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Clinical Status of Patients with Coronary Artery Disease Post COVID-19

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Abstract---*The main goal of our study was to identify the activity of cardiac dysfunction based on the analysis of the main cardiological methods of research, such as ECG, echocardiography, 24-hour ECG monitoring in conjunction with laboratory parameters in patients with coronary artery disease (CAD) who underwent mild and moderate COVID-19, without signs of residual effects of lung tissue damage (fibrotization). 52 patients with coronary artery disease were examined, which were divided into 2 groups depending on the past infection in history: 1 group without COVID-19 in history (n=26) (based on history and results of SARS-CoV-2 antibody titer), 2 a group with a history of COVID-19 (n=26), confirmed by relevant documents (tests), but without oxygen therapy and steroids, in order to avoid the influence of a serious illness and drug exposure. Conclusions: dynamic monitoring of hemostasis parameters after the hospital stage in patients with CAD should be carried out in order to prevent adverse cardiovascular outcomes, even with a history of moderate and mild coronavirus infection. One of the aspects of therapeutic rehabilitation in the post-COVID period in patients with IHD is the use of vitamin D preparations.*
Keywords---*artery disease, clinical status, COVID-19, lung tissue damage, SARS-CoV-2*

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Introduction

Data on the long-term results of COVID-19 treatment began to appear in the literature in the form of clinical cases and in a small sample of patients, however, there is evidence of the development of adverse cardiovascular outcomes after stopping an acute process in the midst of the COVID-19 clinic and during the rehabilitation period (Akhmerov & Marbán, 2020). One of the main reasons for the severe course of cardiovascular diseases (CVD) and the development of complications is also a violation of the hemostasis system (Raxmatillaevna & Karimovich, 2021). Short and long-term prognosis remains an understudied aspect in patients with coronary heart disease (CHD) who have undergone COVID-19. There are enough studies in the literature that present the role of inflammatory mediators in the pathogenesis of CVD (Lubrano & Balzan, 2015; Pasceri et al., 2000; Siti et al., 2015). A pro-inflammatory effect of C-reactive protein (CRP) on the vascular wall has been shown, which increases the formation of other inflammatory mediators, adhesion molecules on the endothelial surface (Lubrano & Balzan, 2015; Siti et al., 2015). Under conditions of SARS-CoV-2 infection, the level of CRP closely correlates with the severity of the course, the volume of affected lung tissue according to computed tomography (CT), progression, and prognosis of COVID-19 (Chikina et al., 2020). The extent to which these changes are expressed in the post-COVID period in patients with CVD is also a topical issue.

In patients with CVD, special vigilance should be exercised against the background of COVID-19 infection, paying equal attention not only to the treatment of the infection but also to the control of risk factors for cardiovascular disease. CVD patients with COVID-19 are at high risk of destabilization due to a combination of stressors, systemic infection, and inflammation. Early studies have shown that people with comorbid conditions such as hypertension, diabetes mellitus suffer increased morbidity and mortality from COVID-19 (Chen et al., 2020; Wang et al., 2020). At the same time, mortality from COVID-19 increases up to five times in people with CVD (Wu & McGoogan, 2020). Clinical and laboratory symptoms of heart damage are detected with COVID-19 quite often; some patients reported chest pain and palpitations even in the absence of typical respiratory symptoms (Shchikota et al., 2020). All this requires maximum cardiological vigilance in the treatment of patients with COVID-19, long-term observation, and timely use of various diagnostic methods in order to prevent early and late cardiovascular complications (CVC).

Materials and Methods

The study was conducted on the basis of the Republican Specialized Scientific and Practical Center for Cardiology. 52 patients with coronary artery disease were examined, which were divided into 2 groups depending on the past infection in history: 1 group without COVID-19 in history (n=26) (based on history and results of SARS-CoV-2 antibody titer), 2 a group with a history of COVID-19 (n=26), confirmed by relevant documents (tests), but without oxygen therapy and steroids, in order to avoid the influence of a serious illness and drug exposure (Sattar et al., 2020; Todurov et al., 2021). The main goal of our study was to identify the activity of cardiac dysfunction based on the analysis of the main cardiological research methods, since electrocardiography (ECG), echocardiography (ECHOCG), 24-hour ECG monitoring in conjunction with laboratory parameters in patients with coronary artery disease who underwent mild and moderate COVID-19, without signs of residual effects of lung tissue damage (fibrotization). The period from the acute period of COVID-19 ranged from 2 weeks to 3 months. All subjects had anginal pain, accompanied by dynamic ECG changes, and there were no manifestations of respiratory failure. The exclusion criterion was a history of diabetes mellitus.

