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Heart rate variability in patients with frontal lobe epilepsy

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ABSTRACT

Objective: To identify autonomic dysregulation in frontal lobe epilepsy (FLE).
Methods: We studied 14 male and 11 female subjects with FLE and an equal number of matched healthy control subjects. Lead I electrocardiograms were obtained for 5 min in the interictal state during daytime. Frequency-domain analysis of heart rate variability was performed and the data subsequently converted to heart rate interval and high frequency (HF; 0.15–0.45 Hz) power which representing vagal or parasympathetic regulation, as well as low frequency (LF; 0.04–0.15 Hz) power and LF/(HF + LF) expressed in normalized units (LF%) (considered to mirror sympathetic regulation). Differences in data between groups were compared using *t*-test.
Results: The epilepsy group had a lower mean heart rate interval and a lower high frequency power.
Conclusions: Patients with FLE have interictally faster heart rates, attributed to lower parasympathetic drive, which may contribute to the higher incidence of sudden death that is seen in this group of patients. This suggests that the mechanism of decreased HRV in patients with FLE is probably different from that in patients with temporal lobe epilepsy.
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Introduction

Impaired autonomic regulation and cardiac arrhythmia are not uncommon in humans with epilepsy.[1,2] Dysregulation of autonomic nervous system (ANS) has been associated with long-term morbidity and mortality in epileptic patients.[3,4] Sudden unexpected death in epileptic patients (SUDEP) is now known to be associated with ANS dysregulation of the heart.[3,5] Previous studies of ANS in epilepsy were mostly confined to temporal lobe epilepsy (TLE) and uncovered mainly sympathetic dysregulation.[1,4] In TLE, most researchers believe that lesions of the insular cortex lead to the ANS dysregulation[6] and temporal lobe resection has been shown to decrease sympathetic and cardiac dysregulation.[7]

The frontal lobe is the second most common site of origin of seizures among localization-related epilepsies.[8] In an animal study, insular area was found to link with multiple regions in the frontal lobe.[9] Seizures of frontal lobe origin are of highly variable types and autonomic symptoms during these seizures have often been reported in literature.[8,10] However, autonomic function in patients with frontal lobe epilepsy (FLE) has rarely been studied and the mechanism of sympathetic and parasympathetic regulation of the heart in these patients remains to be clarified.

Frequency-domain analysis of heart rate variability (HRV) is a sophisticated and noninvasive tool for studying neural regulation of heart rate. The standard procedures and interpretation of HRV analysis were first reported in 1996.[11] We used a modification of this procedure[12] in this study to evaluate sympathetic and parasympathetic regulation of heart rate in patients with FLE.

Methods

Epileptic patients and controls

Fourteen males and 11 females (age 5–34 years; mean age: 16.16 years) who had epilepsies of frontal lobe origin as identified by interictal electroencephalography (EEG) were enrolled. For each

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patient, thorough historical information served to classify the seizure types according to International League Against Epilepsy guidelines (ILAE, 1981). Brain magnetic resonance imaging was used to detect possible structural lesions and EEG was used to determine epileptogenic zones. Clinical features of our epileptic patients are reported in Table 1. None of the patients had arrhythmia, systemic disease, or adverse effects to therapy. Patient numbers 9 and 21 had intracranial arachnoid cysts but the cysts did not correlate with their seizure foci. All patients were classified as idiopathic or cryptogenic epilepsies.

Healthy controls comprised 14 males and 11 females subjects (mean age: 16.20 years). The two groups were well-matched for anthropometric characteristics, such as gender, age, weight, height, and body mass index (BMI).

