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Original Article

Evaluation of Heart Rate Variability in Children With Breath-Holding Episodes

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ABSTRACT

Aim: We evaluated heart rate variability in children with breath-holding episodes (BHEs).
Methods: Sixty children with BHEs were included in the study; these individuals were further subdivided into children with cyanotic BHEs (n = 42) and children with pallid BHE (n = 18). Sixty healthy children of matched age and sex served as a control group. Twenty-four hour Holter monitoring was applied to all included children. Minimum, mean, maximum heart rate, rhythms, and corrected QT were evaluated. Time domain parameters of heart rate variability such as standard deviation of all R-R intervals, standard deviation of the average of R-R intervals in all five-minute segments of the entire recording, mean of the standard deviations of all N-N (normal-normal RR) intervals for all five-minute segments, root mean squares differences between adjacent R-R intervals, percentage of differences between adjacent R-R intervals that are greater than 50 milliseconds were also assessed.
Results: All time domain parameters of heart rate variability were significantly higher in children with pallid BHEs than those with cyanotic BHEs and control group. Minimum, mean, and maximum heart rate were significantly lower in children with pallid BHEs than those with cyanotic BHEs and control group. Asystole was observed in three children with pallid BHEs. Long corrected QT was observed in another two children with pallid BHEs.
Conclusions: Heart rate variability increased significantly in children with pallid BHEs. Evaluation of heart rate variability is crucial for children with BHEs especially those with pallid episodes.

Introduction

Breath-holding episodes (BHEs) are relatively common in otherwise healthy children, affecting one of every 20 children. Nevertheless, the event is often a distressing experience for the parents. Episodes are often initiated by unpleasant or distressing stimuli such as pain, anger, or fright that lead to crying then the child holds his breath involuntarily untill he or she faints. There are two types of BHEs, cyanotic episodes and pallid episodes, and some children have both.[1,2]

In general, BHE is considered a benign disorder that typically resolves as the child matures. However, in rare instances it can be associated with life-threatening bradycardia, seizures, or asystole.[3] The pathophysiology of BHEs is thought to be an autonomic nervous system dysfunction by several studies.[4-6] Pallid episodes differ from cyanotic episodes as they are characterized by loss of consciousness preceded by one to several seconds of asystole.[7]

Cardiac pacing may be necessary for some individuals with BHE. Some studies have demonstrated the importance of cardiac evaluation to discover possible changes in heart rhythm in these patients.[8-10] Cardiac evaluation is necessary in such severe complicated cases. Heart rate variability (HRV) is considered a measure of cardiac beat-to-beat variability, which is largely dependent on the parasympathetic nervous system, namely, the efferents of the vagus nerve to change the heart rate in response to different stimuli and physical status such as inspiration, expiration, exercise, activity, wakefulness, or sleep.[11]

The aim of this study was to assess cardiac rhythm and HRV in children with BHEs using 24-hour Holter monitoring and to compare HRV parameters in children with pallid BHEs and those with cyanotic BHEs.

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Patients and methods

We enrolled 60 children with BHEs as the patient group (group I) who were attending the outpatient clinic of pediatric neurology unit, Tanta University Hospital, during the period from March 2015 to December 2017. Sixty healthy age- and sex-matched children were chosen from the children attending the pediatric clinic for minor complaints served as a control group (group II). The patient group was further subdivided into children with pallid episodes and children with cyanotic episodes. The study was approved by the ethical committee of Faculty of Medicine, Tanta University. A written consent was signed by all the parents of participating children.

Inclusion criteria: children with recurrent BHEs, at least three times in the last three months with loss of consciousness and normal physical and neurological examination. Exclusion criteria: children with congenital or acquired heart disease, children with epilepsy or any neurological illness, drug intake, and positive family history of epilepsy, neurological illness, or cardiac problems.