In order to identify the features of the course of coronary artery disease in the examined, an analysis of the clinical status was carried out, including the main indicators of ECG and hemodynamics (Table 1)

Table 1
Clinical status of CAD patients with and without COVID-19 in history

Indicators	1 group (n=26)		2 group (n=26)		
	M	m	M	m	p
Age, years	60,15	1,64	58,42	1,68	0,464
BMI	27,12	0,60	30,61	0,81	0,001*
Obesity experience (years)	10,94	0,67	12,35	0,99	0,247
AG experience (years)	7,78	0,65	9,70	0,87	0,084
CVD experience (years)	6,32	0,79	7,92	1,03	0,223

SpO2, %	96,04	0,26	95,85	0,25	0,596
SBP, mmHg	131,15	4,24	130,77	4,61	0,951
DBP, mmHg	83,08	1,82	82,31	1,50	0,746
HR on ECG	71,27	2,45	73,08	2,74	0,625
P, ms	0,10	0,00	0,10	0,00	1,000
P-Q, ms	0,15	0,00	0,16	0,00	0,611
QTs, ms	0,35	0,01	0,37	0,01	0,005*

Note: *-significance of differences, $p<0.05$

Abbreviations: BMI-body mass index; AG-arterial hypertension; CVD-cardiovascular disease; SBP-systolic blood pressure; DBP - diastolic blood pressure, HR - heart rate.

In the age aspect, the patients of the studied groups did not differ. The mean age was 60.15±1.64 & 58.42±1.68 years in the 1st and 2nd groups, respectively. As can be seen from the table, a significant difference was noted in the body mass index, which was higher in patients with a history of coronavirus infection. When deciphering the main ECG parameters, lengthening of the corrected Q-T interval (Q-Tc) was noted in patients of group 2, although the average values of this interval were within the reference value (Heusch et al., 2014; Mitrani et al., 2020). Cardiological characteristics of patients are presented in Table 2. In both groups, more than 80% had a history of arterial hypertension, however, at the time of admission, high levels of SBP and DBP were recorded in single patients. The average levels of SBP and DBP in the examined groups did not differ (Table 1), although a more detailed analysis showed that in patients who had a moderate course of COVID-19, the minimum level of SBP was 140 mm Hg.

Table 2
Cardiac characteristics of patients

Parameter n/%	1 group (n=26)	2 group (n=26)	p
AMI / with Q wave/ without Q wave	6 (23,1%) / 2(7,7%) / 4 (15,4%)	1 (3,8%)/-/ 1(3,8%)	0,009*
History of stenting	2 (7,7%)	1 (3,8%)	>0,05*
Cardiac arrhythmias, according to ECG	9 (34,6%)	3 (11,5%)	0,001*

Note: *-significance of differences $p<0.05$

Abbreviations: AMI-acute myocardial infarction

6 patients (23.1%) who had undergone COVID-19 were hospitalized with the diagnosis of AMI, in group 1 (without COVID-19) only in one case AMI was registered. When evaluating the main indicators of ECHOCG, no significant differences were found in the studied groups (Table 3). We can only note a trend towards a decrease in SV in patients who underwent COVID-19 (n.d.).

