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Genetic markers and traditional risk factors in predicting atrial fibrillation in patients with arterial hypertension, focus on the renin-angiotensin-aldosterone system genes

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ABSTRACT

BACKGROUND: Genetic and environmental factors are involved in the development of atrial fibrillation in arterial hypertension. This determines the relevance of studying gene-environment interactions in the occurrence of arrhythmia.

AIM: To evaluate the contribution of the renin-angiotensin-aldosterone system genes polymorphisms to the susceptibility to atrial fibrillation in patients with arterial hypertension, and also to study the combined influence of these polymorphisms and environmental factors on the risk of arrhythmia.

MATERIALS AND METHODS: The study included 60 patients with arterial hypertension and paroxysmal atrial fibrillation (study group), 60 patients with arterial hypertension without atrial fibrillation (comparison group 1) and 20 healthy volunteers (comparison group 2). Angiotensin-converting enzyme (*ACE* (*I/D*)) and angiotensin II type 1 receptor gene (*AGTR1* (*A1166C*)) polymorphisms were analyzed by real-time polymerase chain reaction.

RESULTS: Genotype II and allele I of the *ACE* gene *(I/D)* in patients with arterial hypertension and atrial fibrillation were significantly more frequent compared to patients with arterial hypertension without arrhythmia ($\chi^2 = 4.547$; $p = 0.03$ and $\chi^2 = 4.818$; $p = 0.03$ respectively). Carriage of genotype II in patients with arterial hypertension increased the chance of developing atrial fibrillation by 2.8 times (95% CI 1.19–7.18). The odds ratio (OR) for arrythmia development in patients with arterial hypertension and allele I was 1.8 (95% CI 1.10–3.07). The presence of obesity in patients with arterial hypertension in the presence of genotype II of the *ACE* gene *(I/D)* was associated with an increased risk of developing atrial fibrillation, compared with the genotype alone (OR = 4.16, 95% CI 1.16–19.87). A study of the A1166C polymorphism of the *AGTR1* gene did not reveal a reliable significant relationship between its inheritance and the development of atrial fibrillation.

CONCLUSION: Genotype II and allele I of the *ACE* gene *(I/D)* were statistically significantly more frequent in patients with arterial hypertension and atrial fibrillation. Carriage of genotype II and allele I of the *ACE* gene *(I/D)* increased the chance of developing atrial fibrillation in patients with arterial hypertension. Obesity had a significant effect on the susceptibility to atrial fibrillation in the presence of genotype II of the *ACE* gene *(I/D)* in hypertensive patients.

Keywords: atrial fibrillation; arterial hypertension; renin-angiotensin-aldosterone system; gene polymorphism; risk factor; obesity.

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Генетические маркеры и традиционные факторы риска в прогнозировании фибрилляции предсердий у пациентов с артериальной гипертензией, фокус на гены ренин-ангиотензин-альдостероновой системы

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АННОТАЦИЯ

Актуальность. В развитие фибрилляции предсердий при артериальной гипертензии вовлечены генетические и средовые факторы. Это определяет актуальность изучения генно-средовых взаимодействий при возникновении аритмии.

Цель исследования — оценить вклад полиморфизмов генов ренин-ангиотензин-альдостероновой системы в предрасположенность к фибрилляции предсердий у пациентов с артериальной гипертензией, а также изучить сочетанное влияние данных полиморфизмов и средовых факторов на риск развития аритмии.

Материалы и методы. В исследовании участвовали 140 человек: 60 пациентов с артериальной гипертензией и пароксизмальной формой фибрилляции предсердий (исследуемая группа), 60 пациентов с артериальной гипертензией без фибрилляции предсердий (группа сравнения 1) и 20 здоровых добровольцев (группа сравнения 2). Анализ полиморфизма гена ангиотензинпревращающего фермента (*ACE (I/D)*) и гена рецептора ангиотензина II 1 типа (*AGTR1 (A1166C)*) выполнен методом полимеразной цепной реакции в режиме реального времени.

