Evaluation of autonomic nervous system functions by using tilt table test and heart rate variability in epileptic children

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ABSTRACT

Objective: The value of head-up tilt test (HUTT) for differential diagnosis of epilepsy and the autonomic nervous system functions in epileptic children using heart rate variability (HRV) are studied.

Patients and Methods: The study group consisted of 16 children with idiopatic/criptogenic epilepsy and 12 controls. Heart rate, PR interval, corrected QT (QTc) interval, QT and QTc dispersion were calculated using 12-lead electrocardiogram (ECG), HRV analysis was performed using the Holter recordings obtained both during HUTT and throughout the day. Time domain parameters, standard deviation of all RR intervals (SDNN), the standard deviation of mean NN intervals in five-minutes recording (SDANN), mean standard deviation of NN intervals in five-minutes recordings (SDNNi), root mean square of successive differences (RMSSD), count divided by the total number of all NN intervals (pNN50) and frequency domain parameters low frequency (LF), high frequency (HF), low-frequency/high-frequency ratio (LF/HF) were calculated in both and compared between the two groups.

Results: Head-up tilt test was positive in 4 epileptic children (25%), none of controls were positive. The heart rate of the patients were higher than the controls (p=0.015). LF/HF ratio in 24-hour Holter recordings, were significantly lower (1.13±0.6, 1.83±0.7 respectively, p=0.002); the SDANN during HUTT (28.7±20.2, 18.2 ± 19.9 respectively, p=0.024) were significantly higher in the patients than the controls.

Conclusion: Head-up tilt test positivity is frequent in epileptic children, and cannot be used in differential diagnosis. HRV calculated both from 24 hour Holter recordings and Holter recordings under orthostatic stress were impaired in favour of parasympathetic system in epileptic children.

Keywords: Epilepsy, Syncope, Head-up tilt test, Heart rate variability, Autonomous nervous system, Arrhythmia.

1. INTRODUCTION

Epilepsy is a common paroxysmal childhood disease that is characterized by abnormal cortical electrical activity [1-3]. Epilepsy has a complex relationship with cardiac and autonomic functions. Various rhythm abnormalities both tachyarrhythmia, and bradyarrhythmia can be seen in epileptic patients during seizures [4-7]. Some studies also show that epileptic patients has an increased risk of sudden cardiac death, mostly related to arrhythmia [8,9]. It may be difficult to distinguish seizures of patients with atonic, hypotonic epileptic seizures from neurocardiogenic syncope attacks. Head-up tilt test (HUTT) used in diagnosis of neurocardiogenic syncope may give false positive results in the presence of autonomic dysfunction [10].

Heart rate variability is a beneficial method for evaluating autonomic functions. Time-based and frequency-based parameters can be used to investigate sympathetic or parasympathetic system dominance. Reduction of heart rate variability suggests sympathetic system dominance and an increased risk of arrhythmia and sudden death.

In our study, the utility of HUTT has been investigated in patients with idiopathic and cryptogenic epilepsy and the autonomic function changes both under orthostatic stress and throughout the day have been evaluated using heart rate variability parameters obtained via Holter monitorization.

2. PATIENTS and METHODS

Patient Population

The study group included the patients who were diagnosed to have idiopathic or cryptogenic epilepsy at the Marmara University Pediatric Neurology Department. Patients with systemic or local diseases effecting cardiovascular and central nervous system, psychiatric diseases, genetic syndromes, symptomatic epilepsy, chronic or progressive neurological diseases, and those on cardiotoxic or neurotoxic drug treatment other than antiepileptic treatment were excluded from the study.

Control group consisted of healthy children with similar age and gender characteristics, without any cardiac or neurologic abnormality. Patients between 7 to 18 years who can cooperate for HUTT and Holter monitorization were included in the study. All the patients and the control group underwent echocardiographic examination for exclusion of structural heart disease.

