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Uncontrolled arterial hypertension: role of suffered COVID-19 infection and polymorphisms of genes encoding the renin-agiotensin-aldosterone system

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The aim of the study was to determine the role of polymorphisms of genes encoding components of the renin-angiotensin-aldosterone system (RAAS) and suffered COVID-19 infection in patients with uncontrolled hypertension.

Methods. Clinical examination of 116 patients with stage 2 uncontrolled arterial hypertension was performed. 96 of them had mild to moderate form of coronavirus infection (COVID-19). Clinical examination, studies of polymorphism of genes encoding RAAS components were performed.

Results. Patients in the ongoing symptomatic COVID-19 phase were found to have higher systolic blood pressure (SBP) levels (p1-2=0.03659; p1-3=<0.00001) than in the postcovid syndrome group. We found that diastolic blood pressure (DBP) remained elevated in patients after COVID-19 (p1-3<0.00001; p2-3<0.00001). In the ongoing symptomatic COVID-19 phase, carriage of the homozygous TT genotype of the AGT 704 T>C gene, rs699, was less frequent (p=0.005) than in the control group. There was a weak negative association of TT genotype AGT704 with body mass index with (r=–0.30, p=0.001), SBP (r=-0.42, p=0.0001) and DBP (r=–0.36, p=0.0001).

Conclusion. Uncontrolled AH was a long-term effect of mild to moderate COVID-19. Analysis of time aspects revealed the greatest persistence of destabilization with regard to DBP. The association of BP elevation with the C allele of the AGT gene polymorphism (T704C) was found in patients who had suffered coronavirus infection in the period up to 12 weeks. Identification of the association

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of BP with the AGT gene polymorphism in postvoid syndrome will provide an opportunity to initiate personalized treatment and develop prevention strategies.

Keywords: postcovid syndrome, arterial hypertension, renin-angiotensin-aldosterone system, gene polymorphism, AGT 704 genotype.

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Introduction

A significant proportion of patients recovering from coronavirus infection (COVID-19) report various clinical symptoms of a physical, psychological and cognitive nature despite the ending of SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus 2) replication four weeks after initial infection [1]. The term "postcovid syndrome" (PCS) is now internationally recognized and is widely used to describe these symptoms [2]. The prolonged course of COVID-19 implies many unfavorable outcomes, among which cardiovascular diseases are often noted [3, 4].

Further study of the impact of COVID-19 in patients with arterial hypertension (AH) is required in order to determine the optimal therapeutic and diagnostic measures for this category of individuals [3]. Currently, it is relevant to determine possible markers to identify patients with adverse effects of COVID-19 [3]. The involvement of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of COVID-19 suggests the study of polymorphism of genes encoding RAAS components as a possible factor in the occurrence of uncontrolled AH [4].

The aim of the study was to determine the role of polymorphisms of genes encoding components of the renin-angiotensin-aldosterone system (RAAS) and suffered COVID-19 infection in patients with uncontrolled hypertension.

Methods. 116 patients hospitalized in cardiology department No.1 of the Saratov City Clinical Hospital No.8 for the destabilization of AH were examined. 96 patients had confirmed COVID-19 of mild and moderately severe form more than 4 weeks before admission. Inclusion criteria: patients aged 44–60 years with stage 2 AH and confirmed suffered COVID-19 of mild and moderate form at the outpatient stage more than 4 weeks before the examination. Exclusion criteria: symptomatic AH, other diseases of cardiovascular system, neoplasia, somatic diseases in decompensation stage. Control group: 20 patients with destabilized AH stage 2, who did not have COVID-19. Patients were divided into two groups: up to 12 weeks and more than 12 weeks after the COVID-19 (Table 1).

Clinical study. All patients were evaluated, including clinical examination, general blood count, blood chemistry, electrocardiography, echocardiography (EchoCG), and daily BP monitoring ("Valenta", St. Petersburg). EchoCG was performed on ultrasound scanner HITACHI ALOKA Alpha 7 (Japan). Genes encoding RAAS components (angiotensinogen (AGT: 704 T>C, AGT: 521 C>T), angiotensin II type 1 receptor (AGTR 1: 1166 A>C), angiotensin II type 2 receptor (AGTR 2: 1675 G>A), aldosteron synthase (CYP11B 2: –344 C>T)) were determined using RNS-2 amplifier ("Techne", UK). Patients received complex hypotensive therapy (angiotensin-converting enzyme inhibitors (perindopril 8 mg/day or enalapril 10–20 mg/day), calcium channels antagonist (amlodipine 5–10 mg/day), drugs with central mechanism of action (moxonidine 0.2–0.4 per day).

