95 cm). No statistically significant differences were found in the occlusion index amplitude among the groups, that is, single nucleotide replacements of CYP3A4 had no influence on the system of low-resistance arteries. Conversely, the values of the phase shift between channels (reflecting the condition of large arteries) significantly differed. The G392G polymorphism showed the worst parameters, and minimal changes were observed in the A392A group. Contour analysis demonstrated the highest augmentation index values in the G392G group, reflecting the maximal stiffness of vessels. The CYP3A4 polymorphism had no effect on the parameters of respiratory function in the studied cohort of patients. Spirometry revealed that the obstructive and restrictive parameters were not significant although homozygotes demonstrated the highest forced vital capacity of the lungs (76.5% [71.1% and 82.0%]) and forced expiratory volume for 1 s (84.6% [79.0% and 90.3%]). The maximal parameter of the vital capacity of the lungs in homozygotes for A392A (85.6% [82.3% and 88.8%]).

CONCLUSION: Patients with CRHD homozygous for G392G had the minimum parameters of hypertrophy and dimensions of the left ventricular cavity. They also had the lowest values for the cavities of the right heart. CYP3A4 polymorphism had no effect on the parameters of respiratory function in the studied patients with CRHD.

Keywords: *chronic rheumatic heart disease; mitral stenosis; polymorphism of CYP3A4 isoenzyme*

To cite this article:
Petrov VS, Nikiforov AA, Smirnova EA. Polymorphism of CYP3A4 isoenzyme gene in patients with chronic rheumatic heart disease. *I.P. Pavlov Russian Medical Biological Herald.* 2021;29(2):239–244. DOI: https://doi.org/10.17816/PAVLOVJ65126

Received: 15.04.2021 **Accepted:** 11.06.2021 **Published:** 30.06.2021

Most medical drugs (MDs) entering a human body undergo biotransformation, which leads to a change in pharmacological activity, decrease in lipophilicity, and increase in hydrophilicity of the drug, which eventually aids in its excretion from the body [1]. A significant portion of the biotransformation process occurs in the liver, although the intestines, lungs, kidneys, and skin may also be involved [2]. One of the main biotransformation enzymes is cytochrome P450, which contains more than 1000 isoenzymes, five of which provide up to 90% of the drug metabolism: CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2 [3]. The CYP3A4 isoenzyme provides biotransformation for up to 40%–50% of the MDs used in clinical practice: slow calcium channel blockers [4], macrolide antibiotics, statins (atorvastatin and simvastatin) [5], R-warfarin [6], and direct oral anticoagulants (rivaroxaban, apixaban and, to a lesser extent, edoxaban) [7].

One of the factors influencing the activity of cytochrome P450 isoenzymes is *single nucleotide substitutions*, which have been actively studied in the recent decades in various diseases. More often evaluated factors are polymorphism of the genes of the renin-angiotensin-aldosterone system in cardiac patients [8] or single nucleotide substitutions in arterial hypertension [9]. There are practically no works on the assessment of the association of CYP3A4 isoenzyme gene polymorphism with organic and/or functional changes in the cardiovascular system in patients with chronic rheumatic heart disease (CRHD).

This study **aimed** to identify the associations of CYP3A4 isoenzyme gene polymorphism with echocardiography (EchoCG), spirometry, and endothelial function parameters in patients with CRHD.

MATERIALS AND METHODS

A total of 128 patients (84.4% women and 15.6% men) with a confirmed diagnosis of CRHD (mitral stenosis obligatory) were examined at the Regional Clinical Cardiologic Dispensary (Ryazan) after signing informed consent.

All the participants received drug therapy, including β-blockers, spironolactone, and angiotensin-converting enzyme inhibitors.

The *criteria of exclusion from the study* were the absence of mitral stenosis despite a diagnosis of CRHD, implantation of a pacemaker, surgery on the heart valves, diabetes mellitus, bronchial asthma, and chronic obstructive pulmonary disease.

To objectify the functional class of chronic heart failure (CHF), 6-minute walk test was used.

