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Research Article

STUDY OF HEART RATE VARIABILITY INDICES IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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ABSTRACT

Summary: Heart rate variability (HRV) is a non-invasive electrocardiographic marker that reflects the activity of the sympathetic and vagal components of the autonomic nervous system of the sinoatrial node of the heart [1]. Low heart rate variability indicates a reduction in parasympathetic cardiac function, predicting the risk of mortality after myocardial infarction and, therefore, may contribute to an increased cardiovascular risk in patients with rheumatoid arthritis. Studies to date have shown that heart rate variability is low in patients with rheumatoid arthritis compared to healthy controls, although the mechanisms are not fully elucidated. **Purpose:** To study the indices of heart rate variability in idiopathic juvenile arthritis depending on the activity of the disease, the duration of the disease and the evolutionary variant. **Material and methods:** HRV was performed in 45 children with juvenile idhiopatic arthritis (JIA). HRV indices were correlated with disease activity, homocysteine level and lipid profile (cholesterol, triglycerides) and treatment. **Results:** Following the comparative analysis, a positive correlation was found between PNN50 and the parameters for assessing inflammation, homocysteine, triglycerides, DAS-28 and treatment with corticosteroids and MTX. **Conclusion:** The study found an inverse relationship between HRV indices with inflammatory markers, homocysteine, DAS 28 and treatment.

Keywords: heart rate variability, juvenile idiopathic arthritis, homocysteine, triglycerides.

INTRODUCTION

Autonomic nervous system imbalance has been observed in many chronic autoimmune diseases, including rheumatoid arthritis. Autonomic dysfunction, increased sympathetic tone activity, and decreased parasympathetic tone were associated with an increased risk of cardiovascular disease (CVD) [2,3,4]. Heart rate variability (HRV) is a non-invasive electrocardiographic marker that reflects the activity of the sympathetic and vagal components of the autonomic nervous system of the sinoatrial node of the heart [1]. Low heart rate variability indicates a reduction in parasympathetic cardiac function, predicting the risk of mortality after myocardial infarction and, therefore, may contribute to an increased cardiovascular risk in patients with rheumatoid arthritis. However, there are few data on the factors that contribute to autonomic dysfunction in the population with a high long-term inflammatory burden, such as patients with inflammatory arthritis [5]. From the accessed sources, there are no data on the evaluation of the relationship between risk factors, heart rate variability and CVD in children with JIA. The current study is the first to reveal the correlation of HRV indices with individual CVD risk factors in JIA.

MATERIAL AND METHODS

The prospective clinical study was conducted in the Department of Pediatrics, *Nicolae Testemitanu* SUMPh, between January 2015 and December 2016. The research group included 90 children with JIA, of which 63.3% were girls and 36.7% - boys. The mean age was 10.73 ± 0.46 years. The results were compared according to disease duration and activity, as well as the treatment administered: non-steroidal anti-inflammatory drugs (NSAIDs), costicosteroids, Methotrexate (MTX). Disease activity was assessed according to DAS 28 (Disease Activity Score). DAS 28 = 0.56 · √NSJ28 + 0.28 · NPJ28 + 0.7 · LnESR + 0.014 · EGB, where: NSJ - number of swollen joints, NPJ- number of painful joints, ESR- erythrocyte sedimentation rate, natural logarithm, PGA - Patient global assessment according to visual analog scale of 100 mm (VAS). Thus, DAS 28> 5.1 corresponds to high activity, DAS <3.2 - moderate or minimal activity, DAS <2.6 accounts for disease remission. Acute phase reactants (ESR, CRP) were performed in all children included in the study. C-reactive protein was performed using the cobas 6000 analyzer. Reference values: C-reactive protein 0-5mg / l. Enzymatic spectrophotometry assessed lipid metabolism (total lipids, total cholesterol (TC), triglycerides (TG)) in all children included in the study. Increased values were considered pathological in patients with CT ≥ 5.2 mmol / l and TG> 1.7 mmol / l. Homocysteine was performed in 90 children. Blood was collected from the ulnar vein in the morning on an empty stomach. The blood was collected in an EDTA container, plasma being more suitable for homocysteine test. The assessment method used were: enzymatic, ELISA. Reference values - <12 μmol / L. Detection limit - 2.8 μmol / L. Homocysteine was evaluated in all children included in the study. A 24-hour Holter EKG was used to assess heart rate variability indices. It was performed on 45 children in the research group. Children were distributed according to gender and age. Thus, there were 2 (4.4%) girls aged 6-8 years, 3 (6.6%) boys aged 6-8 years, 4 (9%) girls and 4 (9%) boys aged 9-11 years, 24 (53.3%) girls aged 12-17 years and 8 (17.7%) boys. The children underwent ambulatory electrocardiogram monitoring within 24 hours using the Meditech Card (X) Plore monitor with automated data processing. The portable device was set to start the evaluation at 3-minute intervals during the day and at 60-minute intervals at night. The patient was asked to complete a diary with the symptoms occurring during the recording. Heart rate variability (HRV) is a non-invasive electrocardiographic marker that reflects the activity of the sympathetic and vagal components of the autonomic nervous system (ANS) of the sinoatrial