Table 1. **Characterization of examined patients by groups**

Group and number of patients, n	Mean age, years (M±m)	Amount of males/females, abs. (%)	Period after COVID-19, weeks	Mean number of weeks after COVID-19, weeks (M±m)
Control group (n=20)	54.2±3.6	9(45%)/11(55%)	-	-
Group 1 (n=51)	54.2±4.4	22(43%) /29(57%)	4-12	7.6±2.1
Group 2 (n=45)	52.3±5.3	21(47%) /(53%)	More than 12	19.4±4.5

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Statistical analysis

The data were processed using Microsoft Excel 2016, R-Studio Version 1.1.383. Identification of the nature of data distribution was performed using the Shapiro-Wilk test. The arithmetic mean (M) and standard deviation (m) were determined for descriptive statistics of data with normal distribution. Median, first and third quantiles (Me [1st Qu; 3st Qu]) were determined for non-normal distribution. The Kruskal-Wallis test was used to compare three groups of unrelated continuous variables followed by application of the two-sample Wilcoxon rank-sum test. Pearson's x-square test (χ^2), Fisher's exact test (F) were used to compare groups of independent nominal variables. The established level of statistical significance was $p<0.05$.

Ethical review. The study protocol was approved by the Ethical Committee of the Saratov State Medical University named after V. I. Razumovsky.

Results

A survey of patients who had suffered COVID-19 revealed complaints of increased fatigue, decreased tolerance to physical activity that persisted after the infection. Examination of patients revealed no differences in groups by sex and age (Table 2).

Physical examination (Table 3) revealed greater values of body mass index (BMI) and waist circum-

Table 2. **Age and sex characteristics of patients examined with AH**

Characteristics of the surveyed patients	Control group n = 20	Group 1 n = 51	Group 2 n = 45	P
Age, years	54.2±4.59	55[48.5; 63]	53[43;62]	p1-2=0.325 p1-3= 0.663 p2-3= 0.346
Gender, males/females	9 (45%) /11(55%)	22(43.1%)/ 29(56.9%)	21 (46.7%)/ 24(53.3%)	Comparison of 3 groups (Fisher's test). p = 0.9414 Pairwise comparison of groups p1-2 = 0.887 p1-3 =1 p2-3 = 1

Note. * — parameters have statistically significant differences with the control group; ** — there are statistically significant differences between the first and second groups.

Table 3. **Results of clinical examination of the groups with AH**

Parameters	Group 1 n = 51	Group 2 n = 45	Control group n = 20	p
BMI, kg/m^2	29.21±4.49	29.26±4.85	24.89±3.59*.**	p1-2= 0.959 p1-3= 0.0001 p2-3= 0.001
Waist circumference, cm	94.37±9.84	95.84±11.1	87.37±8.28*	p1-2= 0.496 p1-3= 0.004 p2-3= 0.366
HR, bpm	79.53±8.17	74.51±9.40*	72.7±6.31*.**	p1-2 = 0.022 p1-3<0.00001 p2-3=0.0004
SBP, mmHg	139.6±13.0	131[121;145]*	119.3±15.47*	p1-2=0.036 p1-3= <0.00001 p2-3=0.433
DBP, mmHg	84.45±10.13	81.29±11.24	71.1±5.53*.**	p1-2= 0.153 p1-3<0.00001 p2-3<0.00001
Creatinine, μmol/L	84.82±6.22	80.98±8.47*	79±8.82	p1-2= 0.014 p1-3= 0.076 p2-3= 0.404
Low-density lipoproteins, mmol/l	2.3[1.8; 3.0]	2.1[1.7; 2.6]	2.02±0.28	p1-2= 0.466 p1-3= 0.132 p2-3= 0.336
Uric acid, μmol/l	360.9±86.97	334[313;390]	314.6±48.71	p1-2= 0.223 p1-3= 0.062 p2-3= 0.116
Glucose, mmol/l	5.4[4.95; 5.9]	5.2[4.9; 5.3]	5.12±0.54	p1-2= 0.129 p1-3= 0.054 p2-3= 0.988