Результаты. Генотип II и аллель I гена *ACE (I/D)* у пациентов с артериальной гипертензией и фибрилляции предсердий встречались значимо чаще по сравнению с пациентами с артериальной гипертензией без аритмии ($\chi^2 = 4{,}547$; $p = 0{,}03$ и $\chi^2 = 4{,}818$; $p = 0{,}03$ соответственно). Носительство генотипа II у пациентов с артериальной гипертензией увеличивало шанс развития ФП в 2,8 раза (отношение шансов = 2,83; 95 % доверительный интервал 1,19–7,18). Отношение шансов развития аритмии у пациентов с артериальной гипертензией и аллелем I составило 1,83 (95 % доверительный интервал 1,10–3,07). Наличие ожирения у пациентов с артериальной гипертензией в присутствии генотипа II гена *ACE (I/D)* сопровождалось повышением риска развития фибрилляции предсердий, по сравнению с учетом только генотипа (отношение шансов = 4,16; 95 % доверительный интервал 1,16–19,87). Исследование полиморфизма *A1166C* гена *AGTR1* не выявило достоверно значимой связи между его наследованием и развитием фибрилляции предсердий.

Заключение. Генотип II и аллель I гена *ACE (I/D)* статистически значимо чаще встречались у пациентов с артериальной гипертензией и фибрилляцией предсердий. Носительство генотипа II и аллели I гена *ACE (I/D)* увеличивало шанс развития фибрилляции предсердий у пациентов с артериальной гипертензией. Ожирение оказывало значимое влияние на предрасположенность к фибрилляции предсердий при наличии генотипа II гена *ACE (I/D)* у больных гипертонией.

Ключевые слова: фибрилляция предсердий; артериальная гипертензия; ренин-ангиотензин-альдостероновая система; полиморфизм гена; фактор риска, ожирение.

Как цитировать

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INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia, occurring in 3%–4% of the general population [1]. It frequently manifests along with arterial hypertension (AH). In a Russian study (n = 2577), the prevalence of AH in patients with established AF aged <60 years was 63.8%, whereas in individuals aged >60, it was 90.1% [2]. Similar results were obtained in the Kazakh population, where the prevalence of AH among patients with arrhythmia reached 86.2% [3].

The development of AF in patients with AH is due to the interaction of genetic and environmental factors. Among these, the most common are obesity, smoking, hypercholesterolemia, and hyperuricemia. A meta-analysis of 16 studies involving 123,249 patients demonstrated a correlation between elevated body mass index (BMI) and AF risk. Overweight and obese individuals have a 39% and 87% greater risk of arrhythmia, respectively, compared to those with normal BMI [4]. General and abdominal obesity were found to increase the risk of AF. In patients with AH, increased waist circumference (WC) was identified as a predictor of AF (Odds Ratio (OR) = 1.07; 95% CI: 1.04–1.10) [5]. The Rotterdam Study showed that former and current smokers were equally at risk of developing arrhythmias [6]. The 16-year prospective Atherosclerosis Risk in Communities Study found that former and continuing smokers had a 32% and 105% higher risk, respectively, of developing AF compared with those who had never smoked [5]. The contribution of hypercholesterolemia to the development of AF is uncertain. However, a correlation between reduced levels of high-density lipoprotein cholesterol (HDL-C) and AF has been noted. For example, a Japanese study involving 28,449 people without arrhythmia at inclusion found that low HDL-C levels were associated with the development of AF in women [7]. A meta-analysis of six cohort studies demonstrated a significant association between hyperuricemia and increased AF risk (OR = 1.49; 95% CI: 1.24–1.79; $p < 0.001$) [8].

