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THE STATE OF RESPONSE OF AUTONOMIC NERVOUS SYSTEM IN CHILDREN WITH MITRAL VALVE PROLAPSE

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Ключевые слова: *вегетативная нервная система, вариабельность ритма сердца, кардиоинтервалография, дети, пролапс митрального клапана*

Abstract. The state of response of autonomic nervous system in children with mitral valve prolapse. Mitiuriaeva-Korniyko I.O., Kuleshov O.V., Medrazhevska Ya.A., Fik L.O., Klets T.D. *The article presents summarized materials on connective tissue dysplasia of the heart, primary mitral valve prolapse, dysfunction of the autonomic system. Aim of research: to estimate the condition of autonomic nervous system in children with primary mitral valve prolapse. We examined 106 children with mitral valve prolapse aged from 13 to 17 years old on the clinical base of city hospital "Center of mother and child" in Vinnitsya. Research included time and frequency domain (evaluation with cardiointervalography. Final results were compared with the control group records. The results showed no statistical significance among time domain parameters in the main group of children. All these indices displayed tendency to sympathetic and parasympathetic autonomic nervous system tonus increase in boys. However, sympathicotonia tendency was noted in girls only. Frequency domain parameters showed similar results, compared with the previous. Nevertheless, very low frequency parameters had statistically significant difference in both subgroups of patience with mitral valve prolapse, including males (3205.8±190.9 against 1717±154, p<0.05) and females (3280±220.1 against 1433±811, p<0.05). There were no statistically significant difference among other frequency domain parameters. Conclusions: we estimated that children with mitral valve prolapse have imbalanced autonomic homeostasis manifested by tone disturbances of both autonomic vegetative system branches with sympathetic predominance. Patients with primary mitral valve prolapse generally have increased sympathetic tone - both boys and girls - according to spectral analysis of heart rate variability indices, heart rate oscillation power of a very low frequency in particular (p<0.05). In children with mitral valve prolapse, the tone of parasympathetic nervous system is generally normal; there is a tendency to its increase in boys and decrease in girls. These children should be under close medical supervision by pediatricians and cardiologists.*

Реферат. Стан реагування вегетативної нервової системи в дітей з пролапсом мітрального клапана. Мітюряєва-Корнійко І.О., Кулешов О.В., Медражевська Я.А., Фік Л.О., Клець Т.Д. *У статті наведені загальні дані про дисплазію сполучної тканини серця, первинний пролапс мітрального клапана, дисфункцію вегетативної системи. Метою дослідження було вивчення стану вегетативної нервової системи в дітей з первинним пролапсом мітрального клапана. Проведено дослідження 106 дітей з пролапсом мітрального клапана у віці від 13 до 17 років на базі міської лікарні "Центр Матері та Дитини" м. Вінниці. Обстеження включало визначення статистичних та спектральних показників варіабельності ритму серця за допомогою кардіоінтервалографії. Отримані результати порівнювались з відповідними параметрами групи контролю (здорові діти) ідентичного віку. У результаті була зареєстрована відсутність достовірних відмінностей серед статистичних параметрів досліджуваної групи дітей відносно контрольної. Симпатикозалежні та парасимпатикозалежні показники демонстрували тенденцію до напруги обидвох відділів вегетативної нервової системи в хлопчиків та тенденцію тільки до симпатикотонії в дівчаток. Серед спектральних показників*

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достовірні відмінності мав тільки параметр потужності коливань дуже низької частоти як у хлопчиків (3205,8±190,9 проти 1717±154, p<0,05), так і в дівчаток (3280±220,1 проти 1433±811, p<0,05) відносно групи контролю. Інші показники достовірно від нормативних даних не відрізнялись. Установлено, що для дітей з первинним пролапсом мітрального клапана характерне підвищення тонусу симпатичного відділу вегетативної нервової системи як для хлопчиків, так і для дівчаток, відповідно до даних спектрального аналізу варіабельності ритму серця, зокрема параметр потужності коливань дуже низької частоти (p<0,05). У дітей з пролапсом мітрального клапана, у цілому, тонус парасимпатичної нервової системи в нормі. Має місце тенденція до його підвищення в хлопчиків та до зниження в дівчаток. Ця категорія дітей повинна бути під постійним наглядом педіатрів та кардіологів.

