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ORIGINAL PAPER

Analysis of heart rate variability in paediatric patients with vasovagal syncope

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ABSTRACT

Introduction: The aim of the study was to detect any abnormalities of the autonomic nervous system in children and adolescents with vasovagal syncope.

Material and methods: We studied 56 children, ages eight to 17 years, with a history of vasovagal syncope and 41 healthy volunteers. Heart rate variability was calculated over a 24-hour period for heart rate, standard deviations of the averages of the R-R intervals in all 5-min segments of R-R intervals (SDANN), the root of the 24-hour square (RMSSD), the proportion of adjacent normal R-R intervals < 50 ms (pNN50), the total power (TP), the low frequency index (LF), the high frequency index (HF), and the LF/HF ratio.

Results: Patients with vasovagal syncope had significantly reduced values of 24-hour (256.21 ±190.97 ms, 366.51 ±264.7 ms, $p = 0.048$) and night-time SDANN (168.56 ±140.59 ms, 251.54 ±189.92 ms, $p = 0.034$); 24-hour (292.96 ±226.25 ms, 390.49 ±254.06 ms, $p = 0.046$), daytime (349.52 ±298.32 ms, 479.23 ±350.39 ms, $p = 0.040$), and night-time RMSSD (188.47 ±161.07 ms, 271.05 ±200.70 ms, $p = 0.029$); daytime pNN50 (25.10 ±13.10%, 32.10 ±14.19%, $p = 0.037$); and increased value of night-time LF/HF ratio (1.43 ±1.50, 0.86 ±1.00, $p = 0.015$), in comparison to healthy subjects. In adolescents with vasovagal syncope we found significantly lower values of 24-hour (7578.29 ±5409.74 ms^2, 12236.00 ±5651.45 ms^2, $p = 0.025$) and daytime TP (4776.19 ±4146.56 ms^2, 10488.70 ±8326.43 ms^2, $p = 0.039$), 24-hour (2120.90 ±2057.00 ms^2, 3634.22 ±3026.90 ms^2, $p = 0.015$) and daytime HF (930.10 ±1101.66 ms^2, 7832.90 ±18825.10 ms^2, $p = 0.015$), in comparison with children. Males presented lower values of 24-hour (207.4 ±134.63 ms, 324.00 ±236.95 ms, $p = 0.042$) and daytime SDANN (264.56 ±208.16 ms, 432.65 ±320.52 ms, $p = 0.044$), and daytime RMSSD (282.54 ±248.94 ms, 446.28 ±342.35 ms, $p = 0.041$) compared with females.

Conclusions: Paediatric patients with vasovagal syncope had alterations in basal autonomic balance, which indicated an increased sympathetic modulation. More severe autonomic imbalance occurs in adolescent males.

KEY WORDS:

vasovagal syncope, heart rate variability, autonomic nervous system, children.

INTRODUCTION

Balance between the sympathetic and parasympathetic branches of the autonomic nervous system is essential to maintaining systemic homeostasis and responding effectively to external stressors. The resultant disruption in systemic homeostasis due to autonomic nervous system dysregulation or dysfunction has been associated with organ dysfunction, increased illness severity, and poor

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outcomes [1, 2]. The most common method of objectively assessing autonomic nervous system dysregulation is through measurement of heart rate variability, which reflects the normal, physiologic alterations in the intervals in time between consecutive heart beats that occur when there is a balance of sympathetic and parasympathetic inputs on the electrical conduction system of the heart [3].

Since the early 1970s, when power spectral analysis was applied to explore the physiological basis of intermittent variations in heart rate, a large number of studies addressing heart rate variability were published [4, 5]. Reduced heart rate variability corresponds to the autonomic nervous system imbalance and may be associated with an increased mortality in various disease states among adults [6]. Also in children, depressed heart rate variability may be related to some cardiac and non-cardiac disorders [7]. Numerous studies identified that decreases in heart rate variability precede clinical deterioration, reflect response to therapy, and are associated with poor outcomes in a variety of conditions [8].

Vasovagal syncope is a common clinical event the pathogenetic mechanism of which has not yet been fully clarified. The syncopal symptoms appear to be associated with pathological autonomic cardiac modulation [9]. By evaluating the fluctuations of the autonomic nervous system in vasovagal syncope patients, heart rate variability can be considered as a tool of added value [10, 11]. However, in the literature, there are only a few studies dealing with heart rate variability in children and adolescents with vasovagal syncope. Most of them are quite controversial and studied only a very small group of children [12–14]. The present study was designed to assess the autonomic nervous system imbalance in these patients using a heart rate variability technique, based on 24-hour Holter recordings. The aim of the study was to detect any abnormalities of autonomic nervous system in children and adolescents with vasovagal syncope, and to investigate the relationship between identified heart rate variability abnormalities and other conditions in this group of patients.

