

HEART DISEASE IN YOUNG ELITE ATHLETES HAVING A HISTORY OF COVID-19

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The impact of coronavirus infection (SARS-CoV-2) on cardiac output in underage athletes is uncertain. The study was aimed to determine heart disease in young elite athletes having a history of COVID-19 (SARS-CoV-2). A retrospective analysis of the results of the developed three-phase medical assessment of 236 elite athletes aged 14–17 (16 ± 1), who had had SARS-CoV-2 infection, was performed. The first phase of assessment involved examination, ECG, ECHO, bicycle ergometry (BEM), creatine kinase and creatine kinase MB tests. During the second phase 22 athletes (9.3%) underwent a more thorough assessment that included Holter monitoring (HM) with heart rate turbulence (HRT), microvolt T-wave alternans (MTWA), heart rate variability (HRV) estimation, signal averaged ECG (SAECG), determination of myocardial damage biochemical markers (troponin, NTproBNP) due to alterations revealed. Seven athletes (32%) having alterations revealed during this phase were referred to gadolinium enhancement cardiac magnetic resonance imaging (MRI) (the third phase). Myopericarditis was diagnosed in four cases (1.7% of 236) based on the results. Thus, low myocardial involvement (below 2%) has been revealed in young elite athletes, who have a history of SARS-CoV-2 infection. Cardiovascular assessment algorithm has been developed for such athletes. Detection of cardiac arrhythmias by ECG, BEM, and HM is the most informative. SAECG, HRV, HRT, and MTWA can be used as additional methods to determine indications for MRI as a gold standard of the diagnosis of myocarditis.

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ПОРАЖЕНИЕ СЕРДЦА У ЮНЫХ ЭЛИТНЫХ СПОРТСМЕНОВ, ПЕРЕНЕСШИХ COVID-19

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Влияние коронавирусной инфекции (SARS-CoV-2) на состояние сердца у несовершеннолетних спортсменов остается неопределенным. Целью работы было определение поражения сердца юных элитных спортсменов, перенесших инфекции COVID-19 (SARS-CoV-2). Проведен ретроспективный анализ результатов разработанного трехэтапного медицинского обследования 236 элитных спортсменов 14–17 (16 ± 1) лет, перенесших инфекцию SARS-CoV-2. Первый этап обследования включал осмотр, ЭКГ, ЭХО-КГ, велоэргометрию (ВЭМ), оценку КФК и КФК-МБ. В связи с выявленными изменениями 22-м спортсменам (9,3%) на втором этапе проводили более углубленное обследование, включающее холтеровское мониторирование (ХМ) с оценкой турбулентности ритма сердца (ТРЦ), микровольтной альтернации Т-зубца (МАТ) и вариабельности ритма сердца (ВРС), ЭКГ высокого разрешения (ЭКГ ВР), определение биохимических маркеров поражения миокарда: тропонин, NTproBNP. Семь спортсменов (32%) с выявленными на этом этапе изменениями были направлены на проведение магнитно-резонансной томографии (МРТ) сердца с контрастированием гадолинием (третий этап). По ее результатам в четырех случаях (1,7% из 236) был поставлен диагноз миокардит. Таким образом, отмечена низкая (менее 2%) вовлеченность поражения миокарда у юных элитных спортсменов, перенесших инфекцию SARS-CoV-2. Разработан алгоритм обследования сердца таких спортсменов. Наиболее информативно выявление аритмий сердца с помощью ЭКГ, ВЭМ и ХМ. Дополнительными методами определения показаний к МРТ сердца как золотому стандарту диагностики миокардита могут быть методы ЭКГ ВР, ВРС, ТРЦ и МАТ.