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node of the heart [1]. From a series of instantaneous heart rates or cyclic intervals recorded for 24 hours, statistical data can be obtained being divided into 2 groups: (1) parameters derived from the direct measurement of NN intervals or instantaneous heart rate and (2) parameters derived from differences between NN intervals. The time domain can be analyzed with statistical and geometric methods. The main parameters of the HRV time domain(Time domain) are: MEAN - average of NN intervals in the examined part; SDNN (standard deviation of normal-to-normal (NN) intervals) (sin: CLV and SDRR) - represents the standard deviation of all normal RR intervals [47]. SDNN characterizes the state of heart rate regulation mechanisms. It is an integral parameter that describes HRV in general, dependent on the influences of the sympathetic and parasympathetic nervous system on the sinus node [55]; SDNN-i (index) (ms) (Mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording) - the average of the standard deviations of all NN intervals on 5-minute segments of the entire recording, SDANN (ms) (Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording) - standard deviation of the average of NN intervals on 5 minsegments of the entire recording, rMMSD (The square root of the mean of the sum of the squares of differences between adjacent NN intervals) - the square root of the successive differences between the normal heartbeats, NN50 (Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording, three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer) - number of pairs of adjacent NN intervals which differ by more than 50 ms. Three variants are possible by counting all pairs of intervals or only pairs in which the first or second interval is longer, pNN50% (NN50 count divided by the total number of all NN intervals) - the NN50 number divided by the total number of NN intervals [12,14]. The parameters MEAN, SDNN, SDNN-i and SDANN reflect the analysis of the neighboring RR intervals that follow one after the other.

RESULTS

Following the statistical analysis, the average value of pNN50 was 21.07±15.77, the minimum value being 0.0 and the maximum value - 73.2; the average value of SDANN – 151.14±43.39, the minimum value - 43.0 and the maximum value - 309.0; the average value of SDNN – 147.17±47.43, the minimum value - 46.0 and the maximum value - 265.6 and the average value of rMSSD constituted 55.94±23.89, the minimum value -5.0 and the maximum value -143.7 (tab. 1).

Table 1. Average values of HRV parameters in children with AJI

Parameters	M	SD	V min.	Vmax.
pNN50	21.07	15.77	0	73.2
SDANN	151.14	43.39	43.0	309.0
SDNN	147.17	47.43	46.0	265.6
rMSSD	55.94	23.89	5.0	143.7

Note: pNN50 - NN50 number divided by all NN intervals, SDANN - standard deviation of the average NN intervals on 5 min segments of the entire recording, SDNN - standard deviation of all normal RR intervals, rMSSD - the square mean root of the successive differences between normal heartbeats, M- average value; SD - standard deviation.

Following the comparative analysis, a positive correlation was found between PNN50 and the parameters for assessing inflammation, such as DAS 28 (r = 0.563 **, p <0.01), AVSP (r = 0.435 **, p <0.01) and ESR (r = 0.322 *, p <0.05).

