

# Heart Rate Variability Before and After Seizure Control in Five Patients with Generalized Seizures

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## ABSTRACT

Changes in heart rate variability (HRV) as a result of autonomic dysfunction has been reported in patients with epileptic seizures and this condition is associated with higher morbidity and mortality. Because most studies have been limited to cases of temporal lobe epilepsy, our study focused on cases of generalized epilepsy and examined changes in sympathetic and parasympathetic regulation. Five patients with generalized seizures were enrolled. Before seizure control and for 6 months or more after seizure control, precordial electrocardiograms were taken during an interictal period in the daytime. Frequency-domain analysis of HRV was performed using a nonparametric method of fast Fourier transformation. Each power spectrum was subsequently converted to standard frequency domain measures, including R-R interval (RR), high frequency power (HF; 0.15-0.40 Hz), low frequency power (LF; 0.04-0.15 Hz), and LF/(HF+LF) expressed in normalized units (LF%). After seizure control, there was a significant increase in HF and significant decrease in LF% relative to their levels before seizure control but no changes in RR or LF were noted. Thus, control of generalized seizures was accompanied by a simultaneous increase in parasympathetic regulation and decrease in sympathetic regulation. Our study confirms that seizure control may modulate autonomic function. (*Tzu Chi Med J* 2006; **18**:392-396)

*Key words:* epilepsy, heart rate variability, parasympathetic, sympathetic

## INTRODUCTION

Dysfunction of the autonomic nervous system (ANS) has been reported in humans with epileptic seizures and in animal models of epilepsy [1-7]. This dysfunction results in higher morbidity and mortality in patients with epilepsy than in those without epilepsy [8]. In documented studies, high sympathetic regulation was found to play a causal role in sudden death [6,9,10]. Because most studies have been limited to patients with temporal lobe epilepsy (TLE) [1,2,11,12], we designed this study to investigate changes in parasympathetic and sympathetic regulation in patients with generalized seizures.

Frequency-domain analysis of heart rate variability

(HRV) is a sophisticated and noninvasive tool for detecting autonomic regulation of the heart [2,5,9,13-18]. HRV can be categorized into high frequency power (HF; 0.15-0.40 Hz) and low frequency power (LF; 0.04-0.15 Hz), both of which depend on oscillatory frequency and development mechanism. The LF component is influenced by both parasympathetic and sympathetic regulation. The HF component and LF/(HF+LF) ratio in normalized units (LF%) reflect the extent of vagal (parasympathetic) and sympathetic regulation of the heart, respectively [18]. Standard procedures and interpretation of HRV analysis were first reported in 1996. We used frequency domain analysis to study HRV and measured changes in sympathetic and parasympathetic regulation in patients with generalized seizures.

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## CASE REPORT

## Patients

Five patients with generalized seizures were referred to the epilepsy team of Buddhist Tzu Chi General Hospital, Hualien, Taiwan (Table 1). They were enrolled in our study after approval from the Tzu Chi Hospital Ethics Committee and written informed consents were obtained. According to the official classification of the International League Against Epilepsy (ILAE, 1981), they were diagnosed with generalized tonic seizures or

generalized tonic-clonic seizures. Electroencephalographs (EEG) were used to locate seizure foci. Brain magnetic resonance imaging (MRI) was done to rule out structural lesions in their brains. The Table shows patients and clinical data including gender, age, blood pressure, height, weight, seizure type and focus, and cause and duration of epilepsy. No patient had any arrhythmias, congestive heart failure, coronary artery disease, diabetes mellitus, or structural brain lesions (Fig. 1). Patient 2 was treated with a combination of topiramate and valproate. The other patients were treated with valproate alone (Table 1). All subjects were followed