Among neurohumoral factors, activation of the renin–angiotensin–aldosterone system (RAAS) is associated with the development of AF. RAAS activity is genetically determined. One of the key links of RAAS is angiotensin-converting enzyme (ACE), which forms the main vasoconstrictor — angiotensin II (AT-II). The effects of the latter are mainly induced by the influence on type 1 receptors. The polymorphism of the ACE type I/D gene (*ACE* (*I/D*)) in the 16th intron of chromosome 17 is associated with the activity of the enzyme in the blood. An increase in the latter results in increased AT-II production, which contributes to the development of AF [9]. The gene encoding the type 1 AT-II receptor (*AGTR1* (*A1166C*)) is located on chromosome 3 (3q24). The substitution of adenine (A) for cytosine (C) at position 1166 of the *AGTR1* gene affects the functional activity of the AT-II receptor. Homozygotes for the allelic variant C of this gene shows a higher affinity for AT-II [9]. Data on the effect of polymorphisms of the *ACE* type *I/D* gene and the gene encoding the type 1 AT-II receptor (*AGTR1* (*A1166C*)) on ACE activity and the functional activity of the receptor are inconclusive and contradictory.

This study aimed to assess the role of RAAS gene polymorphisms in predisposition to AF in patients with AH and investigate the combined effect of these polymorphisms and environmental factors on the risk of arrhythmia development.

MATERIALS AND METHODS

Overall, 120 patients with AH grades I and II were examined. Of these, 60 patients had a paroxysmal form of AF and comprised the study group (SG), and 60 had no AF and comprised comparison group 1 (CG-1). Comparison group 2 (CG-2) included 20 healthy volunteers. The exclusion criteria were AH grade III, symptomatic AH, clinically significant forms of ischemic heart disease, non-coronary myocardial diseases, heart defects, heart rhythm disorders (ventricular extrasystole above Lown class 2, Wolff – Parkinson – White syndrome), radiofrequency ablation before the study, acute inflammatory diseases, chronic heart failure with functional class II or higher, thyroid dysfunction, chronic kidney disease with a glomerular filtration rate ⩽60 ml/min/1.73 m^2, liver dysfunction, diabetes mellitus, cancer, and other severe comorbidities that can affect the parameters under study.

The identification of risk factors (RFs) included the assessment of the incidence of smoking, obesity, hypercholesterolemia, and hyperuricemia. Smoking status was determined using a questionnaire. Individuals were considered smokers if they were past or current smokers. All patients were measured for WC, hip circumference (HC), WC/HC ratio, height, and weight, with subsequent BMI calculation. WC was assessed in the standing position by placing a centimeter tape on the midpoint of the distance between the crest of the iliac bones and lower edge of the ribs. HC was measured at the most protruding points of the buttocks. The presence of abdominal obesity was established when the WC was >88 cm in women and >102 cm in men. A BMI ⩾ 30 kg/m^2 indicated obesity [10].

Blood plasma lipid parameters and serum uric acid levels were assessed using Diazens reagents (Belarus) on an automated photometer RA 2600 (CJSC SOLAR, Belarus). Hypercholesterolemia was determined when the total cholesterol level was ⩾ 4.9 mmol/L and/or hypolipidemic therapy was used [10]. Hyperuricemia was defined as an increase in uric acid level of >360 μmol/L [10].

Polymerase chain reaction (PCR) method was used to identify polymorphic markers of RAAS genes: *ACE (I/D)* and *AGTR1* (*A1166C*). Genomic DNA was extracted from collected blood samples using vacuum systems with ethylenediaminetetraacetate and a set of reagents for DNA extraction from whole blood by M-sorb magnetic sorption method (Syntol LLC, Russia). Genotyping was conducted via real-time PCR on a Rotor-Gene Q 5plex HRM thermocycler

system (QIAGEN, Germany). In the analysis of obtained results, the conformity of the control genotypes with the declared ones was verified.