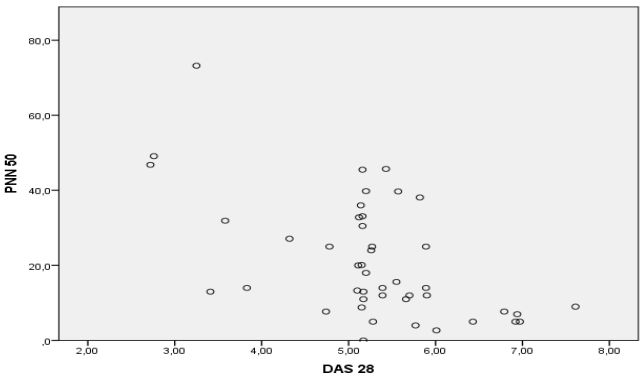

Fig. 1. Correlation between pNN50 and DAS 28

Note: pNN50 - NN50 number divided by all NN intervals; DAS 28-disease activity; ** - p <0.01, value considered highly significant.

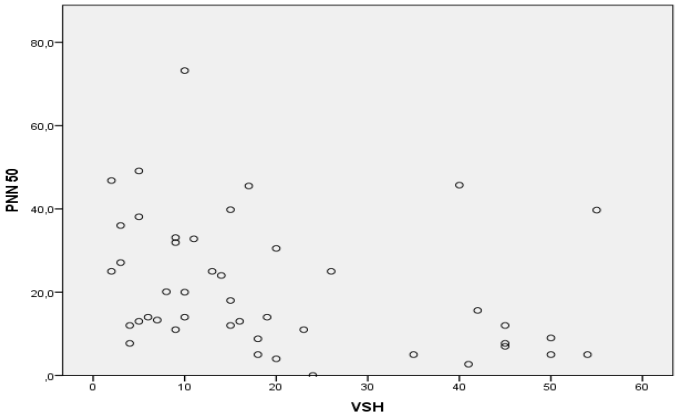

Fig.2. Correlation between pNN50 and ESR

Note: pNN50 - NN50 number divided by all NN intervals, ESR - erythrocyte sedimentation rate; * - p <0.01, value considered significant.

This correlation is significant, given the inflammatory role on the decrease of PNN50. Also, the interrelation between PNN50 and TG (r = 0.297 *, p <0.05) and Hcy (r = 0.398 **, p <0.01) was observed, their increase leading to the decrease of PNN50. The correlation between PNN50 and FCCmin is also essential (r = 0.343 *, p <0.05); SDNN (r = 0.740 **, p <0.01) and rMSSD (r = 0.711 **, p <0.01), the decrease of PNN50 leading to the decrease of the other HRV parameters.

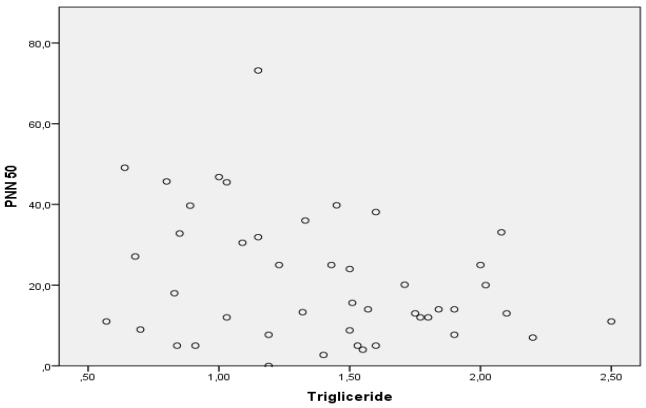

Fig.3. Correlation between pNN50 and triglycerides

Note: pNN50 - NN50 number divided by all NN intervals; * - p <0.05, value considered significant.