Nowadays, conditions accompanied by manifestations of connective tissue dysplasia (CTD) of the heart are quite common in children with cardiovascular pathology. They are recorded in 26-80% of the child population [1].

In practice of pediatrician and pediatric cardiologist, minor heart abnormalities are common, generally mentioned in literature as abnormally located trabeculae, “false” or extra chords in the left ventricle, structural abnormalities of papillary muscles, mitral valve prolapse (MVP) [7].

Modern literature describes close relationship between CTD syndromes, namely its cardiac manifestations, and disturbances in functioning of the autonomic nervous system (ANS) [6] which can lead to aggravation of the child’s state [8, 9]. Dysfunction of autonomic system can also be caused by inherited specific features in the structure and function of limbic-reticular complex resulting in abnormal neuro-vegetative reactions [5]. In some studies both sympathetic and [3] and parasympathetic activity of the nervous system was reported [6].

In view of all this, it should be noted that despite great prevalence rate of MVP in the child population, many diagnostic problems in such adolescents remain to be solved.

Aim of research: to estimate the condition of autonomic nervous system in children with primary mitral valve prolapse considering gender differences.

MATERIALS AND METHODS OF RESEARCH

106 children with primary MVP confirmed echocardiographically were studied. Children with the present of other small cardiac abnormalities were not included in to research. Examined children were divided into subgroups by sex. The first subgroup IA consisted of 62 (58.5%) boys with MVP; the second one IB included 44 (41.5%) girls with MVP. Children with several minor cardiac anomalies and secondary mitral valve prolapse were not included in the study. MVP was verified using known diagnostic criteria [10]. Among children, MVP of the first degree was detected in 90 (84.9%) children, MVP of the second degree – in 16 (15.1%), respectively.

The control group was also divided into subgroups according to the sex: the subgroup of boys IIA consisted of 12 (52.2%) individuals, and that of the girls IIB included 11 (47.8%). All study children were between the ages of 13 and 17. With the help of a clinical examination, it was registered that the physical development of the studied children was within the normal range (height – 163.0±6.3 sm, weight 55.0±3.8 kg).

The studies were carried out in compliance with the basic provisions of the "Rules of Ethical Principles for Conducting Scientific Medical Research with Human Participation" approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEC Directive No. 609 (dated November 24, 1986) , orders of the Ministry of Health of Ukraine No. 690 of 23.09.2009, No. 944 of 14.12.2009, No. 616 of 03.08.2012. Parents or relatives of each patient signed an informed consent to participate in the study. All methods were used to ensure the anonymity of patients.

The study was carried out on the clinical base of the department, in Vinnytsia children's hospital “Center of Mother and Child”. The children were clinically examined and consulted by specialized doctors.

Vegetative homeostasis was assessed using the method of cardiointervalography (CIG) which allows to register sinus heart rate (HR) with subsequent mathematical analysis of its structure [10]. The studies were carried out in children after a 10-minute rest, in conditions of relative rest and in a horizontal position. The initial tone of the autonomic nervous system (ANS) was assessed using the following indicators: 1) Mo, c – mode is the value of the cardiointerval, which occurs most common and indicates the dominant level of sinus node functioning. 2) Amo, % – the amplitude of the mode, which determines the state of activity of the sympathetic part of ANS. 3) ΔX, c – variation range, reflects the level of activity of the parasympathetic part of ANS. 4) VIR, c.u. – vegetative indicator of rhythm (1/Mo*ΔX), allows to characterize the parasympathetic changes within the vegetative balance. 5) IARP – indicator of the adequacy of regulation processes (AMo/Mo), reflects the correspondence between the activity of the sympathetic part of ANS and the leading level of functioning of the sinoatrial node. 6) SI – Baevsky stress index (AMo (%)/2Mo*ΔX), indicates the tension of the body's compensatory mechanisms, reflects the degree of centralization of HR control.

To assess the status of the ANS, heart rate variability (HRV) indices were analyzed using the regimes of time-domain (statistical) and frequency-domain (spectral) analyses in accordance with the International standards of measurement, physiological interpretation and clinical use, developed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [10].

The following parameters were used in time domain analysis: heart rate (HR), mean NN-interval, SDNN, SDSD, rMSSD, pNN50%.

