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FUNCTIONAL FEATURES OF THE CARDIOVASCULAR SYSTEM IN COVID-2019 CHILDREN

Relevance. The consequences of COVID-19 are a serious problem and a cause of health problems for children. Identifying post-COVID-19 health problems to develop rehabilitation and treatment options is an important public health challenge. One of the urgent problems is the violation of the functional parameters of the cardiovascular system in children.

Material and methods. The functional state of the cardiovascular system of children who had COVID-19 in school conditions at the age of 8-12 years was studied. A total of 64 children (32 girls and 32 boys) were studied, 3-6 months after suffering COVID-19. The children were examined by copy-pairs. The study included children in the age range (8-12 years), in which functional indicators have the same reference values according to the methods used. The functional indicators of the cardiovascular system were studied according to the electrocardiogram data using the analysis of heart rate variability according to R.M. Baevsky, as well as with the help of the Martinet-Kushelevsky functional test. The following were studied: adaptive potential, response quality index, Kerdo autonomic index, coefficient of variation, systolic and diastolic blood pressure, pulse pressure, heart pumping function by assessing the stroke and minute volume of the heart, the index of functional changes, the stress index, the total power of the spectrum.

Results. It was shown that one of the mechanisms of functional disorders of the cardiovascular system in the period from 3 to 6 months after COVID-19 is a syndrome of autonomic dysfunction. The manifestations of autonomic dysfunction in children are hypertensive changes in the cardiovascular system in the absence of pronounced clinical manifestations, the presence of functional tension of regulatory systems, unsatisfactory functional status, decreased rates of increase in heart rate power in response to load, low values of sympathetic regulation mechanisms and centralization of the cardiovascular system regulation circuit, a large proportion of the influence of the peripheral regulation circuit.

Conclusion. One of the pathogenetic mechanisms for reducing the functional parameters of the cardiovascular system in children who have had a coronavirus infection is endothelial dysfunction syndrome.

Keywords: children, COVID-19, cardiovascular system, functional parameters, endothelial dysfunction syndrome.

The SARS-COV-2 virus (COVID-19), which has caused the pandemic coronavirus infection, has several features that lead to the development of a multisystemic inflammatory syndrome [1]. According to various authors, the condition does not exclude the paediatric population [6]. According to foreign studies, autonomic dysfunction syndrome should be excluded in children with abdominal pain, signs of gastrointestinal disturbances, respiratory or neurological symptoms of unclear etiology [19].

According to some authors [18, 19, 20, 21], the over-infected patients (COVID-19) have multiple organ involvement, myocardial dysfunction, coagulopathies, and increased inflammatory markers [4]. Often, serious cardiovascular abnormalities in children are asymptomatic and are not recognised in time (6).

Therefore, the study of the effect of coronavirus infection on the health and functional outcomes of children is highly relevant.

Purpose of the study: to identify functional changes in the cardiovascular system in children with coronavirus infection.

Material and methods of investigation. Children aged 8-12 years who had had coronavirus infection during the last 3 months and a control group were investigated. The children in the study group had a mild to moderate coronavirus infection. The disease was diagnosed by an outpatient clinic doctor according to the diagnostic criteria of COVID-19 (main clinical manifestations: nasal congestion, sneezing, headache, weakness, fever) and was confirmed by laboratory PCR test of the mouth and nasopharynx. Children with severe forms of the disease, with clinical manifestations of multinflammatory syndrome, with myocardial infections, and carriers of infection were not included in the study group. Children in the control group were matched by the copy-pair method and had no documented contacts with COVID-19 patients during the last 3 months before the examination. Carriage in children in the control group was excluded by the results of rapid tests administered at school to all students in the follow-up group (8-12 years old) during the period from the beginning of the pandemic to the end of the study. No blood was drawn for antibodies in the observation group. Copies were matched for age and sex. The age group 8-12 years old was investigated, taking into account the grouping of the functional indicators of the techniques that were used, i.e. the age norms of these indicators in children 8-12 years old fell within one age range of the age norm. All children attending the Irkutsk Education Center No. 47. All children of the control and studied groups had no somatic (and other) pathology, including vegetative dysfunction and were in the 1st health group. A total of 64 children were investigated, 32 children who had had a coronavirus infection within the next 3-6 months, and 32 children in the control group (who had not been ill themselves and had no family history of coronavirus infection in their relatives since the beginning of the pandemic). Children who became ill with COVID-19 were not allowed to attend classes im-

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mediately after the first signs of illness. Each group consisted of 16 girls and 16 boys, distributed in copy-pairs.