Ключевые слова: коронавирусная инфекция, SARS-CoV-2, миокардит, юные элитные спортсмены, неинвазивная электрокардиология**Финансирование:** исследование выполнено по гранту № 37B /ЦСМ ФМБА России/22 от 10.08.2022.**Вклад авторов:** Л. М. Макаров — концепция и дизайн исследования, написание текста рукописи, формулировка выводов; В. Н. Комолотова — анализ данных с помощью статистических и математических методов, сбор данных литературы, формулировка выводов; И. И. Киселева — клиническое обследование спортсменов, сбор данных литературы; Д. А. Беспорточный — проведение инструментальных исследований, работа с графическим материалом; А. Г. Акоюн, А. В. Дмитриева — проведение инструментальных исследований; Н. В. Аксенова — отбор групп обследования.**Соблюдение этических стандартов:** исследование одобрено этическим комитетом РНИМУ им. Н. И. Пирогова (протокол № 217 от 18 апреля 2022 г), проведено в соответствии с требованиями Основ законодательства «Об охране здоровья граждан»; все участники подписали информированное согласие на обследование.✉ **Для корреспонденции:** Леонид Михайлович Макаров
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Today, there are extensive data on cardiovascular disease, primarily myocarditis, in patients having a history of COVID-19 (SARS-CoV-2), including in athletes [1–6]. It is well-known that myocarditis often causes sudden cardiac death (SCD) in sports [7–9].

However, the data on the prevalence and clinical significance of heart disease in athletes, who had had the SARS-CoV-2 infection, varied significantly (1.4–56%) depending on the disease assessment criteria, diagnostic methods applied, and other aspects of the study design [3–5]. Cardiac MRI is the gold standard of detecting the heart disease following previous infection [1]. However, this method is costly and cannot be used as a screening tool. The search for additional markers and factors is an extremely topical task, which will make it possible to clarify the category of individuals in need of this procedure. The so-called “triad” testing (ECG, ECHO, troponin measurement) is the most widely used protocol for cardiovascular testing after having SARS-CoV-2 infection in the world [2–6]. Myocarditis of any etiology is a major cause of sudden death in athletes [7–9]. Abnormal “triad” testing results probably associated with SARS-CoV-2 affecting the heart were obtained using ECHO in 24 (0.9%) out 2556, using 12-lead ECG in 21 (0.7%) out 2999, and using troponin measurement in 24 (0.9%) out of 2719 [10].

The study was aimed to determine heart involvement in the elite athletes of higher sports mastery having a history of COVID-19 (SARS-CoV-2).

METHODS

Inclusion criteria: athletes' age 14–17 years; self-reported previous SARS-CoV-2 infection or medical documents confirming the history of SARS-CoV-2 infection; cardiac check-up conducted as part of in-depth medical assessment in the Center for Syncope and Cardiac Arrhythmias, Federal Scientific and Clinical Center for Children and Adolescents of FMBA of Russia.

Exclusion criteria: athletes' age under 14 and over 17 years; no in-depth medical assessment results.

To conduct retrospective analysis of the cardiovascular system assessment results, 236 medical histories of young elite athletes aged 14–17 (16 ± 1), who had reported having SARS-CoV-2 infection between September 1, 2021 and June 31, 2022, out 1505 were selected based on the inclusion criteria. All athletes had cardiac check-up conducted as part of in-depth medical assessment in the Center for Syncope and Cardiac Arrhythmias, Federal Scientific and Clinical Center for Children and Adolescents of FMBA of Russia. The time between infection and check-up was 1–6 months.

The examination program consisted of three phases. During the first phase the following was performed in all athletes as part of in-depth medical assessment: history taking and gathering complaints, examination involving measuring blood pressure, auscultation, cardiac percussion, 12-lead ECG (Mac 5500; GE Healthcare, USA), ECHO (Vivid T8, GE Healthcare, USA) and bicycle ergometry or BEM (CardioSoft 6.5; GE Healthcare, USA), extended biochemical profile. When performing analysis of medical documents, emphasis was placed on previous coronavirus infection, specific symptoms of infection (loss of taste and smell), common symptoms of intoxication associated with infection, duration of fever and the disease. Complaints of palpitation and dyspnea that were non-specific for coronavirus infection, as well as the decreased athletic performance, abnormal heart murmurs, and heart failure assessment were also taken into account. The analysis of previous 12-lead ECG was performed based on the Seattle criteria [11] and

International recommendations [12] for the athletes' ECG analysis; heart rhythm disturbances and the signs of metabolic and ischemic myocardial alterations (T wave, ST segment, QT interval alterations).