The characteristics of those parameters are given below: 1) HR –heart rate; 2) mean NN-interval (normal-to-normal), ms – intervals between normal heart beats; 3) SDNN – standard deviation of all NN intervals (those measured between consecutive sinus beats), ms. This integral variable characterizes HRV in general and depends on the influence of sympathetic and parasympathetic nervous system on SA node. Decreased or increased SDNN value indicates imbalance in one of ANS branches. 4) SDSD – standard deviation of successive differences between adjacent NN intervals, ms. 5) CVr (coefficient of variation), % – coefficient of variation of series of consecutive intervals between heartbeats, calculated by the formula: SDN/NN × 100%. 6) r-MSSD, ms – the root-mean-square successive difference, calculates the square root of the mean of the squared differences between successive NN intervals. 7) pNN50% – the percentage of adjacent NN intervals that differ from each other by more than 50 ms.

The latter two indices measure short-term variations in NN interval because they are entirely based on comparisons between successive beats correlating with high frequency power. They characterize activity of parasympathetic branch of ANS.

The following major frequency domain indices were measured: 1) VLF (very low frequency), (0.003-0.004 Hz) – heart rate oscillation power of a very low frequency characterizing the state of humoral regulation, the activity of central oscillators, metabolic fluctuations, and thermoregulation system. 2) LF (low frequency), (0.04-0.15 Hz) – oscillation power of low frequency. Power in this range is influenced by alterations in both sympathetic (predominantly) and parasympathetic activity. 3) HF (high frequency), (0.15-0.40 Hz) – respiratory waves of the heart rhythm. This index represents the high-frequency component of HRV reflecting parasympathetic activity. 4) LF/HF – sympathovagal index, the ratio between low to high frequency bands being used as metric of sympathetic-parasympathetic balance.

Differences between the results of two samples were evaluated by Student's t-test. Changes in parameters were considered to be reliable at $p<0.05$ [8]. Obtained data were statistically processed using Microsoft Excel tables with Windows-2007 (license No. 00426-OEM-8992662-00400).

RESULTS AND DISCUSSION

Evaluation of the results of the CIG study showed that the IARP indicator was significantly increased in group IA when compared with boys from group IIA (37.07±1.73 vs 22.93±3.53, $p<0.05$), which indicates tension sympathetic division of the ANS. According to the results of this indicator, in boys with MVP, the way of realization of the central stimulation of the ANS is a nervous one. SI in children from group IA was within the normal range, which indicates to satisfactory adaptive mechanisms of the organism (Table 1).

Boys from group IA showed a significantly increased indicator of the variation range (ΔX) when compared with the control group IIA – (0.46±0.05 versus 0.33±0.02 s, $p<0.05$), which indicates to increased initial tone of the parasympathetic part of ANS.

On the background of the increase in the parasympathetic tone of the ANS, an increase in the sympathetic part was also noted, which was manifested by an increase in AMo indicators in boys from IA relative to group IIA (28.57±2.2 vs 20.05±2.56%, $p<0.05$).

Thus, boys with MVP have initial sympathicotonia without tension of the adaptive mechanisms.

Statistical processing of the results of CIG indices in girls from group IB showed that in contrast to the group of boys (group IA), the variation range was within the normal data. Only the average AMo parameters in girls from group IB, indicators had tendency to decrease relative to the control group IIB (16.12±34 vs 21.37±3.01%, $p>0.05$). This indicates the decrease in the activity of the sympathetic part of ANS. There were no other statistically significant differences (Table 1). Thus, the adaptive mechanisms of the body in girls with MVP are not tense, and the control of the heart rate is central. The results of vegetative provision have been presented in previous studies [2].

Under normal physiological conditions the heart rhythm is known to result from rhythmic activity of sinus node and influence of innervation of ANS branches (sympathetic and parasympathetic). In study children of experimental group, decreased time-domain values of HRV were recorded regardless of sex, suggesting the weakening of parasympathetic influences on cardiac activity.

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Table 1

Cardiointervalography indices in children (M±m)

Index	group IA (boys with MVP), n=62	group IIA (boys from the control group), n=12	group IB (girls with MVP), n=44	group IIB (girls from control group), n=11
ΔX, sec	0.46±0.05*	0.33±0.02	0.27±0.03	0.31±0.04
Mo, sec	0.77±0.04	0.68±0.06	0.82±0.03	0.73±0.04
AMo, %	28.57±2.2*	20.05±2.56	16.12±1.34	21.37±3.01
SI, c.u.	78.78±10.1	72.15±5.2	64.46±7.77	72.43±5.63
VIR, c.u.	6.95±0.97	9.65±1.6	7.72±0.7	8.97±1.4
IARP, c.u.	37.07±1.73*	22.9±3.53	20.47±1.88	19.88±3.47

Note. Statistically significant differences as compared to control group ($p<0.05$).

