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Heart rate variability in children with refractory generalized epilepsy

Tomor Harnod [a,b], Cheryl C.H. Yang [b,c], Yue-Loong Hsin [b,d], Kun-Ruey Shieh [b,e], Pen-Jung Wang [b], Terry B.J. Kuo [b,c,*]

[a] *Department of Neurosurgery, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[b] *Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan*
[c] *Institute of Brain Science, National Yang Ming University, Taipei, Taiwan*
[d] *Department of Neurology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[e] *Institute of Neuroscience, Tzu Chi University, Hualien, Taiwan*

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Summary

Objective: Repetitive seizures can alter the regulation of cardiac activity by the autonomic nervous system (ANS), and ANS dysregulation is thought to be associated with higher morbidity and mortality in epileptic patients, especially from sudden unexpected death. Few studies of interictal dysregulation of cardiac activity in children with epilepsy have been performed. In this study we characterize heart rate variability (HRV) in children with refractory generalized epilepsy.
Methods: Fifteen male and 15 female children, average age = 10.9 ± 0.6 years, all with refractory generalized epilepsy were enrolled into the study group. A control group consisted of 15 males and 15 females with average age = 10.6 ± 0.6 years. A lead I ECG was recorded for 5 min in the interictal period during daylight hours from each subject while awake. Frequency-domain analysis of HRV was performed using a non-parametric method of fast Fourier transformation. Changes of HRV were categorized into high frequency power (HF; 0.15–0.45 Hz), which represented vagal regulation, and low frequency power (LF; 0.04–0.15 Hz). LF/(HF + LF) expressed in normalized units (LF%) was considered to mirror sympathetic regulation.
Results: There were significant reductions in RR, LF, and HF in the study group when compared to controls. There was no significant difference in LF% between the two groups.
Conclusions: We postulate that the lower HRV in our patients results from parasympathetic or vagal reduction. This suggests that decreased HRV in epileptic children occurs by a different mechanism than in adults with epilepsy.

* Corresponding author at: Institute of Brain Science, National Yang Ming University, 155 Linung Street, Sec. 2, Taipei 112, Taiwan. Tel.: +886 2 28204760; fax: +886 2 28204761.
E-mail address: cchyang@ym.edu.tw (T.B.J. Kuo).

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Introduction

The autonomic nervous system (ANS) plays a complex and vital role in the homeostasis of the human body. Repetitive seizures can alter the regulation of cardiac activity by the ANS, partly due to a direct spreading of seizure activity to the ANS and partly due to an evolved physiological response by time.[1–8] ANS dysregulation to heart rate variability (HRV) is thought to be associated with higher morbidity and mortality in epileptic patients, especially from sudden unexpected death (SUDEP).[2,5,7,9–11] Many published papers suggest that high sympathetic tone, ictally and interictally, in adult epilepsy is the main cause of lower HRV and SUDEP.[1,2,10] These researchers hypothesize that SUDEP is related to higher sympathetic tone interictally, and an ictal sympathetic surge. Some treatment models have been proposed to decrease the long-term sympathetic regulation in patients and possibly reduce the risk of SUDEP.[10,12]

Relatively few studies of the ANS have been performed in children with epilepsy.[2–5,13] Most of these studies conclude that a seizure could disrupt the normal regulation of cardiac activity during the ictal period by direct inputs to the ANS. Ferri et al.[2] did a study of HRV during sleep in children with partial epilepsy and reported that the study group tended to have lower HRV in both time–domain and frequency–domain autonomic parameters, mostly during rapid eye movement (REM) sleep. Yang et al.[13] conducted a study with frequency–domain analysis of HRV in children with epilepsy and found no significant difference in any indicator of HRV between the study and control groups. The interictal physiological alterations of HRV, however, as well as the alterations of respectively sympathetic and parasympathetic regulation due to seizures, especially generalized seizures in childhood epilepsy, have not been well studied.