Electrocardiography (ECG) [11] and the Martinet-Kushelevsky functional test [9] were used to study the functional parameters of the cardiovascular system.

Electrocardiogram was recorded using 12-channel electrocardiograph POLI-SEKTR-8/EX (Neurosoft Ltd.) equipped with modules for heart rate variability (HRV), stress-ECG, pulse wave velocity (PWV), Q-T dispersion, detection of late ventricular potential (LEP) [5, 6]. ECG was assessed using heart rate variability (HRV) analysis method according to R.M. Baevsky [11], using software included into the module. The system is included in the standard of equipment of functional diagnostics departments according to the orders of the Ministry of Health of the Russian Federation No. 92n dated March 7, 2018 "On approval of the Regulations on organization of primary health care for children" and No. 997n dated December 26, 2016 "On approval of the Rules for functional studies". Six standard leads (according to W. Einthoven and E. Goldberger) [5, 7, 12] were recorded first at rest and then in orthopposition.

The Martinet-Kushelevsky test was performed in a standardised manner with a dosed load of 20 squats for 30 seconds, followed by measurements during recovery.

Functional indices were studied according to age groups [5, 7, 12]. The following parameters were studied: systolic and diastolic blood pressure (SBP and BP), pulse pressure (PPP) were studied by Korotkoff method; ECG analysis by pulsometry according to R.M. Baevsky assessed the heart pump function (by estimating the stroke volume (SBV) and minute blood volume (MOB)), functional change index (FDI), tension index (TI), total power spectrum (TP), adaptive potential (AP), response quality index (RQI), Kerdo vegetative index (CI), coefficient of variation (CV) [5, 12]. All studied indices were validated in Russia [5,7,12].

Shock volume was calculated:

YO=80+0.5×PD - 0.6×(DAD - C),

where AP is pulse blood pressure (mmHg), DAP - diastolic blood pressure (mmHg), B - age (years).

Minute blood volume according to the formula:

MOC = YO × HSF [5, 6],

Index of functional changes by the formula:

IFI = 0.011HSS + 0.014SAD + +0.008DAD + 0.014V + 0.009MT - -0.009R - 0.27 [7, 12],

where HR - heart rate, bpm, SAD - systolic blood pressure, mmHg, DAP - diastolic blood pressure, mm Hg, B - age, years, MT - body weight, kg, P - body length, cm, 0.27- independent coefficient.

The regulatory tension index, which reflects the degree of centralisation of heart rhythm control, was determined according to the formula:

IN=AMo/(2BP×Mo)) [7,12],

Adaptation potential was determined according to the formula:

AP = 0.011HP + 0.014SAD + +0.008DAD + 0.014V + 0.009MT - -(0.009P + 0.27) [7,12],

where B - age, years, MT - body weight, kg, R - height, cm, SBP - systolic blood pressure, mmHg, DAP - diastolic blood pressure, mm Hg, HR - pulse rate per 1 min.

The response quality index in the Martin-Kushelewski test:

PCR = (RD2 - RD1)/(P2 - P1) [7,9,12],

where P1 is resting pulse, PD1 - pulse pressure at rest, P2 - heart rate after exercise, PD2 - pulse pressure after exercise).

The good functional state of the cardiovascular system was taken at PKR = 0.5 to 1.0.

The Kerdo index is calculated according to the formula:

IC = (1-DAD / HSF)×100[7,12],

where DAP is diastolic pressure, HR is heart rate [5].

The basic orientation of the autonomic nervous system (ANS) tone was classified into 5 types according to IR [5, 11]:

1. IR > -31: predominance of parasympathetic tone - marked parasympathicotonia.
2. IR between -16 and -30: intermediate state between normal and parasympathic tone - parasympathicotonia.
3. IR between -15 and +15: sympathetic and parasympathetic balance - normotonia.
4. IR between +16 and +30: intermediate state between normal and sympathetic tone - sympathicotonia.
5. AC > +31: predominance of sympathetic tone - marked sympathicotonia.

In addition, we used clinical pediatric examination to define cardiac boundaries and auscultation.