Statistical analysis was conducted using the Statistica 10.0 application program package. The results are presented as the median (Me) and interquartile range [*LQ*; *UQ*]. The Mann – Whitney *U* test was used to compare two independent groups. Multiple comparisons within groups (more than two) were performed using the Kruskal–Wallis *H*-criterion. The category distributions between groups was compared using Pearson's χ^2 homogeneity criterion. In the case of two compared groups and two categories, the Yates correction for Pearson's χ^2 criterion was used. If the conditions for employing Pearson's chi-squared homogeneity criterion were not met, Fisher's exact test was employed. The ORs of pathology development under and without the influence of RFs were defined as exponents of the corresponding regression coefficients in the logistic regression equations. In these equations, the independent variable was a binary indicator variable (risk factor present/no risk factor present), and the dependent variable was a binary indicator (pathology development present/no pathology development). The 95% CI for ORs was calculated as the exponent of the corresponding CI for the regression coefficients. The threshold value for the statistical significance was assumed to be 0.05. To test the independence of the RFs when accounting for their joint influence on the dependent variable, the generalized variance inflation factor (generalized VIF) was determined. If the condition generalized VIF2 was < 4 was, the RFs were considered independent.

RESULTS AND DISCUSSION

The studied groups did not differ in age and were comparable in gender. Table 1 shows the comparative characteristics of the groups.

The duration of history of AH was significantly higher in SG patients than in CG-1 patients ($p = 0.002$). Regarding BMI, WC, HC, and WC/HC, SG was comparable to CG-1. Healthy volunteers had significantly lower BMI, WC, and HC compared to patients with AH and paroxysmal AF and AH patients without arrhythmia ($p = 0.0000$ for all values). As regards WC/HC, CG-2 was comparable to CG-1 and significantly different from SG ($p = 0.02$).

Table 2 presents the frequency of the primary RFs for cardiovascular disease (CVD). No significant differences were found in the groups by smoking status. However, a tendency for a higher frequency of smoking were noted among patients with AF with/without AH compared to healthy individuals.

Obesity was significantly more common in SG and CG-1 than in CG-2 ($p < 0.05$). Abdominal obesity was equally frequent in SG and CG-1 and was diagnosed less frequently in CG-2 ($p < 0.05$).

Hypercholesterolemia was the most common factor in all studied groups. It was significantly less frequent in CG-2 than in CG-1 ($p < 0.05$). Hyperuricemia was two times more common in SG and CG-1 than in CG-2; however, the differences were not significant.

The distribution of genotype and allele frequencies for polymorphisms of the studied genes in the SG and

Table 1. General characteristics of the examined groups

Patient groups	Study group (*n* = 60)	Comparison group 1 (*n* = 60)	Comparison group 2 (*n* = 20)
Age, years	61 [58; 62.5]	60 [57; 62]	59 [56; 61]
Women, *n* (%)	31 (51.7)	31 (51.7)	10 (50)
Duration of arterial hypertension, years	16 [12; 22.5] [2]	11 [7; 18.5] [1]	–
Arterial hypertension grade I, *n* (%)	24 (40)	23 (38.3)	–
Arterial hypertension grade II, *n* (%)	36 (60)	37 (61.7)	–
Duration of atrial fibrillation, years	5 [3; 8]	–	–
Body mass index, kg/m^2	30.8 [28.1; 34.0][3]	29.7 [27.6; 32.8][3]	24.5 [22.1; 26.3][1.2]
Waist circumference, cm	106.5 [99.0; 111.5][3]	102.0 [96.0; 106.5][3]	92.0 [80.0; 94.5][1.2]
Hip circumference, cm	113.0 [108.5; 121.0][3]	112.0 [107.0; 118.5][3]	102.5 [99.0; 105.0][1.2]
Waist circumference/ hip circumference	0.92 [0.88; 0.96][3]	0.9 [0.85; 0.95]	0.89 [0.83; 0.92][1]

Note: [1] — $p < 0.05$, compared to the study group; [2] — $p < 0.05$, when compared to comparison group 1; [3] — $p < 0.05$, when compared to comparison group 2.