Experimental protocols

At enrollment, each subject underwent a daytime electrocardiogram (ECG) in awake interictal state after an informed consent was obtained. The ECG was recorded for 5 min while each subject lay quietly in a 45° head-up posture and breathed normally. Lead I ECG signals were retrieved 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.[12]

Processing of ECG signals

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 resemblance to a standard QRS template. Stationary *R–R* values were resampled and interpolated at a rate of 7.11 Hz to provide continuity in the time-domain.[12]

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 (288 s; 2048 data points), our algorithm estimated the power spectrum density on the basis of FFT. The resulting 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.[11,12] These included the *R–R* intervals (the intervals between two neighboring *R* waves, RR), high frequency (HF; 0.15–0.45 Hz) power and low frequency (LF; 0.04–0.15 Hz) power. The LF component is formed by both sympathetic and parasympathetic contributions. The HF component is equivalent to the respiratory sinus arrhythmia (RSA) and is considered to reflect vagal (parasympathetic) regulation of the heart.[11] The fraction LF/(HF + LF) expressed as a normalized unit (LF%) is considered to mirror sympathetic regulation.[11] Due to that change of RR might be proportionally linked to HF or LF in algorithm, we calculated high frequency unit ($HF/RR^2 \times 100^2$, HU) and low frequency unit ($LF/RR^2 \times 100^2$, LU) for further correction. The HF, LF, HU and LU data were logarithmically transformed to correct for any skew in the distribution.

Statistical analysis

Data are presented as mean ± standard error (S.E.). The significance of differences between groups was examined using Student's *t*-test for independent continuous variables. If the data were far from normal distribution, the Mann–Whitney Rank Sum test was applied instead. All statistical assessments were two-sided and evaluated at the 0.05 level of significant difference.

Table 1
Clinical features of patients with frontal lobe epilepsy

Patients (no.)	Age (years)/gender	Duration of epilepsy (years)	Type of seizures	Interictal EEG findings, location	Therapy at enrollment
1	7/F	7	Tonic, tonic–clonic	Spikes, sharp waves, spike-wave complexes, left F	CZP, LTG, PB
2	7/F	4	Tonic, tonic–clonic	Spike/polyspike-wave complexes, right F	LTG, VPA
3	8/F	2	Tonic	Spikes, spike-wave complexes, left lateral frontal region	TPM, VPA
4	9/F	3	Tonic	Repeated or isolated spikes, spike-waves, left F	TPM, VPA
5	13/F	8	CPS, sec. GTC	Polyspikes and spike-wave complexes, left F	OXC, VPA
6	14/F	13.5	Tonic–clonic	Paroxysms of sharp-wave complexes, left F	VPA
7	15/F	10	Tonic–clonic	Polymorphic alpha/theta activity, left F	LTG, VPA
8	16/F	15	Tonic, tonic–clonic	Spikes, right frontocentral region	PB, PHT, TPM
9	5/M	2	Tonic–clonic	Trains of sharply contoured 10–11 Hz activity, bilateral F	OXC
10	8/M	2	PS	Sharp wave with following rhythmic theta activity, left F	CZP
11	10/M	4	Tonic–clonic	Slow waves, right frontocentral region	VPA
12	15/M	10	Tonic–clonic	Spikes with phase reversal, left frontocentral region	VPA
13	19/M	15	CPS, sec. GTC	Repeated spikes and polyspikes with phase reversal, right F	CLB, VPA
14	25/M	10	Tonic–clonic	Sharp-contoured alpha and semirhythmic theta activity, left F	OXC
15	27/M	24	CPS, sec. GTC	Isolated spikes, left lateral frontal region	CZP, LTG, VPA
16	31/M	28	Tonic–clonic	Spike-wave complexes and repetitive spikes, left F	VPA
17	32/M	14	CPS	Isolated spikes, left F	OXC
18	8/F	5	Tonic–clonic, absence	Spikes, bilateral F	CBZ, VPA
19	16/F	7	Tonic–clonic	Spike/polyspike with phase reversal, left F	CBZ, TPM
20	23/F	2	CPS	Spikes with phase reversal, left F	CBZ
21	12/M	6	CPS, sec. GTC	Spikes with phase reversal, bilateral frontocentral regions	CBZ
22	16/M	8	Tonic	Sharp waves with phase reversal, right F	CBZ, VGB
23	16/M	10	CPS	Transients of fast alpha activity or sharp waves, left F	CBZ, VGB
24	18/M	8	CPS, sec. GTC	Polyspikes, repeated spikes, spike-wave complexes, right F	CBZ
25	34/M	31	CPS, sec. GTC	Spikes with phase reversal, left F	CBZ, LTG, VPA

EEG, electroencephalography; CPS, complex partial seizure; sec. GTC, secondarily generalized tonic–clonic; PS, partial seizure; F, frontal location; OXC, oxcarbazepine; VPA, sodium valproate; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; CZP, clonazepam; CLB, clobazam; CBZ, carbamazepine; VGB, vigabatrin. Patient no. 9 and no. 21 had intracranial arachnoid cysts which did not correlate with their seizure foci. All the patients were categorized as idiopathic or cryptogenic epilepsy.