MATERIAL AND METHODS

STUDY POPULATION

We studied 56 children, ages eight to 17 years, with a history of vasovagal syncope. The control group consisted of 41 healthy volunteers without a history of vasovagal syncope or any acute and chronic diseases. For the diagnosis of vasovagal syncope the diagnostic criteria of the European Society of Cardiology (2018) were used [15]. Children enrolled in the study had to meet the following inclusion criteria: 1) a minimum of one event of vasovagal syncope during the preceding month, 2) normal response during active standing test, 3) absence of structural heart diseases and electrocardiography findings suggesting arrhythmic syncope, 4) absence of electroencephalography signs of epilepsy, 5) absence of any other evident aetiology for syncope, and 6) no concomitant chronic or acute disease. Patients using drugs or substances affecting heart rate, sympathetic-parasympathetic nervous system activity, and QT interval in electrocardiography were also excluded. Informed consent was obtained from the patients and their parents. The main demographic and clinical characteristics of vasovagal syncope and control groups are presented in Table 1.

This study was approved by the Ethics Committee of the Ivan Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine, and all participants gave their written, informed consent before participation.

EVALUATIONS

The symptoms of orthostatic dysregulation assessed by the questionnaire include five major symptoms and six minor symptoms. A positive questionnaire result was defined according to the criteria proposed by the Japanese clinical guidelines for juvenile orthostatic dysregulation [16], as follows: one major symptom plus three or more minor symptoms, two major symptoms plus

TABLE 1. Demographic and clinical characteristics of patients

Parameter	Vasovagal syncope ($n = 56$)	Control ($n = 41$)
Age, years	14.00 ±2.24	12.5 ±2.66
Sex, M/F	32/24	17/24
Body mass index	19.70 ±2.85	18.8 ±2.44
Number of patients with a past medical history	–	–
Age of the first syncopal event, years	12.70 ±2.88	–
Number of syncopal events	3.38 ±5.29	–
Calgary Syncope Seizure Score	1.50 ±2.2	–
Modified Calgary Syncope Seizure Score	–2.00 ±1.7	–
Number of patients with orthostatic dysregulation (%)	26 (46.43)	3 (0.73)

Values are presented as mean ±standard deviation

more than one minor symptom, or three or more major symptoms.

Active standing test was used for all patients for exclusion of orthostatic hypotension and postural orthostatic tachycardia syndrome [15]. The protocol for the Active Standing Test established by Tanaka *et al.* [16] for use in adolescents was as follows: 1) Rest for 10 min in the supine position. Put a manometer cuff on the arm. A stethoscope should be fixed on the arm around the brachial artery. 2) Measure blood pressure and heart rate three times after a 10-min rest. Determine and record the middle value. 3) Inflate the air to the cuff at the level of the middle value of systolic blood pressure and pinch a rubber tube of the manometer using a clamp in order not to deflate. Use a stethoscope and hear the Korotkoff sounds of the brachial artery, which you can hear very slightly if the instructions have been correctly followed. 4) Tell the child to stand up actively, and start measurement using a stopwatch while listening using a stethoscope. 5) At the beginning of standing, the Korotkoff sounds disappear, and then appear again (after 17 s in average). Stop the stopwatch. The time (s) displayed on the stopwatch corresponds to the recovery time of blood pressure. 6) Take off the clamp and deflate the cuff. 7) Measure blood pressure and pulse rate by conventional method at 1, 3, 5, 7, and 10 min. Normal response for orthostasis is systolic blood pressure ±10 mm Hg, diastolic blood pressure ±5 mm Hg, pulse rate +5–15 beats/minute.

Heart rhythm recordings were conducted for 24 hours both in the patient and control groups using a three-channel rhythm Holter monitorisation device (SDM3, Ukraine). Heart rate variability parameters were analysed using a computer program. After automated QRS detection and classification, very careful direct visual confirmation of beat types and then verification of the edge values of the tachogram was performed manually. Ectopic beats and signal artefacts were corrected by interpolation with the previous and following R-R intervals. After editing, the beats files were analysed for time and frequency-domain indices of heart rate variability. Within time-domain analysis, the following indices were calculated: heart rate, standard deviations of the averages of the R-R intervals in all 5-min segments of R-R intervals (SDANN), the root of the 24-hour square (RMSSD), and the proportion of adjacent normal R-R intervals < 50 ms (pNN50). All the time-domain indices were calculated based on full 24-hour recordings. Frequency-domain analysis was performed on five-minute segments, free of noise and ectopy, selected from daytime alert rest in a supine position and night-time sleep. Four frequency components were calculated: the total power (TP), the low frequency index (LF), the high frequency index (HF), and LF/HF ratio [3].

On the same day 24-hour ambulatory blood pressure monitoring was conducted. Studies were performed with a BAT41-2 device (Ukraine) using a protocol of the European Society of Hypertension (2014) [17]. Automatic measurements were taken every 15 minutes during the day and every 30 minutes during the night.

The paediatric Quality of Life Inventory (PedsQLTM 4.0, MAPI Research Institute, Lyon, France) was used for evaluation health-related quality of life, with the Ukrainian Generic Version. It assesses children's and adolescents' physical (eight items), emotional (five items), social (five items), and school functioning (five items). It generates a total score summarising all four domains: the Total Health Scale, the Physical Health Scale (which refers to physical functioning), and the Psychosocial Health Scale (which summarises the emotional, social, and school domains) [18].