Statistical processing was performed using Statistica Base 10 for Windows. Statistical processing included arithmetic mean (M), standard deviation (s), and error in arithmetic mean (m). Prior to statistical analysis we assessed the distribution of the signs for normality using the Harker-Bera test. Statistical significance of differences in quantitative characteristics having normal distribution was analysed by Student's t-test in the confidence interval > 95%. In case of non-normal distribution of the variation series, the statistical significance of the differences was analysed using Mann-Whitney test. The statistical significance of differences in qualitative variables was analysed using the χ2 test. Dependence between two variables was assessed using Spearman's correlation coefficient. The critical level of significance for statistical hypothesis testing was 0.05.

Results of the study. It was found that the main blood pressure parameters such as systolic and diastolic pressure, pulse pressure and heart rate tended to increase in the COVID-19-treated children, but no statistically significant differences could be found (Figure 1 and Figure 2). This was evident when the values were measured both at rest and after exercise.

There was a trend towards increased stroke and minute blood volume in children with COVID-19 (Table).

Studying the degree of adaptability, functional reserves of organism and predicting negative changes of health by studying the index of functional changes (IFI) in the investigated group was higher than 2,1 conventional units, which shows the presence of functional tension of regulatory systems (p < 0,05). Such indexes of RSI require elimination of risk factors and rehabilitation of children. In the control group, the index was 1.9±0.3 standard units, which corresponds to the norm (p > 0.05) [5].

The study of cardiac rhythm spectrum power index in children, which characterizes the total absolute level of regulatory systems, showed that the index (TP) at rest in the control group was 1.5 lower than in the study group (p < 0.05).

Indicators of shock and minute blood volume in children

Indicator	Study group n=32	Control group n=32	Value of p
Shock volume (SV). beats per minute	65.4±8.4	64.8±6.4	p > 0.05
Minute blood volume (MBV). millilitres per minute	5967.5±1020.8*	5495.3±883.9	p < 0.05

*(p < 0.05).