Results

Clinical features of epileptic patients

Table 1 demonstrates the clinical features of our patients. All the 25 patients had idiopathic or cryptogenic epilepsies (duration range 2–31 years, mean ± S.E.: 9.94 ± 1.57 years). Eight patients were reported to have generalized tonic–clonic seizures (GTC) only. Six patients had generalized tonic seizures (GT) but 3 of them had GTC as well. Complex partial seizures (CPS) were noted in 9 patients and secondary generalization occurred in 6 patients. Patient no. 10 had partial seizure (PS) only and patient no. 18 presented with GTC and absence.

Epileptogenic foci on interictal EEG were: left frontal in 16, right frontal in 6 and bilateral frontal in 3 patients.

Eleven patients were treated with only one anti-epileptic drug (AED): sodium valproate (4 patients), oxcarbazepine (3), clonazepam (1), and carbamazepine (3). Ten patients received two AEDs: lamotrigine and sodium valproate (2), topiramate and sodium valproate (2), oxcarbazepine and sodium valproate (1), clobazam and sodium valproate (1), carbamazepine and sodium valproate (1), carbamazepine and topiramate (1), carbamazepine and vigabatrin (2). Four patients considered resistant to a two-drug combination received three AEDs each: clonazepam, lamotrigine, and phenobarbital (1); Phenobarbital, phenytoin and topiramate (1); clonazepam, lamotrigine, and sodium valproate (2).