ECHO was performed in accordance with the standard protocol involving assessing contractility of myocardium and heart chambers, hemodynamic parameters. Heart dimensions were estimated against body surface area and compared with normal age- and gender-related values considering z-scores of deviations [13]. BEM was performed in accordance with PWC 170 involving assessment of ECG and blood pressure during each phase of the test and the recovery period [14]. The creatine kinase and creatine kinase MB fraction levels were assessed in biochemical profiles of all athletes. The creatine kinase levels of 26–174 U/L and creatine kinase MB levels of 0–24 U/L were considered to be normal.

When detecting abnormalities during the first phase, the athlete was referred to the second-phase assessment that also included signal averaged ECG (SAECG) with ventricular late potentials detection: tot fQRS (normal values are below 114 ms), Last 40 (normal values are over 38 ms), and RMS40 (normal values are over 20 Hz) [14], Holter monitoring with estimation of arrhythmia and the dynamics of ventricular repolarization indicators (ST, T, QT alterations). When assessing the results of Holter monitoring, emphasis was on the signs of electrical myocardial instability: reduced heart rate variability or HRV (values below SDNN 100 ms, pNN50 below 15%) [15], episodes of microvolt T-wave alternans (above 55 μ V) [16], reduced heart rate turbulence (onset over 0% and slope over 6 ms/RR) [17].

At this stage biochemical markers of myocardial damage were also determined: troponin (normal values are below 9 ng/mL) and N-terminal pro-B-type natriuretic peptide (NT-proBNP, normal values are below 125 pg/mL) levels.

When detecting abnormalities during this phase, the athlete was referred to the third-phase assessment involving the gadolinium enhancement cardiac magnetic resonance imaging (MRI).

Statistical data analysis was performed using the Statistica software package for Windows, ver. 7.0 (StatSoft; USA). Nonparametric statistical methods were used for data analysis, the differences were considered significant at $p < 0.05$.

RESULTS

The algorithm and results of the three-phase assessment of underage athletes having a history of SARS-CoV-2 infection are provided in Figure. The majority of athletes had mild and even more often asymptomatic (positive PCR tests performed during the pre-competition examination) SARS-CoV-2 infection, only one athlete developed pneumonia and needed hospital admission. None of the athletes had heart abnormalities according to the data of physical examination. During the first phase, cardiovascular system alterations that required in-depth assessment were found in 22 athletes (9.3%) based on the ECG, BEM, and ECHO data (Table 1). The combinations of several abnormalities were observed in six athletes. We revealed no relationship between the SARS-CoV-2 infection severity according to medical history and the need for second-stage assessment. As mentioned above, one athlete was earlier hospitalized with the COVID-19-associated pneumonia, however, cardiac check-up revealed no heart involvement.

The levels of creatine kinase were estimated in all athletes during the first phase of assessment. The group that needed second-phase assessment had significantly higher total

Table 1. Cardiovascular system alterations in underage elite athletes having a history of SARS-CoV-2 revealed during the first-phase assessment (see Figure). AVB — atrioventricular block; BEM — bicycle ergometry; PVC — ventricular extrasystole; LVEDD — left ventricular end-diastolic diameter; QTc — QT interval corrected using Bazett's formula (QT/√RR)

Alterations detected	n of athletes (% of all group)
Ventricular extrasystole on the resting ECG	2 (0.8%)
AVB, 2nd degree, Mobitz I, on the resting ECG	1 (0.4%)
QTc exceeding 460 ms on the resting ECG	5 (2.1%)
Reduced LV contractility and increased LVEDD	2 (0.8%)
PVC on BEM	18 (7.6%)
T wave inversion on BEM	8 (3.3%)

creatinine kinase levels (525 [155, 684] vs. 325 [74, 422] U/L, $p < 0.05$) and creatine kinase MB levels (27 [5, 34] vs. 21 [7, 24] U/L, $p < 0.05$). No cases of elevated troponin or natriuretic peptide (NT-proBNP) levels were revealed during the second phase.

Ventricular late potentials were reported in two athletes (9%) out of 22 based on all three HRECG parameters (total fQRS — 122 ± 5 ms whereas normal values are below 114 ms, Last 40 — 42 ± 5 ms whereas normal values exceed 38 ms, RMS40 — 18 ± 3 Hz whereas normal values exceed 20 Hz). The presence of these electrical myocardial instability signs suggested possible post-COVID myocarditis and allowed us to refer the athletes to MRI.