In addition to a detailed history of seizures, general medical and family history, a detailed neurologic, cardiac, and systemic physical examination was performed. The antiepileptic medications taken and electroencephalography (EEG) data were recorded.

All the children were evaluated at Marmara University Paediatric Cardiology Department by using electrocardiography, transthoracic echocardiography, 24-hour Holter monitorisation and HUTT.

Standard 12-lead surface electrocardiogram was obtained from all subjects. Heart rate, PR interval, P wave duration, P wave height, P axis, QRS duration, QRS axis, QT interval, maximum and minimum QT intervals were measured and the corrected QT interval (QTc), QT dispersion, and QTc dispersion were calculated using Bazett's formula [11].

Head-up tilt test protocol: All patients were studied during the afternoon in a quiet room with low lightning after 6 hours of fasting. An intravenous line is inserted as a precaution for possible emergency interventions. Children were monitorised by using a standard three lead cardiac monitor and a sphygmomanometer. During the tilt period, vital signs and ECG were continuously monitored and reported at 3-minute interval. After 15 minutes in the supine position, the table was tilted to 60°. Whenever a syncope or presyncope developed and if associated with a blood pressure or heart rate drop of at least 30% of baseline levels, children were returned to supine position immediately. The test was terminated, and the HUTT was considered positive [12]. If hypotension, bradycardia, syncope, or presyncope did not occur, the patient was returned to the supine position after 45 minutes, and HUTT was considered negative.

Participants in both groups underwent a 30-minute 60° HUTT. Holter recordings were obtained during the HUTT. Additionally, 24-hour Holter recordings were obtained. Del Mar Reynolds Holter System (Spacelabs Medical Inc, West Sussex, UK) was used for Holter recordings. The groups were compared in terms of the time-based (SDNN, SDANN, SDNNi, RMSSD, pNN50) and frequency-based (LF, HF, LF / HF) HRV parameters calculated both from HUTT and Holter recordings and 24-hour Holter recordings.

All the patients and the parents were informed about the study, consent forms were signed and Local Ethics Committee has approved the study. (Ethics Committee of Marmara University Medical School, date: 07.04.2011, number: B.30.2.MAR.0.01.02/AEK/58)

Statistical Evaluation

Statistical Package for Social Sciences (SPSS) 17.0 software package was used for statistical analyses to evaluate the study findings. Kolmogorov-Smirnov distribution test was used to investigate normal distribution. Qualitative data between the groups were compared using Pearson's chi-squared and Fisher's exact tests. McNemar's test was used for comparing qualitative data between the groups. parameters with quantitative data were compared with Mann Whitney U test. Quantitative parameters within the group were compared using Wilcoxon signed rank test. The results were evaluated within a 95% confidence interval at $p<0.05$ significance level, and at $p<0.01$ and $p<0.001$ high significance levels.

3. RESULTS

The study group consisted of 16 epileptic children (8 male and 8 female), between 7 and 16 years of age (10.5±2.1). The control group consisted of 12 healthy children (7 male and 5 female) between 7 and 15 years of age (9.6± 3). The diagnosis was rolandic epilepsy in 7, occipital lobe epilepsy in 3 and absence epilepsy in 6 children. Twelve patients were using antiepileptic medication (11 of them Valproic acid, 1 Carbamazepine). EEG records of all of the patients revealed epileptic activity.

Height and weight of all children in the study and the control groups were within the normal range for their age. No statistically significant difference was observed between the groups in terms of height or weight (Table I).

Table I. Demographic comparison

DEMOGRAPHIC DATA		STUDY GROUP	CONTROL GROUP	p-value
Age (years) (Mean±SD)		10.56±2.19	9.67±3.09	0.437
Gender (n (%))	♀	8 (5%)	5 (42%)	0.445
	♂	8 (50%)	7 (58%)	
Height (cm) (Mean±SD)		143.18±12.40	138.83±15.58	0.390
Weight (kg) (Mean±SD)		38.75±10.67	33.50±12.21	0.113
On drug therapy (n (%))		12 (75%)	0	
Not on drug therapy (n (%))		4 (25%)	12 (100%)	<0.001

SD: Standard deviation

The average heart rate, measured during physical examination, was 83.56±11.25 beats/min in the study group and 79.00±7.25 beats/min in the control group. No statistically significant difference was observed between the groups.