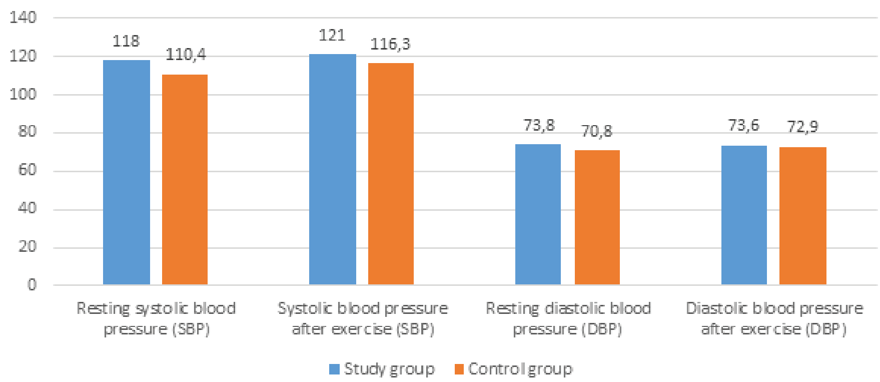

Fig. 1. Indicators of systolic and diastolic pressure in children

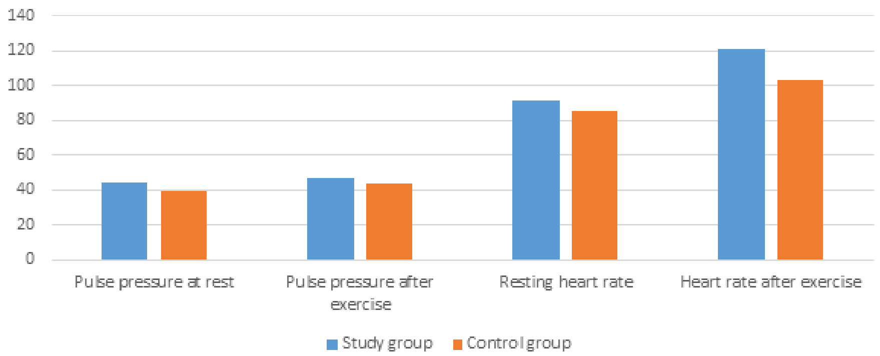

Fig. 2. Indicators of pulse pressure and pulse in children

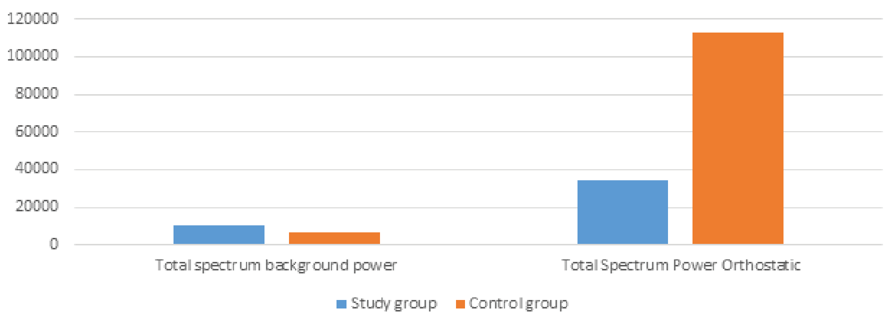

Fig. 3. Spectrum power indicators in children ($p < 0,05$)

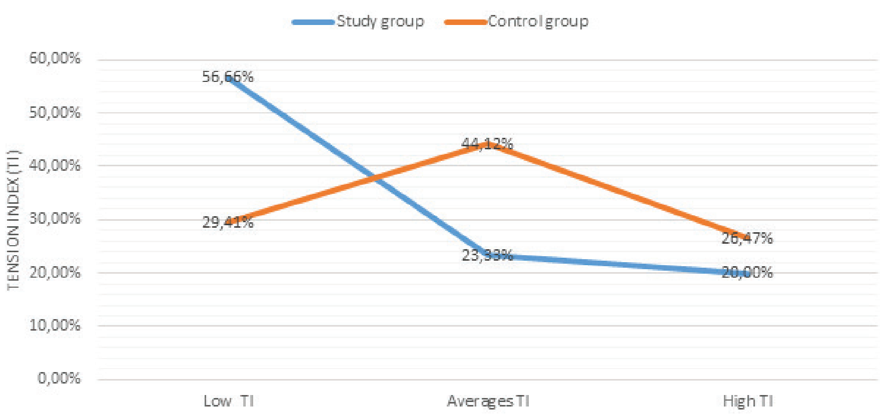

Fig. 4. Tension Index Levels in Children

This indicated the absence of tension of regulatory systems in children without COVID-2019 and insignificant tension at rest in the studied group. During orthostatic test the power of the spectrum increased significantly in the control group (16.5 times) ($p < 0.05$), which indicated effective mobilization of regulatory systems in response to the load. While in the studied TP increased only 3.3 times ($p < 0.05$), i.e. the mobilization of regulatory systems was 5 times lower compared to the control group[5].

The stress index of regulatory systems, which characterizes the activity of sympathetic regulation mechanisms, the state of the central circuit and is calculated on the basis of analysis of the diagram of cardiointervals distribution demonstrated that in the studied group the low activity of the central circuit of sympathetic regulation was registered in most children. The AN level increases with increasing endurance of the organism, the indices of AN level (see Fig. 4) characterized the decrease of endurance and the decreased role of the central circuit regulation in the group of children who underwent COVID-19. In our study, IN values were divided in the groups into low, medium and high. The high IN values were similar in both groups, but the low IN values predominated in the study group, whereas the medium IN values predominated in the study group ($p < 0.05$) [5].

The index of reaction quality in the Martine-Kushelevsky test revealed an unsatisfactory functional state in children in the studied group and was 0.4±1.4 conventional units, while in the control group this index corresponded to a good functional state (0.5±1.4 conventional units) [11].

Adaptation potential is an index of vital functions, the formation of which level depends on a complex of changes in physiological systems of a human organism (state of nervous, pituitary and adrenal hormones, cardiovascular, respiratory and other systems) as well as under the influence of stress factors (physical and mental load, atmospheric pressure, temperature changes, etc.) [11].

In our study, the level of adaptive potential was 3.6±0.8 in the COVID-19 group and 3.2±0.7 in the control group, which corresponds to a more pronounced stress of adaptation mechanisms ($p<0.05$).

After Kerdo index calculation, the autonomic nervous system (ANS) state types were determined, which were classified into 5 tone types

1. IR > -31: predominance of para-

sympathetic tone - pronounced parasympathicotonia.

2. IR between -16 and -30: intermediate state between normal and parasympathic tone - parasympathicotonia.

3. IR between -15 and +15: sympathetic and parasympathetic balance - normotonia.

4. IR between +16 and +30: intermediate state between normal and sympathetic tone - sympathicotonia.

5. IR > +31: predominance of sympathetic tone - expressed sympathicotonia.

In this case the IR values were distributed as follows (see Fig. 5) [5].