Table 3
EchoCG parameters in the studied groups

Parameters	1 group (n=26)		2 group (n=26)		
	M	m	M	m	p
BSA	1,97	0,03	1,98	0,03	0,904
TPWLV sm	1,00	0,02	0,98	0,02	0,325
TIVS mm	1,02	0,02	1,01	0,02	0,750
MMLV, g	188,57	7,26	187,27	7,63	0,902
IMMLV, g/sm2	95,98	3,71	93,15	3,46	0,579
SV, ml	66,88	2,32	63,26	3,17	0,360
EF, %	59,17	0,77	58,89	1,16	0,840
EDS LV, sm	5,01	0,09	5,05	0,10	0,728
EDV LV, ml	109,50	6,55	109,04	6,77	0,961
IEDV LV	55,30	3,12	54,51	3,04	0,858
ESI LV, sm	3,55	0,11	3,56	0,12	0,959
ESV, ml	45,71	4,12	46,10	4,22	0,947
LA, sm width	3,46	0,09	3,46	0,09	1,000
LA, sm length	4,62	0,09	4,52	0,10	0,479

Square	16,13	0,72	15,79	0,74	0,744
Ao, sm	3,10	0,12	3,11	0,12	0,982
RWT LV, unit	0,41	0,01	0,40	0,01	0,517
RV ave.	2,75	0,08	2,73	0,08	0,894
RV base	3,26	0,07	3,25	0,07	0,970
RA sm width	3,18	0,07	3,22	0,07	0,737
RA sm length	4,39	0,07	4,37	0,07	0,831
Wave E [m/s]	0,66	0,03	0,66	0,04	0,963
Wave A [m/s]	0,78	0,03	0,76	0,03	0,724
E/A	0,87	0,06	0,91	0,06	0,709
SP PA	25,50	1,46	24,31	1,51	0,572

Abbreviations: BSA - body surface area; TPWLV-thickness of the posterior wall of the left ventricle; TIVS-thickness of the interventricular septum; MMLV - mass of the myocardium of the left ventricle; IMMLV - MMLV index; SV - stroke volume; EF - ejection fraction; EDS LV- end-diastolic size of the left ventricle; EDV - end-diastolic volume; IEDV - end-diastolic volume index; ESI – end systolic size index; ESV - end systolic volume; LA - left atrium; Ao - aorta; RWT - relative wall thickness; RV- right ventricle; RA- right atrium; SP PA - systolic pressure in the pulmonary artery.

More convincing differences in cardiological parameters between the groups were obtained by us in a detailed analysis of the data of 24-hour ECG monitoring and heart rate variability. Supraventricular arrhythmias, in the form of supraventricular extrasystoles and running supraventricular tachycardias, were more frequent manifestations of arrhythmia in patients with COVID-19 than in patients without a history of COVID-19 (80.7% vs. 46.0%, $p<0.05$), as well as ventricular arrhythmias, in the form of ventricular extrasystoles in the second group (42.3%) versus 15.3%, ($p<0.05$). Analysis of the diurnal dynamics of QTs (Figure 1) showed higher values of the minimum (413 vs. 381 ms, $p<0.01$), mean (457 vs. $p<0.01$) in patients of group 2, compared with group 1. Hourly analysis showed that group 2 patients had consistently longer QTs values than group 1 throughout the day (Thomas et al., 1988; Allen et al., 1978).