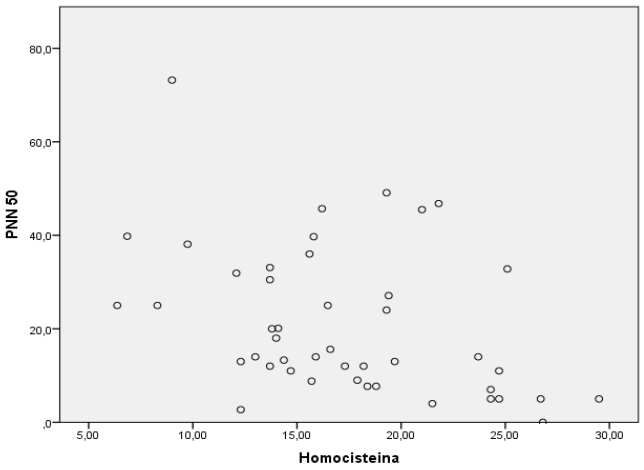

Fig. 4. Correlation between pNN50 and homocysteine

Note: pNN50 - number NN50 divided by all NN intervals ** - p <0.01, value considered highly significant.

When assessing the interrelationship between SDNN and inflammation assessment parameters, a positive correlation was noted with DAS 28 (r = 0.421 **, p <0.01) and AVSP (r = 0.325 *, p <0.05). rMSSD is another essential HRV parameter, a positive correlation with AVSP (r = 0.526 **, p <0.01) being observed, the correlation with other parameters for assessing inflammation being statistically insignificant (p> 0.05). Also, the interrelation between rMSSD and Hcy level is essential, where r = 0.295 *, p <0.05**.** The correlation with other HRV indices was also noted, such as PNN50 (r = 0.711 **, p <0.01), SDANN (r = 0.343 *, p <0.05) and SDNN (r = 0.687 **, p <0.01).

Indices of heart rate variability depending on disease activity, disease duration and treatment

Depending on the disease activity, the mean value of PNN50 in children with DAS 28 <5.1 was 331.97±21.08 (minimum value - 7.7, maximum value - 73.2) compared to 18.34±13.15 (minimum value - 0.0, maximum value - 45.7) in children with DAS 28> 5.1 (F = 5.988, where p <0.01), mean SDANN value - 165.14±31.04 (minimum value -127.0, maximum value - 208.0) in children with DAS 28 <5.1 compared to SDANN - 147.64±45.64 (minimum value -43.0, maximum value - 309.0) in children with DAS 28> 5.1; average SDNN value - 175.71±42.19 (minimum value -131.0, maximum value - 265.6) compared to 140.03±46.47 (minimum value - 46.0, maximum value - 253.9) in children with DAS 28> 5.1 (F = 4.385, where p <0.05) and mean rMSSD was 62.75±19.05 (minimum value - 35.2, maximum value -82.0) in children with DAS 28 < 5.1 compared to 54.24±24.9 (minimum value -5.0, maximum value - 143.7) in children with DAS 28> 5.1 (tab. 2).

Table 2. Mean values of HRV parameters according to disease activity in children with AJI

Parameters	DAS 28 < 5,1		DAS 28 > 5,1		F	p
	M	SD	M	SD		
PNN50	31.97	21.08	18.34	13.15	5.988	< 0,01**
SDANN	165.14	31.04	147.64	45.64	1.176	>0,05
SDNN	175.71	42.19	140.03	46.47	4.385	<0,05*
rMSSD	62.75	19.05	54.24	24.9	0.911	>0,05

Note: DAS 28 <5.1 - moderate or low disease activity; DAS 28> 5.1 - increased disease activity; M- average value; SD - standard deviation; pNN50 - NN50 number divided by all NN intervals; SDANN - standard deviation of the average NN intervals on 5 min segments of the entire recording; SDNN - standard deviation of all normal RR intervals; rMSSD - the mean square root of the successive differences between the normal heartbeats, * - p <0.05 - value considered significant; ** - p <0.01, value considered highly significant; p> 0.05 - insignificant value.