Fig. 5 shows that sympathicotonic responses were less pronounced in children in the study group than in the control group ($p < 0.05$).

Coefficient of variation (CV) in its physiological sense is an index normalised to heart rate and reflects a less artifact-dependent and ectopic heart rate variability (Figure 6) [5].

Figure 6. Coefficient of variation of heart rate (CV) ($p < 0.05$).

It was shown that there were practically no changes of heart rate variability at rest and during exercise in children in the studied group. In the control group, rhythm variation was well expressed in relation to the load received ($p < 0.05$) [5].

Clinical paediatric examination, auscultation and measurement of the boundaries of absolute and relative cardiac dullness showed no abnormalities.

Discussion of results. The study showed that in children who had received COVID-19 there was an increase in the main haemodynamic indices (BP, BP, BP, HR, OI, IOC), indicating hypertensive changes in the cardiovascular system. However, this increase has no statistically significant differences between the study and control groups. A tendency towards hypertension has also been shown by many authors in COVID-19 sufferers [15,17].

The absence of clinical manifestations, changes of cardiac boundaries and auscultatory abnormalities of the cardiovascular system showed that the changes were of a functional nature. This was evidenced by an increase in the index of functional changes (IFI), which determined the presence of functional stress of the regulatory systems in children who had had COVID-19, which is consistent with the findings of other authors [14].

Reaction quality index in the Martine-Kushelevsky test revealed a poor functional state in children in the study group compared to the control group ($p < 0.05$).

Changes in the level of adaptive potential in the COVID-19 group of children also indicated a marked strain on adaptation mechanisms.

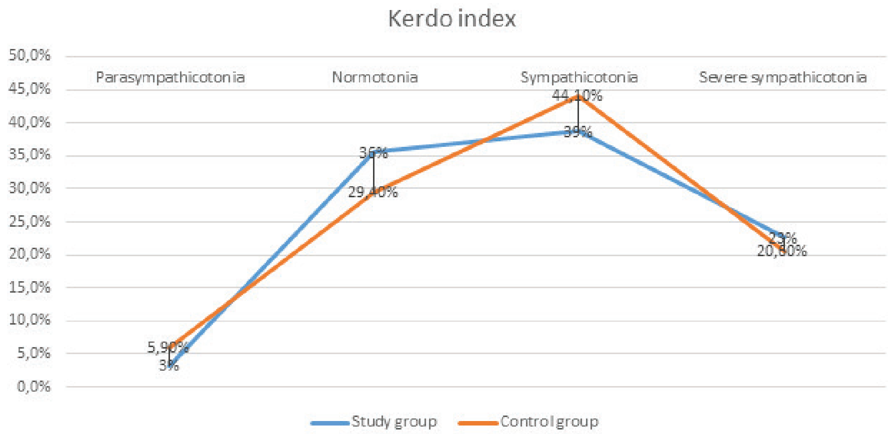

Fig. 5. Vegetative Kerdo index

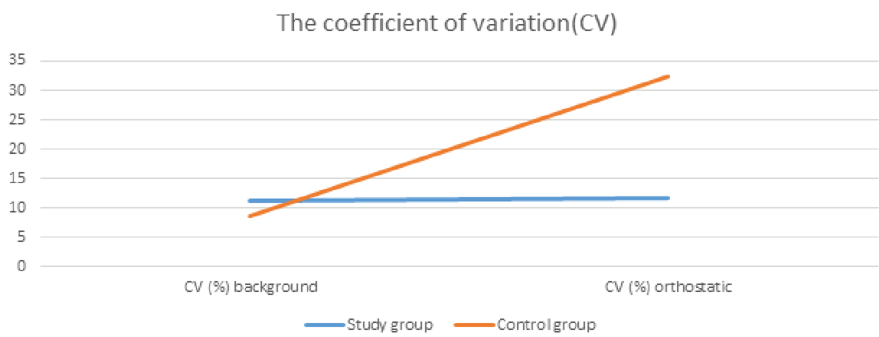

Fig. 6. Coefficient of heart rate variation (CV)

Functional changes in the study group were associated with an initial increase in total spectrum power, which increased 5-fold less in response to exercise than in the control group ($p < 0.05$). Such values of total spectrum power may be associated with depletion of mechanisms (or structures) responsible for an adequate response to load.