The analysis of time-domain indices of HRV in children with MVP revealed the diversity of their values as compared to corresponding average values of healthy children of similar age. Decreased NN value was detected in both subgroups of children, with no significant differences as compared to the controls – boys (768±37.6 versus 823.5±54.5 ms) and girls (726.3±29.7 versus 740.2±52.1 ms). Decreased SDNN indices were found in both subgroups as well, with no statistically significant differences as compared to the controls – boys (111.6±15.4 versus 158.2±25.6 ms) and girls (136.4±22.4 versus 163.5±11.6 ms). The absence of significant differences between those parameters probably suggests only a tendency towards predominant influence of sympathetic ANS branch on the heart rhythm and the organism as a whole. When analyzing mean CVr values, only the tendency to its decrease was noted as well, with no statistical significance as compared to the control groups of boys (6.2±0.7 versus 7.9±1.2%) and girls (7.4±1.1 versus 8.1±1.5%).

The obtained results of all the above HRV parameters can suggest only predisposition to increased sympathetic influence on the heart rhythm and the body of a child with MVP as a whole. The average heart rate values showed no statistically significant deviations from the normal indices as well (Table 2).

No significant differences were found between other time-domain variables responsible for parasympathetic branch of ANS in the patients with MVP and those in the control group.

There were no significant differences in SDSD values in both groups of children with primary MVP as compared to the control group. rMSSD index showed a week tendency to increase in the subgroup of boys with MVP (84±3.7 versus 82.5±12.3 ms) and decreasing tendency in girls (72.3±5.7 versus 77.1±7.8 ms).

The analysis of pNN50 index showed the similar pattern. Its insignificant increase was noted in experimental male group (49.6±2.2 versus 42.7±6.8%) and a tendency to decrease in female group (38±3 against 39.9±6.8%) as compared to normal indices.

Thus, the data obtained demonstrated that average values of SDSD, rMSSD, pNN50 indices did not practically differ from normal ones. Therefore, activation of parasympathetic branch of ANS should not be thought of in this case. However, it should be noted that in subgroups of patients with MVP there was a tendency to moderate increase of parasympathetic tone (parasympathicotonia) in boys and its decrease in girls.

Summarizing study results on ANS status by time-domain indices of heart rate variability in children with primary MVP, the following could be noted: there were no statistically significant differences in average HRV variables between boys and girls as compared to the control group. At the same time, decrease in sympathetic-dependent parameters and partial increase in parasympathetic-dependent parameters were recorded, reflecting the tendency to activation of both ANS branches, particularly in the male group. To conclude, all time domain parameters had no significant differences as compared to normal indices ($p>0.05$).

But time-domain indices are not enough to make final conclusions about ANS general status in such patients. Because of that, spectral analysis was performed as a valuable tool for assessment of cardiovascular autonomic function. The data obtained made it possible to evaluate sex-dependent autonomic activity in children with primary MVP.

Table 2

Time-domain indices of heart rate variability in children with MVP (M±m)

Index	group IA (boys with MVP), n=62	group IIA (boys from the control group), n=12	group IB (girls with MVP), n=44	group IIB (girls from control group), n=11
HR, min	62±2.1	74.0±6.5	67.5±1.6	72±4.3
NN-interval, ms	768.0±37.6	823.5±54.5	726.3±29.7	740.2±52.1
SDNN, ms	111.6±15.4	158.2±25.6	136.4±22.4	163.5±11.6
CVr,%	6.2±0.7	7.9±1.2	7.4±1.1	8.1±1.5
SDSD, ms	66.2±3.5	65.5±18.1	70.2±4.2	72.1±2.3
rMSSD, ms	84.0±3.7	82.5±12.3	72.3±5.7	77.1±7.8
pNN50, %	49.6±2.2	42.7±6.8	38±3	39.9±6.8

Analyzing the results of HRV frequency parameters, only a tendency to an increase in low-frequency waves (LF) was noted relative to the control in children of both subgroups (IA and IB) (Table 3). LF parameter is known to be a marker of sympathetic modulation associated with regulation of average level of blood pressure, and it is thought by some authors to reflect both sympathetic and parasympathetic influences [6]. Therefore, the state of the sympathetic nervous system cannot be estimated only by the results of LF component values because of insignificant differences between experimental and control groups of children both among boys (2076.8±206.3 versus 1386±1035 ms²) and girls (1547.4±243.9 versus 1479.0±1420.0 ms²).