HM revealed sinus bradycardia in almost all athletes, only three athletes (16%) out of 22 had HR exceeding normal (sinus tachycardia) [15]. Reduced HRV was reported in two of them. One athlete had his HR back to normal after a month of rest, therefore, sinus tachycardia revealed by HM was considered as a sign of overtraining. None of 18 athletes showing exercise-induced ventricular extrasystole during BEM showed frequent ventricular extrasystoles during HM; the extrasystole rate varied between single extrasystoles and 105 extrasystoles per day (less than 1%), it was associated with elevated HR in the diurnal cycle (diurnal type). Reduced heart rate turbulence, the indicator associated with malignant extrasystole against the background of possible myocardial involvement, was

revealed in two athletes out of 18 (11.1%). A short run of nonsustained ventricular tachycardia of three QRS complexes was recorded during HM in the morning in one athlete, who also needed MRI. HM revealed the values of microvolt T-wave alternans exceeding 55 μ V in three patients with exercise-induced ventricular extrasystole. All eight athletes, who showed abnormal ventricular repolarization (negative T waves) during BEM (Table 1), had similar episodes during HM in the form of deep T-wave inversion, mainly against the background of sinus tachycardia. The analysis of previous check-ups of these athletes revealed similar alterations found during the in-depth medical assessment performed before the infection in three individuals (37.5%), thereby allowing us to exclude post-COVID-19 alterations. The patients with the combination of abnormal ventricular repolarization and exercise-induced ventricular extrasystole were referred to MRI. Thus, after the second phase of assessment seven athletes (32%) out of 22 were referred to the contrast-enhanced cardiac MRI (Table 2) that was performed in six of them. One athlete failed to provide MRI results, and his further sports fate is unknown. Myopericarditis was diagnosed in four athletes (1.7% of 236) based on MRI results. MRI revealed no alterations in the athlete, who had shown a run of nonsustained ventricular tachycardia. Four athletes with confirmed myocarditis were suspended from training for six months in accordance with the existing guidelines [18].

Table 2. Results of third-phase assessment of athletes having a history of SARS-CoV-2 infection (contrast-enhanced heart MRI). AVB — atrioventricular block; HRC — heart rate variability; BEM — bicycle ergometry; VT — ventricular tachycardia; PVC — ventricular extrasystole; LVEDD — left ventricular end-diastolic diameter; MTWA — microvolt T wave alternans; MRI — magnetic resonance imaging; HRT — heart rate turbulence; EF — ejection fraction; HM — Holter monitoring

	Age, gender, sports	ECG	ECHO	BEM	HM	MRI
1	17, f, field hockey	Tachycardia, QT prolongation (QTc > 460 ms)	normal	Abnormal ventricular repolarization, exercise-induced PVC	Tachycardia, abnormal ventricular repolarization, rare PVC, reduced HRT, MTWA	Data confirming subacute myopericarditis
2	16, f, badminton	PVC	normal	PVC during testing	MTWA, tachycardia, reduced HRV	No alterations detected
3	16, m, hockey	AVB, 2nd degree, Mobitz I	normal	AVB, 1st degree, at the beginning of the test and during the recovery period	Frequent episodes of AVB, 2nd degree, Mobitz I and II	Acute myopericarditis
4	15, m, boxing	Abnormal ventricular repolarization (ST depression up to 0.5 mm in V4-V6)	Reduced contractility (EF 53%), diastolic dysfunction	Abnormal ventricular repolarization worsens under load	Abnormal ventricular repolarization	No data
5	16, m, volleyball	QT prolongation (QTc > 460 ms)	LV dilatation (LVEDD up to 61 mm), normal EF	normal	Tachycardia, reduced HRV, 1st degree AVB, episodes of 2nd degree AVB	Data confirming acute myocarditis
6	15, f, artistic gymnastics	normal	normal	Abnormal ventricular repolarization, exercise-induced PVC	Abnormal ventricular repolarization, rare PVC, reduced HRT	Data confirming myopericarditis
7	16, m, swimming	normal	normal	Abnormal ventricular repolarization	Run of polymorphic VT, MTWA	No alterations detected

