ORIGINAL ARTICLES

УДК 616.98:578.834.1]-06:616.24-002:616.127
https://doi.org/10.20538/1682-0363-2024-1-94-104

Changes in the cardiovascular profile in patients 3 and 12 months after COVID-19 pneumonia: parameters of arterial stiffness, global longitudinal strain, and diastolic function of the left ventricle

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ABSTRACT

Aim. To study changes in the brachial – ankle pulse wave velocity (baPWV), ankle – brachial index (ABI), diastolic function, and global longitudinal strain of the left ventricle (LV) 3 and 12 months after COVID-19 pneumonia.

Materials and methods. The dynamics of vascular age and LV global longitudinal strain was studied in 154 patients 3 and 12 months after COVID-19 pneumonia (51 ± 12 years, 48% were women). The control group consisted of 55 sex- and age-matched individuals.

Results. During the follow-up, the average baPWV decreased (13.2 [11.8; 15.1] cm / sec vs. 13.0 [11.8; 14.1] cm / s; $p < 0.001$), and the frequency of its elevated values declined (45.4 vs. 35.1%; $p = 0.008$). The average ABI increased (1.09 [1.04; 1.14] vs. 1.11 [1.06; 1.17]; $p = 0.012$), but remained within the normal range. LV global longitudinal strain (LV GLS) (–19.6 ± 2.2 and –19.7 ± 2.5%; $p = 0.854$) and the frequency of reduced LV GLS (21.4 and 26.6%; $p = 0.268$) did not change significantly and did not differ from values in the control group. Global longitudinal strain in the LV basal inferoseptal segment improved (–19.2 ± 3.6% vs. –20.1 ± 4.0%; $p = 0.032$). The early diastolic mitral annular velocity decreased (8.4 ± 3.0 cm / s vs. 8.0 ± 2.5 cm / s; $p = 0.023$). The LV isovolumic relaxation time was greater than in the control group (101.8 ± 22.3 ms at the 1st visit vs. 92.9 ± 21.5 ms; $p = 0.012$; 105.9 ± 21.9 ms vs. 92.9 ± 21.5 ms at the 2nd visit; $p < 0.001$). A positive correlation was found between baPWV ($r = 0.209$; $p = 0.009$) and ABI ($r = 0.190$; $p = 0.021$) and strain parameters of the LV basal segments 12 months after discharge.

Conclusion. Patients with optimal visualization on echocardiography at 12 months after COVID-19 pneumonia, compared to the results of the examination 3 months after the disease, had deteriorated parameters of LV diastolic function. LV GLS was within the grey zone and did not change significantly. An improvement in arterial stiffness was noted, associated with an improvement in the strain of basal LV segments.

Keywords: COVID-19, pulse wave velocity, ankle – brachial index, echocardiography, longitudinal myocardial strain

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that hey received no funding for the study.

Conformity with the principles of ethics. All individuals signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Tyumen Cardiology Research Center, Tomsk NRMC of the Russian Academy of Sciences (Protocol No. 159 of 23.07.2020).

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Для цитирования: Yaroslavskaya E.I., Shirokov N.E., Krinochkin D.V., Migacheva A.V., Korovina I.O., Osokina N.A., Sapozhnikova A.D., Petelina T.I. Changes in the cardiovascular profile in patients 3 and 12 months after COVID-19 pneumonia: parameters of arterial stiffness, global longitudinal strain, and diastolic function of the left ventricle. *Bulletin of Siberian Medicine.* 2024;23(1):94–104. https://doi.org/10.20538/1682-0363-2024-1-94-104.

Динамика сердечно-сосудистого статуса пациентов через 3 и 12 месяцев после пневмонии COVID-19: показатели сосудистой жесткости, диастолической функции и продольной деформации левого желудочка

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РЕЗЮМЕ

Цель: изучить динамику скорости пульсовой волны (brachial-ankle pulsewave velocity, baPWV), лодыжечно-плечевого индекса (ankle-brachialindex, ABI), диастолической функции и продольной деформации левого желудочка (ЛЖ) через 3 и 12 мес после пневмонии COVID-19.

Материалы и методы. Динамика показателей сосудистого возрастаи продольной деформации ЛЖ изучена у 154 пациентов через 3 и 12 мес после пневмонии COVID-19 (51 ± 12 лет, 48% женщин). Группу контроля составили 55 сопоставимых по полу и возрасту пациентов.

Результаты. За время наблюдения снизилась усредненная baPWV (13,2 [11,8; 15,1] см/сек против 13,0 [11,8; 14,1] см/с, p < 0,001) и частота выявления ее повышенных значений (45,4 против 35,1%, p = 0,008). Усредненное значение ABI выросло, оставаясь в пределах нормы (1,09 [1,04; 1,14] против 1,11 [1,06; 1,17], p = 0,012). Глобальная продольная деформация ЛЖ (LV GLS) (19,6 ± 2,2% и –19,7 ± 2,5%; p = 0,854) и частота выявления сниженной LV GLS (21,4 и 26,6%; p = 0,268) значимо не изменились и не отличались от полученных в группе контроля. Продольная деформация базального нижне-перегородочного сегмента ЛЖ улучшилась (–19,2 ± 3,6% против –20,1 ± 4,0%; p = 0,032). Раннедиастолическая скорость септальной части митрального кольца снизилась (8,4 ± 3,0 см/с против 8,0 ± 2,5 см/с, p = 0,023). Время изоволюмического расслабления ЛЖ было больше, чем в группе контроля (на 1-м визите 101,8 ± 22,3 мс против 92,9 ± 21,5 мс; p = 0,012; на 2-м визите 105,9 ± 21,9 мс против 92,9 ± 21,5 мс; p < 0,001). Выявлена положительная корреляционная связь baPWV (r = 0,209; p = 0,009) и ABI (r = 0,190; p = 0,021)) с параметрами деформации сегментов базального уровня ЛЖ через год после выписки.