So, increased sympathetic influence on heart rate was established as evidenced by averaged results of VLF frequency spectrum: increased values in patients with MVP, both boys (3205.8±190.9 versus 1717.0±154.0 ms², $p<0.05$) and girls (3280.0±220.1 versus 1433±811 ms², $p<0.05$) as compared to control subgroups. Given that VLF-component of frequency spectrum represents the system of humoral mechanisms as well as the presence of statistically significant results in both subgroups of patients strongly suggest the heart rhythm in study children to be influenced by hormone and metabolic effects, variations in heart period being largely dependent on higher divisions of the brain [4].

Predisposition to reduction of vagal influence in the subgroup of girls with MVP, with no significant differences, can be regarded as one of the causes of sympathicotonia. This is evidenced by decreased high-frequency components of HF spectrum (1023.4±109.7 versus 1644.0±1462.0 ms²), in contrast to their increased values in the subgroup of boys with PMC (2007.1±206.3 versus 1952.0±1740.0 ms²) as compared to the control. Such indices of HF spectrum suggest the tendency to sympathicotonia.

It is noteworthy that changes in rMSSD and pNN50% indices correspond to variability of high-frequency fluctuations. Those parameters had the tendencies to increase and decrease as compared to standards in both subgroups of study children. Increased rMMSD and pNN50% indices in boys with MVP, as compared to the control subgroups, were accompanied by increase of HF, respectively. Similar indices, but with opposite results, were recorded in girls: decreased rMMSD and pNN50% indices were accompanied by decrease of high-frequency (HF) components of the HRV spectrum.

Insignificant increase of LF/HF in both subgroups of children with primary MVP confirms the activation of sympathetic nervous system (Table 3).

Thus, according to spectral indices of HRV in children with MVP, there was an increase in sympathetic tone in both subgroups – boys and girls, as well as a tendency to increase of parasympathetic tone of the ANS in boys and its decrease in girls.

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Table 3

Frequency-domain indices of heart rate variability in children with MVP (M±m)

Index	group IA (boys with MVP), n=62	group IIA (boys from the control group), n=12	group IB (girls with MVP), n=44	group IIB (girls from control group), n=11
VLF, ms²	3205.8±190.9	1717.0±154*	3280.0±220.1*	1433.0±811.0
LF, ms²	2076.8±206.3	1386.0±1035.0	1547.4±243.9	1479.0±1420.0
HF, ms²	2007.1±206.3	1952.0±1740.0	1023.4±109.7	1644±1462.0
LF/HF	1.8±0.3	1.2±0.9	2.2±0.4	1.4±1.7

Note. * – tatistically significant differences as compared to control group ($p<0.05$).

CONCLUSIONS

1. According to cardiointervalography mathematical analysis data, children with mitral valve prolapse have imbalance of autonomic homeostasis, which has an important diagnostic value.
2. In children with mitral valve prolapse, there are differences in the initial tone, taking into account gender features: in boys with MVP, according to these parameters (ΔX, AMo, IARP, ($p<0.05$)) – initial sympathicotonia and parasympathicotonia; in girls – relative parasympathicotonia on the background of the sympathetic part of ANS decreased activity, which manifested itself as decrease in the average AMo parameters ($p<0.05$).
3. Spectral analysis of heart rate variability indicators in children with MVP indicates the prevalence of the tone of the sympathetic division of the autonomic nervous system in both boys and girls. There is an increase in cerebral ergotropic influences with increased ($p<0.05$) VLF relative to control data and decrease in the activity of segmental systems (VLF>LF>HF), which causes the tension of the adaptive and regulatory systems.
4. The results obtained indicate the necessity to include diagnostic methods for assessing the state of the autonomic nervous system in a comprehensive examination of children with mitral valve prolapse (regardless of gender) for further changes predicting in intracardiac hemodynamics.

Conflict of interests. The authors declare no conflict of interest.

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