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FEATURES OF THE COURSE OF ISCHEMIC HEART DISEASE IN PATIENTS WITH COVID-19

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic has been going on for more than two years and is significantly affecting routine clinical practice. Despite the numerous publications on heart damage in the acutephase of COVID-19, there is not enough data regarding the dynamics of cardiovascular system condition in coronary artery disease (CAD) patients after the infection caused by SARS-CoV-2. The infl uence of the long-term consequences of the disease on cardiovascular system condition of patients who have had infection requires careful study.
Goal. To assess the clinical and laboratory picture and coronary lesion nature in CAD patients with mild or moderate course of COVID-19 infection after at least 12 weeks.
Materials and methods. The analysis of clinical, laboratory parameters and coronary angiography of 118 CAD patients aged 46–67 years (mean age 60.2 ± 6.1 years) after a serologically confi rmed SARS-CoV-2 infection at the lapse of 12 weeks was carried out. The patients were divided into 2 groups: group 1 included 60 patients with a mild COVID-19, group 2 included 58 patients with a moderate COVID-19 course.
Results. CAD patients with a moderate course of COVID-19 in the acute period had higher values of office blood pressure, higher incidence of uncontrolled arterial hypertension, major multivessel lesions of coronary arteries and lesions of the main vessels than CAD patients with mild COVID-19. When comparing echocardiographic parameters in patients with moderate COVID-19, the lower parameters of the left ventricular ejection fraction were found which is quite consistent with the higher NT-proBNP values in these patients.
Conclusion. CAD patients, who have had moderate COVID-19 in the acute phase of infectious process, constitute a special risk group for a subsequent more severe course of the underlying disease.

Keywords: COVID-19, post-COVID syndrome, coronary artery disease, coronary angiography.

INTRODUCTION

The consequences of a novel coronavirus infection are one of the main challenges to the world health care. Currently, data are accumulating which show a high incidence of cardiorespiratory symptoms and an increased risk of developing and decompensating cardiovascular diseases

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(CVD) inт patients in the long-term period of SARS-CoV-2 infection [1, 2].Post-COVID syndrome, also known as long COVID, is a multisystem symptom complex characterized by the presence of symptoms that have developed more than 12 weeks after the onset of COVID-19, and are not associated with other diseases [3, 4].

The relevance of studying post-COVID syndrome is determined by the fact that there are more and more people with this pathology and they have a very mosaic clinical picture [5]. It is no coincidence that the WHO introduced a special U09 code in the ICD- 10 – Post COVID-19 condition [6]. The syndrome acquires special clinical characteristics in patients with verified CVD, since their prognosis may worsen in comparison with COVID-19 patients without cardiovascular pathology. This statement is confirmed by an increase in the number of patients seeking treatment for blood pressure (BP) destabilization and coronary artery disease (CAD), as well as an increase in cardiovascular mortality [7, 8]. According to the national ACTIV SARS-CoV-2 registry, 79.8% of patients with COVID-19 had comorbidities, most often cardiovascular: arterial hypertension (AH) – 55.4%, obesity – 35.5%, CAD – 20.6%, type 2 diabetes mellitus – 17.5%, chronic heart failure (CHF) – 16.3%. Patients with *de novo* CVD due to SARS-CoV-2 infection had a more severe form of COVID-19, were older, and were more likely to be obese compared with patients without newly diagnosed diseases [9]. A retrospective Great Britain cohort study analyzed the health status of nearly 48 000 people hospitalized for COVID-19. The evaluation was carried out within 140 days after discharge from the hospital in comparison with patients hospitalized for other reasons (control), similar in demographic and clinical characteristics.

It turned out that the risk of re-hospitalization and death within a year after COVID-19 was 3.5 and 7.7 times higher, respectively, than in the control group. Per 1000 people discharged from the hospital after COVID-19, 66 new cases of severe cardiovascular complications were diagnosed during the year [10]. Worsening of the course of chronic CVD may be due to their decompensation as a result of a mismatch between increased metabolic requirements and a decrease in cardiac reserve, a greater likelihood of atherosclerotic plaque rupture in virus induced inflammation, a high risk of thrombotic complications, including stent thrombosis due to the procoagulant effect of inflammation [11–13,] a significant impairment of blood coagulation parameters [14], which is due to the multifactorial pathophysiological nature of the disease [15]. Despite the numerous publications on heart damage in the acute phase of COVID-19, there are insufficiently systematized data regarding the dynamics of the condition in CAD patients during the post- COVID period, and there are no clinical guidelines for the management of such patients.