STATISTICAL ANALYSIS

All data were expressed as mean ±standard deviation (SD). The Mann-Whitney *U* test was used for comparing the values of different groups. Relationships between variables were examined using Spearman linear correlation analysis. For all analyses, a p value < 0.05 was considered statistically significant. All statistics were analysed using the SPSS 12.0 package program.

RESULTS

The values of time and frequency domain analysis of heart rate variability are presented in Table 2. Patients with vasovagal syncope had significantly reduced values of 24-hour and night-time SDANN, 24-hour and daytime RMSSD, daytime pNN50, and increased value of night-time LF/HF ratio, in comparison to healthy ones.

For better understanding of heart rate variability peculiarities depending on the age, all patients were differentiated as adolescents (ages 13–17 years) and children (8–12 years). There was no statistically significant difference between adolescents and children in any parameter of time domain heart rate variability indexes (Table 3). In adolescents with vasovagal syncope we found significantly lower values of 24-hour and daytime TP, and 24-hour and daytime HF, in comparison with vasovagal syncope children. There was no difference between adolescents and children in any heart rate variability indexes in the control group ($p < 0.05$).

Detailed analysis of heart rate variability measurements in adolescents showed us significantly lower values of 24-hour RMSSD, 24-hour, and daytime pNN50, and higher values of night-time LF/HF ratio, in comparison with the control group. In children with vasovagal syncope and the control group the heart rate variability measurements were evaluated as being not significantly different (Table 4).

The next step of the study was to assess heart rate variability in vasovagal syncope patients depending on gender. It helped us find significantly reduced values of

TABLE 2. Comparison of heart rate variability between vasovagal syncope and control groups

Heart rate variability index	Vasovagal syncope ($n = 56$)	Control ($n = 41$)	p-value
Time domain			
Heart rate (bpm)			
24-hour	76.95 ±15.06	77.95 ±10.39	0.772
daytime	83.98 ±10.60	85.49 ±10.18	0.663
night-time	68.84 ±11.46	67.72 ±12.44	0.549
circadian rhythm	1.24 ±0.15	1.29 ±0.20	0.231
SDANN (ms)			
24-hour	256.21 ±190.97	366.51 ±264.7	0.048
daytime	332.60 ±269.13	449.13 ±357.86	0.121
night-time	168.56 ±140.59	251.54 ±189.92	0.034
RMSSD (ms)			
24-hour	292.96 ±226.25	390.49 ±254.06	0.046
daytime	349.52 ±298.32	479.23 ±350.39	0.040
night-time	188.47 ±161.07	271.05 ±200.70	0.029
pNN50 (%)			
24-hour	31.16 ±1.91	36.46 ±15.80	0.181
daytime	25.10 ±13.10	32.10 ±14.19	0.037
night-time	40.15 ±16.6	45.08 ±20.36	0.187
Frequency domain			
TP (ms^2)			
24-hour	8626.28 ±5739.62	9183.86 ±7489.43	0.950
daytime	6169.49 ±5887.53	8696.63 ±7669.84	0.191
night-time	10086.70 ±7030.04	10303.10 ±8740.13	0.832
LF (ms^2)			
24-hour	3130.93 ±3717.05	3521.92 ±6400.24	0.473
daytime	1829.46 ±1699.74	2638.26 ±2553.34	0.182
night-time	3060.43 ±2030.21	2781.06 ±2388.55	0.404
HF (ms^2)			
24-hour	2461.40 ±2354.53	2858.81 ±2744.35	0.755
daytime	2613.71 ±9468.54	1963.20 ±2081.59	0.146
night-time	3112.85 ±2849.45	3619.11 ±3424.34	0.746
LF/HF ratio			
24-hour	1.50 ±1.40	1.13 ±0.83	0.348
daytime	1.69 ±1.60	1.66 ±1.82	0.836
night-time	1.43 ±1.50	0.86 ±1.00	0.015

Values are presented as mean ±standard deviation. Mann-Whitney U test was used

24-hour and daytime SDANN, and daytime RMSSD. No significant differences were noted between male and female heart rate variability values in the control group (Table 5).

Comparison of heart rate variability between patients of vasovagal syncope and healthy groups found lower values of daytime pNN50, daytime TP, daytime LF, and daytime HF in males. There was no significant difference between vasovagal syncope and healthy females in any time and frequency domain heart rate variability parameter, except for increased night-time LF/HF index of sympathovagal balance (Table 6). We also did not identify any differences of time and frequency domain heart rate variability indices between vasovagal syncope patients with one and more than one syncopal event in their life ($p > 0.05$).