Depending on the disease duration, the mean PNN50 value was 20.20±15.19 (minimum value - 0.0, maximum value - 49.1) in children with disease duration greater than 24 months, compared to 22.81±17.29 (minimum value -4.0, maximum value -73.2) in children with disease duration of less than 24 months; the mean SDANN value was 153.55±47.17(minimum value - 43.0, maximum value - 309.0) in children in group I compared to 146.31±35.65 (minimum value -86.8, maximum value - 208.0) in children in group II; the mean SDNN value in children with the highest disease rate was 146.80±54.05 (minimum value - 46.0, maximum value -265.6) compared to 147.91±31.92 (minimum value – 78, maximum value -203.7) in children with a shorter disease duration and mean value of rMSSD in children with a longer disease duration was 54.83±26.63 (minimum value - 5.0, maximum value -143.7) compared with children with a lower disease duration, where the average value of rMSSD was58.17±17.80 (minimum value - 23.0, maximum value - 85.4). Statistically significant differences in disease duration were not observed (p> 0.05). Statistically significant differences of HRV parameters were observed in children treated with corticosteroids. Thus, the mean PNN50 value was 13.49±11.07 (minimum value - 0.0, maximum value - 45.7) in children who received corticosteroids compared to 30.54±15.85 (minimum value - 7.7, maximum value - 73.2) in children who were not treated with corticosteroids (F = 18.004, p <0.001); the mean SDANN value was 150.90±52.85 (minimum value - 43.0, maximum value -309.0) compared to 151.44±28.84 (minimum value - 86.8, maximum value -207.8) in children who were not treated with corticosteroids; the mean SDNN value was 128.45±46.25 (minimum value - 46.0, maximum value - 253.9) in children who received corticosteroids, compared to 170.57±38.36 (minimum value -90.2, maximum value - 265.6, F = 10.687, p <0.001) and the mean value of rMSSD was 44.22±18.49 (minimum value - 5.0, maximum value -80.9) in children who received corticosteroids, compared to 70.61±21.98 (minimum value - 35.2, maximum value - 143.7) in children who did not receive corticosteroids, F = 19.132, where p <0.001 (tab.3).

Table 3. HRV parameters depending on corticosteroid treatment in children with AJI

Parameters	With Cs		Without Cs		F	p
	M	Dev.std.	M	Dev.std.		
PNN50	13.49	11.07	30.54	15.85	18.004	< 0.001**
SDANN	150.90	52.85	151.44	28.84	0.002	>0.05
SDNN	128.45	46.25	170.57	38.36	10.687	<0.001**
rMSSD	44.22	18.49	70.61	21.98	19.132	<0.001**

Note: with Cs - children who received corticosteroids; without Cs - children who did not receive corticosteroids; M- average value; dev. std.- standard deviation; pNN50 - NN50 number divided by all NN intervals; SDANN - standard deviation of the average NN intervals on 5 min segments of the entire recording; SDNN - standard deviation of all normal RR intervals; rMSSD – the mean square root of the successive differences between the normal heartbeats; ** - p <0.001, value considered highly significant; p> 0.05 - insignificant value.

Also, a significant decrease in HRV parameters was reported in patients receiving MTX treatment, compared to patients not receiving MTX. Thus, the mean PNN50 value in patients receiving MTX was

15.13±12.10 (minimum value - 0.0, maximum value - 49.1) compared to 31.82±16.27 (minimum value -7.7, maximum value - 73.2) in children who were not treated with MTX (F = 15.285, p <0.001); the mean SDANN value in children in group I was 151.91±49.48 (minimum value -43.0, maximum value - 309.0), compared to 149.74±30.80 (minimum value -86.8, maximum value - 207.8) in children in group II (F = 0.025, p> 0.05); the mean SDNN value was 134.09±45.36 (minimum value -46.0, maximum value - 253.9) in children receiving MTX, compared to 170.87±42.76 (minimum value -90.2 and maximum value -265, 6) in children not receiving MTX (F = 7.052, p <0.01) and the mean value of rMSSD in children receiving MTX was 47.93±20.7 (minimum value -5.0, maximum value- 82. 0), compared to 70.47±22.92 (minimum value - 43.4, maximum value - 143.7) in children who did not receive MTX (F = 11.325, p <0.001) (tab.4).