At the same time, the stress index of regulatory systems related to the activity of sympathetic regulation mechanisms and the state of central regulation circuit in the studied group showed lower values in comparison with the control group, which can be connected with the contribution of a greater part of regulatory mechanisms by the peripheral regulation circuit, and thus related to the state of the vascular system [14].

This phenomenon was also indicated by less pronounced sympathicotonic responses in the children in the study group, where the Kerdo index showed a flatter curve when allocating the children to groups according to the type of autonomic tone (see Fig. 5). The absence of variation in heart rate variability at rest and during exercise in children in the study group indirectly confirmed the depletion of central regulatory mechanisms and the predominance of adverse peripheral influences [3].

In this regard, it can be assumed that the main impairments of functional parameters on the part of the cardiovascular system in children who have undergone COVID-19 are associated with changes in the nervous system (general toxic lesion, cerebrovascular disorders, hypoxia) [16], the heart muscle (adenosine-converting enzyme-2 mediated cardiac lesion, hypoxia, cardiovascular disorders, systemic inflammatory response syndrome) [14] and the vascular bed (endothelial dysfunction syndrome, increased blood coagulation) [2, 3, 20, 21].

If we assume that the main mechanism of functional disorders of the cardiovascular system in our study is toxic action or hypoxia, then hypotensive reactions would be observed. If systemic inflammatory response syndrome was the main mechanism in this process, then indirect signs of inflammation of the heart muscle (changes in heart boundaries, cardiac murmurs) could have been observed. However, this was not observed in our study, due to the fact that it was conducted between 3 and 6 months after the disease.

Our study has shown the importance of investigating the functional state, physical and neuro-psychological development of children who have had coronavirus infection. This problem is of particular importance in the context of school intensification [8,16].

Conclusion. Our study revealed functional dysfunction in children with COVID-19. This is indicated by the pattern of changes in the functional parameters of the cardiovascular system in children between 3 and 6 months after COVID-19. The findings will help to suggest effective treatments for functional impairment in children.

Reference

1. Baklaushev V.P., Kulemzin S.V., Gorchakov A.A. [et al.] COVID-19. Etiologiya, patogenez, diagnoz i lechenie [COVID-19. Etiology, pathogenesis, diagnosis and treatment]. Klinicheskaya praktika [Clinical practice. 2020;11(1): 7-20 (In Russ.).] doi.org/10.17816/clinpract26339

2. Bolevich C.B., Bolevich S.S. Kompleksnyj mekhanizm razvitiya SOVID-19 [Comprehensive mechanism for the development of COVID-19]. Sechenovskiy Bulletin. 2020; 11(2): 50–61 (In Russ.).] https://doi.org/10.47093/2218-7332.2020.11.2.50-61.

3. Bubnova M.G., Aronov D.M. COVID-19 i serdechno-sosudistye zabolevaniya: ot epidemiologii do reabilitacii [COVID-19 and cardiovascular disease: from epidemiology to rehabilitation]. Pul'monologiya [Pulmonology. 2020; 30(5): 688–699 (In Russ.).] DOI: 10.18093/0869-0189-2020-30-5-688-699

4. Galstyan G.M. Koagulopatiya pri COVID-19 [Coagulopathy in COVID-19]. Pul'monologiya [Pulmonology. 2020;30(5):645-657 (In Russ.).] https://doi.org/10.18093/0869-0189-2020-30-5-645-657

5. Efimova N.V., Mylnikova I.V. Regional'nye pokazateli fizicheskogo razvitiya, funkcional'nogo sostoyaniya i adaptivnyh vozmozhnostej kardiorespiratornoj sistemy detej i podrostkov Irkutskoj oblasti: metodich. Rekomendacii [Regional indicators of physical development, functional state and adaptive capabilities of the cardiorespiratory system of children and adolescents in the Irkutsk region]. Guidelines. Angarsk: VSEIMI, 2016. – 44.

6. Zaplatnikov A.L., Svintsiskaya V.I. COVID-19 i deti [COVID-19 and children. Breast cancer. 2020;1(*):1–3 (In Russ.).]

7. M.B. Kuberger and et al. Kardiointervalografiya v ocenke reaktivnosti i tyazhesti sostoyaniya bol'nyh detej: metodicheskie rekomendacii [Cardiointervalography in assessing the reactivity and severity of the condition of sick children: guidelines. M., 1985; 15 (In Russ.).]