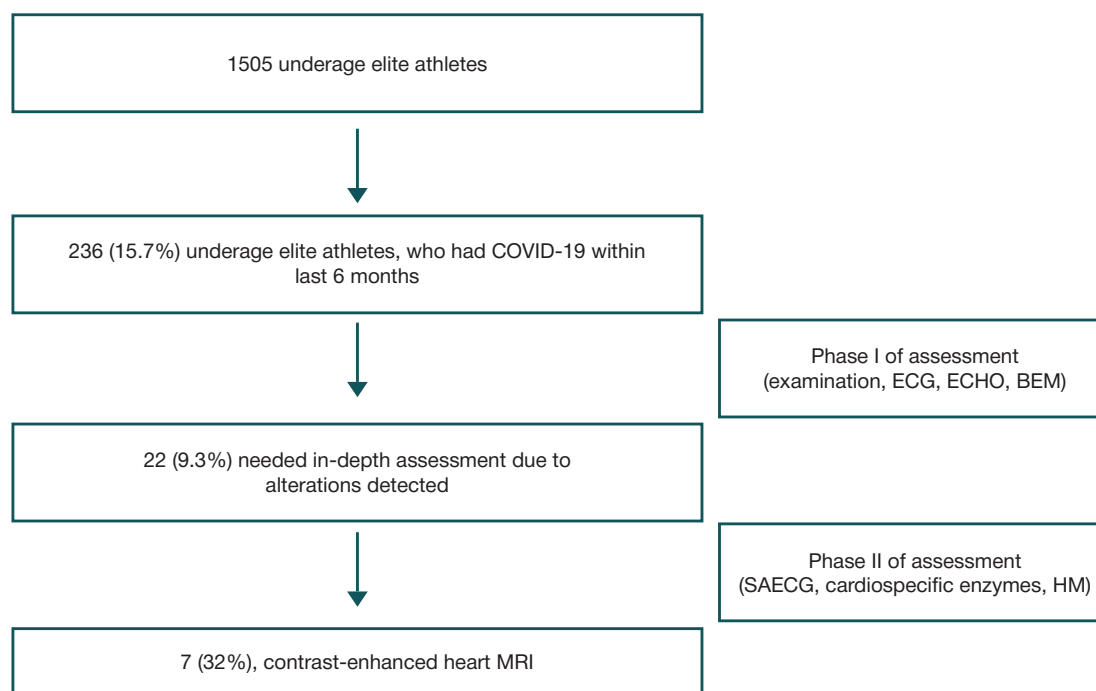


Fig. Algorithm and results of the three-phase assessment of underage elite athletes aged 14–17, who have had SARS-CoV-2 infection

DISCUSSION

Complications of SARS-CoV-2 infection affecting all systems of the body are reported in athletes. Cardiovascular system turned out to be the most vulnerable [18]. However, the prevalence and clinical manifestations of heart involvement in athletes having a history of SARS-CoV-2 infection vary considerably between studies [2–5, 18, 19]. Our findings showed that the prevalence of myocardial inflammation following previous SARS-CoV-2 infection in young athletes turned out to be low (1.7%) relative to the data of the sample of adult patients with severe disease (non-athletes, average age 64 years, 33% females) [20]. According to our data, reduced left ventricle contractility was observed in only one young athlete; unfortunately, he failed to provide the data of MRI he was recommended. In general, according to some reports, the detection rate of definite or probable heart involvement in young athletes was 2.7% [10], which was significantly lower compared to adult patients [1].

The symptoms of previous infections usually did not determine the course severity and complications. Thus, in one of the studies the clinically significant disease symptoms were reported in 27% of athletes, while myocarditis was found in 46% [4]. Other authors reported symptoms in 70–77% of cases, while no cases of myocarditis were revealed [2, 19]. Similar data were obtained during our study: among 236 athletes, only one had moderate disease. He was admitted to hospital due to pneumonia, but later had no cardiovascular alterations. In contrast, all athletes with confirmed myopericarditis had mild novel coronavirus infection (loss of taste or smell only). The fact of previous novel coronavirus infection is not always the cause of cardiac abnormalities detected. Such alterations in young elite athletes are often caused by the “overtraining” syndrome [21]. It is sometimes difficult to reveal the relationship between the alterations detected and previous infection, the analysis of previous assessment is often helpful. In our study, the analysis of previous documents in three athletes with abnormal repolarization during exertion out of eight made it possible to exclude coronavirus infection as the cause of alterations detected. One female athlete (patient 2; Table 2) had

a combination of ventricular extrasystole, sinus tachycardia, and reduced HRV, however, no alterations were revealed by MRI. HR and HRV were back to normal after the short rest.