Заключение. У лиц с оптимальной визуализацией при эхокардиографии через год после пневмонии COVID-19 в сравнении с результатами обследования через 3 мес отмечается ухудшение параметров диастолической функции ЛЖ. LV GLS находилась в пределах «серой зоны» и значимо не изменилась. Отмечено улучшение показателей сосудистой жесткости, связанное с улучшением деформации сегментов базального уровня ЛЖ.

Ключевые слова: COVID-19, скорость распространения пульсовой волны, лодыжечно-плечевой индекс, эхокардиография, продольная деформация миокарда

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

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

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом Тюменского кардиологического научного центра, Томского НИМЦ (протокол № 159 от 23.07.2020).

Для цитирования: Ярославская Е.И., Широков Н.Е., Криночкин Д.В., Мигачева А.В., Коровина И.О., Осокина Н.А., Сапожникова А.Д., Петелина Т.И. Динамика сердечно-сосудистого статуса пациентов через 3 и 12 месяцев после пневмонии COVID-19: показатели сосудистой жесткости, диастолической функции и продольной деформации левого желудочка. *Бюллетень сибирской медицины.* 2024;23(1):94–104. https://doi.org/10.20538/1682-0363-2024-1-94-104.

INTRODUCTION

Increased arterial stiffness is known to impair myocardial relaxation and increase left ventricular (LV) end-diastolic pressure [1]. The study of the relationship between arterial stiffness and myocardial strain properties is of sustained interest. A chronic increase in afterload has been shown to accelerate LV remodeling and development of heart failure [2]. A study of 248 individuals without structural heart disease revealed an independent relationship between brachial – ankle pulse wave velocity (baPWV) and LV global longitudinal strain (GLS) [3]. J.W. Hwang et al. demonstrated that increased baPWV contributed to impaired LV GLS in patients with arterial hypertension (AH) and preserved LV ejection fraction (LVEF) [4].

Arterial stiffness is naturally associated with aging but may be accelerated by concomitant metabolic and cardiovascular pathology. One of the mechanisms that underlies changes in blood vessels during aging and cardiovascular diseases is a decrease in the number of elastic fibers and an increase in collagen content. Another mechanism is endothelial dysfunction, which develops as a result of inflammation, oxidative stress, and changes in smooth muscle tone in muscular arteries. COVID-19 is a multisystem disease with extensive damage to the cardiovascular system, causing increased arterial stiffness [5]. Today, complications of the experienced infectious process come to the forefront; most of these complications directly affect the vascular system. A significant number of COVID-19 survivors have been shown to develop persistent metabolic changes with vascular wall damage similar to that seen in AH, type 2 diabetes mellitus, and metabolic syndrome [6]. Mild inflammatory components play a role in the development of early vascular aging after COVID-19 [7, 8].

All of these may lead to the onset or progression of both AH and atherosclerotic vascular wall damage, especially after a complicated course of COVID-19. Considering that functional disorders develop faster than structural ones, the study of arterial stiffness after COVID-19 is very relevant, but such studies are still few. I. Ikonomidis et al. proposed to use the ratio of carotid – femoral pulse wave velocity (PWV) to LV GLS as a parameter for assessing ventricular – arterial coupling, which in turn affects LV diastolic function, the severity of concentric hypertrophy, and the degree of impairment of coronary flow reserve [9].

We hypothesized that in patients who have had a complicated course of COVID-19 in the long term after the disease, arterial stiffness increases, and LV GLS parameters worsen in comparison with the examination data in the early recovery period, which could be a reflection of early vascular aging.

The aim of the study was to determine changes in and relationships between baPWV, ankle – brachial index (ABI), and LV GLS 3 and 12 months after COVID-19 pneumonia.

MATERIALS AND METHODS

The study included patients of the “Prospective Registry of COVID-19-Associated Pneumonia Survivors” (state registration certificate No. 2021622535 of 18.11.2021). The study complied with the ethical standards of the Declaration of Helsinki as amended in 2000 and the “Rules of good clinical practice in the Russian Federation”, approved by Order of the Ministry of Health of the Russian Federation No. 266 of 19.06.2003. The study was approved by the local Ethics Committee (Protocol No. 159 of 23.07.2020) and registered in international clinical trials registry clinicaltrials.gov (No. NCT04501822). Patients were identified according to the 1C medical information system of infectious disease hospitals in the period from April 2020 to January 2021. Inclusion criteria: laboratory-confirmed diagnosis of COVID-19 pneumonia, age 18 years or older, and patient’s consent to participate in the study. Non-inclusion criteria: exacerbation of chronic diseases, hemodynamically significant heart defects, history of cancers younger than 5 years, tuberculosis, other diseases accompanied by pulmonary fibrosis, chronic hepatitis, HIV. Exclusion criteria: pregnancy, cancer detected during the follow-up period, refusal to participate in the study, suboptimal echocardiography (Echo) imaging. All patients signed an informed consent to participate in the study.

