Heart rate variability during asymptomatic periods in children with recurrent neurocardiogenic syncope

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Neurocardiogenic syncope (NS) is a common clinical problem during childhood. In order to characterize the autonomic profile in syncopal children, we evaluated heart rate variability (HRV) of 27 patients, ages 8-17 years, in an asymptomatic period. HRV was calculated over a 24-hour (h) period for the time-domain indices and frequency-domain indices. The obtained results were compared to values in 27 healthy children, ages 10-17 years. Patients with syncope did not have significantly different HRV values in comparison to healthy children. After behavior modification and education, HRV assessment was repeated six months later in the symptomatic group under follow-up, and we found no significantly different values.

We conclude that there was no significant difference in baseline autonomic values between children with NS and the healthy control group. After behavior modification and education, none of the patients with NS under follow-up experienced syncope or presyncope during the follow-up period. The major complaint had disappeared but did not reflect the HRV values. There was no significant difference in baseline HRV values of the patients in follow-up. We conclude that patients are predisposed to faint by a triggering autonomic stress, without having constant autonomic instability.

Key words: heart rate variability, neurocardiogenic syncope, asymptomatic periods.

Syncope can be defined as a temporary loss of consciousness and postural tone secondary to a lack of adequate cerebral blood perfusion[1]. Neurocardiogenic syncope (NS) is the most common cause of unexplained syncope in children[2]. NS is diagnosed by typical history, absence of other proven causes of syncope and a positive response to head-upright tilt-table (HUTT) test[3]. In children, the exact mechanism of NS has not been described definitively, but the probable theory is supposed to be the overstimulation of central reflex (Bezold-Jarisch reflex) by orthostatic stress and venous pooling[4]. Recently, heart rate variability (HRV) has been defined and used for evaluating the health status of the heart and also its sympathetic and parasympathetic innervation[5]. HRV, which is used during HUTT, has given important proofs to define the mechanism of syncope in children[6-8]. HRV derived from the patients with NS during asymptomatic periods produced different results in children and in adults[9-15]. The purpose of this study was to evaluate baseline autonomic function by assessment of 24-hour (h) HRV in children with recurrent NS and compare the results with the children who had no history of syncope, in order to assess the sympathovagal balance, to follow the patients with recurrent NS with education and physical counter-maneuvers, and to compare the HRV responses after behavior modification.

Material and Methods

Study Population

Our study population consisted of 27 children (18 girls, 9 boys; mean age: 14.1 years) with recurrent NS. The control group consisted of 27 healthy volunteers (14 girls, 13 boys; mean age: 13.8 years) without a history of NS or

presyncope or any medication. The patients were referred to the Department of Pediatric Cardiology during the period February 2004 and June 2005 for evaluation and treatment of recurrent syncope. Children enrolled in the study had to meet the following inclusion criteria: 1) recurrent syncope or presyncope episodes; recurrence is defined as at least two typical attacks of NS within the last six months or one syncope and three presyncope attacks in a year[16], 2) absence of any other evident etiology for syncope or presyncopal attacks, and 3) no concomitant chronic or acute disease. Written informed consent was obtained from all participants in this study. The university's ethics committee approved this study (Approval: April 5, 2004, number: 49-1238).

Evaluations

The following was performed in all patients: Medical history, physical examination (auscultation, blood pressure measurement in supine and upright positions), 12-lead ECG, chest X-ray, transthoracic echocardiography, HUTT, 24-h ambulatory ECG, and a complete neurological examination. None of the patients or the control group was taking neurally active or vasoactive medication at the time of the evaluation. HUTT was not performed in the control patients for ethical reasons. The entire evaluation parameters except for HUTT were completed in the control group as well.

Head-Upright Tilt-Table (HUTT) Test

The test was conducted between 10 a.m. and 2 p.m., at least 3 h after a light meal, in a quiet room with dimmed lighting, on an electrically driven table with a foot board. A peripheral intravenous cannula was placed for emergency intervention before starting the test. The ECG was monitored continuously and oscillometric blood pressure measurement was done noninvasively with a manual arm sphygmomanometer of appropriate size, once in the supine position, at 1 and 3 minutes (min) after tilting, and then at 3-min intervals and in case of any clinical symptoms. The patients were positioned at a 60-degree angle from the horizontal plane after allowing them to rest in the supine position for 15 min. The test was ended after 45 min if no symptoms were observed. Neither medication nor stimulation was used during the test. Whenever symptoms were observed during HUTT, the table was lowered to the horizontal position and the test was terminated. A positive response was defined as sudden development of syncope or presyncope associated with hypotension, bradycardia, or both. Vasodepressor response was defined as marked fall in systolic blood pressure without bradycardia. Cardioinhibitory response was defined as an abrupt drop in the heart rate to below 40 beats/min for longer that 10 seconds (s) or asystole lasting more than 3 s. Mixed response was characterized by both blood pressure and heart rate decrease. A negative test was defined as the absence of hypotension, bradycardia, syncope, or presyncope.