TABLE 3. Comparison of heart rate variability between adolescents and children in vasovagal syncope and control groups

Heart rate variability index	Vasovagal syncope			Control		
	Adolescents ($n = 39$)	Children ($n = 17$)	*p*-value	Adolescents ($n = 21$)	Children ($n = 20$)	*p*-value
Time domain						
Heart rate (bpm)						
24-hour	75.76 ±9.28	80.55 ±23.56	0.093	76.81 ±10.13	79.15 ±10.79	0.514
daytime	67.13 ±10.26	73.25 ±12.81	0.151	68.25 ±13.97	67.16 ±10.95	0.255
night-time	82.61 ±10.52	87.50 ±10.41	0.147	83.45 ±8.24	87.63 ±11.73	1.00
circadian rhythm	1.25 ±0.16	1.21 ±0.13	0.616	1.25 ±0.18	1.33 ±0.21	0.431
SDANN (ms)						
24-hour	255.28 ±197.63	258.91 ±179.13	0.978	353.57 ±217.82	380.10 ±311.66	0.885
daytime	330.87 ±269.53	337.46 ±281.05	0.954	406.10 ±281.94	494.42 ±426.87	0.704
night-time	178.93 ±160.33	140.27 ±57.51	0.713	236.75 ±152.169	267.105 ±226.29	0.911
RMSSD (ms)						
24-hour	294.00 ±234.106	289.91 ±212.31	0.911	396.57 ±239.44	384.10 ±274.69	0.784
daytime	349.28 ±291.64	350.17 ±228.04	0.751	464.45 ±326.66	494.79 ±382.18	0.989
night-time	201.65 ±182.46	154.42 ±80.67	0.597	270.00 ±174.78	272.16 ±229.75	0.877
pNN50 (%)						
24-hour	30.13 ±11.83	34.18 ±14.56	0.297	37.43 ±17.36	35.45 ±14.36	0.824
daytime	23.55 ±12.63	29.45 ±14.12	0.213	34.00 ±14.96	30.11 ±13.44	0.593
night-time	38.7 ±15.86	44.09 ±18.69	0.296	45.55 ±23.51	44.58 ±17.07	0.642
Frequency domain						
TP (ms^2)						
24-hour	7578.29 ±5409.74	12236.00 ±5651.45	0.025	7998.47 ±6366.83	10508.70 ±8405.55	0.326
daytime	4776.19 ±4146.56	10488.70 ±8326.43	0.039	8206.32 ±7444.75	9278.88 ±8134.17	0.803
night-time	9387.97 ±6985.05	12183.00 ±7101.71	0.325	8597.00 ±8103.34	12329.10 ±9289.16	0.150
LF (ms^2)						
24-hour	3067.35 ±4187.66	3349.89 ±1234.43	0.105	2274.32 ±1957.36	4916.29 ±9021.22	0.428
daytime	1546.00 ±1257.66	2708.20 ±2536.42	0.163	2469.42 ±2656.57	2838.75 ±2495.96	0.655
night-time	2956.90 ±2070.30	3371.00 ±1976.64	0.408	2334.05 ±2255.21	3193.13 ±2548.51	0.297
HF (ms^2)						
24-hour	2120.90 ±2057.00	3634.22 ±3026.90	0.049	2560.63 ±2859.00	3192.06 ±2656.29	0.358
daytime	930.10 ±1101.66	7832.90 ±18825.10	0.015	1736.00 ±1902.29	2233.00 ±2310.00	0.619
night-time	2805.8 ±2640.1	4034.00 ±3386.38	0.254	3273.16 ±3813.83	4029.94 ±2965.31	0.240
LF/HF ratio						
24-hour	1.57 ±1.56	1.42 ±0.88	0.783	1.05 ±0.88	1.22 ±0.78	0.293
daytime	1.85 ±1.76	1.37 ±1.08	0.738	1.15 ±0.93	2.30 ±2.42	0.083
night-time	1.54 ±1.71	1.21 ±0.85	0.888	0.97 ±1.29	0.72 ±0.43	0.949

Values are presented as mean ±standard deviation. Mann-Whitney U test was used

The strength of the association between heart rate variability indexes and main clinical parameters of vasovagal syncope in children and adolescents via Spearman's correlation is represented in Table 7.

DISCUSSION

Heart rate variability is a key indicator of the sympathetic and the parasympathetic nervous system activity, and the autonomic imbalance is often caused by increased

TABLE 4. Comparison of heart rate variability between vasovagal syncope patients and healthy ones in the groups of adolescents and children