An outpatient examination of 350 patients meeting all the criteria was performed 3 months ± 2 weeks (92 [82–99] days) and 12 months ± 3 weeks (367 [362–381] days) after discharge. Of the 380 patients included in the study, 28 were excluded for various reasons. At the first visit, 271 patients had optimal visualization quality during echocardiography, and at the second visit – 244 patients. Of the remaining examined subjects, vascular age parameters were assessed after 3 months (1st visit) in 339 (97%) subjects and after 12 months (2nd visit) in 286 (82%) subjects. The parameters of LV GLS and LV segmental longitudinal strain were studied 3 months after pneumonia in 271 (77%) patients with optimal visualization during echocardiography and after 12 months in 244 (70%) patients. Changes in vascular age indices and LV strain properties could be assessed in 154 (44%) patients (main group). The control group consisted of 55 sex- and age-matched patients with optimal visualization quality during echocardiography. They were included in the study at the same time as the main group and had neither a single positive result of the polymerase chain reaction identifying SARS-CoV-2 nor clinical manifestations of COVID-19.

Data from the acute phase of COVID-19 were assessed using discharge summaries from medical records. The average proportion of lung tissue damage in the examined patients according to computed tomography (CT) during hospitalization was 50.0%; 8.5% of patients were treated in intensive care units, 45.7% received hormonal therapy, 5.9% – biologically active therapy. 17.0% of patients had mild pneumonia, 31.3% – moderate, 38.1% – severe, and 13.6% – extremely severe pneumonia.

During the visits, all the study participants underwent determination of elastic properties of the peripheral arterial wall by volumetric sphygmography on the VaSera VS-1000 Series sphygmomanometer (Fukuda Denishi, Japan). We assessed baPWV on the right and left; ABI on the right and left as the ratio of systolic blood pressure (BP) at the ankle to systolic BP at the arm. The averaged values between the right and left sides were analyzed. In accordance with the specified hardware conditions for interpretation of the results, baPWV was considered to be normal at < 13.5 cm / sec; normal ABI values were considered to be $1.0 \leq$ ABI < 1.3 (vascular age was not assessed in the control group, since it was determined in less than half of the patients in this group). Echo was performed on the best-in-class Vivid S70 ultrasound diagnostic system with data storage in DICOM format and subsequent data analysis on the Intelli Space Cardiovascular workstation using the TomTec software (Philips, USA). LV GLS > –18% was considered to be reduced [10, 11]. The symptoms of anxiety – depressive disorders (according to the GAD7 and PHQ9 scales), stress disorders (according to the Perceived Stress Scale (PSS-10)), and the quality of life (according to the SF-36 questionnaire) were assessed.

Statistical analysis was carried out using the SPSS 21 software application package (SPSS Inc., Chicago, IL, USA) and Statistica 12.0. The distribution of variables was assessed using the Kolmogorov – Smirnov test. For normal distribution of quantitative variables, parameters were presented as the mean and the standard deviation ($M \pm SD$). For distribution other than normal, parameters were presented as the median and the interquartile range Me [Q_{25}; Q_{75}]. The significance of differences in continuous variables was assessed depending on the data distribution using the Student's *t*-test for dependent variables or the Wilcoxon test. To compare qualitative variables, the McNemar test was used. Correlations between pairs of quantitative variables were assessed using the Pearson's chi-squared test for normal distribution, and Spearman's rank correlation coefficient for non-normal distribution. Comparison with the control group was performed using the Kruskal – Wallis test or one-way analysis of variance for quantitative variables, and by the $\chi 2$ test or Fisher's exact test for qualitative parameters. The results were considered statistically significant at $p < 0.05$.

RESULTS

The mean body mass index (BMI) in the main group corresponded to overweight at both visits and increased over the follow-up period (Table 1). The number of smokers decreased by 9.2%, but drinking alcohol several times a week increased by 5%. Symptoms of anxiety – depressive and stress disorders and subjectively perceived quality of life did not change significantly. The prevalence of cardiovascular diseases increased due to the newly identified 7 cases of AH and 6 cases of coronary artery disease (CAD). At the same time, no significant change in BP and heart rate was registered. The average baPWV decreased by 0.2 cm / sec, and the frequency of detection of its elevated values decreased by 10.3%. The average value of ABI increased by 0.02, remaining within the normal range. The number of patients with normalization of lung CT data increased by 5.4%.

The main group did not differ from the control group in age and sex composition, significant differences in BMI appeared only at the end of the observation period. Individuals who had COVID-19 pneumonia in the early recovery period drank alcohol less frequently, more often showed symptoms of anxiety, and had worse physical characteristics of health than the control group. Patients of the main group did not differ from the control group in the frequency of AH, but 3 months after discharge, they showed a trend toward higher systolic BP than in the control group, and their diastolic BP was higher throughout the observation. In the control group, only one patient had diabetes mellitus, and there were no diagnosed cases of CAD.

