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Immune-Inflammatory Reactions of The Cardiovascular System: Antigenic Determinants in Patients After Covid-19

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ABSTRACT
The study studied the levels of autoantibodies in the cardiovascular system and their relationship not only with the previous coronavirus infection but also with clinical and laboratory parameters in patients with coronary heart disease (CHD). Damage to the coronary arteries and the clinical course of coronary artery disease were taken into account. 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 (analysis), but without oxygen therapy and steroids, to avoid the influence of a serious illness and drug exposure.\ An increase in autoantibodies to β2-GP in patients with coronary artery disease who underwent COVID-19 indicates that, despite the absence of any symptoms related to coronavirus infection, inflammation processes can persist in the body for up to 3 months, dystrophic processes in myocardium and violations of hemostasis, aggravating the severity of the course of coronary artery disease.
Keywords*: post-COVID-19, SARS-CoV-2, coronary artery disease*

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INTRODUCTION

The management of patients with cardiovascular diseases (CVD) in the context of the COVID-19 pandemic is an urgent problem of modern medicine. This is important not only in the acute period of the disease but also during the rehabilitation period because the short-term and long-term prognosis remains an insufficiently studied aspect in patients with coronary artery disease who have undergone COVID-19 [1]. Data on anti cardiac antibodies in patients with COVID-19 have begun to appear in the literature. Mortality among the examined 34 patients with severe and moderate COVID-19 was 9.3% with a hospital stay of 14 days and significantly correlated with the level of antibodies to antigens of cardiomyocytes and smooth muscles [2].

Conducting structural-functional and immunological studies of the heart with COVID-19, both at the height of the disease and during the recovery period, may indicate ongoing and latently developing dysfunctions. The detection of high titers of antibodies to the cardiovascular system (CVS) against the background of COVID-19 is important in terms of prioritizing treatment tactics.

Coagulopathy associated with COVID-19 is of particular interest because it represents multiple mechanisms of development, as in coagulopathy caused by sepsis, disseminated intravascular coagulation, hemophagocytic syndrome, thrombotic microangiopathy and antiphospholipid syndrome (APS) [3,4]. Clinically, APS is often manifested by thromboembolism, miscarriage, or illness during pregnancy, as well as other symptoms associated with APS, such as thrombocytopenia and pulmonary hemorrhage [5]. Infection is possibly a trigger for the occurrence of APS, stimulating the production of APA through molecular mimicry, for example, human immunodeficiency virus, hepatitis B, and C viruses. Against the background of COVID-19, there was a tendency for a temporary increase in lupus anticoagulants [6]. A retrospective study for the presence of APS in 25 patients with COVID-19 complicated by ARDS treated in the intensive care unit showed especially high values of lupus anticoagulant in 92%, anticardiolipin in 52%, and anti-β2 glycoprotein in 72% of cases, respectively [7]. PE was observed in 6 patients, the levels of all APA in which were also high. Comparison of critically ill patients with COVID-19 with patients with severe

illness unrelated to COVID-19 showed approximately the same level of APA, only lupus anticoagulant was higher in COVID-19 [8].

Another question that needs to be answered concerns the close similarities in the pathogenesis of COVID-19 and APS, moreover, whether COVID-19 infection can also induce APS. This issue is primarily related to the pathogenetic pathways of coagulopathy in COVID-19, and stimulated hypercoagulability in patients with COVID-19, which suggests that the production of APA and subsequent APS may be the cause of thrombosis as a previously unrecognized mechanism in critical conditions of the disease [9]. When saying "APS caused by COVID-19", it is necessary to take into account the presence of criteria for APS. The revised Sapporo classification requires at least one clinical criterion and one laboratory criterion [10], therefore, on the one hand, patients with clinical criteria for vascular thrombosis should be considered. On the other hand, laboratory criteria requiring two successful APA measurements 12 weeks apart, which was not done in the studies described above. Therefore, the question of APS caused by COVID-19 remains open and should be approached with further studies, which include examination of patients with thrombotic complications and in the post-COVID rehabilitation period. In addition, high levels of lupus anticoagulant, which is very often found in patients with COVID-19, may be due to an increased level of CRP, as a marker of severe inflammation in severe COVID-19 [11]. It is also problematic to interpret APA values measured during anticoagulant therapy with unfractionated heparin or vitamin K antagonists [12]. Given the above, a more in-depth study of the presence of antibodies should be carried out to confirm the possible disappearance or persistence of antibodies after the acute phase of infection [13]