CGs corresponded to the Hardy – Weinberg equilibrium ($p > 0.05$). Table 3 shows the results obtained by analyzing the genotypes and alleles of the *ACE* gene (*I/D*). Genotype II was more common in patients with AH and AF than in patients with AH without arrhythmia (33.3% and 15.0%, respectively; $\chi^2 = 4.547$; $p = 0.03$). No significant difference was noted in the frequency of genotype II between SG and CG-2 (33.3% and 30%, respectively; $\chi^2 = 0.000$; $p = 1.0$). However, allele I was significantly more frequent in SG than in CG-1 ($\chi^2 = 4.818$; $p = 0.03$). The high frequency of genotype II and allele I in healthy volunteers compared to that in CG-1 was notable (30% vs. 15% and 55% vs. 41.7%, respectively); however, these differences were not significant.

The OR of AF development in patients with AH and genotype II of the *ACE* gene (*I/D*) was 2.83 (95% CI, 1.19–7.18), respectively. Consequently, patients with AH and genotype II of the *ACE* gene (*I/D*) were 2.8 times more likely to develop AF compared to patients with AH and genotype ID or DD. Furthermore, carriage of allele I in patients with AH increased the risk of AF by 1.8-fold (OR = 1.83; 95% CI, 1.10–3.07).

Table 4 displays the frequency of genotypes and alleles of the *AGTR1* (*A1166C*) gene. Differences in the frequency of occurrence of genotypes and alleles of *AGTR1* (*A1166C*) gene between groups were not significant.

In the subsequent phase of the study, the correlation between the *ACE* gene I/D polymorphism and *AGTR1* gene

Table 2. Frequency of cardiovascular diseases risk factors in the examined groups

Parameters	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
Smoking status	23	38.3	20	33.3	4	20
Abdominal obesity	47	78.3[3]	47	78.3[3]	4	20[1, 2]
Obesity	37	61.7[3]	29	48.3[3]	0	0[1, 2]
Increased total cholesterol	52	86.7[3]	51	85[3]	12	60[1, 2]
Hyperuricemia	20	33.3	21	35	3	15

Note: [1] — $p < 0.05$, compared to the study group; [2] — $p < 0.05$, when compared to comparison group 1; [3] — $p < 0.05$, when compared to comparison group 2.

Table 3. Distribution of genotypes and alleles of the *ACE (I/D)* gene in patients of the studied groups

Genetic variant	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
DD genotype	12	20	19	31.7	4	20
ID genotype	28	46.7	32	53.3	10	50
II genotype	20*	33.3	9*	15.0	6	30
D allele	52	43.3	70	58.3	18	45
I allele	68*	56.7	50*	41.7	22	55

Note: * — statistically significant differences ($p < 0.05$) of genotype and allele frequencies in the study group compared to those in comparison group 1.

Table 4. Distribution of genotypes and alleles of the *AGTR1 (A1166C)* gene in patients of the studied groups

Genetic variant	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
CC genotype	9	15	4	6.7	4	20.0
AC genotype	26	43.3	23	38.3	9	45.0
AA genotype	25	41.7	33	55.0	7	35.0
C allele	44	36.7	31	25.8	17	42.5
A allele	76	63.3	89	74.2	23	57.5

A1166C polymorphism and AF onset was examined, with consideration of the influence of traditional RFs. Table 5 illustrates the distribution of *ACE* gene genotypes (*I/D*) across the studied groups, in the presence or absence of specific factors including smoking, hypercholesterolemia, hyperuricemia, and general and abdominal obesity.

In the context of obesity, genotype II was 3.2 times more prevalent ($p < 0.05$) in SG than in CG-1. Furthermore, in the presence of hypercholesterolemia, genotype II was 2.2 times more frequent ($p < 0.05$) in SG than in CG-1. Notably, no differences were observed in the frequency of *ACE* gene genotypes among smoking patients in SG and CG-1. However, genotype II was significantly more common among never-smoking patients with AH and paroxysmal AF than in those with AH without arrhythmia ($p < 0.05$).

