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Decreased Cardiac Parasympathetic Regulation in Late-Onset Adulthood Epilepsy

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Abstract

Background: We used frequency-domain analysis of heart rate variability (HRV) to evaluate cardiac sympathetic and parasympathetic regulation in patients with adult-onset epilepsy.

Methods: Nineteen male and 16 female patients, having epilepsy with unknown etiology and ever experiencing generalized onset seizure (age range: 18-67 years), were enrolled retrospectively. Data of daytime electrocardiograms for 5 min was recorded in each patient and was quantified into the heart rate variables: High frequency power (0.15 Hz to 0.45 Hz, HF, reflect parasympathetic regulation), low frequency power (0.04 Hz to 0.15 Hz, LF, contributed by mixed sympathetic and parasympathetic divisions), and LF% (LF/(HF + LF) in normalized units, mirrors sympathetic regulation). The significance was analyzed using paired t-tests. Pearson correlation analysis and stepwise regression were applied for further analysis.

Results: In the patients with epilepsy, the rate of decline in HF was significantly correlated with the onset age of epilepsy (r=-0.438, p=0.009), but not with patient age, epilepsy duration, seizure frequency and number of anti-epileptic drug. We categorized the patients into three groups according to their onset age of epilepsy: early onset (18-24 years), middle onset (25-39 years) and late onset (40-66 years) groups. HF was significantly lower in the late onset group.

Conclusions: Cardiac parasympathetic regulation is decreased in adulthood patients with epilepsy, which is correlated with their onset age of epilepsy.

Keywords: Autonomic nervous system; Epilepsy; Heart rate variability

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Introduction

Autonomic dysregulation has been reported to be associated with long-term co-morbidity and premature mortality in patients with epilepsy [1-4]. Some risk factors of cardiac autonomic dysregulation usually associated with a higher mortality include generalized tonic-clonic (GTC) seizures, early-onset or chronic epilepsy, multiple antiepileptic drugs (AEDs), and refractory epilepsy with frequent seizures [4,5].

A change in heart rate is primarily determined by cardiac autonomic regulation by parasympathetic (via the vagus nerve) and sympathetic divisions. Heart rate variability (HRV) is defined by irregularities in the interval between normal sinus beats [6,7]. Frequency-domain analysis of HRV is a sophisticated and non-invasive tool for respectively studying sympathetic and parasympathetic regulation of heart rate. The standard procedures and interpretation of HRV analysis were first reported in 1996 [8]. We have previously applied a modification of these procedures to investigate cardiac autonomic dysregulation in children with epilepsy [9]. In this retrospectively case-control study on a cohort of adult-onset epilepsy, we used applied frequency-domain analysis of HRV from the digitalized electrocardiograms (ECG) data to evaluate the respective changes in cardiac sympathetic and parasympathetic regulations.

Materials and Methods

Study population

Nineteen male and 16 female adult patients, who presented with repetitive seizures for more than 1 year, were retrospectively enrolled in the study at the Epilepsy Center of Hualien Tzu Chi General Hospital. The patients were recorded their epilepsy and seizure types according to the classification of the International League Against Epilepsy Guidelines (ILAE, 2017) [10]. Brain

Table 1: Clinical features and heart rate variables of epilepsy and control groups.

	Epilepsy	Control	p value
Gender	19 M / 16 F	19 M / 16 F	
Age (year)	47.171 ± 2.033	47.171 ± 2.033	
Epilepsy duration (year)	14.229 ± 1.942	-	
Onset age (year)	32.914 ± 2.170	-	
SBP (mmHg)	122.114 ± 1.861	124.280 ± 1.947	0.558
DBP (mmHg)	76.229 ± 1.272	78.120 ± 1.264	0.335
RR (ms)	771.600 ± 15.271	798.889 ± 22.273	0.316
LF (ln [ms^2])	4.673 ± 0.189	5.039 ± 0.247	0.247
LF% (nu)	57.780 ± 3.374	50.952 ± 2.761	0.089
HF (ln [ms^2])	3.843 ± 0.172	4.639 ± 0.284	0.011*

*p<0.05; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; RR: Interval between two neighboring R waves; LF: Low Frequency power; LF%: LF/(HF+LF) in normalized units; HF: High Frequency power

Table 2: Correlations of HF with patient age, epilepsy duration, onset age, seizure frequency and AED number.