HRV Analysis

A standard ambulatory Holter recording system with a three-channel recorder was used. In order to minimize the impact of stress connected with various tests, Holter monitoring did not overlap other cardiovascular tests and was performed from 2 to 4 days after the HUTT. All the recordings were of very good quality, and none of the patients had a significant number of ectopic beats. The ECG was obtained through continuous electrocardiographic recordings and stored in a personal computer. HRV was automatically analyzed by the spectral program using Reynolds Medical Pathfinder 700 Model Ambulatory Holter Analysis System with a sampling rate of 1024 Hz. HRV was assessed in two ways: 1) time-domain analysis and 2) frequency-domain analysis. Within 6 time–domain analyses, we calculated the following indices: Mean R-R interval, standard deviation of all R-R intervals (SDNN), standard deviation of the averages of the R-R intervals in all 5-min segments of R-R intervals (SDANN), the mean of all 5-min means SDs of R-R intervals (SDANNI), the root of the mean square of the difference of successive R-R intervals (rMSSD), and the proportion of adjacent normal R-R intervals $<$50 ms (pNN50%). The first four parameters show the sympathetic and parasympathetic influence on HRV, while rMSSD and pNN50 reflect the vagal control on heart rate. The first four parameters reflect the heart rate, and their increase is related with a decrease in the heart rate and parasympathetic control.

Their decrease is related with an increase in the heart rate and sympathetic control[17].

The 24-h frequency-domain analysis was done in 5-min segments (repeat interval was 60 min). Artifact- and ectopic-free segments were not used for analysis. Two frequency components were calculated: 1) The high frequency (HF) component, i.e. the value of the power (ms^2) in the band from 0.16 to 0.40 Hz, mainly due to vagal activity; 2) The low frequency (24-h LF) component, i.e. the value of the power (ms^2) in the band from 0.04 to 0.15 Hz and thought to show both sympathetic and vagal activity. The 24-h LF/HF ratio is an index of the sympathovagal interplay. The values of HRV of the symptomatic group were compared with those of the healthy control group.

Follow-Up and Treatment

The patients were educated regarding the possible predisposing factors for NS. In order to avoid dehydration, it was suggested to the patients to intake adequate fluid and salt. It was also suggested that they avoid the predisposing factors such as standing up for an extended period, especially in hot and crowded environments. Prodromic symptoms such as dizziness, nausea and sweating were described and the physical counter-maneuvers were shown in order to manage them. In most patients with orthostatic intolerance, immobility can worsen symptoms, whereas bending forward, sitting or moving around can improve them[4]. On the basis of these observations, several physical maneuvers that reduce venous pooling were described. Patients were educated to apply maneuvers (leg-crossing, squatting, bending forward, arm-tugging) as soon as symptoms began[18,19]. Twenty-one patients were evaluated six months later and HUTT and Holter ambulatory monitoring were repeated. The other six patients were excluded because they could not complete the six months of the evaluation period during the study.

Statistical Analysis

Data were expressed as proportions or median and minimum and maximum values. The Mann-Whitney U test was used for comparing the values of the patients and controls. Wilcoxon test was used to compare the baseline and control values of the patients. Kruskal-Wallis test was used to evaluate the relationship of HRV with the other parameters. For all analyses, a p value <0.05 was considered statistically significant. All statistics were analyzed using the SPSS 11.0 package program.

Results

1. Head-Up Tilt Test (HUTT)

This study group included 18 females and 9 males with a median age of 14.1 years. Among the 27 NS patients, 24 (88.9%) had a positive response to the baseline HUTT, while 3 had a negative test. Ten of them (37%) were mixed responses, 7 (25.9%) were cardioinhibitory responses, and only 1 patient (3.7%) showed a vasodepressor response. Six of them (22.2%) experienced presyncopal episodes during HUTT.

2. Analysis of HRV Indices: 24-Hour Ambulatory ECG Recording

The 24-h time-domain and resting spectral HRV parameters were compared with the healthy controls (Table I).