In this study, we analyzed electrocardiogram (ECG) signals to characterize HRV in 30 children with epilepsy and in 30 healthy controls. Our null hypothesis was that neither sympathetic nor parasympathetic regulation would be affected by refractory generalized seizures in childhood epilepsy.

Methods

Subjects

Thirty children (15 males and 15 females, aged 6–17 years, average age = 10.9 ± 0.6 years), with recurrent monthly seizures despite regular use of antiepileptic drugs (AEDs) were defined as having refractory epilepsy and enrolled into the study group (Table 1). Their seizure diaries were reviewed and 24-h video-electroencephalographies were performed to document the type and severity of seizures. Seizure types were classified according to the recommendations of the International League Against Epilepsy.[14] All of the patients were found to have generalized tonic or generalized tonic–clonic seizures.

Thirty healthy children (15 males and 15 females, aged 6–17 years, average age = 10.6 ± 0.6 years) were enrolled as controls (Table 1). No individuals in either group had a history of cardiac arrhythmia, diabetic neuropathy, use of carbamazepine[10,15] or other medications such as vasopressors or vagolytic agents that might affect autonomic function.

Experimental protocols

After obtaining informed consent from the parents, a lead I ECG was taken in the interictal period during daylight hours from each subject while awake. The ECG was recorded for 5 min with each subject laying in a head-up posture (head at 30–45°) while quiet and breathing normally. ECG signals were recorded using an analog-to-digital converter with a sampling rate of 512 Hz. The digitized ECG signals were analyzed on-line and were simultaneously stored on a hard disk for off-line analysis and verification.[13,16]

Processing of ECG signals

Signal acquisition, storage, and processing were performed on an IBM-compatible personal computer. Our computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template.[13,16] Stationary R–R values were re-sampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain.[13,16]

Table 1 Basic data of the control and refractory epilepsy groups

	Age (years)	Gender	Duration of epilepsy (years)	Height (cm)	Weight (kg)
Control (n = 30)	10.6 ± 0.6	15M/15F	–	140.3 ± 3.4	35 ± 2.4
Epilepsy (n = 30)	10.9 ± 0.6	15M/15F	6.1 ± 0.7	140.4 ± 3	39.5 ± 3.5

Frequency—domain analysis of HRV

Frequency—domain analysis was performed using a non-parametric method of fast Fourier transformation (FFT). The direct current component was deleted and a Hamming window was used to attenuate the leakage effect. For each time segment (288 s; 2048 data points), our algorithm estimated the power spectrum density based on FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency—domain measurements as defined previously.[13,17,18] The frequency—domain measurements included the R—R intervals (RR, the interval between two neighboring R waves), HF power (0.15—0.45 Hz), LF power (0.04—0.15 Hz), and LF/(HF + LF) expressed in normalized units (LF%). The HF power and LF power were logarithmically transformed to correct for the skewing of the distribution.

The LF component is contributed by both parasympathetic and sympathetic regulation. The HF component is equivalent to the well-known respiratory sinus arrhythmia (RSA) and may represent vagal (parasympathetic) regulation of heart rate. LF% is considered to mirror sympathetic regulation.[16—18]

Statistical methods

Values are expressed as means ± S.E. Data between the two groups were compared with one-way ANOVA, followed by Fisher's least significant difference test. Differences were considered statistically significant at $P < 0.05$.

Results

There was no significant difference in age, gender, height, and weight between the study and control groups (Table 1). Fig. 1 illustrates representative ECG sequences during a 5-min recording from a male and a female in both the study and control groups. Note the heart rates in epileptic children are faster and less variable than controls.

Fig. 2 demonstrates that there are significant reductions in RR, LF, and HF in the study group as compared to controls. There is no significant difference in LF% between the study and control groups.