		Age (year)	Duration (year)	Onset age (year)	Seizure frequency (no / month)	AED number
HF	Pearson correlation	-0.291	0.182	-0.438*	0.181	0.119
	p value	0.090	0.295	0.009	0.307	0.495

*p<0.05; HF: High Frequency power; AED: Anti-Epileptic Drug

magnetic resonance imaging was analyzed to rule out any epilepsy with structural etiology, and electroencephalography (EEG) data was used to detect the possible seizure foci and epileptiform discharges in the patients. All of the patients were diagnosed with adult-onset focal epilepsy with unknown etiology and they all experienced generalized onset seizure ever. The seizure frequency was that 19 patients had less than 6 seizures in past one year, and 4 patients had 1 seizure, 6 patients had 2 seizures, 4 patients had 3 seizures, 2 patients had 5 or more seizures per month in average.

The number of AED taken by patients was that 23 patients had 1 AED, 10 patients had 2 AEDs, and 2 patients had 3 AEDs at the enrollment. None of the enrolled patients had evidence of arrhythmia, ischemic heart disease, heart failure, or diabetes mellitus, which can affect heart rate recording and HRV [11]. Patients with prominent mental retardation and those who seemed uncooperative toward the study were excluded from the study. Clinical features of enrolled patients are listed in Table 1.

Data of thirty-five healthy subjects with matched sex and age were enrolled as the control group, and they were anthropometrically matched to the epilepsy group. There was no history of physical or psychological disease in the controls. The study protocol was approved by the Institutional Review Board of the Buddhist Tzu Chi Hospital. All of the subjects gave their written informed consent at enrollment.

Blood pressure, heart rate recording and frequency-domain analysis of HRV

Systolic and diastolic blood pressure (SBP and DBP), heart rate and daytime ECG were recorded for 5 min when each subject lay quietly awake in the head-up 45-degree position. Using an analog-to-digital converter with a sampling rate of 512 Hz, frequency-domain analysis was performed using a nonparametric method of fast fourier transformation (FFT) from the lead I ECG data. The direct current component was deleted and a Hamming window was used to attenuate the leakage effect. For each time segment (288 s; 2,048 data points), our algorithm estimated the power spectrum density on the basis of FFT. The power spectrum was corrected for attenuation resulting from the sampling and the Hamming window [12]. The power spectrum was subsequently quantified into standard frequency-domain measurements as defined by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Those included R-R interval (the intervals between two neighboring R waves, RR (also mean 1/heart rate × 60,000 ms)) and heart rate variables by spectral analysis: high frequency power (0.15 Hz to 0.45 Hz, HF), low frequency power (0.04 Hz to 0.15 Hz, LF), and LF% (LF/(HF+LF) in normalized units). The HF and LF data were logarithmically transformed to correct for skewed distribution. LF is produced by mixed sympathetic and parasympathetic divisions. HF was considered to reflect vagal (parasympathetic) regulation and LF% was considered to reflect sympathetic regulation [8,9,12].

Statistical analysis

The mean and standard error (SE) was calculated for all measures. Clinical features and heart rate variables between matched epilepsy and control groups were analyzed by the paired t-test. Among the 35 patients with adult-onset idiopathic epilepsy, Pearson's correlation coefficient (r) was used to measure the correlation between patient age, epilepsy duration, onset age (the age of epilepsy being diagnosed), seizure frequency, AED number at enrollment and heart rate variables, such as LF, HF, and LF%. In addition, analysis of variance (ANOVA) and stepwise regression analysis were conducted to identify those factors associated with heart rate variables. All statistical assessments were evaluated at the 0.05 level of significant difference. All analyses were performed using SPSS (now called PASW) version 17.0 (SPSS, Chicago, IL).

Results

There was no difference in SBP, DBP, and heart rate interval between the epilepsy and control groups. The epilepsy group had a significantly lower HF (3.843 ln [ms^2] ± 0.172 ln [ms^2] vs. 4.239 ln [ms^2] ± 0.284 ln [ms^2], p=0.011) compared with the age- and sex-matched control group (Table 1). There were no differences in LF and LF% between the two groups. In the epilepsy group, Pearson correlation

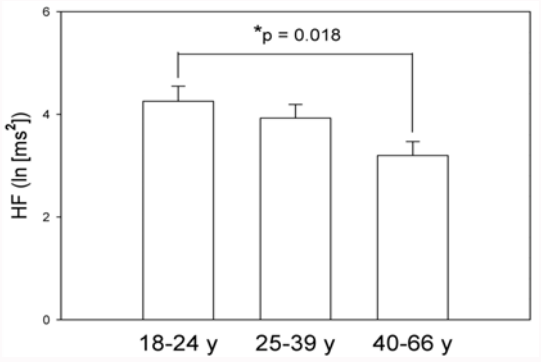

Figure 1: Comparison of HF between different onset ages of idiopathic epilepsy. A significant difference between the early onset (18-24 years) group and late onset (40-66 years) group was observed.
HF: High Frequency power.