MATERIAL AND METHODS

The study was conducted based on the Republican Specialized Scientific and Practical Center for Cardiology. 52 patients with coronary heart 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 (analysis), but without oxygen therapy and steroids, to avoid the influence of a serious illness and drug exposure. The main goal of our study was to identify the activity of cardiac dysfunction based on the analysis of the main clinical and laboratory parameters in conjunction with the presence of autoantibodies to CVS in patients with coronary artery disease who had a mild and moderate course of 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. The principle of the method for determining autoantibodies to CVS is to carry out the tablet method. Investigated DNA Antigen - DNA-antigenic component of any cell type. Its increase is associated, more often with an active infectious process (usually viral); exacerbation of herpes infection. Less commonly, a systemic autoimmune disease (SLE, RA, scleroderma, etc.) or a variant of a paraneoplastic reaction in various forms of a malignant tumor process. The β2-GP antigen is the main phospholipid-binding protein in blood plasma. It increases with transient antiphospholipid syndrome (APS; accompanies any acute infectious process or exacerbation of a chronic infection), less often, with systemic autoimmune diseases or a variant of a paraneoplastic reaction in various forms of a malignant tumor process.

Collagen. The growth of antibodies to collagen occurs mainly in inflammatory lesions of the CVS.

CoM-02 antigen is a component of cardiomyocyte membranes. An increase in AT to this component occurs with myocardial dystrophy.

Beta1-adrenergic receptors are a component of the autonomic nervous system of the heart, involved in the regulation of the frequency and strength of heart contractions, as well as the tone of the coronary arteries. An increase in AT to this component leads to the development of arrhythmias.

The CoS-05 antigen is a component of the cytoplasm of cells in the myocardium. An increase in AT to this component occurs with functional disorders in the activity of the heart.

Protein cardiomyosin L. An increase in the serum content of AT to it is characteristic of dystrophic changes in the myocardium of various origins.

TrM antigen - platelet membrane antigen; changes in the number and functions of platelets (can lead to both hyper- and hypocoagulation).

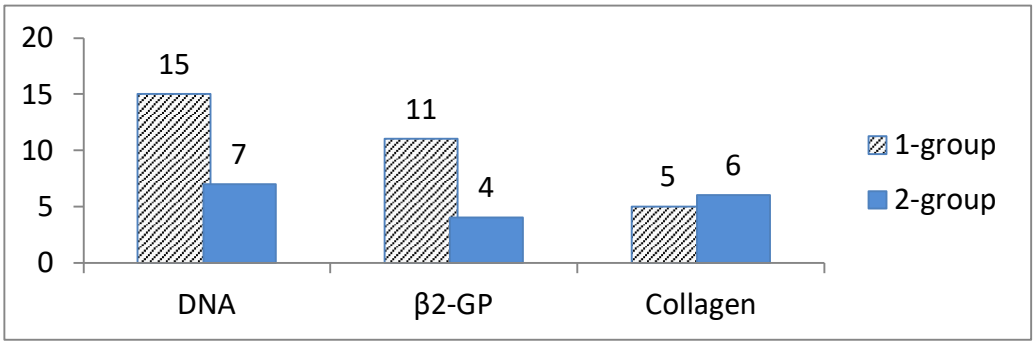
The c-ANCA antigen is a strongly anionic component of the cytoplasm of neutrophils and vascular endothelial cells; an increase in the serum content of antibodies to it is typical for various kinds of vasculitis.