Time-domain analysis: Statistical analysis of the results showed a significant increase in the median SDNN and SDANN values in the NS group compared to the control group ($p<0.01$). However, the other time-domain indices revealed no significant differences between the patients and the control group ($p<0.05$). Because all of the parameters did not reflect statistical significance, the results were evaluated as being not significantly different.

Frequency-domain analysis: There was no statistically significant difference between the two groups in any parameter ($p<0.05$).

3. Relation Between 24-Hour Baseline HRV and the Pattern of Syncope During HUTT

The HRV indices were classified for the responses to HUTT (Table II). Patients with cardioinhibitory response had significantly higher values of rMSSD and HF compared to the other responses to HUTT ($p<0.05$).

4. Follow-Up Evaluations

Twenty-one patients were evaluated six months later and no patient had a history of syncope or presyncopal attacks. The HUTT and HRV parameters were repeated in this

Table I. Baseline HRV Values of the Patients and Controls

Parameter	Patients n: 27 Median (Min-Max)	Controls n: 27 Median (Min-Max)	p
Mean RR (ms)	723 (537-869)	724 (480-869)	0.863
SDNN (ms)	162 (97-266)	121 (37.6-182)	0.001
SDANNI (ms)	73 (35-133)	70 (28-131)	0.769
SDANN (ms)	135 (89-226)	73 (23.1-159)	0.000
rMSSD (ms)	53 (13-128)	51 (20-125)	0.678
pNN50 (%)	20.4 (0.6-43.2)	19.7 (4.77-45.06)	0.651
LF (ms^2)	486.73 (112.98-1487.98)	549.92 (85.39-1463.52)	0.869
HF (ms^2)	412.94 (42.53-1367.73)	226.96 (67.93-1983.20)	0.938
LF/HF	2.73 (1.52-6.04)	2.63 (1.07-7.54)	0.836

Mean RR: Mean R-R interval. SDNN: Standard deviation of all R-R intervals. SDANN: Standard deviation of the averages of R-R intervals in all 5-min segments of R-R intervals. SDANNI: Mean of all 5-min means SDs of R-R intervals. rMSSD: Root of the mean square of the difference of successive R-R intervals. pNN50%: Proportion of adjacent normal R-R intervals <50 ms. LF: Low frequency. HF: High frequency.

period. Seventeen patients (81%) experienced negative response to HUTT. Three patients had presyncopal attacks and only one had syncope during HUTT. These HRV parameters were compared to the first baseline HRV indices, and significant increases in SDNN and SDANN were found ($p<0.05$) (Table III). However, there were no significant differences in other time-domain indices (particularly in rMSSD and pNN50) and frequency-domain indices in the follow-up.

Discussion

Although the pathophysiology of NS is still poorly understood, the autonomic nervous system is thought to play a major role. HUTT is used extensively in evaluation of patients with NS. The studies designed in children revealed that specificity and sensitivity of the HUTT differs from 25-48.5% and from 93.5-100%, respectively[3,19]. The positive test response varies from 14% to 50%[20]. In this study, we found the positive test response as 88.9%, despite the lower angle of HUTT and not using any provocative medication. The most relevant response in HUTT was mixed type followed by cardioinhibitory type response, concordant with the previous studies that have been carried out in children[21,22].

In recent years, a large number of valuable studies have used spectral analysis of HRV to investigate the role of the autonomic nervous system in the pathogenesis of NS. Some of these studies investigated the autonomic nervous system under baseline conditions (over a 24-h period), and others studied the changes in the autonomic nervous system during HUTT and just before the syncope[7,10,23-25]. Different age groups, different HUTT protocols and the variation in the time of HRV recordings confuse all the results and comments.

Recently, the relationship between the daily baseline cardiac autonomic activity and the mechanism of predisposing factors for NS was investigated. There are a few studies that were interested in daily baseline cardiac autonomic activity during childhood[7,9,15,23,26]. They have reported conflicting results, with some authors suggesting that patients have normal resting autonomic tone and others suggesting that they have alterations in baseline autonomic activity[7,9,15,23,26]. In this study, we evaluated the baseline autonomic activity using traditional HRV indices. The time-domain indices of SDNN and SDANN were significantly higher in patients with NS compared with healthy children. According to earlier reports, SDNN and SDANN are more often associated with untoward outcome for cardiovascular diseases,