Table 1

Changes in clinical parameters of patients after COVID-19 pneumonia and the control group

Parameter		Patients after COVID-19 pneumonia		p	Control group, n = 55	p *	p**
		After 3 months, n = 154	After 12 months, n = 154				
Age, years, $M \pm SD$		51.3 ± 11.5	–	–	51.8 ± 10.8	0.943	–
Female gender, %		48.1	–	–	56.4	0.290	–
Body mass index, kg / m², $M \pm SD$		28.5 ± 4.4	29.3 ± 4.8	<0.001	27.4 ± 4.2	0.093	0.013
Smoking or recently quit, n (%)		62 (40.3)	46 (31.1)	0.002	15 (41.7)	0.877	0.266
Alcohol drinking, n (%)	do not drink	34 (22.4)	39 (26.7)	0.302	5 (13.9)	0.259	0.107
	several times a year	70 (46.1)	53 (36.3)	0.002	18 (50.0)	0.670	0.131
	several times a month	42 (27.6)	40 (27.4)	0.690	7 (19.4)	0.314	0.329
	once/several times a week	6 (3.9)	13 (8.9)	0.039	6 (16.7)	0.013	0.220
Identifying anxiety symptoms using the GAD7 scale, n (%)		47 (30.7)	36 (25.4)	0.185	4 (11.1)	0.017	0.067
Identifying depression symptoms using the PHQ9 scale, n (%)		49 (32.0)	36 (25.4)	0.262	8 (22.2)	0.249	0.697
Identifying stress symptoms using the Perceived Stress Scale-10, n (%)		16 (10.5)	12 (8.5)	1.000	2 (5.6)	0.533	0.738
Generalized scores of the SF-36 questionnaire, Me [Q_{25}; Q_{75}]	Physical component	48.5 [43.5; 51.6]	48.7 [44.1; 52.4]	0.143	50.0 [45.7; 52.7]	0.096	0.282
	Mental component	66.7 [59.7; 71.4]	67.7 [59.3; 71.9]	0.341	67.0 [60.9; 71.3]	0.855	0.879
Arterial hypertension, n (%)		111 (72.1)	118 (77.1)	0.039	38 (69.1)	0.671	0.238
Coronary artery disease, n (%)		21 (13.6)	27 (17.6)	0.031	0 (0.0)	0.004	0.001
Type 2 diabetes mellitus, n (%)		20 (13.0)	21 (13.6)	1.000	1 (1.8)	0.018	0.014
Congestive heart failure according to NYHA, n (%)	FC I	51 (71.8)	55 (72.4)	0.388	15 (88.2)	0.219	0.244
	FC II	17 (23.9)	18 (23.7)	1.000	2 (11.8)	0.344	0.348
	FC III	3 (4.2)	3 (3.9)	1.000	0 (0.0)	1.000	1.000
Office blood pressure, mm Hg, Me [Q_{25}; Q_{75}]	Systolic	129 [117; 140]	128 [116; 139]	0.511	120 [110; 135]	0.068	0.081
	Diastolic	82 [75; 92]	85 [80; 92]	0.164	80 [70; 81]	0.011	0.001
Heart rate per minute, Me [Q_{25}; Q_{75}]		63 [58; 70]	62 [56; 68]	0.400	72 [66;78]	0.857	0.183
Normalization of lung CT data, %		38.8	44.2	<0.001	–	–	–
Parameters of vascular wall elasticity							
Average baPWV value, cm / sec, Me [Q_{25}; Q_{75}]		13.2 [11.8; 15.1]	13.0 [11.8; 14.1]	<0.001	–	–	–
Frequency of detection of elevated baPWV (≥ 13.5 cm / sec), n (%)		69 (45.4)	54 (35.1)	0.008	–	–	–
Average ABI value, Me [Q_{25}; Q_{75}]		1.09 [1.04; 1.14]	1.11 [1.06; 1.17]	0.012	–	–	–
Detection of reduced ABI (less than 1), n (%)		44 (29.7)	35 (23.5)	0.451	–	–	–
Detection of increased ABI (1.3 and above), n (%)		3 (2.1)	3 (2.1)	1.000	–	–	–

Note. NYHA – New York Heart Association; FC – functional class; CT – computed tomography, p – level of statistical significance of differences between the groups of patients.

p* – significance of differences between the control group and those who had COVID-19 pneumonia 3 months after discharge; p** – significance of differences between the control group and those who had COVID-19 pneumonia 12 months after discharge.

During hospitalization, the reference values of C-reactive protein (CRP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) (moderate increase), alanine aminotransferase (ALT) were significantly exceeded with subsequent normalization (with the exception of CRP: its average values after discharge decreased, but did not reach the normal value) (Table 2). At 12 months after discharge, there was a significant decrease in levels of total cholesterol (TC), triglycerides, and low-density lipoprotein cholesterol (LDL-C). At the same time, the mean values of these parameters in the outpatient setting were higher than the reference values except for triglycerides. During outpatient follow-up, the liver function tests worsened, the levels of creatine phosphokinase, creatinine, leukocytes, CRP, including high-sensitivity CRP, ferritin, and interleukin (IL) 1 and 6 increased. There was a trend toward a decrease in the level of glycated hemoglobin, its average value approached the normal ones. The N-terminal pro b-type natriuretic peptide (NT-proBNP) level decreased. The frequency of use of beta-blockers (34.0 vs. 42.5%; p = 0.027) and statins (46.9 vs. 59.5%; p = 0.001) increased over the follow-up period. The frequency of use of the following groups of drugs did not change: adenosine-converting enzyme inhibitors (26.5 and 30.1%; p = 0.327), antiplatelet agents (aspirin / clopidogrel) (19.0 and 19.6%; p = 0.754), diuretics (46.3 and 49.7%; p = 0.458), hypoglycemic agents (11.7 and 12.3%; p = 1.000).