The average systolic blood pressure of the cases in the study group (110.44±9.36) was significantly higher than the control group (102.17±11.79) (p<0.05). There was no significant difference between the study (63.63±5.69) and the control (63.17±9.50) groups in terms of their diastolic blood pressure.

Twelve-lead electrocardiogram

Heart rate, measured in the surface ECG, was significantly higher in the study group (93.7±11.3 beats/minute) compared to the control group (80±14.5 beats/minute) (*p<0.05*). There was no statistically significant difference in terms of PR interval, P wave duration, P wave height, P wave axis, QRS axis, and QRS duration between the groups. The QT interval in the study group (325±26.3 msec) was significantly lower than the QT interval the control group (360±38.2 msec) (p<0.05). The longest QT interval was 360.7±25 msec in the study group and 384.4±36.6 msec in the control group; there was no significant difference between the groups. The shortest QT interval was 291.5±30.7 msec in the study group and 337.2±41 msec in the control group, and this difference was statistically significant (p<0.01). While the QT dispersion and QTc values were higher in the study group than in the control group, no statistically significant difference was observed in terms of these parameters. The longest QTc was 449.5±23.5 msec in the study group and 428±30.4 msec in the control group and the difference between the groups was statistically significant (p<0.05) (Table II).

Table II. Comparison of the ECG results

	Study Group (n=16)		Control Group (n=12)		P value
	Mean	SD	Mean	SD	
Heart rate	93.750	11.375	80.000	14.510	**0.015**
PR distance	0.121	0.014	0.130	0.013	0.089
P wave duration	0.074	0.016	0.080	0.009	0.156
P wave height	1.388	0.492	1.267	0.401	0.669
P wave axis	40.625	21.747	31.250	17.726	0.315
QRS duration	0.058	0.010	0.065	0.015	0.153
QRS axis	47.500	22,.876	47.083	24.445	0.963
QT distance	325.000	26.331	360.417	38.209	**0.013**
Maximum QT distance	360.750	25.093	384.417	36.600	0.088
Minimum QT distance	291.500	30.783	337.250	41.083	**0.003**
QT dispersion	58.063	16.060	47.167	11.839	0.085
QTc	404.375	16.354	396.750	28.010	0.724
Maximum QTc	449,500	23.509	428.000	30.466	**0.049**
Minimum QTc	356.250	31.323	367.750	28.062	0.245
QTc dispersion	73.375	22.387	60.250	16.961	0.125

SD: standard deviation

Head-up Tilt Test

Four patients in the study group had positive HUTT results. All of the patients with positive HUTT results had a mixed type positive response. None of the control group participants had a positive Tilt response. No significant difference was observed between the groups in terms of Tilt test positivity (p=0.089). HUTT positivity occurred in one patient at 15th minute, in two patients at 18th minute, and in another patient at 21st minute (Table III).

Table III. Comparison of head-up tilt test results

HEAD-UP TILT TEST RESULTS				
		STUDY GROUP (Mean±SD)	CONTROL GROUP (Mean±SD)	p-value
Tilt positive patients (N (%))		4 / 25%	0 / 0%	0.089
Tilt negative patients (N (%))		12/ 75%	20/ 100%	
Average Heart Rate (beats/min)		98.25±9.97	96.75±11.88	0.693
Minimum Heart Rate (beats/min)		70.81±11.2	71.92±10.77	0.727
Maximum Heart Rate (beats/min)		123.56±17.24	120.33±12.21	0.963
SDNN		61.13±28.47	57.92±22.92	0.940
SDANN		28.69±20.23	18.25±19.91	0.024
SDNNi		49.00±15.82	53.33±16.04	0.429
rMSSD		26.25±11.13	29.08±12.8	0.625
PNN50		7.25±8.15	9.67±11.36	0.575
LF		669.63±397.45	976.62±568.6	0.144
HF		271.44±242.07	359.83±229.97	0.164
LF/HF		2.75±2.11	3.13±1.5	0.400
ARRHYTHMIA (N/%)	Present	1/ 6%	0/ 0%	0.378
	Absent	15/ 94%	12/ 100%	