Table 3 continuation

Parameters	Group 1 n = 51	Group 2 n = 45	Control group n = 20	p
Left ventricle (LV) myocardial mass index, g/m^2	99.81±11.90	97.07±15.43	98.27±12.56	p1-2= 0.338 p1-3= 0.163 p2-3= 0.320
LV end-diastolic dimension, mm	4.93±0.33	4.85±0.31	4.83±0.29	p1-2= 0.218 p1-3= 0.173 p2-3= 0.129
Left atrium size, mm	4[3.71; 4.14]	3.97±0.26	3.89±0.32	p1-2= 0.874 p1-3= 0.743 p2-3= 0.692

Note. *— parameters have statistically significant differences with group 1; ** — parameters have statistically significant differences with group 2.

ference in patients with COVID-19 than in the control group. Obesity was also more frequent in these groups (p = 0.032; χ^2= 6.857; p1-2 = 0.719; p1-3 = 0.029; p2-3 = 0.013).

Heart rate (HR) in the COVID-19 survivor groups was higher than in the control group. HR was highest in patients during the period of ongoing symptomatic COVID-19 (p1-3 <0.00001). Systolic blood pressure (SBP) in this group also exceeded values in control and second groups (p1-2=0.036; p1-3= <0.00001). Diastolic blood pressure (DBP) in the COVID-19 groups exceeded the control values (p1-3<0.00001; p2-3<0.00001).

Laboratory examination revealed a slightly elevated creatinine level in group 1. EchoCG parameters in the compared groups did not differ significantly.

Table 4. **Results of the study of polymorphism of genes encoding RAAS components**

Gene name	Genotypes	Group 1 n = 51	Group 2 n = 45	Control group n = 20	P		
		Abs. number/%	Abs. number /%	Abs. number /%	Pairwise comparison by genotype	Pairwise comparison of groups	A 3-group analysis
AGT704	TT	23*/45.1	25/55.6	15*/75	p1-2 = 0.413 p1-3 = 0.033 p2-3 = 0.173	P1-2 = 0.434 p1-3 = 0.064 p2-3 = 0.401	0,194
	TC	16/31.4	14/31.1	4/20	p1-2 = 1 p1-3 = 0.394 p2-3 = 0.549		
	CC	12/23.5	6/13.3	1/5	p1-2 = 0.295 p1-3 = 0.092 p2-3 = 0.422		
AGT521	CC	38/74.5	26/57.8	10/50	p1-2 = 0.189 p1-3 = 0.055 p2-3 = 0.588	p1-2 = 0.471 p1-3 = 0.020 p2-3 = 0.102	0,059
	CT	13/25.5	18/40.0	9/45	p1-2 = 0.192 p1-3 = 0.065 p2-3 = 0.788		
	TT	0/0	1/2.2	1/5	p1-2 = 0.468 p1-3= 0.5621 p2-3 = 0.436		
AGTR1	AA	37/72.5	35/77.8	17/85	p1-2 = 0.639 p1-3 = 0.361 p2-3 = 0.738	p1-2 = 0.737 p1-3 = 0.185 p2-3 = 0.121	0,3253
	AC	11/21.6	9/20	1/5	p1-2 = 1 p1-3 = 0.158 p2-3 = 0.156		
	CC	3/5.9	1/2.2	2/10	p1-2 = 0.620 p1-3 =1 p2-3 = 0.524		
AGTR2	AA	20/39.2	20/44.4	9/45	p1-2 = 0.680 p1-3 = 0.789 p2-3 =1	p1-2 = 0.114 p1-3 = 0.858 p2-3 = 0.428	0,29
	GA	26/51.0	25/55.6	10/50	p1-2 = 0.686 p1-3 =1 p2-3 = 0.789		

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Table 4 continuation

Gene name	Genotypes	Group 1 n = 51	Group 2 n = 45	Control group n = 20	P		
		Abs. number/%	Abs. number /%	Abs. number /%	Pairwise comparison by genotype	Pairwise comparison of groups	A 3-group analysis
	GG	5/9.8	0/0	1/5	p1-2 = 0.058 p1-3 = 0.668 p2-3 = 0.077		
CYP11B2	CC	23/46.1	27/60	10/50	p1-2= 0.681 p1-3= 0.794 p2-3 = 0.588	p1-2= 0.307 p1-3 = 0.741 p2-3 = 0.601	0,549
	CT	25/49.0	17/37.8	10/50	p1-2 = 0.306 p1-3 =1 p2-3 = 0.419		
	TT	3/5.9	1/2.2	0/0	p1-2 = 0.620 p1-3 = 0.553 p2-3 = 1		

Note. *— parameters have statistically significant differences with group 1; ** — parameters have statistically significant differences with group 2.