Table II. Comparison of HRV Indices Classified to the Response to HUTT

Parameter	Cardio-inhibitory n: 7	Vaso-depressor n: 1	Mixed n: 10	Presyncope n: 6	Negative n: 3	p*
Mean RR (ms)	770 (637-803)	723 (723-723)	665 (546-735)	767 (537-869)	713 (673-751)	NS
SDNN (ms)	183 (130-266)	192 (192-192)	123 (103-186)	153 (97-214)	163 (133-220)	NS
SDANNI (ms)	99 (58-133)	62 (62-62)	57 (36-87)	55 (35-85)	82 (51-98)	NS
SDANN (ms)	156 (118-226)	184 (184-184)	110 (89-172)	118 (90-201)	143 (120-203)	NS
rMSSD (ms)	75 (39-128)*	39 (39-39)	35 (18-68)	45 (13-68)	27 (27-27)	0.038
pNN50	25.1 (5.4-43.2)	7 (7-7)	15.95 (1.3-35)	15.2 (0.6-25)	21.1 (7.3-27.7)	NS
LF (ms^2)	687.25 (426.89-1487.98)	286.63 (286.63-286.63)	350.74 (138.86-661.14)	332.85 (112.98-442.68)	974.96 (146.91-978.74)	NS
HF (ms^2)	790.846 (204.622-1367.731)*	121.461 (121.461-121.461)	182.374 (42.538-535.281)	243.501 (43.904-591.864)	117.230 (117.230-117.230)	0.04
LF/HF	2.73 (1.59-4.22)	5.04 (5.04-5.04)	2.77 (1.75-3.89)	3.15 (2.25-6.04)	3.73 (2.38-4.66)	NS

NS: Not significant. Mean RR: Mean R-R interval. SDNN: Standard deviation of all R-R intervals. SDANN: Standard deviation of the averages of R-R intervals in all 5-min segments of R-R intervals. SDANNI: Mean of all 5-min means SDs of R-R intervals. rMSSD: Root of the mean square of the difference of successive R-R intervals. pNN50%: Proportion of adjacent normal R-R intervals <50 ms. LF: Low frequency. HF: High frequency.

while rMSSD and pNN50 are related more with autonomic activity[27,28]. SDNN and SDANN are also affected by sudden and large changes in R-R intervals, caused either by physiologic reflexes or by artefacts. Sosnowski et al.[29] introduced a new index of HRV, named HRV fraction, which was easy to compute and robust, and may overcome the limitations that belong to the standard HRV measures. However, the other time-domain indices (particularly rMSDD and pNN50) and the frequency-domain indices were not significantly different in our patients with NS. Since these HRV indices tend to reflect the autonomic control of the heart more than SDNN and SDANN, these results support that the baseline autonomic activity of the heart in children with NS is normal.

Zygmunt et al.[15] compared the baseline HRV indices in 73 children with NS to those of the healthy controls. They emphasized that sympathetic autonomic activity is predominant in children with syncope and this is thought to be responsible for activating the Bezold-Jarisch reflex[15]. Zygmunt et al.[15] and Guzman et al.[6] found that the patients who had vasodepressor type response during HUTT had sympathetic predominancy in baseline HRV parameters. Longin et al.[23] measured short-term HRV indices in children with NS or presyncopal symptoms to compare with healthy children, and they also found sympathetic predominancy. We found no difference in frequency-domain indices of HRV in 24-h Holter recording among healthy subjects and the symptomatic patients.

Table III. HRV Parameters of Patients in the First Evaluation and in the Follow-Up

Parameter	First evaluation n: 21 Median (Min-Max)	Follow-up n: 21 Median (Min-Max)	p
Mean RR (ms)	724 (623-869)	726 (605-864)	0.7
SDNN (ms)	130 (52-182)	154 (107-213)	0.002
SDANNI (ms)	70 (49-131)	72 (47-110)	0.883
SDANN (ms)	105 (34-159)	142 (97-196)	0.000
rMSSD (ms)	51 (21-125)	51 (22-92)	0.776
pNN50 (%)	19.7 (4.77-45.06)	17.6 (2.9-37.4)	0.951
LF (ms^2)	549.92 (196.60-1463.52)	565.02 (189.81-1039.90)	0.581
HF (ms^2)	226.96 (95.72-1983.20)	348.38 (70.75-777.13)	0.300
LF/HF	2.77 (1.07-7.54)	3.40 (1.49-7.05)	0.978

Mean RR: Mean R-R interval. SDNN: Standard deviation of all R-R intervals. SDANN: Standard deviation of the averages of R-R intervals in all 5-min segments of R-R intervals. SDANNI: Mean of all 5-min means SDs of R-R intervals. rMSSD: Root of the mean square of the difference of successive R-R intervals. pNN50%: Proportion of adjacent normal R-R intervals <50 ms. LF: Low frequency. HF: High frequency.