Nitride oxide synthetase (e-NOS) is involved in the regulation of vascular tone; an increase in the serum content of antibodies to it is typical for vegetative-vascular dystonia and other forms of dysregulation of vascular tone.

Plasminogen is a marker of the anticoagulant system of the blood. Disorders of blood coagulability and disturbances in the formation of reserve blood flow.
PAPP-A protein. An increase in the serum content of antibodies to the PAPP-A protein is observed in atherosclerotic lesions.

RESULTS AND DISCUSSIONS

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. According to objective indicators, a significant difference was noted in the body mass index, which was higher in patients with a history of coronavirus infection ($p<0.05$). 6 patients (23.1%) who had undergone COVID-19 were hospitalized with the diagnosis of Acute stroke, in group 1 (without COVID-19) only in one case Acute stroke was registered. When evaluating the ECHOCG parameters in the studied groups, no significant differences were found. In the course of the study, the levels of autoantibodies to CVS and their relationship were studied not only with the previous coronavirus infection but also with clinical and laboratory parameters. Damage to the coronary arteries, and the clinical course of ischemic heart disease were taken into account.
Having an important prognostic and clinical significance, the bars of the histogram of the level of AT, which went into the zone outside the optimal values (+ 10%), were significantly higher in group 2 in terms of DNA (DNA-antigenic component of any cell types), indicating an active infectious process (usually viral) in 10 patients (38.4%) and 5 patients (19.2%) with a low level of autoantibodies, indicating a gradual attenuation of the active process against the background of the release of a high level of antigens. Comparative characteristics of the number of patients in terms of the level of AT markers of infectious-inflammatory, cicatricial adhesions, and autoimmune processes in the groups are shown in Figure 1, with an increased level and a reduced level of AT.



Picture. 1. Comparative characteristics of AT-markers of infectious-inflammatory, cicatricial adhesions and autoimmune processes that go into the zone outside the optimal values (+10%) and (-15%).

Table 1: The frequency of occurrence of increased and decreased levels of autoantibodies in the surveyed groups

AT to antigen	1-group (n=26)	2- group (n=26)	χ2
DNA	7 (26,9%)	15 (57,7%)	5,042*
β2-GP	4 (15,4%)	11 (42,3%)	4,591*
Collagen	6 (23,0%)	5 (19,2%)	≠
Com	3 (11,5%)	10 (38,5%)	5,026*
β1-Adreno-Rc	2 (7,7%)	2 (7,7%)	≠
Cos	4 (15,3%)	6 (23,0%)	≠
CardioM	4 (15,3%)	9 (34,6%)	≠
TrM	5 (19,2%)	5 (19,2%)	≠
ANCA	3 (11,5%)	4 (15,3%)	≠
NOS	1 (3,8%)	4 (15,3%)	≠
Plasminogen	4 (15,3%)	4 (15,3%)	≠
PAPP-A	5 (19,2%)	5 (19,2%)	≠

Note: *-significance of differences $p<0.05$; ≠ significance of differences $p>0.05$

Especially, values exceeding +15% in the level of autoantibodies to DNA were recorded in 5 out of 15 patients, which may indicate an ongoing active infectious process that can develop into clinically significant

symptoms with long-term preservation of changes. An increase in autoantibodies to the β2-GP-basic phospholipid-binding protein of blood plasma, indicating the presence of an active phospholipid syndrome, was observed in 11 patients of group 2, while in group 1 it was increased only in 3 patients. A high level of antibodies to collagen type II, the main protein of the connective tissue matrix, was more common in patients without a history of COVID-19 (Table 1).

Significant differences in the levels of autoantibodies between patients were noted only concerning autoantibodies to DNA (DNA-antigenic component of any cell types) ($\chi 2=5.042$; $p<0.05$), β2-GP - the main phospholipid-binding protein of blood plasma, indicating the presence of an active phospholipid syndrome ($\chi 2=4.591$; $p<0.05$), Com - antigen of the surface membrane of cardiomyocytes, indicating dystrophic processes in the myocardium ($\chi 2=5.026$; $p<0.05$) (Figure 2).