The results of the OR calculation indicated an association between cardiovascular risk factors and the risk of AF development in *ACE* genotype II carriers (*I/D*). The risk of AF development at genotype II carriage in patients with AH and hypercholesterolemia was 2.8 (OR = 2.79; 95% CI, 1.13–7.38). Consequently, including cholesterol levels in the evaluation of carriers of this genotype did not result in an increased risk of arrhythmia compared to that in the evaluation of genotype II alone (OR = 2.83; 95% CI, 1.19–7.18). Obesity was associated with a greater increase in the risk of AF in genotype II carriers with AF than in genotype II carriers alone (OR = 2.83; 95% CI, 1.19–7.18).

The simultaneous accounting of the influence of two RFs on the probability of AF development can be achieved by developing a two-factor logistic regression model. In this model, the binary variable "no AF/have AF" is considered to depend on two predictors: the binary variables "genotype not II/genotype II" and "no obesity/have obesity". Table 6 presents the statistics of regression coefficients and AUC of this model.

Because only 24% of the subjects were carriers of genotype II, the weight function *W* was used to determine the coefficients of the regression equation, with a value of 3 assigned to subjects who were carriers of genotype II and 1 to subjects who were not (the sample was balanced with respect to the variables "no AF/have AF" and "no obesity/have obesity").

To test the hypothesis on the independence of variables in the above equation, the generalized VIF for this regression

Table 5. Occurrence of risk factors in the studied groups depending on the genotype of the *ACE* (*I/D*) gene

Risk factor or lack thereof	Study group ($n = 60$)			Comparison group 1 ($n = 60$)			Comparison group 2 ($n = 20$)		
	DD	*ID*	*II*	*DD*	*ID*	*II*	*DD*	*ID*	*II*
Smoking, *n* (%)	5 (21.7)	12 (52.2)	6 (26.1)	6 (30.0)	11 (55.0)	3 (15.0)	1 (25.0)	3 (75.0)	– (0.0)
Nonsmokers, *n* (%)	7 (18.9)	16 (43.2)	14* (37.8)	13 (32.5)	21 (52.5)	6* (15.0)	3 (18.75)	7 (43.75)	6 (37.5)
Abdominal obesity, *n* (%)	7 (14.9)	24 (51.1)	16 (34.0)	16 (34.0)	24 (51.1)	7 (14.9)	1 (25.0)	3 (75.0)	–
Normal waist circumference, *n* (%)	5 (38.5)	4 (38.75)	4 (38.75)	3 (23.1)	8 (61.5)	2 (15.4)	3 (18.75)	7 (50.0)	6 (46.15)
Obesity, *n* (%)	7 (18.9)	18 (48.6)	12* (32.4)	9 (31.0)	17 (58.6)	3* (10.3)	– (0.0)	– (0.0)	– (0.0)
No obesity, *n* (%)	5 (21.7)	10 (43.5)	8 (34.8)	10 (32.3)	15 (48.4)	6 (19.3)	4 (20.0)	10 (50.0)	6 (30.0)
Hyperuricemia, *n* (%)	6 (30.0)	7 (35.0)	7 (35.0)	6 (28.6)	12 (57.1)	3 (14.3)	2 (66.7)	1 (33.3)	– (0.0)
Normal uric acid levels, *n* (%)	6 (15.0)	21 (52.5)	13 (32.5)	13 (33.3)	20 (51.3)	6 (15.4)	2 (11.8)	9 (52.9)	6 (35.3)
Hypercholesterolemia, *n* (%)	10 (19.2)	24 (46.2)	18* (34.6)	17 (33.3)	26 (51.0)	8* (15.7)	1 (8.3)	6 (50.0)	5 (41.7)
Normal total cholesterol levels, *n* (%)	2 (25.0)	4 (50.0)	2 (25.0)	2 (22.2)	6 (66.7)	1 (11.1)	3 (37.5)	4 (50.0)	1 (12.5)

Note: *— significant differences ($p < 0.05$) in the frequency of occurrence of genotypes and alleles in the study group compared to comparison group 1.