All children were subjected to the following evaluations:

1. A thorough history, including age of onset of first attack, type of attack, and frequency of attacks
2. Careful physical and neurological examination
3. Complete blood count
4. Echocardiography was performed to exclude congenital or acquired heart disease
5. Electroencephalography was performed to exclude patients with abnormal or increased electrical activity
6. Electrocardiogram (EKG) was performed to detect arrhythmias and to measure corrected QT (QTc) interval
7. Twenty-four hour EKG monitoring (Holter): continuous ambulatory EKG monitoring using a compact digital Holter was recorded for a 24-hour period during which subjects were free to practice their normal daily activities. Rhythm, mean, minimum, and maximum heart rate, and HRV parameters were recorded. The standard time domain measures of HRV included standard deviation of all R-R intervals (SDNN), standard deviation of the average of R-R intervals in all 5-minute segments of the entire recording (SDANN), mean of the standard deviations of all R-R intervals for all five-minute segments (SDNNI), root-mean square differences of successive R-R intervals (RMSSD), percentage of differences between adjacent R-R intervals that are greater than 50 milliseconds (PNN50). Only normal R waves were used in the aforementioned measurements (N-N) that stands for normal-normal R interval.

The time domain parameters namely RMSSD and PNN50% reflected the parasympathetic activity, whereas SDNN and SDANN reflected both sympathetic and parasympathetic inputs.[12]

The primary outcome was to evaluate HRV in children with BHEs. The secondary outcome was to compare HRV parameters between children with pallid episodes and those with cyanotic episodes.

Statistical analysis

Raw data were fed to the computer and statistical analysis using IBM SPSS software package version 17 (SPSS Inc, Chicago, IL, USA) was performed. Quantitative data were described using the mean and standard deviation. Qualitative data were described using numbers and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution of the obtained results. Comparing mean between two groups was performed using the Student *t* test. Comparison of qualitative data was performed using chi-square test. Comparing mean of more than two groups was performed using the analysis of variance test. Correlation between variable was performed using the Spearman correlation coefficient. Significance was judged when *P* value is less than 0.05.

Results

Our study included 60 children with BHEs with mean age 2.67 ± 1.17 years and mean weight 13.8 ± 3.8 kg; there were 36 males and 24 females. The healthy control subjects comprised 60 children with mean age 2.4 ± 1.3 years and mean weight 13.5 ± 3.5 kg; there were 32 males and 28 females. The patient and the control groups were comparable in regard to age, sex, and weight. Age of onset of BHEs in the patient group was less than six months in six patients, between six and 18 months in 42 patients, and more than 18 months in 12 patients. Family history was positive for BHEs in only nine patients, whereas family history was negative in 51 patients (Table 1).

Table 2 demonstrates that cyanotic episode was present in 42 of 60 patients (70%), whereas pallid episode was presented in 18 of 30 patients (30%). There was no significant difference between children with pallid episode and those with cyanotic episode groups as regards age, sex, weight, age of onset of BHE, and number of BHEs/month ($P > 0.05$).

There was a significant decrease in mean, minimum, and maximum heart rate in the patient group than the control group ($P < 0.05$). In addition, there was a significant increase in all time domain parameters of HRV including SDANN, SDNNI, SDANN, PNN50, and RMSSD in the patient group than the control group ($P < 0.05$) (Table 3).

There was a significant decrease in mean, minimum, and maximum heart rate in patients with pallid episodes than those with cyanotic episodes ($P < 0.05$). Moreover, there was a significant increase in SDANN, SDNN, SDNNI, PNN50, and RMSSD in patients with pallid episodes than those with cyanotic episodes ($P < 0.05$) (Table 4).

There was a significant difference between the three groups as regards mean heart rate, minimum heart rate, maximum heart rate, SDNN, SDANN, SDNNI, PNN50, and RMSSD ($P < 0.05$). Moreover, there was a significant difference between children with pallid episodes and healthy control subjects as regards mean heart rate, minimum heart rate, maximum heart rate, SDNN, SDANN, SDNNI, PNN50, and RMSSD ($P < 0.05$). However, there was no significant difference between children with cyanotic episodes and healthy control subjects as regards mean heart rate, minimum heart rate, maximum heart rate, SDNN, SDANN, SDNNI, PNN50, and RMSSD ($P > 0.05$) (Table 5).