SD: Standard deviation, SDNN: standard deviation of all RR intervals, SDNNi: mean standard deviation of NN intervals in 5-minutes recordings, SDANN: the standard deviation of mean NN intervals in 5-minutes recording, RMSSD: root mean square of successive differences, pNN50: NN50 count divided by the total number of all NN intervals, LF: low frequency, HF: high frequency, LF/HF,: low-frequency/high-frequency ratio

Twenty-four-hour Holter Monitorization

There was no significant difference between the study and the control groups in terms of lowest heart rate (study group: 52.94±4.8; control group: 54.67±12.4 beats/minute), highest heart rate (study group: 164.06±16.9; control group: 155.2±16.6 beats/minute), and average heart rate (study group: 88.1±8.3; control group: 88.08±10.4 beats/minute), observed in the 24-hour Holter monitorization. Supraventricular and ventricular premature beats (varying between 1 or 2 observances per case) were observed in 6 children in the study group and 2 children in the control group. Atrioventricular block, sinus pause, RR interval longer than 2.5 seconds, supraventricular tachycardia (SVT), or ventricular tachycardia (VT) attack was not observed in either groups. No significant difference was present according to the arrhythmia rates between the groups (p>0.05).

Heart Rate Variability

Time based heart rate variability parameters SDNN, SDANN, SDNNi, RMSSD, and pNN50 obtained from the 24-hour Holter recordings did not differ between the two groups. However, LF/HF ratio was significantly lower in the study group (study group: 1.13±0.62; control group: 1.83±0.70, p<0.01) while LF and HF values were comparable, indicating parasympathetic system dominance in epileptic children.

In comparison of heart rate variability during HUTT; SDANN values were higher in the study group (28.6±20.2 msec) than in the control group (18.2±19.9 msec) (p=0.024), while other time domain parameters SDNN, SDNNi, RMSSD, and pNN50 values did not differ significantly, indicating the parasympathetic system dominance was also present during HUTT.

The study and the control groups did not have statistically significant differences in terms of their LF, HF, LF/HF values obtained from Holter recordings obtained during the HUTT (Table IV).

Table IV. Comparison of the 24-hour Holter monitorization results

24-HOUR HOLTER MONITORIZATION RESULTS			
	STUDY GROUP (Mean±SD)	CONTROL GROUP :(Mean±SD)	p-value
Minimum Heart Rate (beats/min)	52.94±4.88	54.67±12.42	0.675
Maximum Heart Rate (beats/min)	164.06±16.93	155.25±16.60	0.15
Average Heart Rate (beats/min)	88.19±8.37	88.08±10.40	0.963
SDNN	124.69±22.62	131.33±48.55	0.693
SDANN	106.81±22.68	112.42±53.90	0.693
SDNNi	59.69±16.32	67.17±22.29	0.285
RMSSD	41.25±15.02	44.83±19.53	0.816
PNN50	17.88±10.35	18.67±11.74	0.944
LF	726.31±304.69	1009.67±509.03	0.210
HF	498.56±257.53	645.25±420.79	0.577
LF/HF	1.13±0.62	1.83±0.70	0.002
ARRHYTHMIA — Present	(6 / 40%)	(2 / 17%)	0.187
ARRHYTHMIA — Absent	(10 / 60%)	(10 / 83%)	