Table 6. Statistics of the regression coefficients and AUC of the model

Indicators	Score	Standard deviation	*p*	OR	95% CI for OR	AUC (95 % CI)
Constant term	–0.6748	0.2857	0.0018	–	–	0.631 (0.538–0.724)
Genotype II "yes"	1.1105	0.3218	0.0006	3.04	1.63–5.78	
Obesity "yes"	0.7535	0.3208	0.0188	2.12	1.14–4.02	

Note: CI — confidence interval; OR — odds ratio.

Table 7. Occurrence of risk factors in the studied groups depending on the genotype of the *AGTR1 (A1166C)* gene

Risk factor or lack thereof	Study group (*n* = 60)			Comparison group 1 (*n* = 60)			Comparison group 2 (*n* = 20)		
	CC	*AC*	*AA*	*CC*	*AC*	*AA*	*CC*	*AC*	*AA*
Smoking, *n* (%)	4 (17.4)	11 (47.8)	8 (34.9)	2 (10.0)	8 (40.0)	10 (50.0)	1 (25.0)	3 (75.0)	– (0.0)
Nonsmokers, *n* (%)	5 (13.5)	15 (40.5)	17 (46.0)	2 (5.0)	15 (37.5)	23 (57.5)	3 (18.75)	6 (37.5)	7 (43.75)
Abdominal obesity, *n* (%)	8 (17.0)	19 (40.4)	20 (42.6)	3 (6.4)	18 (38.3)	26 (55.3)	– (0.0)	3 (75.0)	1 (25.0)
Normal waist circumference, *n* (%)	1 (7.7)	7 (53.8)	5 (38.5)	1 (7.7)	5 (38.5)	7 (53.8)	4 (25.0)	6 (37.5)	6 (37.5)
Obesity, *n* (%)	7 (18.9)	13 (35.1)	17 (45.9)	2 (6.9)	11 (37.9)	16 (43.2)	– (0.0)	– (0.0)	– (0.0)
No obesity, *n* (%)	2 (8.7)	13 (56.5)	8 (34.8)	2 (6.5)	12 (38.7)	17 (54.8)	4 (20.0)	9 (45.0)	7 (35.0)
Hyperuricemia, *n* (%)	2 (10.0)	10 (50.0)	8 (40.0)	1 (4.8)	8 (38.1)	12 (57.1)	1 (33.3)	2 (66.7)	– (0.0)
Normal uric acid levels, *n* (%)	7 (17.5)	16 (40.0)	17 (42.5)	3 (7.7)	15 (38.5)	21 (53.8)	3 (17.6)	7 (41.2)	7 (41.2)
Hypercholesterolemia, *n* (%)	9 (17.3)	21 (40.4)	22 (42.3)	4 (7.8)	20 (39.2)	27 (52.9)	3 (25.0)	3 (25.0)	6 (50.0)
Normal total cholesterol levels, *n* (%)	– (0.0)	5 (62.5)	3 (37.5)	– (0.0)	3 (33.3)	6 (66.7)	1 (12.5)	6 (75.0)	1 (12.5)

model was calculated, which was 1.02. generalized VIF^2 was < 4, indicating that the predictors in the equation that consider their joint influence on the outcome (presence of AF) are mathematically independent.

Table 7 illustrates the prevalence of *AGTR1* (*A1166*) genotypes in relation to the presence of environmental factors. However, no significant differences were observed between the subgroups when environmental factors were included.