EchoCG was performed on the Affinity 50 apparatus (Philips, the Netherlands) with an assessment of the linear dimensions of the heart, its valves, and the level of regurgitation at the valves, including:

- end-diastolic dimension (EDD) of the left ventricle (LV),
- end-systolic dimension (ESD) of the LV,
- dimension of the left atrium (LA),
- dimension of the right atrium (RA),
- dimension of the right ventricle (RV),
- thickness of the interventricular septum (TIVS),
- thickness of the posterior wall (TPW) of the LV,
- mitral orifice area (SMo),
- ejection fraction (EF) of LV,
- regurgitation at the mitral, tricuspid, and aortic valves.

Endothelial function was studied on the AngioScan01 apparatus (AngioScan-Electronics, Russia). Respiratory function was evaluated on SpiroLab II spirometer (MIR Medical, Italy) with evaluation of the following parameters:

- vital capacity of the lungs (VCL),
- reserve inspiratory volume (RIV),
- reserve expiratory volume (REV),
- inspiratory capacity (IC),
- forced VCL (FVCL),
- forced expiratory volume-1sec (FEV1),
- FEV1/FVCL ratio (Gensler index),
- peak flow rate (PFR),
- minute pulmonary ventilation (MPV).

Genotyping for A392A, A392G, G392G polymorphic markers was performed by the PCR method with SNP-EXPRESS electrophoretic scheme (NPF Litekh, Russia) of detection of the result after isolation of DNA from the leukocytes of venous blood. The study was conducted on the base of the Central Research Laboratory of Ryazan State Medical University.

The frequency of CYP3A4 (A392A in rs2740574 locus) was: A392A–85.94% (110 participants), A392G–7.81% (10 participants), and G392G–6.25% (8 participants). The genotype frequency did not follow the Hardy–Weinberg equilibrium ($\chi 2 = 41.87$, $p = 0.001$). The studied patients in the groups were comparable in gender, height, body weight, and age ($p > 0.05$); frequency of arterial hypertension ($\chi 2 = 5.708$, $p = 0.058$); and atrial fibrillation ($\chi 2 = 4.220$, $p = 0.121$).

Statistical processing was performed using IBM SPSS Statistics 23.0 software. The assessment of the normality of the distribution of quantitative parameters was conducted using the Shapiro–Wilk test. The arithmetic mean (M), the error of the mean (m), 95% confidence interval (CI) for the mean, and the achieved level of significance (p) were calculated. The ANOVA method was used for multiple comparisons. Qualitative parameters in the groups were compared using the $\chi 2$ test. Logistic analysis was performed to determine Exp B. Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The studied groups were comparable in terms of the 6-minute walk test distance: CYP3A4 A392A–327.47 ± 6.71 m, A392G–303.63 ± 26.19 m, and G392G–338.87 ± 20.12 m (p = 0.505).

Comparison of EchoCG parameters in patients with CYP3A4 polymorphism revealed the largest LV dimensions in the A392A and A392G groups (Table 1). Patients in these groups were comparable in terms of SMo. Valve insufficiency studies showed the lowest degree of regurgitation at the mitral and aortic valves in the G392G CYP3A4 group. With this, patients with G392G also had the smallest LV dimensions:

• A392G: for ESD Exp B 0.088 (0.010; 0.736), p = 0.025; for EDD Exp B 8.119 (1.783; 36.690), p = 0.007.

• G392G: for ESD Exp B 0.003 (0.001; 0.105), p = 0.003; for EDD Exp B 2.125 (0.210; 21.480), p = 0.523), and also the minimum parameters of the severity of LV hypertrophy (TIVS and TPW LV).

The lowest EchoCG values in the G392G group were the values for the right heart (RV and RA):

• A392G: for RV Exp B 8.794 (0.941; 8.176), p = 0.057; for RA Exp B 0.317 (0.052; 1.922), p = 0.212.

• G392G: for RV Exp B 0.002 (0.001; 0.278), p = 0.013; for RA Exp B 0.731 (0.258; 2.067), p = 0.554.

The maximal linear dimensions of LV and RV cavities were noted in the A392G group.