Table 2

Changes in laboratory parameters of individuals with optimal Echo visualization after COVID-19 pneumonia

Parameter	Hospitalization period, n =154	3 months after discharge, n = 154	12 months after discharge, n = 154	p between 3 and 12 months
TC, mmol / l, Me [Q_{25}; Q_{75}], $M \pm SD$, N 0–5	4.0 [3.3; 4.8]	5.5 ± 1.4	5.1 ± 1.3	<0.001
TG, mmol / l, Me [Q_{25}; Q_{75}], N 0–1.7	–	1.3 [0.9; 1.7]	1.1 [0.8; 1.6]	0.039
HDL, mmol / l, $M \pm SD$ N males ≤40; females ≤31	–	1.4 ± 0.4	1.3 ± 0.3	0.514
LDL, mmol / l, $M \pm SD$ N 0–3	-	3.1 ± 1.2	3.1 ± 1.0	0.004
ALT, units / l, Me [Q_{25}; Q_{75}], N males ≤40; females ≤31	32.0 [17.3; 57.1]	21.0 [15.9; 27.5]	24.0 [18.6; 30.8]	0.008
AST, units/l, Me [Q_{25}; Q_{75}], N males ≤38; females ≤32	32.7 [23.9; 46.0]	19.4 [16.0; 24.2]	21.9 [18.6; 25.8]	0.002
Lactate dehydrogenase, units / l, Me [Q_{25}; Q_{75}], N 0–248	421.5 [292.0; 592.0]	183.9 [159.9; 204.3]	181.6 [159.0; 200.4]	0.064
Creatine phosphokinase, units/l, Me [Q_{25}; Q_{75}], N males ≤190; females ≤167	108.0 [63.0; 227.0]	100.0 [72.1; 139.6]	118.0 [84.1; 165.1]	<0.001
Creatinine, μmol/l, Me [Q_{25}; Q_{75}], N males 62–106; females 44–80	80.0 [69.0; 97.0]	74.5 [65.3; 83.2]	77.2 [67.4; 87.2]	<0.001
Fasting glucose, mmol / l, Me [Q_{25}; Q_{75}], N 3.3–6.1	7.2 [6.5; 9.1]	5.4 [5.0; 5.9]	5.4 [5.0; 6.0]	0.806
Glycated hemoglobin, %, Me [Q_{25}; Q_{75}], N 4.5–6.0	–	6.7 [5.7; 8.0]	5.8 [5.5; 6.2]	0.070
Leukocytes, 10^9 / l, Me [Q_{25}; Q_{75}], N 4.0–9.0	5.9 [4.4; 7.8]	5.2 [4.3; 6.4]	5.5 [4.6; 6.5]	0.001
Lymphocytes, %, $M \pm SD$, Me [Q_{25}; Q_{75}], N 19–37	23.0 ± 11.3	1.8 [1.5; 2.2]	1.9 [1.6; 2.2]	0.387
CRP, mg / l, Me [Q_{25}; Q_{75}], N ≤3	58.5 [15.9; 115.6]	3.5 [1.7; 6.2]	4.2 [2.9; 7.6]	<0.001
hsCRP, mg / l, Me [Q_{25}; Q_{75}], N ≤3	–	3.8 [1.7; 7.0]	4.1 [2.6; 7.5]	<0.001
Ferritin, mg / ml, Me [Q_{25}; Q_{75}], N males 20–300; females 10–120	–	67.8 [24.5; 151.6]	106.8 [37.9; 184.2]	0.002
D-dimer, μg/ml, Me [Q_{25}; Q_{75}], N 0.1–0.5	0.4 [0.2; 0.6]	0.3 [0.1; 0.4]	0.1 [0.1; 0.2]	0.527
NT-proBNP, pg/ml, Me [Q_{25}; Q_{75}], N under 75 years <125, over 75 years <400	–	67.4 [29.1; 155.8]	58.7 [30.9; 98.1]	0.007
Interleukin 8, pg / ml, Me [Q_{25}; Q_{75}], N≤8.11	–	13.7 [10.3; 17.3]	13.8 [10.3; 17.2]	0.739
Interleukin 1, pg / ml, Me [Q_{25}; Q_{75}], N 0–5 pkg/ml	–	2.0 [1.6; 2.8]	2.2 [1.6; 3.1]	0.001
Interleukin 6, pg / ml, $M \pm SD$, N ≤9.7	–	3.0 ± 1.2	3.5 ± 0.9	<0.001

Note. HDL – high-density lipoproteins; LDL – low-density lipoproteins; ALT – alanine aminotransferase; AST – aspartate aminotransferase; hsCRP – high-sensitivity C-reactive protein, N – normal values.