DISCUSSION

The associations between genotype II and allele I of the *ACE* gene (*I/D*) and risk of developing AF differed from those observed in other populations. In the Tunisian population, the DD genotype was associated with a 3.41-fold increased risk of AF (OR = 3.41; 95% CI, 1.39–8.34; $p < 0.007$) [11]. A meta-analysis of 23 studies involving 9,262 patients demonstrated the association between the DD genotype of the *ACE* gene (*I/D*) and AF risk [12]. In contrast, a recent study in a Russian population revealed that carriage of genotype II and allele I increases the risk of developing AF (OR = 3.165; 95% CI, 1.403–7.137 and OR = 2.552; 95% CI, 1.558–4.181, respectively) [13]. This indicates interpopulation differences and underscores the need for further research in the Belarusian population.

However, data on the effect of the *A1166C* polymorphism of the *AGTR1* gene are limited and contradictory. A Russian study found no significant differences in the development of AF from the polymorphism of this gene [14]. Moreover, Chinese scientists obtained data indicating that carriage of the C allele increases the risk of AF development by 1.43 times [15].

Our findings indicate a potential synergistic effect of genotype II and obesity in the pathogenesis of PD through RAAS activation. Currently, adipose tissue is recognized as an active endocrine organ, secreting a multitude of substances, including RAAS components [16].

Moreover, none of the CG-2 patients were obese, and genotype II of the *ACE* gene was not found in factors such as smoking and hyperuricemia. This may further indicate the role of gene-mediated interactions in the development of CVD. Thus, despite the equal frequency of *ACE* gene genotype II in patients with AH and paroxysmal AF and healthy volunteers, the latter do not develop arrhythmias owing to the lack of potentiating effect of environmental factors.

CONCLUSIONS

The presence of genotype II and allele I of the *ACE* gene (*I/D*) in patients with AH increased the risk of AF development by 2.8 and 1.8 times, respectively. Furthermore, obesity in carriers of this genotype was found to increase the risk of AF development by 4.2 times. These findings show that genetic (carriage of genotype II of the *ACE* gene) and environmental factors, primarily obesity, play a significant role in the development of AF in patients with AH. Additionally, the results obtained for *ACE* gene polymorphism (*I/D*) differ from those in other studies, which is probably due to interpopulation differences and requires testing on larger

samples. A better understanding of the relationship between genetic polymorphisms and traditional cardiovascular RFs provides more opportunities for personalized diagnosis and identification of patients at high risk for AF.

ADDITIONAL INFORMATION

Author contribution. All authors made significant contributions to the conception, research and preparation of the article, and read and approved the final version before publication. Personal contribution of the authors: N.V. Bukvalnaya — collection of the material, statistical processing, results interpretation of the results obtained, text writing; L.V. Yakubova — concept and design of the article, text editing; A.V. Kapytski — statistical processing, text editing; L.V. Kezhun — collection of the material, results interpretation; O.V. Gorchakova — definition of polymorphisms, text editing; D.G. Karnialiuk — collection of the material, results interpretation; E.Yu. Charnetskaya — determination of total cholesterol and uric acid levels in blood serum; V.A. Snezhitskiy — literature review, final approval of the manuscript for publication.

Competing interests. The authors declare that they have no competing interests.

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Informed consent for publication. Written consent was obtained from the patients and healthy volunteers for publication of medical data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: Н.В. Буквальная — сбор материала, статистическая обработка, интерпретация полученных результатов, написание текста; Л.В. Якубова — концепция и дизайн статьи, редактирование текста; А.В. Копыцкий — статистическая обработка, редактирование текста; Л.В. Кежун — сбор материала, интерпретация полученных результатов; О.В. Горчакова — определение полиморфизмов, редактирование текста; Д.Г. Корнелюк — сбор материала, интерпретация полученных результатов; Е.Ю. Чернецкая — определение уровня общего холестерина и мочевой кислоты в сыворотке крови; В.А. Снежицкий — обзор литературы, окончательное утверждение рукописи для публикации.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Заключение этического комитета. Протокол исследования был одобрен комитетом по биомедицинской этике и деонтологии УО «Гродненский государственный медицинский университет» (протокол № 1 от 11.01.2021).

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