Table 1. Parameters of EchoCG in CYP3A4 Polymorphism in Patients with CRHD (n = 128), M (95% CI)

Parameter	A392A	A392G	G392G	p
LA, cm	4.8 (4.7;4.9)	5.8 (4.7;6.9)	4.9 (4.4;5.4)	0.144
EDD LV, cm	5.7 (5.6;5.8)	5.9 (5.2;6.6)	4.8 (4.7;5.0)	0.001
ESD LV, cm	3.8 (3.7;3.8)	3.76 (3.2;4.3)	2.97 (2.8;3.1)	0.001
EF LV, %	61.4 (60.4;62.3)	64.0 (62.4;65.7)	68.7 (65.7;71.7)	0.001
TIVS, mm	10.2 (9.8;10.5)	11.1 (10.2;12.0)	8.8 (8.1;9.5)	0.001
TPW LV, mm	10.2 (9.8;10.5)	9.1 (9.0;9.2)	8.8 (8.1;9.5)	0.004
RV, cm	2.7 (2.6;2.8)	2.9 (2.8;3.1)	2. 5 (2.3;2.6)	0.001
RA, cm	4.6 (4.4;4.8)	4.4 (4.0;4.8)	4.1 (3.6;4.6)	0.040
SMo, cm2	1.7 (1.7;1.8)	1.7 (1.5;1.9)	1.7 (1.7;1.8)	0.214
Mitral valve (MV) regurgitation, degree	2.3 (2.2;2.4)	2.3 (1.9;2.7)	1.3 (1.0;1.6)	0.001
Aortic valve (AV) regurgitation, degree	2.3 (2.2;2.4)	1.8 (1.7;2.0)	1.50 (1.0;2.0)	0.001
Tricuspid valve (TV) regurgitation, degree	2.0 (1.9;2.1)	2.2 (2.0;2.4)	2.3 (2.0;2.7)	0.255

There were no statistically significant differences in the occlusion index amplitude in the groups; no effect of single nucleotide substitutions of CYP3A4 on the system of small resistance arteries was found, while the phase shift values between the channels (that reflect the state of large conducting arteries) differed significantly (Table 2). G392G polymorphism was characterized by the worst parameters: minimal changes were noted in the A392A group. The results of contour analysis showed the highest augmentation index values in the G392G group, reflecting maximum vascular stiffness.

The main parameters of respiratory function: VCL, FVCL, FEV1, did not show differences in the study groups (Table 3). The significance of the differences in REV is controversial since the groups showed a wide range of CIs. An increase in IC in the A392A group may be associated with single nucleotide substitutions and changes in the functional state of the heart (see EchoCG parameters, Table 1) in the CYP3A4 A392A group. However, without statistically significant changes in the RIV and VCL, it is difficult to correlate the obtained data with CHF.

Table 2. Parameters of Endothelial Function in CYP3A4 Polymorphism in Patients with CRHD (n = 128), M (95% CI)

Parameter	A392A	A392G	G392G	R
Occlusion index in terms of amplitude	1.8 (1.7;1.9)	1.8 (1.4;2.2)	1.8 (1.1;2.4)	0.434
Phase shift between channels, ms	-6.2 (-7.3;-5.2)	-10.8 (-13.3;-8.4)	-16.5 (-20.6;-12.5)	0.001
Augmentation index, %	11.6 (9.8;13.5)	11.70 (1.1;22.3)	19.2 (11.7;26.6)	0.005
Age of the vascular wall, years	68.2 (65.0;71.4)	66.7 (55.1;78.3)	67.7 (60.7;74.7)	0.458

DOI: https://doi.org/10.17816/PAVLOVJ65126

Table 3. Main Parameters of Spirometry in CYP3A4 Polymorphism in Patients with CRHD (n = 128), M (95% CI)