Larger values of LV volume during hospitalization can be explained by the infusion load, which was pathogenetically justified in the acute period of the disease. The larger anteroposterior dimension of the right ventricle (RV) can be explained by the load on the pulmonary circulation caused by pneumonia (Table 3). During the observation period, the area of RV decreased; the fraction of change in the area of RV increased, indicating structural and functional recovery of the RV. However, such parameters of RV function as tricuspid annular plane systolic excursion (TAPSE), peak tricuspid regurgitation velocity, S' tricuspid annular velocity, acceleration time of blood flow in the RV outflow tract in the main group, though being within the normal range, did not reach the values of the control group in dynamics, which indicates limitation of RV function after COVID-19 pneumonia.

In terms of LV parameters, COVID-19 pneumonia survivors showed a significant decrease in LV end-systolic volume and a slight increase in LV ejection fraction at one year after discharge, suggesting an improvement in LV systolic function in the late recovery period. However, the deterioration of LV diastolic function parameters draws attention: early diastolic mitral annular velocity at the septal annulus (e' sept) significantly decreased (and one year after discharge, it showed a trend toward a lower value than in the control group), there was a trend toward a decrease in LV early diastolic filling deceleration time (DT) and the ratio of the early diastolic velocity of transmittal flow to the early diastolic velocity of the mitral annulus (E/e'). The worse diastolic function compared to the control group is also evidenced by the longer LV isovolumic relaxation time (IVRT) during the whole observation period in the main group.

Table 3

Changes in the echocardiography parameters of persons after COVID-19 pneumonia and the control group, *M* ± *SD*

Parameter		Hospitalization period, *n* = 154	Patients after COVID-19 pneumonia		*p*	Control group, *n* = 55	*p* *	*p* **
			After 3 months, *n* = 154	After 12 months, *n* = 154				
LV end-diastolic volume (EDV)	ml	113.1±24.1	90.2±22.8	89.3±20.6	0.521	88.1±21.7	0.620	0.664
	ml / m^2	–	46.5±9.9	45.6±8.6	0.167	46.2±9.1	0.950	0.585
LV end-systolic volume (ESV)	ml	36.4±12.3	29.3±10.7	27.4±7.3	0.031	28.6±10.1	0.608	0.849
	ml / m^2	–	15.1±4.9	14.0±3.1	0.009	14.9±4.5	0.902	0.346
LV myocardial mass according to the area-length method	g	–	145.9±34.6	148.9±32.3	0.449	136.4±33.8	0.055	0.009
	g / m^2		75.6±15.2	76.1±13.1	0.736	71.2±12.3	0.039	0.012
LV ejection fraction (2D Simpson), %		68.2±5.8	68.1±4.8	69.4±3.9	0.004	68.3±4.8	0.832	0.062
Time of blood flow deceleration in LV outflow tract, ms		–	215.0±32.2	215.7±30.9	0.889	209.7±29.5	0.292	0.217
LV isovolumic relaxation time, IVRT, ms		–	101.8±22.3	105.9±21.9	0.113	92.9±21.5	0.012	<0.001
DT, ms		–	216.6±61.9	205.8±51.5	0.054	194.4±39.7	0.123	0.338
LV early diastolic filling velocity, E, cm /s		–	71.2±15.5	69.4±14.6	0.137	71.8±16.2	0.823	0.313
LV late diastolic filling velocity, A, cm / s		–	68.8±16.3	68.4±15.4	0.731	66.2±14.2	0.284	0.476
Early diastolic velocity at the lateral part of the mitral annulus, e' later, cm/s		–	11.0±3.6	10.9±3.4	0.349	11.1±3.0	0.578	0.552
Early diastolic velocity at the septal part of the mitral annulus, e' sept, cm/s		–	8.4±3.0	8.0±2.5	0.023	8.8±2.6	0.272	0.076
E/e'		–	9.7±3.1	9.5±2.8	0.051	9.9±2.4	0.303	0.180
Maximum left atrial volume	ml	–	47.9±13.6	48.3±12.9	0.474	47.1±12.2	0.823	0.412
	ml / m^2	–	24.8±6.6	24.7±5.9	0.953	24.7±5.2	0.674	0.895
Anteroposterior dimension of the RV	mm	26.9±3.3	25.5±2.4	25.8±2.7	0.539	25.3±2.4	0.631	0.440
	mm / m^2	–	13.3±1.5	13.3±1.5	0.319	13.4±1.6	0.918	0.727
Diastolic area of the RV	cm^2	–	15.7±4.0	14.8±3.3	<0.001	14.9±3.1	0.289	0.723
	cm^2 / m^2	–	8.1±1.7	7.5±1.4	<0.001	7.9±1.5	0.354	0.129
Fraction of change in RV area, %		–	50.8±8.8	53.0±8.4	0.004	52.9±8.3	0.117	0.678
TAPSE, mm		–	22.7±2.5	22.7±2.3	0.973	24.2±2.4	<0.001	<0.001
Peak tricuspid regurgitation velocity, cm / s		–	2.1 [1.8; 2.3]	2.1 [1.9; 2.3]	0.553	1.9 [1.6; 2.1]	0.004	<0.001
Velocity S' of the tricuspid annulus, cm/s		–	9.8±2.6	9.7±2.7	0.289	12.6±1.8	<0.001	<0.001
Acceleration time of blood flow in RV outflow tract, ms		–	113.2±22.9	113.7±21.3	0.929	123.2±26.2	0.003	0.007

Note. DT – deceleration time of LV early diastolic filling.