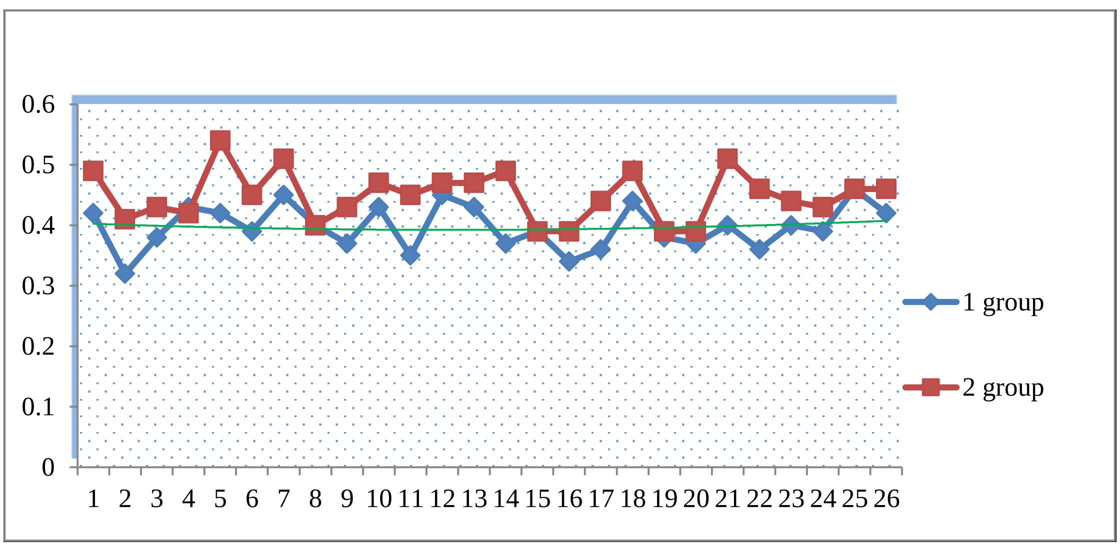

Figure 1. Average QTs parameters in examined patients based on the results of daily ECG monitoring

In patients after coronavirus infection, hyperactivation of the sympathetic nervous system (SNS) was observed, expressed in an increase in LF/HF up to 2.8 rel. units, against the background of a decrease in the activity of the parasympathetic nervous system (PSNS) (decrease in SDNNi to 38.6 ms, $p<0,01$) with a persistent disruption of circadian interactions of these parts of the autonomic nervous system, manifested in an increase in sympathetic influences on the heart rhythm and an insufficient increase in PSNS activity at night (CI LF/HF 1.1 rel. units) (Table 4). The low circadian index (CI) in the second group may have been due to the fact that patients after coronavirus infection experienced hyperactivation of the SNS at night (Scoccia et al., 2021; Angeli et al., 2021)

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Table 4
Indicators of heart rate variability in the examined patients

Parameters	1 group (n=26)	2 group (n=26)
SDNNi, ms	45,2±0,97	38,6±0,85*
LF/HF	2,1	2,8*
CI LF/HF	1,6	1,1*

Note: *- significance of differences p<0.05
Abbreviation: LF/HF - Low Frequency/High Frequency ratio, CI - circadian index

Analysis of hemostasis parameters in the patients with coronary artery disease examined by us revealed a significant difference in the PTI rate of 93.8% versus 97.5% in groups 1 and 2, respectively (p=0.041) (Table 5).

Table 5
Indicators of the hemostasis system and acute-phase blood proteins

Show	1 group (n=26)		2 group (n=26)		
	M	m	M	m	p
APTT sec. - [23,4-36,2]	26,94	0,41	26,96	0,38	0,968
INR - [0,85-1,15]	1,04	0,02	1,04	0,01	0,910
Fibrinogen g/l - [1,8-3,5]	2,53	0,08	2,75	0,11	0,124
PTI % - [70-100]	93,78	1,34	97,52	1,17	0,041*
PTR sec. - [13-18]	13,92	0,17	13,89	0,14	0,903
Prothrombin ratio [0,9-1,3]	1,02	0,01	1,02	0,01	0,872
CRP mg/l - [до 5,0-(отр.)]	2,61	0,12	4,08	0,31	0,000*

Note: [norm]; *-significance of differences p<0.05
Abbreviations: APTT-activated partial thrombin time; INR - international normalized ratio; PTI - prothrombin index; PTR - prothrombin ratio; CRP - C-reactive protein

It should be noted that in patients with increased body weight, a shortening of the PTT by more than 12.7% correlated with a higher level of functioning of the sympathetic nervous system (LF/HF>2.1 rel.u) according to the data of daily ECG monitoring. In addition, patients with an increase in daily LF/HF>2.1 relative units had higher (by 15.2%) hematocrit values. An inflammation marker, CRP, showed significant differences between the study groups, its concentration in group 2 was almost 1.5 times higher than in patients without a history of COVID-19 (p=0.000). In patients who recovered from COVID-19, indicators of ALT, AST, uric acid (p>0.1, n.d.), glomerular filtration rate (GFR), and total bilirubin (p>0.1, n.d.) had only an upward trend, but the level of total protein was statistically significant (p<0.001). Meanwhile, the levels of urea and creatinine in the blood serum also showed a slight difference between the study groups (p>0.1, n.d.) (Figure 2).