Table 4. HRV parameters according to MTX treatment in children with AJI

Parameters	With MTX		Without MTX		F	p
	M	Dev.std.	M	Dev.std.		
PNN50	15.3	12.10	31.82	16.27	15.285	< 0.001**
SDANN	151.91	49.48	149.74	30.80	0.025	>0.05
SDNN	134.09	45.36	170.87	42.76	7.052	<0.01**
rMSSD	47.93	20.7	70.47	22.92	11.325	<0.001**

Note: with MTX - children who received methotrexate; without MTX - children who did not receive methotrexate; M- average value; dev. std. - standard deviation; pNN50 - NN50 number divided by all NN intervals; SDANN - standard deviation of the average NN intervals on 5 min segments of the entire recording; SDNN - standard deviation of all normal RR intervals; rMSSD - the mean square root of the successive differences between the normal heartbeats; ** - p <0.001, value considered highly significant; p> 0.05 - insignificant value.

DISCUSSIONS

Consistent with other studies, the study found an association between HRV indices and triglycerides, given the association between lipid metabolism and ANS [11]. Thus, an inverse correlation between pNN50 and triglycerides was observed (r = 0.297, p <0.05). The inverse correlation between PNN50 and homocysteine was also observed. This is a less common association in literature. There are studies that have not found any association between inflammation, disease activity and autonomic function in RA [9]. Some studies have reported an association of PCR with autonomic dysfunction [4,6,7,9]. In some studies, similar to inflammation, disease activity (DAS 28) has been associated with autonomic function [10]. In other studies, this association was not observed [11]. It is difficult to compare different studies, given the different methods used to assess the autonomic function [7,11,14,15]. Of the available studies, it is noteworthy that studies that did not report any association between autonomic function and inflammation used the Ewing test as an assessment method, while those that reported an association measured autonomic function using HRV. [1,2]. Therefore, it could be argued that HRV is a more sensitive test in assessing parasympathetic function. The mechanisms underlying the reduction of HRV indices observed in RA have remained obscure so far. Involvement of inflammatory cytokines could be one mechanism, which can lead to a decrease in HRV indices through several pathways. [6,5]. In the present study we observed an inverse association between HRV indices and inflammatory markers. In other studies, such as the study by Aeschbacher *et al.,* close associations between PCR and HRV indices have been reported. A strong independent and inverse relationship was found between reported pain and HRV. These findings are broadly consistent with the studies that have shown that HRV is reduced in chronic pain. One of the studies in question is the study conducted by Tracy et al., that reported an inverse association between chronic pain and decreased rates of HRV, pNN50 and SDNN. Moreover, experimentally induced pain in healthy individuals results in a reduction in HRV indices consistent with decreased parasympathetic cardiac activity (Koenig *et al.,*) and increased sympathetic nerve activity (Bruchl *et al.,*). Previous studies evaluating the correlation between disease characteristics and HRV have shown variable and contradictory results. Anichkov *et al.,* obtained significant correlations of SDNN and SDANN with the number of swollen joints, DAS 28 and disease duration. While another study found no correlation of HRV with disease activity, disease duration, and ESR. In terms of age correlation with HRV in patients with RA, it has been shown that HRV is significantly related to age, sex and 24-hour heart rate [13,14,15]. In the study conducted by Kumar et al., HRV indices decreased significantly with increasing disease activity and age in patients with RA [12]. The relationship between HRV and disease characteristics cannot be fully explained, given the insufficient data available to date.

CONCLUSION

This study demonstrated an increased sympathetic control of the heart, as observed in other autoimmune diseases. Thus, the indices of heart rate variability were clearly low in children with elevated disease activity, as well as in children with high levels of homocysteine, triglycerides, and in children who were on long-term treatment with corticosteroids and methotrexate. The present study complements the previous studies, being primary in children with idiopathic juvenile arthritis.

Competing interests

There was no conflict of interest declared by authors.

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