The absence of significant differences in LV GLS in comparison with the control group and the frequency of detection of reduced LV GLS comparable to the control group (Table 4) allows to evaluate the state of LV systolic function in the main group as satisfactory. Improvement in segmental strain values was noted in the inferior and lateral segments of the LV basal level, with this improvement reaching statistical significance in the basal inferoseptal segment (Table 4). It is worth noting that the value of longitudinal strain in this particular segment 3 months after discharge tended to be lower than in the control group. There was some improvement in the values of segmental strain of LV middle level segments, but it did not reach statistical significance. The strain of the apical level segments worsened insignificantly.

Table 4

Changes in LV strain parameters in individuals 3 and 12 months after COVID-19 pneumonia and the control group, %, *M±SD*

Longitudinal strain parameter, %	Patients after COVID-19 pneumonia		*p*	Control group, *n* = 55	*p* *	*p* **
	After 3 months, *n* = 154	After 12 months, *n* = 154				
Global (LV GLS)	–19.6 ± 2.2	–19.7 ± 2.5	0.854	–19.9 ± 2.7	0.556	0.653
Global strain > –18%	33 (21.4)	41 (26.6)	0.268	15 (27.3)	0.376	0.926
Basal anterior segment	–17.3 ± 4.2	–16.7 ± 4.0	0.156	–17.3 ± 4.0	0.965	0.435
Basal anteroseptal segment	–16.8 ± 3.3	–16.7 ± 3.4	0.727	–17.3 ± 3.5	0.494	0.316
Basal inferoseptal segment	–19.2 ± 3.6	–20.1 ± 4.0	0.032	–20.1 ± 3.9	0.060	0.851
Basal inferior segment	–16.6 ± 3.0	–16.8 ± 3.2	0.596	–16.5 ± 3.2	0.728	0.435
Basal inferolateral segment	–17.3 ± 3.8	–17.7 ± 4.1	0.321	–17.5 ± 3.6	0.787	0.502
Basal anterolateral segment	–18.2 ± 4.2	–18.0 ± 4.0	0.459	–18.5 ± 4.6	0.484	0.474
Middle anterior segment	–17.6 ± 4.2	–17.4 ± 4.0	0.556	–17.8 ± 4.5	0.970	0.720
Middle anteroseptal segment	–20.8 ± 3.6	–20.5 ± 3.4	0.424	–20.8 ± 3.6	0.926	0.850
Middle inferoseptal segment	–21.2 ± 3.4	–21.9 ± 3.3	0.093	–22.2 ± 3.5	0.125	0.808
Middle inferior segment	–20.4 ± 3.0	–20.3 ± 3.1	0.925	–20.3 ± 3.0	0.699	0.984
Middle inferolateral segment	–17.9 ± 3.7	–18.0 ± 3.9	0.974	–17.7 ± 3.7	0.482	0.343
Middle anterolateral segment	–19.1 ± 3.4	–19.2 ± 3.7	0.838	–19.1 ± 3.9	0.664	0.787
Apical anterior segment	–21.3 ± 5.2	–21.3 ± 5.0	0.792	–21.8 ± 5.1	0.846	0.912
Apical septal segment	–24.0 ± 4.7	–23.9 ± 4.6	0.954	–24.3 ± 4.0	0.647	0.620
Apical inferior segment	–23.2 ± 4.6	–23.0 ± 4.5	0.472	–23.8 ± 4.1	0.658	0.701
Apical lateral segment	–21.2 ± 4.6	–20.9 ± 5.0	0.539	–21.1 ± 4.1	0.836	0.879
Apical segment	–22.5 ± 4.0	–22.3 ± 4.2	0.324	–22.8 ± 3.9	0.887	0.746
Basal level	-17.6 ± 2.2	–17.7 ± 2.6	0.448	–17.9 ± 2.7	0.400	0.627
Middle level	–19.5 ± 2.0	–19.6 ± 2.5	0.734	–19.6 ± 2.6	0.722	0.865
Apical level	–22.5 ± 4.0	–22.3 ± 4.2	0.693	–22.7 ± 3.8	0.639	0.489

Our study did not reveal the previously described [2, 3] associations of arterial stiffness parameters with LV GLS, which may be due to dysregulation of arterial – ventricular interaction caused by COVID-19. One year after discharge, arterial stiffness parameters (average baPWV (r = 0.209, *p* = 0.009) and average ABI (*r* = 0.190, *p* = 0.021) demonstrated a positive correlation with parameters of segmental strain of the LV basal level.

DISCUSSION

In the in-hospital period, CRP values were many times higher than the reference values, indicating extremely high activity of the inflammatory process and severity of tissue damage. In the recovery period, CRP values never reached the norm and, moreover, increased at one year after discharge, indicating a persistent potential for an increased inflammatory response in the late recovery period of the disease. High levels of high-sensitivity CRP and IL-8 during the recovery period, as well as increased levels of IL-1 and IL-6, indicate a persistent vascular inflammatory process, which may imply a threat of vascular complications.