Heart rate variability index	Adolescents			Children		
	Vasovagal syncope ($n = 39$)	Control ($n = 21$)	*p*-value	Vasovagal syncope ($n = 17$)	Control ($n = 20$)	*p*-value
Time domain						
Heart rate (bpm)						
24-hour	75.76 ±9.28	76.81 ±10.13	0.703	80.55 ±23.56	79.15 ±10.79	0.371
daytime	67.13 ±10.26	68.25 ±13.97	0.817	73.25 ±12.81	67.16 ±10.95	0.174
night-time	82.61 ±10.52	83.45 ±8.24	0.630	87.50 ±10.41	87.63 ±11.73	0.839
circadian rhythm	1.25 ±0.16	1.25 ±0.18	0.743	1.21 ±0.13	1.33 ±0.21	0.224
SDANN (ms)						
24-hour	255.28 ±197.63	353.57 ±217.82	0.102	258.91 ±179.13	380.10 ±311.66	0.302
daytime	330.87 ±269.53	406.10 ±281.94	0.320	337.46 ±281.05	494.42 ±426.87	0.263
night-time	178.93 ±160.33	236.75 ±152.169	0.100	140.27 ±57.51	267.105 ±226.29	0.127
RMSSD (ms)						
24-hour	294.00 ±234.106	396.57 ±239.44	0.043	289.91 ±212.31	384.10 ±274.69	0.409
daytime	349.28 ±291.64	464.45 ±326.66	0.132	350.17 ±228.04	494.79 ±382.18	0.223
night-time	201.65 ±182.46	270.00 ±174.78	0.125	154.42 ±80.67	272.16 ±229.75	0.100
pNN50 (%)						
24-hour	30.13 ±11.83	37.43 ±17.36	0.048	34.18 ±14.56	35.45 ±14.36	0.984
daytime	23.55 ±12.63	34.00 ±14.96	0.014	29.45 ±14.12	30.11 ±13.44	1.00
night-time	38.7 ±15.86	45.55 ±23.51	0.181	44.09 ±18.69	44.58 ±17.07	0.949
Frequency domain						
TP (ms^2)						
24-hour	7578.29 ±5409.74	7998.47 ±6366.83	0.952	12236.00 ±5651.45	10508.70 ±8405.55	0.435
daytime	4776.19 ±4146.56	8206.32 ±7444.75	0.174	10488.70 ±8326.43	9278.88 ±8134.17	0.654
night-time	9387.97 ±6985.05	8597.00 ±8103.34	0.531	12183.00 ±7101.71	12329.10 ±9289.16	0.833
LF (ms^2)						
24-hour	3067.35 ±4187.66	2274.32 ±1957.36	0.576	3349.89 ±1234.43	4916.29 ±9021.22	0.435
daytime	1546.00 ±1257.66	2469.42 ±2656.57	0.259	2708.20 ±2536.42	2838.75 ±2495.96	0.979
night-time	2956.90 ±2070.30	2334.05 ±2255.21	0.334	3371.00 ±1976.64	3193.13 ±2548.51	0.712
HF (ms^2)						
24-hour	2120.90 ±2057.00	2560.63 ±2859.00	0.889	3634.22 ±3026.90	3192.06 ±2656.29	0.767
daytime	930.10 ±1101.66	1736.00 ±1902.29	0.108	7832.90 ±18825.10	2233.00 ±2310.00	0.732
night-time	2805.8 ±2640.1	3273.16 ±3813.83	0.870	4034.00 ±3386.38	4029.94 ±2965.31	0.916
LF/HF ratio						
24-hour	1.57 ±1.56	1.05 ±0.88	0.217	1.42 ±0.88	1.22 ±0.78	0.535
daytime	1.85 ±1.76	1.15 ±0.93	0.210	1.37 ±1.08	2.30 ±2.42	0.317
night-time	1.54 ±1.71	0.97 ±1.29	0.043	1.21 ±0.85	0.72 ±0.43	0.206

Values are presented as mean ±standard deviation. Mann-Whitney U test was used

sympathetic activities and/or reduced parasympathetic activities. Improvement in heart rate variability may be associated with autonomic nervous system homeostasis, and decreased heart rate variability indicates the imbalance in autonomic tone [3, 19]. Therefore, there is an opportunity to identify a non-invasive marker that may be an indicator of future risk of cardiovascular diseases and chronic diseases in general [20].

Although the pathophysiology of vasovagal syncope is still poorly understood, the autonomic nervous system is thought to play a major role. A lot of studies conducted in adults with vasovagal syncope showed that 24-hour base-

TABLE 5. Comparison of heart rate variability between males and females in vasovagal syncope and control groups