On the other hand, Massin et al.[7] and Alehan et al.[30] did not find any changes in resting autonomic tone in children with NS, also concordant with our results.

It is known that mean HRV parameters over a 24-h period are greatly influenced by day-to-night differences. Khalil et al.[9] studied 32 children with NS, and compared the baseline HRV indices and also the 3-h and 6-h period changes during the whole day with healthy controls. They found time-dependent increased sympathetic or decreased parasympathetic tone in patients, and interpreted this as the autonomic imbalance during asymptomatic time periods. Most of the studies designed in adults showed that 24-h baseline HRV indices during asymptomatic periods revealed no significant difference as compared with healthy controls[11,12]. However, Hosaka et al.[27] and Kochiadakis et al.[31] had reported that basal HRV indices were augmented by parasympathetic predominancy in adult syncopal patients as compared to the healthy controls. There are major differences between the results of the studies designed with children and adults. Ruiz et al.[12] demonstrated that age was an important factor influencing the HRV indices during HUTT in pediatric and adult patients. It is certain that age affects HRV, and there is a significant increase in SDNN and rMSSD with increase in age[32]. Zygmunt et al.[15] confirmed that mean RR, SDNN and SDNNi indices significantly increase with an increase in age. Some other studies have also proven that mean RR, SDNN and SDNNi parameters significantly increase with age[33,34]. Massin et al.[7] found that children who had positive response during HUTT had different responses in HRV according to the age groups. They emphasized that all of the time-domain indices and also the frequency-domain indices were found to be higher in children older than 10 years.

There are a few studies concerned with the HUTT responses and the baseline HRV indices in patients with NS. Guzman et al.[6] studied 24 patients with NS, and found an increased parasympathetic activity shown by significant increase in rMSSD in patients with cardioinhibitory type response, and sympathetic

activity predominancy by significant decrease in rMSSD in vasodepressor type response. Zygmunt et al.[15] found that the patients with cardioinhibitory response in HUTT had significantly lower SDNN indices. We compared the HUTT responses and baseline HRV indices in patients, and showed that the patients with cardioinhibitory response had significantly higher rMSSD and HF parameters that reflect the parasympathetic activation, as shown by Guzman et al.[6]. The patients with negative response had lower indices, which confirms the concordance of the autonomic system.

Our patients who are diagnosed as having recurrent NS are followed with education and a conservative approach. The education and conservative approach is supposed to be the most successful treatment option in patients with NS, at 80-85%. In case of failure in treatment, some pharmacological treatment options are considered[35]. The success of the conservative management over the pharmacological options is proven. Alegria et al.[36] followed 463 patients with recurrent NS with two options and showed that the patients using beta-blockers had significantly high rates of recurrences. In the present study, the patients were followed with education on the predisposing factors, on the ways to avoid situations that cause fainting and on the physical maneuvers to manage presyncope and syncope. The follow-up period was six months, and during this period, none of the patients experienced presyncope or syncope. In the follow-up evaluation of HRV indices, no significant difference in autonomic activity was found between the parameters. We concluded that there was no significant disturbance in the baseline autonomic functions in children with NS whether or not they fainted in the follow-up period. No difference occurred in HRV with concomitant change in the history of presyncope and syncope rates. These results were interpreted as indicating that an autonomic stress induces NS and not baseline autonomic activity. These results were not compared with previous studies because no previous study evaluated the HRV parameters in the same population of patients after a period of time.

Study Limitations

Since the HRV indices for the symptomatic patients during HUTT are not available, the results of HRV during HUTT were not compared to values during the asymptomatic periods. The healthy control group did not have HUTT, which could also be viewed as a certain limitation of the present study.

It was not possible to compare the HRV changes in tilt-negative and tilt-positive patients because of the small number of patients with tilt-negative response.

Six patients were lost to follow-up, and their history of syncope or presyncope is not known. The follow-up period was relatively short.

It is known that patients with NS exhibited an imbalance in the autonomic nervous system especially in the morning. The circadian rhythm in QTc dispersion is shown, and significantly high values in early morning and late night were found in children with HUTT-positive NS, suggesting the correlation between QTc dispersion and time of syncope[37]. However, the HRV analysis of 3- and 6-h segments and circadian rhythm in HRV in asymptomatic periods were not recorded in this study.

In conclusion, these findings suggest that baseline autonomic functions are normal in both healthy children and patients with NS. In this study, we particularly evaluated the baseline autonomic activity in the same population six months later. We found that the baseline autonomic activity was similar between the frequent fainters and non-fainters. Therefore, we think that baseline autonomic activity alone might not explain why some individuals faint and others do not.

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