The so-called “triad” testing (ECG, ECHO, troponin measurement) is the most widely used protocol for detection of cardiac involvement after having SARS-CoV-2 infection in the world [18]. That is why our study involved assessment of troponin levels during the second phase, however, no cases of elevated levels were revealed. Perhaps, this is due to the fact that the time between the infection and the check-up was 1–6 months, despite elevated troponin levels can persist within 52 ± 17 days after the infection [22]. In one of the largest studies focused on assessing the course and effects on the heart of young athletes having a history of acute coronavirus infection, abnormal results of the “triad” testing probably associated with the heart disease after SARS-CoV-2 were detected by ECHO in 24 individuals (0.9%) out of 2556, by 12-lead ECG in 21 individuals (0.7%) out of 2999, by troponin measurement in 24 individuals (0.9%) out of 2719. A total of 65 athletes had at least one abnormal test, two athletes had two abnormal tests (ECG, ECHO), none of the athletes had three normal tests [10]. Myocarditis following previous SARS-CoV-2 infection was revealed in 81 athletes (2.7%) based on the “triad” testing and MRI, in 56 athletes (1.9%) the alterations detected were not associated with previous infection. According to the study, the “triad” testing turned out to be a highly sensitive marker of heart involvement in patients having a history of SARS-CoV-2 infection (OR: 37.4; CI: 13.3–105.3) [10]. We believe that the “triad” testing can be useful for detection of heart involvement in athletes, since in our study 75% of individuals with confirmed myocarditis had abnormalities on ECG and 25% had abnormalities on ECHO. One more study of athletes having a history of COVID-19 has shown that MRI was 7.4 more informative in terms of detecting heart involvement than other tests [23]. However, the value of MRI as a tool for mass screening of all athletes, who have had SARS-CoV-2 infection, is still unknown [18].

In our study, ECG, BEM, and HM were the most informative tests for detection of heart involvement before conducting MRI

(Table 1). In our opinion, such noninvasive electrocardiology methods, as SAECG and assessment of heart rate turbulence and variability, can be used as additional informative methods.

The wider use of MRI and additional methods for assessment of athletes having a history of SARS-CoV-2 infection will enable a more accurate determination of the heart disease prevalence in this group, since the issue of efficiency and informativeness of MRI-based screening in all athletes, who have had SARS-CoV-2 infection, relative to the study based on certain indications is a matter of debate [10]. The diversity of clinical manifestations, lack of strong associations between the previous infection severity and the development of complications raise many questions about the possibility of admitting athletes having a history of SARS-CoV-2 infection to training.

Retrospective design and lack of possibility to compare the levels of anti-SARS-CoV-2 antibodies and PCR tests at the disease onset with the later detected alterations, as well as short follow-up period not allowing one to estimate the long-term follow-up history, are the study limitations. The association of the disease with the athletes' anthropometric data, experience in athletics, training stage, previous injuries,

etc., was not included in the analysis, which can be considered in further studies.

CONCLUSIONS

Low prevalence (up to 2%) of hearth involvement after the infection is observed in underage elite athletes having a history of SARS-CoV-2 infection. A three-phase algorithm for assessment of cardiovascular system in athletes, who have had SARS-CoV-2 infection, has been developed. Detection of cardiac arrhythmia by ECG, bicycle ergometry or Holter monitoring is the most informative in terms of determining probable heart involvement in young athletes. Detection of ventricular late potentials by SAECG, as well as reduced heart rate variability and turbulence, microvolt T-wave alternans, can be considered as additional methods to determine indications for MRI. Gadolinium enhancement cardiac MRI is the gold standard of myocardial involvement diagnosis in underage elite athletes having a history of SARS-CoV-2. However, the value of this method as a tool for mandatory screening of all convalescent athletes is still a matter of debate.

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