Heart rate variability index	Vasovagal syncope			Control		
	Males ($n = 32$)	Females ($n = 24$)	*p*-value	Males ($n = 17$)	Females ($n = 24$)	*p*-value
Time domain						
Heart rate (bpm)						
24-hour	75.19 ±9.21	79.5 ±20.89	0.108	77.06 ±12.29	75.58 ±9.05	0.491
daytime	66.46 ±8.85	72.47 ±14.10	0.157	68.59 ±15.11	67.05 ±10.24	0.977
night-time	83.04 ±10.03	85.41 ±11.56	0.345	84.00 ±12.48	86.64 ±8.10	0.396
circadian rhythm	1.26 ±0.13	1.21 ±0.18	0.136	1.25 ±0.18	1.32 ±0.21	0.479
SDANN (ms)						
24-hour	207.4 ±134.63	324.00 ±236.95	0.042	285.88 ±189.59	423.62 ±297.65	0.122
daytime	264.56 ±208.16	432.65 ±320.52	0.044	360.06 ±285.39	517.96 ±397.86	0.183
night-time	142.68 ±43.83	209.00 ±216.27	0.688	201.47 ±122.3	290.23 ±224.23	0.288
RMSSD (ms)						
24-hour	242.12 ±151.05	363.56 ±291.85	0.278	316.24 ±204.02	443.08 ±276.30	0.153
daytime	282.54 ±248.94	446.28 ±342.35	0.041	396.82 ±300.94	542.91 ±378.70	0.257
night-time	158.77 ±58.59	233.88 ±243.13	0.775	225.53 ±154.60	306.23 ±227.38	0.223
pNN50 (%)						
24-hour	31.84 ±11.38	30.22 ±14.26	0.712	38.35 ±16.64	35.13 ±15.39	0.525
daytime	24.56 ±13.21	25.88 ±13.36	0.848	32.59 ±14.08	31.73 ±14.59	0.766
night-time	40.68 ±13.93	39.31 ±20.57	0.957	47.65 ±21.73	43.01 ±19.52	0.497
Frequency domain						
TP (ms^2)						
24-hour	8355.71 ±4990.9	9032.13 ±6867.72	0.923	10901.60 ±7008.57	7809.70 ±7750.83	0.119
daytime	4596.88 ±3508.47	8626.69 ±7885.27	0.186	10646.90 ±7516.20	7054.32 ±7603.36	0.105
night-time	9945.04 ±6778.20	10322.60 ±7669.27	0.889	11333.60 ±7959.23	9435.26 ±9474.29	0.289
LF (ms^2)						
24-hour	2533.71 ±1429.30	4026.75 ±5600.33	0.609	3048.75 ±2180.28	3900.45 ±8447.84	0.191
daytime	1383.84 ±971.79	2525.75 ±2311.97	0.131	3262.69 ±2832.65	2112.42 ±2233.76	0.185
night-time	3039.44 ±1878.24	3095.40 ±2330.72	0.148	3163.63 ±2333.52	2458.89 ±2449.28	0.275
HF (ms^2)						
24-hour	2352.96 ±2176.27	2624.06 ±2665.47	0.836	3309.38 ±2928.92	2498.35 ±2606.42	0.340
daytime	994.00 ±1415.67	5144.50 ±14988.80	0.112	2234.50 ±2107.43	1734.74 ±2088.79	0.354
night-time	2966.04 ±2780.30	3357.53 ±3043.70	0.780	3912.50 ±3325.88	3372.05 ±3576.37	0.427
LF/HF ratio						
24-hour	1.56 ±1.58	1.49 ±1.19	1.00	1.09 ±0.57	1.17 ±1.01	0.737
daytime	1.82 ±1.81	1.59 ±1.31	0.820	1.56 ±0.92	1.74 ±2.39	0.318
night-time	1.43 ±1.68	1.50 ±1.31	0.675	0.8 ±0.35	0.90 ±1.35	0.199

Values are presented as mean ±standard deviation. Mann-Whitney U test was used

line heart rate variability indices revealed no significant difference as compared with healthy ones [21, 22]. However, some of them [23, 24] reported that basal heart rate variability measurements were augmented by parasympathetic predominance in adult patients with vasovagal syncope.

Unlike adults, heart rate variability in children and adolescents with vasovagal syncope has been evaluated only infrequently. Shim *et al.* [12] indicated that children with syncope had a decreased sympathetic tone and increased vagal tone compared to healthy children. Zygmunt and Stanczyk [13] concluded that based on heart rate variabil-

TABLE 6. Comparison of heart rate variability between vasovagal syncope patients and healthy ones in male and female groups

Heart rate variability index	Males			Females		
	Vasovagal syncope ($n = 32$)	Control ($n = 17$)	*p*-value	Vasovagal syncope ($n = 24$)	Control ($n = 24$)	*p*-value
Time domain						
Heart rate (bpm)						
24-hour	75.19 ±9.21	77.06 ±12.29	0.737	79.5 ±20.89	75.58 ±9.05	0.633
daytime	66.46 ±8.85	68.59 ±15.11	0.950	72.47 ±14.10	67.05 ±10.24	0.188
night-time	83.04 ±10.03	84.00 ±12.48	0.920	85.41 ±11.56	86.64 ±8.10	0.799
circadian rhythm	1.26 ±0.13	1.25 ±0.18	0.990	1.21 ±0.18	1.32 ±0.21	0.092
SDANN (ms)						
24-hour	207.4 ±134.63	285.88 ±189.59	0.228	324.00 ±236.95	423.62 ±297.65	0.438
daytime	264.56 ±208.16	360.06 ±285.39	0.299	432.65 ±320.52	517.96 ±397.86	0.590
night-time	142.68 ±43.83	201.47 ±122.3	0.179	209.00 ±216.27	290.23 ±224.23	0.220
RMSSD (ms)						
24-hour	242.12 ±151.05	316.24 ±204.02	0.282	363.56 ±291.85	443.08 ±276.30	0.253
daytime	282.54 ±248.94	396.82 ±300.94	0.109	446.28 ±342.35	542.91 ±378.70	0.455
night-time	158.77 ±58.59	225.53 ±154.60	0.238	233.88 ±243.13	306.23 ±227.38	0.198
pNN50 (%)						
24-hour	31.84 ±11.38	38.35 ±16.64	0.218	30.22 ±14.26	35.13 ±15.39	0.485
daytime	24.56 ±13.21	32.59 ±14.08	0.041	25.88 ±13.36	31.73 ±14.59	0.257
night-time	40.68 ±13.93	47.65 ±21.73	0.127	39.31 ±20.57	43.01 ±19.52	0.605
Frequency domain						
TP (ms^2)						
24-hour	8355.71 ±4990.9	10901.60 ±7008.57	0.288	9032.13 ±6867.72	7809.70 ±7750.83	0.454
daytime	4596.88 ±3508.47	10646.90 ±7516.20	0.012	8626.69 ±7885.27	7054.32 ±7603.36	0.585
night-time	9945.04 ±6778.20	11333.60 ±7959.23	0.530	10322.60 ±7669.27	9435.26 ±9474.29	0.405
LF (ms^2)						
24-hour	2533.71 ±1429.30	3048.75 ±2180.28	0.552	4026.75 ±5600.33	3900.45 ±8447.84	0.258
daytime	1383.84 ±971.79	3262.69 ±2832.65	0.011	2525.75 ±2311.97	2112.42 ±2233.76	0.608
night-time	3039.44 ±1878.24	3163.63 ±2333.52	0.862	3095.40 ±2330.72	2458.89 ±2449.28	0.260
HF (ms^2)						
24-hour	2352.96 ±2176.27	3309.38 ±2928.92	0.415	2624.06 ±2665.47	2498.35 ±2606.42	0.787
daytime	994.00 ±1415.67	2234.50 ±2107.43	0.011	5144.50 ±14988.80	1734.74 ±2088.79	0.830
night-time	2966.04 ±2780.30	3912.50 ±3325.88	0.504	3357.53 ±3043.70	3372.05 ±3576.37	0.862
LF/HF ratio						
24-hour	1.56 ±1.58	1.09 ±0.57	0.573	1.49 ±1.19	1.17 ±1.01	0.361
daytime	1.82 ±1.81	1.56 ±0.92	0.747	1.59 ±1.31	1.74 ±2.39	0.739
night-time	1.43 ±1.68	0.8 ±0.35	0.228	1.50 ±1.31	0.90 ±1.35	0.034