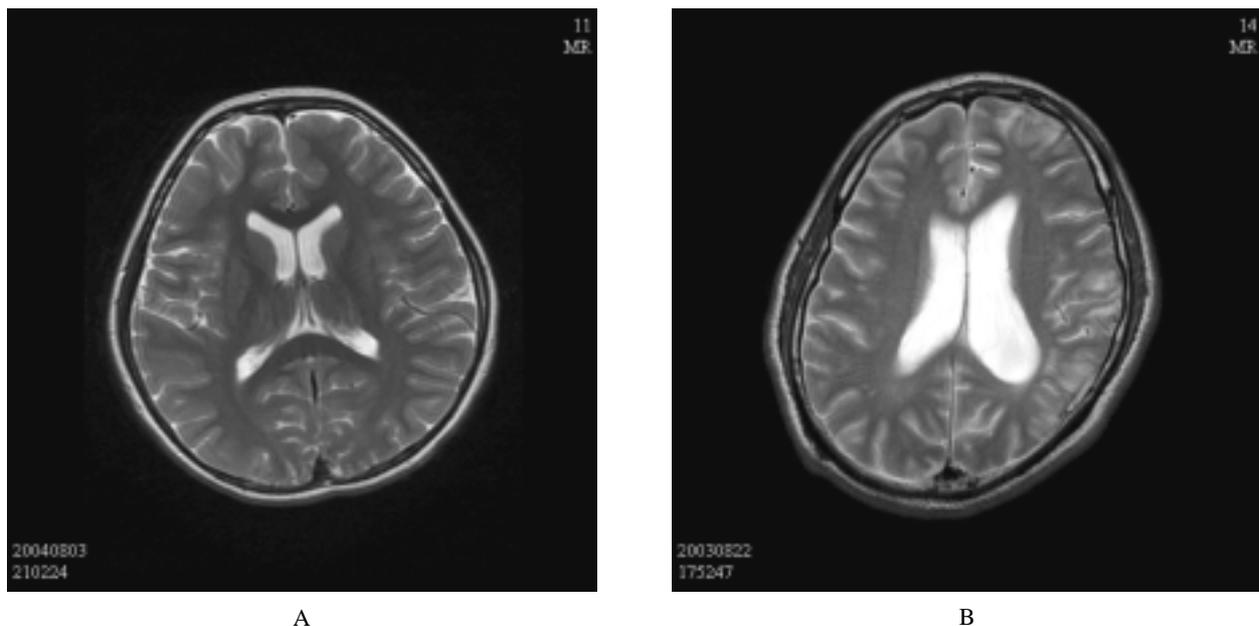


Fig. 1. Brain MRI of (A) patient 2 with a seizure focus in the left frontal lobe and (B) patient 5 with a seizure focus in the right parietal lobe. There were no structural lesions associated with their seizure foci.

Table 1. Patients' Data at Enrollment

Patient	1	2	3	4	5
Sex	Male	Female	Male	Female	Male
Age (years)	8	8	16	25	46
SBP (mmHg)	98	76	103	108	110
DBP (mmHg)	52	60	54	76	80
Height (cm)	125	136	167	153	150
Weight (Kg)	21	33	62	59	60
Seizure type	GTC	GT	GTC	GTC	GT
Seizure focus	Multi-foci*	Left frontal	Multi-foci*	Multi-foci*	Right parietal
Cause of epilepsy	Idiopathic	Idiopathic	Idiopathic	Idiopathic	Traumatic brain injury
Duration of epilepsy (years)	2	2	4	10	0.3
Anti-epileptic drugs	Valproate	Topiramate, valproate	Valproate	Valproate	Valproate

GT: general tonic seizure; GTC: generalized tonic-clonic seizure; \*: EEG cannot localize the seizure to a particular focal region of the brain

for more than 12 months. At the end of follow-up, we defined "seizure control" as one or no disabling seizures per month for more than 6 months.

**Experimental protocols**

At the time of enrollment (i.e., before seizure control), each awake subject received the first precordial electrocardiogram (ECG) during an interictal period in the daytime. An ECG was taken for 5 min while each subject lay quietly, in the supine position, with head elevated 30-45 degrees, while 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. We recorded the second ECG for 5 minutes at various times after seizure control for at least 6 months. The same signal digitization and storage techniques were used before and after seizure control.

**Processing of ECG signals**

The detailed procedures for HRV analysis have been previously reported [14,15,17]. The digitized ECG signals were stored for off-line verification. 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. Stationary R-R values were resampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain.

**Frequency-domain analysis of HRV**

Frequency-domain analysis was performed using a nonparametric 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 (288s; 2,048 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. Those included the R-R intervals (the intervals between 2 neighboring R waves, RR), HF (0.15-0.40 Hz), LF (0.04-0.15 Hz), and LF%. The HF and LF were logarithmically transformed to correct for the skewness of the distribution.

**Statistical methods**

Values are expressed as mean + SE. Data between two groups were compared using paired t-tests. Differences were considered statistically significant at  $p < 0.05$ .