analysis revealed that the rate of decline in HF was significantly correlated with the onset age of epilepsy (r=-0.438, p=0.009), but not with patient age, epilepsy duration, seizure frequency and AED number (Table 2). Using stepwise regression analysis, the decline in HF was significantly correlated with onset age with a slope of -0.035 ln [ms^2] per year (95% confidence interval, -0.009, -0.060; p=0.009). The patients were further divided into three groups according to their onset age of epilepsy. Seven males and four females had early onset of epilepsy (18-24 years), seven males and eight females had middle onset age (25-39 years) and five males and four females had late onset of their epilepsy (40-66 years). HF was significantly lower in the late onset group (3.197 ln [ms^2] ± 0.815 ln [ms^2]) compared with that in the early onset group (4.255 ln [ms^2] ± 0.970 ln [ms^2]) (Figure 1).

Discussion

Both cardiac sympathetic and parasympathetic dysregulation have been reported in patients with various types of epilepsy [1-5,13-15]. Most previous studies concluded that both the sympathetic and parasympathetic divisions of the autonomic nervous system are affected by repetitive epileptic seizures. Among sympathetic and parasympathetic dysregulation in different target organs, an abnormal increase in sympathetic tone in the heart is thought to have a close relationship with mortality in patients with epilepsy [1,2,15-18]. However, our previous study in children with epilepsy [9] and the current study on adult-onset epilepsy showed that cardiac autonomic dysregulation during the interictal period might result more from a decrease of parasympathetic (HF) activity. Taking together with the similar results from Metcalf et al. [1], these implied that adulthood patients with epilepsy with unknown etiology would have reduced parasympathetic activity and then change the sympathovagal balance of their cardiac autonomic control. Furthermore, the findings that children with epilepsy have lower RR and LF, as well as lower HF in our previous study, suggested that children with epilepsy would have more prominent impairment of HRV indicators of the autonomic nervous system than adult-onset epilepsy patients [9].

A simultaneous physiological decline of HRV variables in the sympathetic and parasympathetic divisions from middle age to old age has been reported in the aging process [12,19]. Our results showed that higher decrease in parasympathetic division with sympathovagal imbalance was observed in patients with late (older than 40 years) onset epilepsy than whom with epilepsy onset in younger age. Our results were very different from previous reports that higher risk for cardiac autonomic dysregulation was noted in patients with early onset or long duration of epilepsy. After carefully comparing the design of these studies with ours, the discrepancy between studies could be because previous studies enrolled refractory or untreated epilepsy patients, but all the patients that we enrolled were under AED treatment, and most of them were under seizure control. Therefore our results could demonstrate the usual condition of patients' daily autonomic function, in that patients having AED to control their epilepsies. Meanwhile, since we believed that frequent generalized onset seizures with propagation to deep structures in the brain would affect autonomic control centers [20], we excluded patients who did not experience generalized onset seizure from this study. All of these inclusion criteria at enrollment would be supposed to affect the study results. However, there was no evidence that seizure frequency or AED number was correlated with any change of heart rate variable in this study.

The major limitations of this study are: (1) AED itself can be a confounding factor for studying cardiac autonomic regulation in patients [21]; and (2) short-term heart rate recording with HRV spectral analysis is practically efficient but not a perfect design to obtain circadian data in a single subject [3,9,16]. In this study, all heart rate variables were recorded and analyzed during the daytime to avoid major circadian effects [22]. Obtaining recordings and heart rate variables in sex- and age-matched subjects in the same posture can minimize inter-individual anthropometric and posture confounding effects [23]. Therefore, although we enrolled a limited number of subjects in this case-control study, our statistical results indicated that the sample size was sufficient for achieving a significant interpretation of the observed phenomena and explained the mechanism of HRV dysregulation in adult-onset epilepsy.

Conclusions

Cardiac parasympathetic regulation is decreased in patients with adulthood epilepsy. In patients with onset age of epilepsy older than 40 years, parasympathetic dysregulation is more prominent than whom with epilepsy onset at younger ages. It might be associated with the mechanism of HRV dysregulation in patients with late onset epilepsy.

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Competing Interests

The authors declare that they have no competing interests.

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