Values are presented as mean ±standard deviation. Mann-Whitney U test was used

ity analysis children and adolescents with neurocardiogenic syncope had alterations in basal autonomic balance, which indicated an increased sympathetic modulation in these patients. The findings of Akcaboy *et al.* [14] suggest that the baseline autonomic functions are normal in both healthy children and patients with neurocardiogenic syncope. In this study they evaluated the baseline autonomic activity in the same population six months later and found that it was similar between frequent fainters and non-fainters. Therefore, they concluded that baseline autonomic activity alone might not explain why some individuals faint and others do not. Topcu and Akalın [25]

TABLE 7. Level of correlation between heart rate variability indexes and main clinical parameters of vasovagal syncope ($n = 56$)

Clinical parameter of vasovagal syncope	24-hour heart rate	24-hour SDANN	24-hour RMSSD	24-hour pNN50	24-hour TP	24-hour LF	24-hour HF	24-hour LF/HF ratio
Sex	0.31	0.32	–	–	–	–	–	–
Age	0.30	–	–	–	0.36	–	0.32	–
Body mass index	–	–	–	–	–	–	–	–
Age of the first syncopal event	–	–	–	–	–0.43	–	–0.36	–
Number of syncopal events	–	–	–	–	–	–	–	0.40
Calgary Syncope Seizure Score	–	–	–	–	–	–	–	–
Modified Calgary Syncope Seizure Score	–	–	–	–	–0.33	–	–	–
Orthostatic dysregulation	–	–0.35	–0.35	–	–	–	–	–
24-hour mean systolic blood pressure	0.30	0.31	–	–	–	0.31	–	–
24-hour mean diastolic blood pressure	0.31	0.36	–	–	–	0.30	–	–
PedsQL 4.0 Generic Core Scale								
Total Health Scale	–	–	0.30	0.31	–	–	–	–
Physical Health Scale	–	–	–	0.34	–	–	–	–
Psychosocial Health Scale	–	–	–	–	–	–	–	–
Emotional Functioning	–	–	–	–	–	–	–	–
Social Functioning	–	–	–	–	–	–	–	–
School Functioning	–	–	–	–	–	–	–	–

Values are the Spearman's correlation coefficient. Only significant correlations ($p < 0.05$) are reported

also confirmed that autonomic functions in children with neurocardiogenic syncope are similar to those in healthy children.

The results of our present study demonstrated decreased heart rate variability in vasovagal syncope paediatric patients. The time domain indices of SDANN (24-hour, and night-time measurements), RMSSD (24-hour, daytime, and night-time measurements), and pNN50 (daytime measurement) were significantly decreased in patients with vasovagal syncope compared with healthy patients. Such changes in the examined patients reflect the decrease in the total effect of autonomous blood circulation regulation, associated with the increase of sympathetic regulation, which inhibits the activity of autonomous circuit. Moreover, in the frequency-domain analysis they exhibited a significantly higher LF/HF ratio, which is also a reflection of vegetative imbalance toward increase of sympathetic regulation. The autonomic imbalance with the weakening of the parasympathetic and domination of the sympathetic tone of the nervous system obviously leads to the weakening of the overall adaptive capacities of the organism, and it demonstrated the expected development of cardiovascular disorders even before the appearance of significant changes of central haemodynamics [26].

It is well known that heart rate variability is changing during childhood and adolescence, which may reflect developmental alterations in the autonomic nervous system activity [27]. Thus, in order to follow these changes, values of heart rate variability were comparable between children and adolescents in the vasovagal syncope and the control group. The results of our study showed that adolescents and preadolescents in the control group were not significantly different in terms of heart rate variability. Unlike in healthy patients, we registered significantly lower values of TP (24-hour, and daytime measurements) and HF (24-hour, and daytime measurements) indexes in adolescents, compared with children in the vasovagal syncope group. These results indicate more severe reflection of vegetative imbalance toward increase of sympathetic regulation in adolescents with vasovagal syncope and are in stark contrast to the results of Shim *et al.* [12]. These researchers have shown that adolescents with vasovagal syncope experienced more severe activation of vagal sinus modulation than preadolescents.