SD: Standard deviation, SDNN: standard deviation of all RR intervals, SDNNi: mean standard deviation of NN intervals in 5-minutes recording, SDANN: the standard deviation of mean NN intervals in 5-minutes recordings, RMSSD: root mean square of successive differences, pNN50, NN50: count divided by the total number of all NN intervals, LF: low frequency, HF: high frequency, LF/HF: low-frequency/high-frequency ratio

4. DISCUSSION

Epilepsy is a paroxysmal chronic disease group that occurs frequently during childhood. It has an incidence between 0.4 to 1.9%. Etiology can be identified in only 1/4 or 1/3 of the cases. About 2/3 of the cases are idiopathic or cryptogenic and believed to occur due to genetic causes [2, 13, 14]. The remaining causes are congenital abnormalities, trauma, infections, vascular, neoplastic, and degenerative diseases [2, 15].

It may be difficult to differentiate atonic or hypotonic epileptic seizures from syncopal attacks. HUTT is used for diagnosis of neurocardiogenic syncope, however in our study 25% of the epileptic patients were tilt positive while none of the healthy control group had positive tilt table test result. Although, this difference was not statistically significant, it is much higher than the expected tilt table test positivity for the normal population (7-10%) [16,17]. HUTT positivity among the patients with neurocardiogenic syncope range between 27-75% [18]. In the study conducted by Topcu et al., within our department, 54% of the patients with neurocardiogenic syncope had positive HUTT [10]. Therefore, HUTT may provide direct observation of the syncopal attacks and the vital changes during syncope but is not suitable for differentiation of epileptic seizures from vasovagal syncope. Sabri et al. [19], also found 30% HUTT positivity rate within a proven epileptic group in accordance to our study. High HUTT positivity rate in epileptic patients compared to the normal population can be an indicator of the impaired autonomic functions among these patients.

Our study showed increased resting heart rate and systolic blood pressure in epileptic children comparing the healthy control group,

which may be due to the higher emotional pressure experienced in patients with a chronic illness, during routine tests. Absence of any difference in terms of the heart rates obtained in the Holter recordings between the groups also validates this.

Maximum QTc value was higher among epileptic children compared to healthy children and QTc dispersion was higher in the epileptic patients compared to the control group in this study, however the difference was not statistically significant. However, a prior study conducted in our clinic by Akalin et al., found that QT dispersion in epileptic patients is significantly higher than that in healthy children [20]. The lack of a significant QTc dispersion difference in this study may be due to the small sample size and that most of the patients were receiving antiepileptic drug-therapy. These findings may be significant in terms of arrhythmia risk. Both prolonged QT interval and increased QTc dispertion may suggest increased risk of rhythm abnormalities and sudden cardiac death. Arrhythmia can be observed in epileptic children during ictal and interictal periods. Many studies have been conducted to investigate the causes, frequency, and the dysrhythmia-based risks of arrhythmia observed in epileptic children [8,9] . The reason for this effort is that the unexplained sudden death in epilepsy (SUDEP) risk, as demonstrated by autopsy and clinical studies, is 0.7-1.3/1000, which is 24 times higher than the normal population, especially in case of idiopathic and cryptogenic epilepsy [21]. Electrical stimulation of different locations within the brain was found to induce dysrhythmia such as tachyarrhythmia, bradyarrhythmia (time to time), asystole (rarely), AV block, and ventricular fibrillation [9,22,23]. Seizures affecting the temporal lobe, insular cortex, and amygdala tend to cause dysrhythmia more frequently [24]. The rate of dysrhythmia during seizures vary between 10-60% and about 5-20% of them are serious dysrhythmias [25]. It is known that the heart rate and heart rate variability increase during the ictal period [9,25]. However, the ECG data of epileptic patients obtained during the interictal period are not different than that of the normal population [16,26,27]. Common genetic basis affecting electrical activity both in the central nervous system and the conduction system of the heart is still remains to be clarified.