Discussion

Lower HRV has been documented in epileptic patients, but interictal alterations of respectively sympathetic and parasympathetic regulation in childhood epilepsy have not been published.[1,2,6,8,10,19] We used a power spectrum and frequency—domain analysis to study sympathetic and parasympathetic control of heart rate.[13,16,17] We also sought to understand the nature of autonomic physiological responses in epileptic children. In newly developed treatment models, although the efficacy of vagus nerve stimulation (VNS) has been documented in reduction of seizure frequency among patients with refractory epilepsy, and until now there has been no strong evidence that VNS would change the indicators of HRV.[12,20,21] Further studies are necessary to clarify the long-term effects of VNS or other neuromodulation models on morbidity and mortality in individuals with epilepsy.

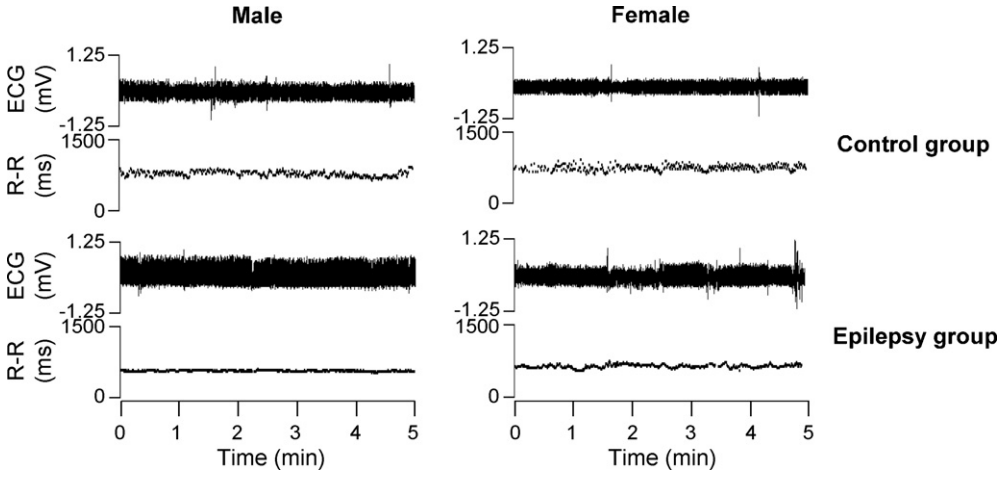

Figure 1 Sample recordings of 5-min ECGs and R—R intervals (time between two neighboring R waves) from a male and a female subject in both the study and control groups.

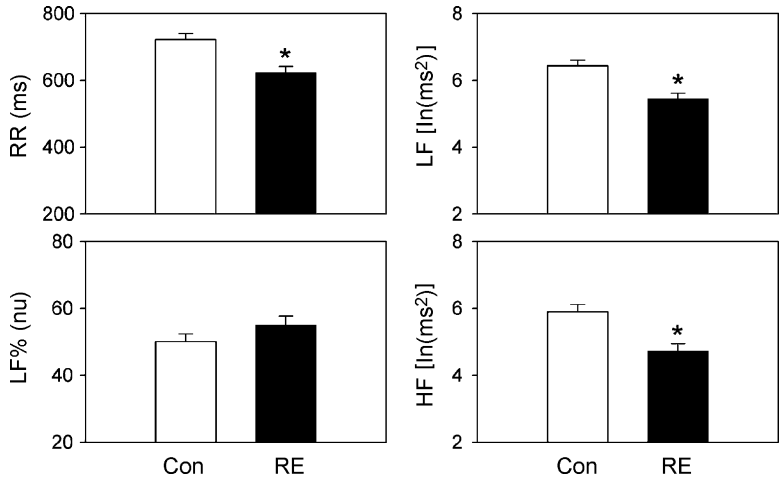

Figure 2 RR, LF, LF%, and HF of the control (Con) and refractory epilepsy (RE) groups. Data are expressed as means ± S.E. RR, the interval between two neighboring R waves; LF, low frequency power; LF%, LF/(HF + LF) expressed in normalized unit; HF, high frequency power. $^{*}P < 0.05$ vs. the control group by one-way ANOVA.