The deterioration of the cardiovascular status during the observation period is evidenced by both the increase in the incidence of cardiovascular diseases (AH – by 5%, CAD – by 4%) and the need to prescribe beta-blockers, which increased by 8.5%, and statins – by 12.6%. The latter explains the fact that lipid profile values improved, but liver function tests worsened and the level of creatine phosphokinase increased.

The data on normalization of RV function obtained by us are in agreement with positive dynamics of CT lung data in our patients. The improvement of LV systolic function was indicated by the revealed decrease in LV end-systolic volume and a slight increase in LVEF, but the improvement of LV GLS was insignificant, and LV diastolic function deteriorated, as evidenced by the dynamics of tissue and pulse-wave Doppler parameters. Taking into account the worse parameters of LV diastolic function in the main group in comparison with the control group, COVID-19 can be considered as a pathogenetic factor of LV diastolic function disorders in our patients along with the progression of cardiovascular pathology.

Patients in the present study showed some improvement in arterial stiffness parameters during the follow-up period, as evidenced by a small but statistically significant decrease in baPWV, as well as a 10.3% decrease in the frequency of its elevated values. The increase in average ABI within normal values does not contradict this conclusion. These results can be interpreted as a return to baseline (before COVID-19) values of functional parameters of the vascular wall. However, the frequency of detection of abnormalities at the 2nd visit was still high (baPWV – 35.1%, ABI – 25.6%). Considering the negative dynamics we found in diastolic function parameters, as well as the high incidence of disturbances in arterial stiffness parameters one year after COVID-19 pneumonia, longer-term follow-up is necessary to study the degree of reversibility of vascular changes and their prognostic consequences.

The improvement of arterial stiffness parameters according to our results is associated with improvement of LV basal segmental strain. Since it was previously shown that in the early recovery period after COVID-19, a decrease in LV segmental strain is characteristic mainly for LV basal segments [12], this result can be interpreted as the restoration of LV strain properties, impaired in the acute period of COVID-19.

We found the only study with 1-year follow-up of arterial stiffness and LV GLS after COVID-19. Greek researchers I. Ikonomidis et al. examined 70 patients (54.5 years) 4 and 12 months after the diagnosis of COVID-19 and 70 individuals without COVID-19 matched by basic clinical characteristics [13]. The mean values of carotid – femoral PWV in the group after COVID-19 decreased insignificantly in the dynamics (12.09 and 11.19 m / s, $p = 0.883$), but still there was a trend toward higher values than in the control group (11.19 vs. 10.04 m / s, $p = 0.057$). Twelve months after COVID-19, LV GLS values showed a trend toward improvement compared to values at 4 months (–19.55 vs. –20.32%, $p = 0.069$), although they remained lower than in the control group (–20.32 vs. –21.98%, $p = 0.003$) [13].

We also found an insignificant improvement in LV GLS 12 months after COVID-19, and its value was closer to the data of group of I. Ikonomidis et al. 4 months after COVID-19 infection. This can probably be associated with a more severe course of COVID-19 in our patients: in the acute period, they all required hospitalization and 8.5% of them required mechanical ventilation, while in 34.3% of patients in the study by I. Ikonomidis et al., the course of the disease was mild and did not require hospitalization, and none of the Greek patients required mechanical ventilation. The LV GLS values obtained in our study can be attributed to the so-called grey zone, when the values can be regarded as both normal and pathological (LV GLS from –18% to –20%) [11]. It should be noted that according to the Greek researchers' data, the RV function parameters significantly improved, and one year after COVID-19 reached the parameters of the control group [13], which is fully consistent with our results.

The clinical significance of our study lies in identifying the negative dynamics of LV diastolic function in the long term after a complicated course of COVID-19. The assessment of arterial stiffness and LV diastolic function in this population may be an important prognostic factor and a marker of an increased risk of cardiovascular complications and thus will help identify a group of patients who need additional measures of secondary prevention.

A limitation of the study is the lack of data on arterial stiffness, LV longitudinal strain, and diastolic function before COVID-19 and during the acute period of the disease. It should be taken into account that the identified disorders, in addition to the direct effect of the virus, may be caused by its indirect effect through the development of new and aggravation of already existing cardiovascular diseases. In addition, our sample is limited to individuals with optimal Echo imaging.

CONCLUSION

Patients with optimal visualization on echocardiography one year after COVID-19 pneumonia, compared with the results of the examination after 3 months, have worsening parameters of LV diastolic function. LV GLS was within the "grey zone" and did not change significantly. An improvement in vascular stiffness was noted, associated with an improvement in the longitudinal strain of LV basal segments.

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Authors' contribution

Yaroslavskaya E.I. – conception and design, justification of the manuscript, critical revision of the manuscript for important intellectual content. Shirokov N.E., Krinochkin D.V. – analysis and interpretation of echocardiography data. Migacheva A.V. – analysis and interpretation of arterial stiffness parameters. Korovina I.O. – analysis and interpretation of the pulmonologist examination data, computed tomography of the lungs. Osokina N.A. – analysis and interpretation of the echocardiography data. Sapozhnikova A.D. – statistical data analysis. Petelina T.I. – final approval of the manuscript for publication.

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Received 29.03.2023;
approved after peer review 28.09.2023;
accepted 16.11.2023