Heart rate variability is a measure of cardiac autonomic function, indicating the cyclic variations of heartbeat intervals [28]. It reflects the complex relationship between the parasympathetic and sympathetic innervation of the heart. Decreased HRV is known to be associated with susceptibility to cardiac arrhythmias [29,30]. This study investigated HRV based on the Holter recordings obtained both during the 24-hour recordings and during the HUTT. Among the time domain measurements, SDNN, SDANN, and SDNNi indicate the sympathetic and parasympathetic effects; and the vagal control is indicated by RMSSD and pNN50. Numerically lower values in all these indexes indicate reduced HRV [31-37]. Decreased HRV means a heart that has relatively faster pulse and lost its diurnal rhythm. This suggests lost parasympathetic tone and sympathetic tone dominance [28]. While SDNN is informative of the whole autonomic structure of the heart, it fails to provide significant information regarding the sympathetic or the parasympathetic

activities separately [29]. On the other hand, RMSSD and PNN50 generally accompany vagal activity. The frequency domain measurement LF is associated mainly with the sympathetic activity and HF with vagal activity [30]. LF/HF ratio on the other hand, reflects the balance between the sympathetic and the parasympathetic autonomic nervous systems. Increases in the ratio suggest sympathetic activity dominance and decreases suggest parasympathetic activity dominance [31,32].

In this study, the 24-hour recordings yielded higher LF/HF ratios and increased SDANN values during HUTT in epileptic children compared to healthy children; this suggests that both under orthostatic stress and throughout the day, the heart rate variability of these patients is increased compared to the control group and that their autonomic functions are impaired in favor of parasympathetic system. On the other hand, our prior study demonstrated increased sympathetic system activity in children with neurocardiogenic syncope during orthostatic stress [10]. Thus, while both epilepsy and neurocardiogenic syncope may cause HUTT positivity and autonomic dysfunction is present in both groups, the underlying mechanism and autonomic factors are different.

El-Sayed et al. has evaluated autonomic functions of children with idiopathic epilepsy during the interictal period. In all age groups, SDNN was decreased, and in the older children, pNN50 and RMSSD were decreased compared to the control group [33]. Similarly, the SDNN values were found to be decreased in patients with temporal lobe epilepsy in other studies [33-35]. Ferri et al., reported a decline in both the time-based and frequency based HRV parameters of epileptic children throughout their sleep [35]. Massetani et al., reported significantly reduced R-R variability among adult epilepsy patients [36]. Increased heart rate variability in this study is not consistent with these studies. However, the consistency between the data collected during the HUTT and the 24-hour Holter monitorization suggest that these findings are reliable. The difference between the findings of this study and the literature may be due to the differences in the epilepsy type and localization or the drug-therapies received. In addition, similar to our findings, Yang TF et al,, have also reported increased heart rate variability in epileptic patients compared to healthy children, though not significant [38]. Raju et al's study reported reduced pNN50 values in children with refractory epilepsy, and in well-controlled patients HRV parameters were similar to those in healthy children [39]. The study group in this study had a very specific type of epilepsy, all were well-controlled, did not have a seizure within the past 6 months, and were receiving antiepileptic drug therapy. Additionally, physiologically the sympathetic system is dominant within the first 10 years of life; parasympathetic system dominance is observed starting from adolescence and throughout adulthood [40, 41]. The children in both the study and the control group being at this transition period may also be the reason for obtaining inconsistent results.

This is the only study where heart rate variability is examined over a 24-hour period and under stress via 24-hour Holter monitorization and the HUTT is applied.

The head-up tilt test had higher positivity among epileptic patients compared to healthy children in this study and their autonomic nervous system functions were impaired in favor of parasympathetic system both under orthostatic stress and during rest. These findings suggest that the HUTT is not suitable for use in syncope-epilepsy differentiation. More comprehensive studies are needed to investigate the effects of different types of epilepsy and antiepileptic therapies on the autonomic nervous system.

Compliance with Ethical Standards

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