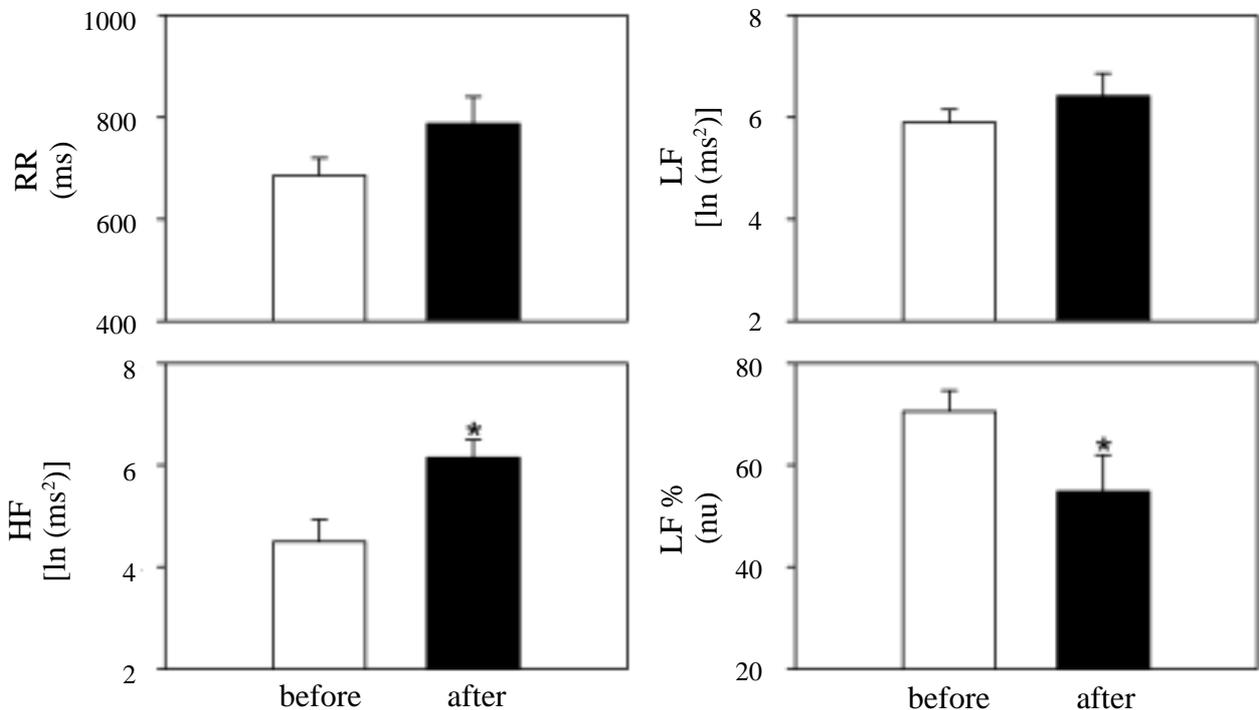


Fig. 2. Changes in the RR, LF, HF, and LF% before and after seizure control. Data are expressed as mean ±SE. \* :  $p < 0.05$  by paired t-test.

## RESULTS

After seizure control, HF was significantly increased ( $p=0.042$ ) and LF% significantly decreased ( $p=0.016$ ) relative to their levels before seizure control, but no significant changes in RR ( $p=0.104$ ) and LF ( $p=0.408$ ) were found (Fig. 2).

## DISCUSSION

We demonstrated that HF increases while LF% decreases after seizure control in patients with generalized seizures. Many studies have reported that seizure control in epileptic patients is associated with a reduction in the sympathetic indicator but failed to mention any changes in the parasympathetic indicator. Most researchers attribute higher mortality in epileptic patients compared to controls mainly to higher sympathetic regulation [6,9,10]. Reduction in sympathetic regulation is the proposed benefit of many seizure treatment models [4, 11,13,19]. Some authors even reported that carbamazepine might suppress both parasympathetic and sympathetic regulation [19]. However, carbamazepine was not used in this study. A study of HRV related to cardiac disease suggested that high parasympathetic or vagal regulation might have an anti-fibrillation effect [20]. Results of a few clinical trials have suggested that the increase in HF of HRV improves patients' health [15, 17]. Although our data are from a limited number of subjects, longitudinal monitoring of HF changes, before and after seizure control, showed HF increased over time. This increase is probably an indicator of seizure control and improvement in patients' health in addition to reduction of sympathetic regulation.

In 2005, Persson et al reported their cross-sectional observation of the linkage between decreased impairment of ANS in patients with TLE and good outcome after temporal resection [12]. Only a few studies of seizures other than TLE have been done so far [3,9]. Darbin et al. reported that severity of generalized convulsive seizures triggered by maximal electroshock in rats played a key role in impairment of cardiovascular neural regulation [3]. However, further studies that examine seizure types individually will be needed to clarify the mechanism of autonomic regulation in the epileptic brain. We are going to study more patients with generalized seizures in the future.

In conclusion, frequency-domain analysis of HRV showed that seizure control in patients with generalized seizures was accompanied by a significant increase in parasympathetic regulation and a significant decrease in sympathetic regulation. Our study confirms that sei-

zure control may modulate the autonomic function.

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