Parameter	A392A	A392G	G392G	R
FVCL, %	73.8 (71.8;75.8)	74.4 (69.2;79.5)	76.5 (71.1;82.0)	0.294
FEV1, %	81.9 (79.7;84.1)	78.1 (72.3;83.8)	84.6 (79.0;90.3)	0.543
FEV1/FVCL	118.5 (117.0;120.0)	115.4 (111.0;119.7)	119.0 (116.7;121.4)	0.068
PFR, %	104.1 (100.7;107.5)	99.8 (83.5;116.2)	100.2 (93.3;107.1)	0.986
RIV,%	87.0 (83.5;90.5)	75.3 (73.8;76.7)	83.9 (75.4;92.3)	0.174
REV, %	22.1 (19.0;25.3)	8.3 (4.7;11.8)	31.7 (10.0;53.4)	0.024
IC, %	111.9 (107.6;116.2)	89.9 (82.3;97.4)	107.9 (103.1;112.8)	0.002
VCL, %	85.6 (82.3;88.8)	75.3 (73.8;76.7)	83.9 (75.4;92.3)	0.359
MPV, %	66.0 (63.0;67.9)	56.2 (42.0;70.3)	66.3 (59.1;73.4)	0.070

Since cytochrome P450 is involved in the metabolism of most MDs, in a situation of comparable frequency of MD use and concomitant pathology, it can be *suggested that the obtained changes in the discussed parameters may be associated with CYP3A4 polymorphism*. For example, with homozygosity for G392G, the values of the linear dimensions of the LV and RV and the parameters of LV hypertrophy were the lowest, as were the parameters of regurgitation on the MV and AV.

With this, the activity of the enzyme is assumed to be higher in heterozygotes for A392G and homozygotes for G392G and, since there was a comparable frequency of use of MDs in the treatment of CHF in the groups, *it can be suggested that, in some cases, standard therapy may negatively influence the values of EchoCG in patients with CRHD*. In the G392G group, the activity of the enzyme increased, which may reduce the effectiveness of pharmacological therapy [2]. Since there were no significant changes between the groups in SMo (influences EchoCG parameters), it can be *suggested that changes of linear dimensions of the heart chambers and the evidence of hypertrophy of the LV were associated with gene polymorphism*. On the other hand, a probable cause of dilatation of the left and right heart chambers and the evidence of hypertrophy of the LV may be the identified *higher extent of regurgitation at the AV and TV.* This may be a more logical explanation of the increase in EchoCG parameters, although the parameters in the A392A and A392G groups were similar. In other words, in the case of CYP3A4 polymorphism, *the influence of single nucleotide substitutions on the dimensions of the heart chambers cannot be excluded*.

The obtained results of changes in the arterial bed were slightly different from the values of EchoCG. Thus, homozygotes for A392A had the best results for vascular stiffness in the system of large arteries in comparison with the A392G and G392G groups, which is probably due to a *higher activity of P450 in the last two groups, that reduced the «protective» effect of MD on the vessel wall* [8]. Here, no significant differences in the parameters of the occlusion test in small resistance arteries were obtained.

Analysis *of the main values of spirometry did not reveal any changes*; however, there are works in the literature on assessment of the contribution of gene polymorphism to the development of pulmonary pathology [9]. The authors also expected changes in spirometry parameters due to CHF since, in the last few years, changes in respiratory function are considered to be a sensitive predictor of CHF decompensation.

CONCLUSION

Thus, in the examined patients with CRHD homozygous for G392G, minimal hypertrophy and minimal dimensions of LV and right heart chambers were noted.

No statistically significant differences were found in the amplitude of the occlusion index in the groups, that is, no effect of single nucleotide substitutions of CYP3A4 on the system of small resistance arteries was revealed, while the values of the phase shift between the channels (reflecting the state of large conducting arteries) differed significantly. G392G polymorphism had the worst parameters while minimal changes were noted in the A392A group. The results of the contour analysis showed the highest augmentation index values in the G392G group, reflecting the maximum vascular stiffness.

CYP3A4 polymorphism in the studied cohort of patients was not found to affect the parameters of respiratory function.

DOI: https://doi.org/10.17816/PAVLOVJ65126

ADDITIONALLY

Financing of study. Budget of Ryazan State Medical University.

Conflict of interests. The author declares no actual and potential conflict of interests which should be stated in connection with publication of the article.

Participation of authors. *V.S. Petrov* — the concept and design of the study, clinical examination of patients, mathematical and statistical processing of results, writing the text, *A.A. Nikiforov* — performing laboratory tests, *E.A. Smirnova* — analyzing the results, editing the text.

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