Lower HRV or life-threatening tachycardia can result from either a higher sympathetic or a lower parasympathetic physiological response. Enhanced vagal activity has been reported to provide protective antifibrillatory effects.[16,22] Reports of changes in the sympathetic indicator and in other parameters of HRV during the ictal period of childhood epilepsy[2] stimulated us to investigate parasympathetic as well as sympathetic indicators during the interictal period.

Our study suggests that children with refractory generalized epilepsy have lower RR and LF, but have no significant change in LF%. The lower RR and LF are likely a result of vagal reduction rather than a sympathetic increase. Compared to previous studies in adult epilepsy patients,[1,6,10] pediatric patients with refractory generalized epilepsy have vagal reduction but no sympathetic change. The mechanism of vagal reduction in childhood epilepsy is very different from the mechanism of decreasing HRV in adult epilepsy.

A previous study in epileptic children reported that there were no significant differences in all parameters of HRV compared to controls.[13] This study differed from our own study in that it did not focus on any specific seizure type and did not separate out patients with refractory epilepsy. Because the risk factors for SUDEP in epileptic patients are young age, early onset or longer duration of epilepsy, generalized tonic—clonic seizures, poorly controlled epilepsy, male sex, and being confined to bed,[3,23] we excluded children with partial seizures or controlled epilepsy. Furthermore, we selected patients with a long mean duration of epilepsy (6.1 years). Because alterations of heart rate are controlled by the ANS, changes in HRV would be expected with more severe disease and longer duration of epilepsy. We believe that our inclusion and exclusion criteria account for the differences reported between our study and the aforementioned (Yang et al.)[13] study.

Other studies reveal that dysfunction of the ANS can produce lethal tachyarrhythmias or cardiac ischemia in epilepsy patients.[1,4,5,7] We propose that indicators of HRV can offer adequate and convenient tools to guide the effects of epilepsy treatment upon cardiovascular autonomic regulation. In previous studies, a decrease in the sympathetic indicator of HRV was observed after temporal lobe resection and was though to be associated with decreasing complications of epilepsy.[6,10] Persson et al.[6] reported the HF of HRV, a parasympathetic indicator, would be another indicator to guide the surgical results. In following the health of epileptic patients and effects of medical or surgical treatment, we are planning to carefully observe the changes of both sympathetic and parasympathetic indicators in our patients.

Frequency—domain analysis of HRV of a 5-min ECG recording is a simple method for investigators and comfortable for sick children.[2,13] A recording can be obtained repeatedly in a single subject to follow his or her serial changes in autonomic function, and can be done in a ward, clinic, hospice, or a patient's home to minimize the effects of stress from the study itself. The digitalized data of a 5-min recording is relatively small and can be transmitted via the Internet. This technology is especially valuable for patients who cannot cooperate with a 24-h ECG recording, for example, young children or those in school, mentally handicapped children or those with behavior problems.

A 24-h ECG recording with analysis of HRV is superior to a 5-min recording in that it can be

applied in a sleep center to analyze the HRV in daylight wake, nighttime wake, sleep, and REM stages.[2] This is valuable because changes of HRV with circadian rhythm may be important in the pathophysiology of SUDEP, which occurs mostly in young children during sleep.[23] However, a 5-min ECG with frequency—domain analysis of HRV is a highly assessable tool to evaluate sympathetic and parasympathetic regulation in an epileptic patient,[24] and an abnormal result will prompt an in-depth 24-h analysis.

Conclusions

In this study, we used frequency—domain analysis of HRV obtained from a 5-min ECG recording to demonstrate that children with refractory generalized epilepsy have lower HRV during the interictal period. We postulate that the lower HRV in our patients results from parasympathetic or vagal reduction. This suggests that the mechanism of decreased HRV in children with epilepsy is different than in adults with epilepsy. In the future, additional studies in adult and pediatric patients with different seizure types, having different severities and durations of epilepsy, may help us to understand the odds ratio and priority of each risk factor.

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