8. Kuchma V.R., Tkachuk E.A. Ocenka vliyaniya na detej informatizacii obucheniya i vospitaniya v sovremennyh usloviyah [Assessment of the impact on children of informatization of education and upbringing in modern conditions]. Rossijskij pediatricheskij zhurnal [Russian pediatric journal. 2015; 18(6): 20-24 (In Russ.).]

9. Kuchma, V. R. Gigiena detej i podrostkov : uchebnik [Hygiene of children and adolescents: textbook]. Moskva : GEOTAR-Media, 2012. 480 (In Russ.).] ISBN 978-5-9704-2319-6.

10. Melekhina E.V., Gorelov A.V., Muzyka A.D. Klinicheskie osobennosti techeniya COVID-19 u detej razlichnyh vozrastnyh grupp [Clinical features of the course of COVID-19 in children of different age groups]. Voprosy prakticheskoj pediatrii [Issues of practical pediatrics. 2020;15(2): 7–20 (In Russ.).]

11. Mikhailov V.M. Variabel'nost' ritma serdca: opyt prakticheskogo primeneniya metoda [Heart rate variability: experience of practical application of the method]. Ed. second, revised and additional: Ivanovo: Ivan. State Med. Academy, 2002; 290 (In Russ.).]

12. Spravochnik po funkcional'noj diagnostike v pediatrii [Handbook of functional diagnostics in pediatrics]. Ed. Yu.E. Veltishcheva, N.S. Kislyak. M.: Medicine, 1979: 242-244 (In Russ.).]

13. Tkachuk E.A., Tarmaeva I.YU. Nervno-psihicheskoe razvitie detej doshkol'nogo vozrasta v usloviyah informatizacii [Neuropsychic development of preschool children in the context of informatization]. Gigiena i sanitariya [Hygiene and sanitation. 2014; 93 (6): 23-26 (In Russ.).]

14. Fisun A.YA., Lobzin YU.V., Cherkashin D.V., Tyrenko V.V., Tkachenko K.N., Kachnov V.A., Kutelev G.G., Rudchenko I.V., Sobolev A.D. Mekhanizmy porazheniya serdechno-sosudistoj sistemy pri COVID-19 [Mechanisms of damage to the cardiovascular system in COVID-19]. Vestnik RAMN [Bulletin of RAMS. 2021;76(3):287–297 (In Russ.).] doi.org/10.15690/vramn1474

15. Chazova I.E., Blinova N.V., Nevzorova V.A. i dr. Konsensus ekspertov Rossijskogo medicinskogo obshchestva po arterial'noj gipertonii: arterial'naya gipertoniya i COVID-19 [Expert Consensus of the Russian Medical Society on Arterial Hypertension: Arterial Hypertension and COVID-19]. Sistemnye gipertenzii [Systemic hypertension. 2020; 17(3):35–41 (In Russ.).] DOI: 10.26442/2075082X.2020.3.200362

16. Shepeleva I.I., Chernysheva A.A., Kir'yanova E.M., Salnikova L.I., Gurina O.I. COVID-19: Porazhenie nervnoj sistemy i psihologo-psihiatricheskie oslozhneniya [COVID-19: Damage to the nervous system and psychological and psychiatric complications]. Social'naya i klinicheskaya psihiatriya [Social and Clinical Psychiatry 2020; 30: 4 76-82 (In Russ.).]

17. Chen Y., Guo Y., Pan Y., et al. Structure analysis of the recep_tor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020 Feb 17; 525(1): 135–40. DOI: 10.1016/j.bbrc.2020.02.071

18. Liu W., Zhang Q., Chen J. et al. Detection of COVID-19 in Children in Early January 2020 in Wuhan, China. N Engl J Med. 2020; Mar 12. DOI: 10.1056/NEJMc2003717

19. Ludvigsson J.F. Systematic review of COVID-19 in children show milder cases and a better prognosis than adults. Acta Paediatr. 2020 Mar 23. DOI: 10.1111/apa.15270.

20. Abdurahimov A. Kh., Khegay L. N., Yusupova Sh. K. COVID-19 i ego oslozhneniya // Re-health journal [COVID-19 and its complications]. Re-health journal 2021; 4 (12) (In Russ.).]

21. Bubnova M.G., Aronov D.M. COVID-19 i serdechno-sosudistye zabolevaniya: ot epidemiologii do reabilitacii [COVID-19 and cardiovascular diseases: from epidemiology to rehabilitation]. Pulmonology. 2020; 30(5): 688–699 (In Russ.).] DOI: 10.18093/0869-0189-2020-30-5-688-699