TABLE 1.
Demographic Data in the Study Groups

Variables	Group 1 (Patient Group) N = 60	Group II (Control Group) N = 60	*P* Value
Age (years)	2.67 ± 1.17	2.4 ± 1.3	0.401
Sex (male:female)	36:24	32:28	0.602
Weight (kg)	13.8 ± 3.8	13.5 ± 3.5	0.741
Age of onset of BHE			
<6 months	6	—	
6-18 months	42	—	
>18 months	12	—	
Family history			
Positive	9	—	
Negative	51	—	

TABLE 2.
Demographic and Clinical Data in Group I

Variables	Patients With Cyanotic Episode (N = 42)	Patients With Pallid Episode (N = 18)	*P* Value
Age (years)	2.6 ± 1.5	2.3 ± 1.3	0.607
Sex (male:female)	26:16	10:8	0.919
Weight (kg)	14.5 ± 4.2	12.5 ± 2.3	0.179
Age of onset of BHE (months)	11.8 ± 1.3	12.2 ± 1.5	0.782
Number of BHEs/month			
<15 Attacks/month	27	12	0.321
>15 Attacks/month	15	6	

Abbreviation:
BHE = breath-holding episode

Sinus pause lasting for more than two seconds was observed in three cases with pallid BHEs (16.7% of the cases with pallid BHEs). Long QTc was observed in another two cases of pallid BHEs.

There was a significant negative correlation between the mean heart rate and SDNN, PNN50, and RMSSD. Moreover, there was a significant positive correlation between frequency of BHEs/month and SDNN, SDNNI, and RMSSD (Table 6).

Discussion

BHE is a well-known event in infants and children in whom the exact cause is not clearly understood.[13] BHEs occur in 5% of otherwise healthy children. Most pediatricians have offered parents the reassurance that these alarming episodes are not life threatening and are likely to resolve spontaneously with time.[14] However, in some severe complex cases, the episodes can be dramatic and unresponsive to medication and are associated with seizures, life-threatening arrhythmias, and even asystole,[3] which draws our attention to the importance of evaluating cardiac rhythm changes.

BHEs are of two types, cyanotic and pallid types, according to the color of the child during the episode.[1] They cyanotic episode is the commonest type accounting for more than 60% of the cases, whereas the pallid type occurs in only 20% to 30% of the cases.[15] Our study revealed that 70% of our patients had the cyanotic type, while 30% of the patients had the pallid type.

Various studies have shown that the underlying pathophysiology of BHEs is generalized autonomic dysregulation.[16-18] This autonomic dysregulation can be evaluated by several methods such as Valsalva maneuver, diastolic blood pressure response to tilt table test or continuous isometric contraction, heart rate response to deep inspiration or standing position, and HRV.[19,20] Most of these methods are difficult to apply in infants and young children with BHEs, so the most practical method in such patients is HRV measured by 24-hour Holter monitoring. HRV can evaluate both the sympathetic and parasympathetic autonomic nervous system effects on the heart. HRV is considered now a good tool for evaluation of autonomic dysregulation in several studies.