AIM OF THE RESEARCH

To evaluate the clinical and laboratory picture and the nature of coronary lesion in CAD patients with mild or moderate COVID-19 infection after more than 12 weeks from its onset.

MATERIALS AND METHODS

In order to assess the clinical, laboratory parameters and the state of the coronary artery bed of CAD patients who had serologically confirmed COVID-19, more than 12 weeks ago, 118

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patients aged 46–67 years (mean age 60.2 ± 6.1 years; 77 men and 41 women) with classes I–III stable angina were examined on the basis of the Novosibirsk Regional Clinical Cardiology Dispensary. The diagnosis of CAD was made taking into account the clinical manifestations (anginal pain, effectiveness of nitrates) in combination with one or more of the following characteristics: verified acute myocardial infarction (MI) more than 6 months ago, positive stress test; myocardial ischemia confirmed by Holter monitoring; coronary lesion detected by coronary angiography.

All patients signed a informed consent to participate in the study in accordance with the International Ethical Guidelines of the WHO (Geneva, 1993).

The severity of COVID-19 in the acute period was determined according to the Temporary Guidelines for the Prevention, Diagnosis and Treatment of a Novel Coronavirus Infection (Version 15) dated February 22, 2022 [16]. Mild severity corresponded to fever up to 38°C, coughing, weakness, sore throat and the absence of criteria for moderate and severeь course. Moderate course was diagnosed in fever up 38°C; respiration rate > 22 per 1 min; shortness of breath during physical exertion; changes in computed tomography (CT) (radiography), typical of virus-related lesion; SpO2 < 95%; serum C-reactive protein (CRP) > 10 mg/l; PaO2/FiO2 ≤ 300 mm Hg; impaired consciousness, systolic blood pressure (SBP) < 90 mm Hg or diastolic blood pressure (DBP) < 60 mm Hg, diuresis less than 20 ml/h. The examined patients were divided into two groups. Group 1 included 60 patients with mild COVID-19 in the acute phase (mean age 56.3 ± 6.6 years), group 2 included 58 patients with moderate COVID-19 in the acute phase (mean age 60.9 ± 5.6 years). The history of CAD in group 1 was 4.2 ± 0.5 years, in group 2 it was 3.9 ± 0.6 years ($p > 0.05$). Previously, 17 (28.3%) patients of the 1st group and 14 (24.0%) patients of the 2nd group underwent coronary angioplasty. Exclusion criteria were acute coronary syndrome or verified MI < 6 months ago, post-infarction left ventricular aneurysm, any form of atrial fibrillation, severe heart disease, CHF with reduced ejection fraction (EF), morbid obesity, implanted cardiac pacemaker, severe anemia, severe pulmonary hypertension, oncological diseases and other clinically significant comorbidities. Laboratory examination, in addition to conventional tests, included the determination of the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) by enzyme immunoassay and D-dimer. Clinical diagnostics included exercise stress test (treadmill test) or myocardial scintigraphy and cardiac ultrasound using an Acuson Aspen ultrasound machine (USA). All patients underwent diagnostic coronary angiography according to M. Judkins (1967) using a Philips INTEGRIS BH 3000angiographic system. Statistical data processing was carried out using jamovi 2.2.5 and MS Excel. The methods of parametric and non-parametric statistics were used. The significance of differences between the qualitative indicators of the compared groups was determined using the $\chi 2$ test. Verification of the normality of the distribution of the quantitative indicators was carried out using the Kolmogorov-Smirnov test. In case of nonnormal distribution, the non-parametric Mann- Whitney *U*-test was used. To detect differences between quantitative variables, the distribution of which did not diff er from normal, Student's *t*-test was used for independent samples. The significance of the difference coefficients was taken at a value of $p < 0.05$.

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RESULTS

The duration of COVID-19 infection was 3–15 months before the inclusion of patients in the study. Thirty three (56.8%) patients of the 2nd group were hospitalized; patients of the 1st group were treated on an outpatient basis.