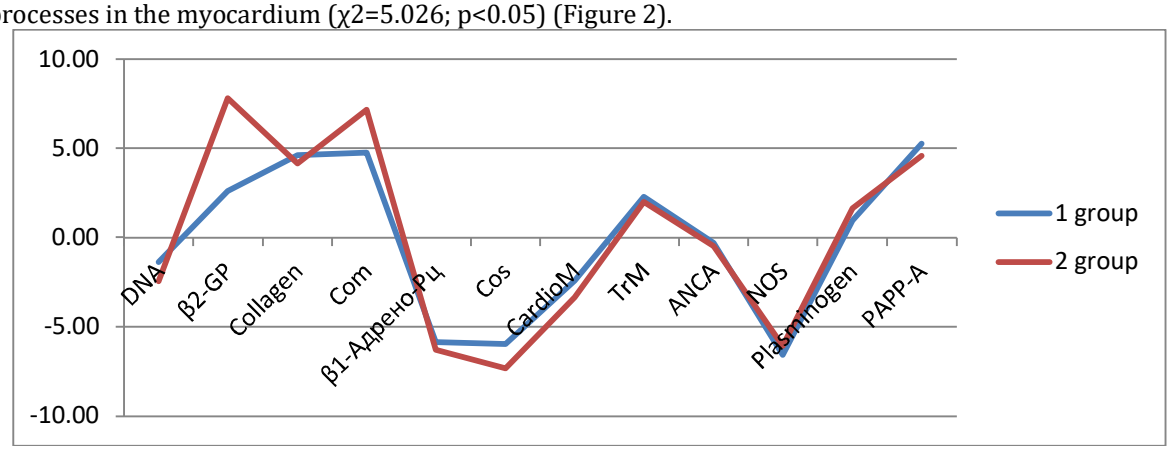


Figure 2. Autoantibody profile in patients without and with a history of COVID-19

Significant correlation differences between the level of antibodies to DNA and the following indicators were revealed: left ventricular ejection fraction ($r=-0.46$, $p<0.05$); identified hemodynamically significant stenosis of the coronary vessels ($r=0.62$, $p<0.05$); blood glucose level 2 hours after eating ($r=0.46$, $p<0.05$). Significant correlations were also determined in terms of hemostasis indicators (Table 2).

Table 2: Correlations between the level of autoantibodies to β2-GP and hemostasis in patients after COVID-19

Indicators	β2-GP	
	r	P
Prothrombin index	0,54*	<0,05
prothrombin time	-0,47*	<0,05
prothrombin ratio	-0,48*	<0,05

Therefore, an increase in autoantibodies to β2-GP in patients with coronary artery disease who underwent COVID-19 indicates that, despite the absence of any symptoms related to coronavirus infection, inflammation processes can persist in the body for up to 3 months, dystrophic processes in myocardium and violations of hemostasis, aggravating the severity of the course of coronary artery disease.

CONCLUSION

Undoubtedly, patients who have had COVID-19, especially in moderate and severe forms, with cardiovascular disorders, need medical rehabilitation and the formation of rehabilitation programs for such patients, taking into account their functional status. In terms of this issue, there is enough research in the literature. The advantage of our work is the study of the characteristics of the course of coronary artery disease in patients who underwent COVID-19 without complications, without taking steroids and oxygen therapy in history, which justifies the purity of the data obtained. The results obtained showed that manifestations of antiphospholipid syndrome can persist in patients of this category of patients without a pronounced manifestation of coronavirus infection in the next 3 months. The severity of the process was associated with being overweight, which may be the reason for frequent CVCs in this category of people with COVID-19. Dynamic monitoring of hemostasis parameters, and inflammatory markers such as CRP during the rehabilitation period should be carried out to prevent adverse cardiovascular outcomes.

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