TABLE 3.
Mean, Minimum, Maximum Heart Rate, and Time Domain HRV Parameters in the Studied Groups

Variables	Group I (Patient Group) (N = 60)	Group II (Control Group) (N = 60)	*P* Value
Mean HR (beats/minute)	111.2 ± 15.8	121.8 ± 12.9	0.006*
Minimum HR (beats/minute)	69 ± 13.4	79.1 ± 11.1	0.002*
Maximum HR (beats/minute)	156.1 ± 26.4	170.6 ± 20.5	0.002*
SDNN (milliseconds)	107.1 ± 48.7	84.7 ± 35.9	0.04*
SDANN (milliseconds)	58 ± 30.4	60.5 ± 21.7	0.723
SDNNI	64.1 ± 34	47.8 ± 23.9	0.03*
PNN50	13.4 ± 9.3	8.8 ± 3	0.01*
RMSSD (milliseconds)	52.7 ± 26.8	39.6 ± 14.9	0.02*

Abbreviations:
HR = heart rate
PNN50 = Percent of the number of pairs of successive beat-to-beat intervals that differ by N50 milliseconds
RMSSD = Root-mean square differences of successive R-R intervals
SDANN = Standard deviation of all R-R intervals in successive 5 minutes
SDNN = Mean standard deviation for all R-R intervals
* Statistical significance.

TABLE 4.
Mean, Minimum, and Maximum Heart Rate in Patients With Cyanotic and Pallid Episodes

Variables	Patients With Cyanotic Episode (N = 42)	Patients With Pallid Episode (N = 18)	*P* Value
Mean HR (beats/minute)	116.6 ± 14.5	98.8 ± 11.3	0.003*
Minimum HR (beats/minute)	75.1 ± 14.8	64.1 ± 8.1	0.01*
Maximum HR(beats/minute)	165.1 ± 26.8	138.1 ± 11.2	0.007*
SDNN (milliseconds)	88.5 ± 35.8	157.1 ± 28	<0.001*
SDANN (milliseconds)	64.4 ± 33.7	43.2 ± 13	0.01*
SDNNI	53 ± 24.7	90 ± 39.9	0.004*
PNN50	10.3 ± 3.9	20.7 ± 13.9	0.003*
RMSSD (milliseconds)	45.2 ± 10.8	69.9 ± 42.8	0.01*

Abbreviations:
HR = heart rate
PNN50 = percent of the number of pairs of successive beat-to-beat intervals that differ by N50 milliseconds
RMSSD = root-mean square differences of successive R-R intervals
SDANN = standard deviation of all R-R intervals in successive 5 minutes
SDNN = mean standard deviation for all R-R intervals
* Statistical significance.

Our study showed that all-time domain HRV parameters including SDNN, SDNNI, RMSSD, and PNN50 were significantly increased in children with BHEs compared with healthy control subjects. In addition, mean, minimum, and maximum heart rate were significantly lower in children with BHEs than control group especially those with pallid episodes when compared with those with cyanotic BHEs and control group. Moreover, our study revealed that HRV time domain parameters were significantly higher in children with pallid BHEs than those with cyanotic BHEs and control group. These results are in agreement with that of Yilmaz et al.[21] who found an increase in HRV parameters in children with pallid BHEs than those with cyanotic episodes and control group. However, they found no significant difference between children with BHEs and control group as regards minimum, mean, or maximum heart rate, and HRV parameters. This finding could be explained by lower percentage of children with pallid episodes in their study than ours (17.6% versus 30%).

This alteration of HRV in children with pallid episodes indicates that there was autonomic nervous system dysfunction in these children. This autonomic dysfunction was evidenced by significantly higher SDNN, which measures the total HRV and reflects total autonomic nervous system function but provides no information regarding isolated sympathetic and parasympathetic activity. Moreover, the increased SDANN gives information about sympathetic and parasympathetic imbalance.[22] On the other hand, the increased RMSSD and PNN50 in our study in children with pallid BHEs indicate increased vagal tone because they are mainly influenced by vagal activity.[23] Thus our results demonstrated greater effects of parasympathetic influences on HRV in pallid BHEs than identified in either cyanotic BHEs or control subjects suggesting that cyanotic BHEs may have another pathophysiology.[24,25] This finding was in accordance with previous studies.[21] In contrast to the results of the present study, Azab et al.[26] did not find a significant difference in EKG data between cyanotic and pallid BHEs,