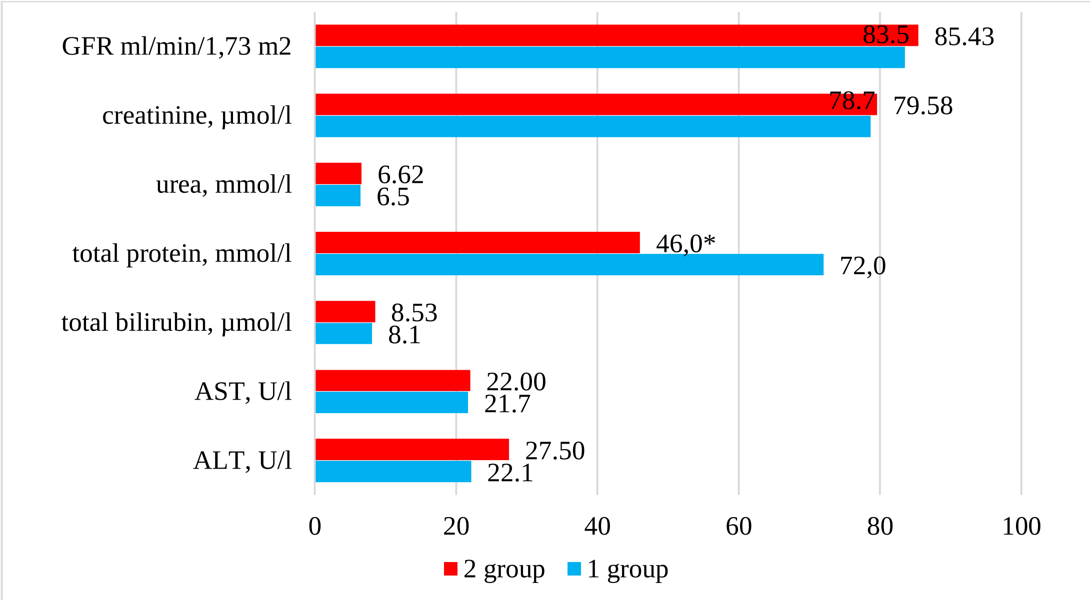

Figure 2. Biochemical parameters of the examined groups
*-significance of differences p<0.05

The level of vitamin D was significantly reduced in patients of group 2 (p=0.000). We found an inverse relationship between the level of vitamin D and the postponed period of COVID-19, i.e. the longer the period from the height of the disease, the higher the level of vitamin D in the blood, although it would be logical to assume lower levels in the initial periods of the post-COVID period.

Discussion

The obtained changes in the hemostasis system confirm the concept of the relationship between inflammation and thrombosis, the so-called “immunothrombosis”, associated with an increase in the activation of the blood coagulation system, against the background of severe inflammation in the midst of COVID-19 and during the decline in the activity of the process (Yavelov & Drapkina, 2020). What “dictates” further monitoring of hemostasis parameters in patients who have undergone COVID-19 in the long-term period. The concentration of CRP in patients with a history of COVID-19 was almost 1.5 times higher than in patients without a history of COVID-19 (p = 0.000), which indicates the presence of a persistent long-term residual inflammatory process even with moderate and mild coronavirus infection.

According to the results of daily ECG monitoring, the low circadian index (CI) in the second group may have been due to the fact that patients after coronavirus infection experienced hyperactivation of the SNS at night. COVID-19 leads to changes in hemostasis and contributes to hyperactivation of the SNS, a "vicious circle" is created, and both processes exacerbate each other. As a result, the thrombotic process and the risk of cardiovascular events increase. The severity of the process was associated with overweight, which may be the reason for frequent CVCs in this category of people with COVID-19. The revealed changes in vitamin D values can be explained by low levels of vitamin D in the acute period of the disease, as a result of infection, and a tendency to increase in the post-COVID period as a result of the restoration of the immune system. The foregoing dictates the need for the use of vitamin D preparations during the rehabilitation period (Gupta et al., 2021; Jang et al., 1994; Hussin et al., 2021).

Conclusions

- Dynamic monitoring of hemostasis parameters after the hospital stage in patients with CAD should be carried out in order to prevent adverse cardiovascular outcomes, even with a history of moderate and mild coronavirus infection.
- One of the aspects of therapeutic rehabilitation in the post-COVID period in patients with CAD is the use of vitamin D preparations.

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