Arterial hypertension occurred in the vast majority ьof patients of group 1 (57 people – 95.0%) and group 2 (57 people – 98.2%) groups. The history of AH was 12.3 ± 9.3 and 15.5 ± 9.7 years in groups 1 and 2, respectively. Controlled AH occurred in 35 (58.0%) patients in group 1 and in 28 (48.0%) patients in group 2. Uncontrolled AH occurred signifycantly more often in patients of group 2 – 29

(60.3%) versus 22 (36.6%) in group 1 ($p < 0.05$). SBP was significantly higher in the group with moderate COVID-19. The body mass index (BMI) in patients of group 1 was 28.8 ± 4.9 kg/m2, in patients of group 2 it was 31.4 ± 4.2 kg/m2 ($p < 0.05$), however, the incidence of obesity in the groups did not differ significantly. The clinical characteristics of the examined patients are presented in In the post-COVID period, in 21 (35.0%) patients of the 1st group and in 22 (37.9%) patients of the 2ndgroup, the course of stable CAD worsened, which was manifested by a decrease in exercise tolerance, an increase in frequency and severity of anginal attacks, and an increase in the nitrates requirements. Effort angina was diagnosed for the fi rst time in the post- COVID period in 10 (16.6%) patients of group 1 and in 11 (18.9%) patients of group 2. When analyzing the course of CAD in the post- COVID period, eff ort angina class III was diagnosed in 29 (50.0%) patients of the 2nd group and in 17 (28.3%) patients of the 1st group ($p < 0.05$). In four patients in each group, microvascular angina was verified. Prior to COVID-19, 15 (25.0%) patients of group 1 and 17 (29.3%) patients of group 2 had MI. In the 1stgroup, 15 (25.0%) patients had type 2 diabetes mellitus, and 6 (10.0%) patients had glucose intolerance (GI). Among patients of group 2, diabetes mellitus occurred in 14 (24.1%) patients, GI – in 5 (8.6%). Chronic kidney disease (CKD) was detected in all patients of both groups, while stage 3b CKD was found only in patients with a moderate course of COVID-19 (6 people – 10.3%); and stage 3a CKD was diagnosed in 19 (31.6%) patients with mild COVID-19 and in 16 (27.5%) with moderate one; finally, stage 2 CKD – in 41 (68.2%) patients in the 1st group and in 36 (62.0%) in the 2nd group. Chronic obstructive pulmonary disease and bronchial asthma occurred in 2 (3.3%) patients in group 1 and in 6 (10.3%) patients in group 2. Atherosclerotic lesions of the brachiocephalic arteries, hemodynamically insignificant, were detected in 29 (48.3%) patients of the 1st group and in 34 (58.6%) patients of the 2nd group. In all patients of the 1st group, the contractility of the left ventricle (LV) was preserved, and in 6 (10.3%) patients of the 2nd group, CHF was detected with a slightly reduced EF. Class I CHF was diagnosed in 46 (76.0%) patients of the 1st group and in 32 (55.1%) patients of the 2nd group, class 2A CHF – in 23(39%) patients of the 1st group and in 14 (23.3%) patients of the 2nd group; class 2B CHF – only in 2 (3.4%) patients of the 2nd group. In the 1st group, 55 (91.6%) patients received drug therapy for CAD and AH in the post-COVID period, in the 2nd group – 54 (93.1%) patients. Therapy included antiplatelet agents, statins, β-blockers, slow-channel calcium blockers, angiotensin-converting enzyme inhibitors, sartans, long-acting nitrates in individual combinations and dosages.

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In patients of both groups, no significant differences were found in the values of the main biochemical parameters – total cholesterol (CH), low-density lipoprotein (LDL) cholesterol, triglycerides and basal glycemia (Table 2). In the vast majority of patients, the lipid spectrum did not reach the target values.

The plasma NT-proBNP concentration in patients of both groups was beyond the reference values, but the values of NT-proBNP in patients of the 2nd group (510.6 ± 56.7 mmol/l) significantly exceeded those in patients of the 1st group (213.7 ± 87.6 mmol/l), $p < 0.005$. The levels of basal glycemia did not differ significantly between the groups (6.0 ± 1.8 mmol/l and 6.2 ± 1.9 mmol/l, respectively), the value of postprandial glycemia in patients of the 1st group (7.0 ± 1.9 mmol/l) was significantly lower than in patients of the 2nd group (7.9 ± 2.0 mmol/l). The concentration of glycated hemoglobin in patients of both groups was beyond the reference values, but did not differ significantly. The plasma fibrinogen level in patients of group 2 (5.1 ± 0.8 g/l) was significantly higher than in patients of group 1 (3.7 ± 0.8 g/l) ($p < 0.005$) (see Table 2).