TABLE 5.
Patients Characteristics and Heart Rate Variability Parameters (Time Domain) in Patients With Cyanotic and Pallid Episodes and Control Group by Holter

Variables	Patients With Cyanotic Episode (N = 42)	Patients With Pallid Episode (N = 18)	Control Group (N = 60)	ANOVA *P* Value	P1 (Cyanotic vs Control)	P2 (Pallid vs Control)
Mean HR (beats/minute)	116.6 ± 14.5	98.8 ± 11.3	121.8 ± 12.9	0.001*	0.139	0.001*
Minimum HR (beats/minute)	71.1 ± 14.8	64.1 ± 8	79.1 ± 11.1	0.004*	0.09	0.001*
Maximum HR (beats/minute)	165.1 ± 26.8	138.1 ± 11.2	170.6 ± 20.5	0.001*	0.132	0.001*
SDNN (milliseconds)	88.5 ± 35.8	157.1 ± 28	84.7 ± 35.9	0.001*	0.723	0.001*
SDANN (milliseconds)	64.4 ± 33.7	43.2 ± 13	60.5 ± 21.7	0.02*	0.804	0.01*
SDNNI	53 ± 24.7	90 ± 39.9	47.8 ± 23.9	0.001*	0.454	0.001*
PNN50	10.3 ± 3.9	20.7 ± 13.9	8.8 ± 3	0.001*	0.505	0.02*
RMSSD (milliseconds)	45.2 ± 10.8	69.9 ± 42.8	39.6 ± 14.9	0.001*	0.683	0.001*

Abbreviations:
ANOVA = analysis of variance
HR = heart rate
PNN50 = percent of the number of pairs of successive beat-to-beat intervals that differ by N50 milliseconds
RMSSD = root-mean square differences of successive R-R intervals
SDANN = standard deviation of all R-R intervals in successive 5 minutes
SDNN = mean standard deviation for all R-R intervals
* Statistical significance.

and they believed that both types of BHEs share the same pathophysiologic mechanism.

In our study, there was a significant correlation between HRV parameters and the frequency of BHEs. Azab et al.[26] also revealed a significant positive correlation between the frequency of BHEs and the frequency of respiratory sinus arrhythmia that represented HRV with respiration and is considered another method to measure autonomic dysregulation in such children.

Our study showed that three children had asystole (cessation of cardiac electrical activity detected by EKG) more than two seconds and another two patients had long QTc that predispose to life-threatening arrhythmias and cardiac arrest. The association of sudden infant death because of cardiac asystole caused by vigorous vagal stimulation was observed in children with pallid BHEs in many studies.[27-29] So the need for permanent cardiac pacemaker in some children with pallid BHEs presenting with bradycardia, fainting, and prolonged asystole was evaluated in several studies,[3,8,9,30] which explains the importance of HRV study in patients with BHE especially the pallid type.

The limitations of the study are the small number of children with pallid BHEs.

TABLE 6.
Correlation Between HRV Parameters and Frequency of BHEs/Month and Mean Heart Rate

Variables	Mean Heart Rate		Frequency of BHEs/Month	
	r	*P*	*r*	*P*
SDNN	−0.118	0.02*	0.456	0.01*
SDANN	−0.324	0.08	0.271	0.174
SDNNI	−0.37	0.845	0.273	0.02*
PNN50	−0.364	0.04*	0.361	0.08
RMSSD	−0.238	0.02*	0.367	0.04*

Abbreviations:
BHE = breath-holding episode
HRV = heart rate variability
PNN50 = percent of the number of pairs of successive beat-to-beat intervals that differ by N50 milliseconds
RMSSD = root-mean square differences of successive R-R intervals
SDANN = standard deviation of all R-R intervals in successive 5 minutes
SDNN = mean standard deviation for all R-R intervals
* Statistical significance.

Conclusions

HRV increased significantly in children with pallid BHEs. Thus evaluation of HRV is crucial for children with BHEs especially those with pallid type.

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