To confirm predominance in vagal tone of adolescent patients, Shim *et al.* [12] also analysed the differences of heart rate variability pattern by age. The time and frequency domain of heart rate variability analysis in adolescent age show the activation of parasympathetic tone and the inhibition of sympathetic tone in adolescent patients. From the results of our study, in adolescents with vasovagal syncope, we found lower values of RMSSD (24-hour measurement), pNN50 (24-hour and daytime measurements), and higher value of LF/HF ratio (night-time measurement), in comparison with the control group. These data confirm sympathetic predominance in adolescents with vasovagal syncope.

While comparing heart rate variability to gender, in males we found significantly lower values of SDANN (24-hour, and daytime measurements) and RMSSD (daytime measurement). However, there were no significant differences in heart rate variability indices between males and females in the control group. In addition, in males with vasovagal syncope we found lower values of pNN50 (daytime measurement), TP (daytime measurement), LF (daytime measurement), and HF (daytime measurement), in comparison with healthy males. Such results indicated that in males with vasovagal syncope sympathetic hyperactivity is more greatly expressed compared with females.

Our findings are partially comparable with other studies. Silva *et al.* revealed that girls presented significantly higher values than the boys for SDNN and HF in the supine position [28]. In the study of Silvetti *et al.* males showed SDNN and SDANN values that were significantly higher than in females, while for SDNN-i, rMSSD, and pNN50 there were no significant differences between sexes [29].

We did not find any differences in time and frequency domain heart rate variability indices between patients with vasovagal syncope with one and more than one syncopal event in their life. However, 24-hour LF/HF index of sympathovagal balance was correlated with number of syncopal events in the lives of children and adolescents. We have not found any comparable studies in this area.

Since heart rate variability is under the influence of a number of factors, we conducted correlative analysis between heart rate variability indexes (24-hour measurements) and some clinical parameters of vasovagal syncope in paediatric patients. A significant correlation was found between age of the first syncopal event and TP and HF indices. The results indicated the same tendency of more severe dysbalance of the autonomic nervous system in syncopal adolescents in comparison with children.

Despite the abundant data available for the impact of body mass index on heart rate variability [30], we did not find any relationship between body mass index and any of the time and frequency domain heart rate variability indices in children and adolescents with vasovagal syncope.

However, orthostatic dysregulation was associated with lower values of SDANN and RMSSD in patients with vasovagal syncope. Sato *et al.* showed that patients with orthostatic dysregulation had less variability of the parasympathetic nervous system as well as hyperactivity of the sympathetic nervous system [31]. In this sense, the results of our studies also coincide.

It is well known that autonomic nervous function plays a significant role in the circulatory system and in blood pressure regulation. Heart rate variability techniques may provide a seemingly low-effort approach to assessing cardiovascular autonomic function in hypertension, hypotension, and other circulatory disease states; the techniques are not yet for general use but remain within the domain of research requiring interpretation within the context of the overall circulatory state [32]. Gui-Ling *et al.* provided evidence that heart rate variability is reduced and the circadian rhythm is weakened in hypertensive children, and they hypothesise that reduced heart rate variability is a potential pathophysiological mechanism linking childhood hypertension and adulthood cardiovascular diseases [33]. In our patients with vasovagal syncope we observed a tendency for decreasing SDANN and LF with decreasing 24-hour mean systolic and diastolic blood pressure. The data suggest that children with vasovagal syncope may exhibit differences in heart rate variability measurements depending on the kind of vasovagal response.

It is well-known that evaluation of quality of life is an excellent tool to assess the impact of acute or chronic disease on health outcomes in children and adolescents [34]. A few studies have addressed the quality of life of children with vasovagal syncope. Their findings suggest that paediatric patients with syncope, although typically of benign aetiology, had low health-related quality of life compared with healthy controls [18]. It is of interest that a decreased value of pNN50 index was associated with low health-related quality of life in the group of patients with vasovagal syncope. These results were not compared with previous studies because no previous study evaluated the heart rate variability parameters in the same population of patients.

CONCLUSIONS

The analysis of heart rate variability patterns with vasovagal syncope remains controversial. On the one hand, heart rate variability must be carefully interpreted in context because measurements are greatly influenced by experimental conditions, respirations, and other biologic signals. Nonetheless, heart rate variability techniques offer a relatively simple and painless window on autonomic control and have been extensively used. The results of heart rate variability analysis can be conflicting because the pathophysiology of syncope remains unclear. Further studies are needed including larger numbers of patients and heart rate variability indices values depending on the kind of vasovagal response observed during head-up tilt test.

In conclusion, these findings suggest that paediatric patients with vasovagal syncope had alterations in basal autonomic balance, which indicated an increased sympathetic modulation. More severe autonomic imbalance occurs in adolescent males.

DISCLOSURE

The authors declare no conflict of interest.

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