When analyzing the echocardiographic data, there were no significant differences in most indicators. However, the left ventricular ejection fraction (Simpson's method) in patients of the 1st group (63.2 ± 4.8%) was significantly higher than in patients of the 2nd group (54.4 ± 3.6%) ($p < 0.05$), although its values in both groups were within the reference range.

During angiography, an analysis was made of the frequency and severity of lesions of the coronary vessels, primarily the main arteries. No lesions in coronary arteries were found in 5 (8.3%) patients of the 1st group and in 4 (6.8%) patients of the 2nd group. Hemodynamically significant lesions of the coronary arteries (>70%) occurred in (63.3%) patients of the 1st group and in 44 (75.8%) patients of the 2nd group. In patients of the 1st group, single-vessel coronary artery disease was most common (16–26.6%), two-vessel coronary artery disease occurred in 8 (13.3%) patients, and multivessel coronary artery disease occurred in 6 (10.0%) patients. In the 2ndgroup hemodynamically significant multivessel coronary artery disease was found in 10 (17.2%) patients; two-vessel coronary artery disease – in 10 (17.2%), and single-vessel – in 16 (27.5%) patients (Table 4). In patients of the 1st group, the lesions of the main trunk of the left coronary artery were not detected, while 4 (6.8%) patients of the 2nd group had the lesions of the above mentioned localization. Besides, in patients of the 1st group, compared with patients of the 2nd group, the other main arteries were less often affected (anterior interventricular diagonal, circumflex), although the significance of the differences was determined only in relation to the frequency of lesions of the right coronary artery (RCA) The frequency of in-stent restenosis after previous percutaneous coronary interventions (PCI) in the post-COVID period did not differ significantly in patients of both groups and amounted to 8 (47.0%) in group 1 and 5 (35.7%) in group 2 ($p > 0.005$). All these patients underwent reintervention.

DISCUSSION

The course of CAD in the post-COVID period has its own characteristics in patients with mild to moderate COVID-19 infection. CAD patients with a moderate course of COVID-19 had a history of significantly higher office SBP, a higher incidence of uncontrolled hypertension, and a higher class of eff ort angina compared with patients with a mild course of COVID-19. In the

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post-COVID period, the concentration of NTproBNP, as an early marker of myocardial dysfunction, in CAD patients group with the moderate course of COVID-19 was significantly higher than in CAD patients with the mild course of infection in the acute phase, although the values of NT-proBNP in both groups of patients went beyond the reference indices. Hyperfibrinogenemia is the most common marker of the acute COVID-19-associated coagulopathy, and has been found in patients hospitalized for COVID-19 [13]. We found a significantly higher plasma fibrinogen level which was beyond the reference range in CAD patients with moderate COVID-19, compared with patients who had mild COVID-19, but already in the post-COVID period. When comparing echocardiographic parameters in CAD patients who had moderate COVID-19 in the acute period, a lower left ventricular ejection fraction was found, which is consistent with their higher NTproBNP values. In the post-COVID period, in CAD patients with the moderate course of COVID-19 infection, the hemodynamically significant lesions of the coronary bed are more often detected, and the main vessels, primarily the RCA, are affected more frequently.

However, there were no significant differences in the frequency of in-stent restenosis in comparison with the mild COVID-19 convalescents.

CONCLUSION

The data obtained indicate that CAD patients, who have had moderate COVID-19 in the acute phase of the infectious process, constitute a special risk group for the subsequent more severe course of the underlying disease. It is possible that the aggravation of the course of CAD in a setting of previous coronavirus infection is associated with the addition of respiratory failure typical for this disease, fibrotic changes in lung tissue with aggravation of cardiopulmonary failure and coagulopathy. CAD patients who had COVID-19 in the long-term (post-COVID) period require special attention and timely assessment of the cardiovascular system to prevent cardiovascular complications, one of the predictors of which is the severity of the disease in the acute phase.

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