The results of the study of genes polymorphism encoding RAAS components are presented in Table 4.

Significant differences were obtained when comparing AGT 704 gene genotypes in COVID-19 and non-COVID-19 subjects (p1-3 = 0.033). Carriage of the homozygous TT genotype was less frequent in COVID-19 survivors (p=0.005). There was a weak negative association of BMI with TT genotype AGT704 (r=–0.30; p=0.001), SBP (r=–0.42; p=0.0001) and DBP (r=–0.36; p=0.0001). There was a weak correlation of glomerular filtration rate (r=0.42; p=0.0001) with this genotype.

Discussion

Lack of BP control is associated with adverse cardiovascular events in the short term [1]. To date, the specific impact of severe COVID-19 on BP during and after the acute phase of infection has been established [5–7]. In our data, even 12 weeks after moderate to mild COVID-19, BP destabilization persisted in patients with pre-existing hypertension.

A population-based Hamburg Health Study including 432 patients after mild COVID-19 with at least 4 months of follow-up after COVID-19 found a significant increase in DBP in this category (+4.7 mmHg, 95 % CI 3.97–5.7, p<0.001) [5]. For SBP, a trend toward higher values was found (+1.4 mmHg, 95 % CI 0.4–3.2, p= 0.120).

A retrospective cohort study of patients after COVID-19 who were admitted to the Washington University Cardiology Clinic with cardiovascular symptoms found elevations in both SBP and DBP [8]. However, the time factor after COVID-19 was not taken into account when examining the patients. Based on the results of our study, we found that even 12 weeks after COVID-19, patients still had elevated DBP levels (p1-3<0.00001; p2-3<0.00001). Elevated SBP was recorded only in the ongoing COVID-19 group (p1-2=0.036; p1-3=<0.00001). Maximum HR values were noted in the same group (p1-3<0.00001).

A search for risk factors for PCS has revealed a higher prevalence of its occurrence in women [9–11]. However, our study showed no differences in groups by gender. According to a study that included medical records of more than 1 million COVID-19 patients, obese, overweight patients had a higher risk of developing PCS [9, 10]. In our study, abdominal obesity was also detected more frequently in COVID-19 survivors compared to non-infected patients (p = 0.032, χ^2= 6.857).

BP elevation after COVID-19 is presumably associated with tissue RAAS activation. Disruption of ACE upregulation by the introduction of SARS-CoV-2, causes vasoconstriction, inflammation and cellular damage [12]. There is growing evidence supporting the persistence of endothelial dysfunction after COVID-19 [14, 15] as a possible mechanism for the occurrence of the "cardiovascular" phenotype of PCS [8]. However, the etiology of PCS remains unknown to date [13].

In 2023, a new paradigm of PCS was proposed with the inclusion of biological, psychological, and social factors integrated in complex relationships [14]. In this regard, the study of gene dysregulation as part of the biological component of the syndrome is of particular importance. On the other hand, the genetic architecture of BP includes monogenic mutations and genetic polymorphisms that contribute to the occurrence of AH [15]. Considering the fact of involvement of RAAS components in COVID-19, we can assume an association of the occurrence of uncon-

trolled AH in PCS with polymorphisms of genes of the above system. Studies confirm the association of AGT level with the severity of COVID-19 [16].

Information on the role of polymorphisms of genes encoding AGT in the development of PCS is currently lacking. We identified an association of BP level with the C allele of the AGT gene (T704C) in patients with the ongoing symptomatic COVID-19. In the phase of ongoing symptomatic COVID-19, carrying the homozygous TT genotype of the AGT gene 704T>C, rs699 was less frequent (p=0.005) than in the control group. There was also a weak negative association of TT genotype AGT704 with BMI (r=–0.30, p=0.001), SBP (r=–0.42, p=0.0001) and DBP (r=–0.36, p=0.0001).

Conclusion

To date, the association between COVID-19 and AH remains poorly understood. According to the results of our study, uncontrolled AH was a long-term effect of mild to moderate COVID-19. Analysis of time aspects revealed the greatest persistence of destabilization in DBP values. Identification of the association of BP with AGT gene polymorphism in PCS will provide an opportunity to initiate personalized treatment and develop prevention strategies.

Conflict of interests: none declared.

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