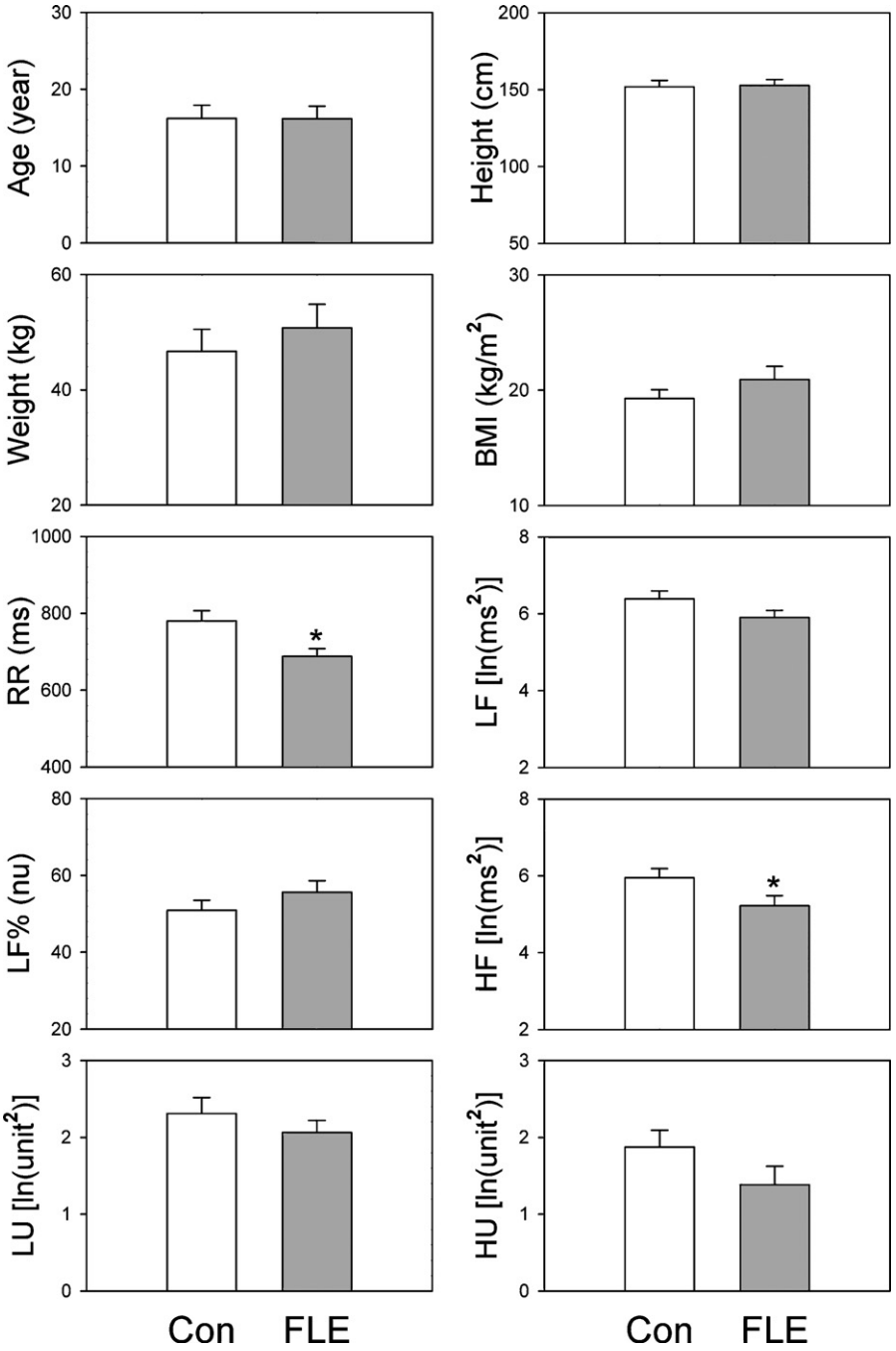

Fig. 1. Age, height, weight, BMI, RR, LF, LF%, HF, LU and HU of control (Con) and frontal lobe epilepsy (FLE) groups. Data expressed as mean ± S.E. BMI, body mass index; RR, interval between 2 neighboring *R* waves; LF, low frequency power; LF%, LF/(HF + LF) expressed in normalized unit; HF, high frequency power; LU, low frequency unit; HU, high frequency unit. $^{*}P < 0.05$ *vs.* control group by Student's *t*-test.

Table 2
Comparisons of anthropometric characteristics and heart rate variables between with and without carbamazepine (CBZ) using groups

	With CBZ (5M, 3F)	Without CBZ (9M, 8F)	*P*-Value
Age (years)	17.88 ± 2.77	15.35 ± 2.1	0.268
Height (cm)	159.13 ± 6.84	149.82 ± 4.7	0.449
Weight (kg)	54.25 ± 5.65	49.06 ± 5.52	0.568
Duration of epilepsy (years)	9.63 ± 3.17	10.09 ± 1.84	0.727
RR (ms)	747.5 ± 21.17	659.65 ± 25.08	0.037*
LF (ln(ms^2))	6.23 ± 0.34	5.75 ± 0.22	0.241
LF% (nu)	56.75 ± 6.03	55.06 ± 3.5	0.799
HF (ln(ms^2))	5.49 ± 0.62	5.09 ± 0.27	0.498

Data expressed as mean ± S.E.; *$P < 0.05$.

Table 3
Comparisons of anthropometric characteristics and heart rate variables between poly- and mono-therapy groups

	Polytherapy (5M, 9F)	Monotherapy (9M, 2F)	*P*-Value
Age (years)	15.07 ± 2.09	17.55 ± 2.75	0.622
Height (cm)	151.29 ± 5.4	154.73 ± 5.81	0.784
Weight (kg)	48.93 ± 5.35	53.0 ± 6.68	0.634
Duration of epilepsy (years)	10.64 ± 2.2	9.05 ± 2.32	0.625
RR (ms)	662.93 ± 22.37	719.36 ± 34.05	0.164
LF (ln(ms^2))	5.72 ± 0.28	6.13 ± 0.22	0.291
LF% (nu)	53.86 ± 3.73	57.82 ± 5.01	0.523
HF (ln(ms^2))	5.09 ± 0.4	5.38 ± 0.33	0.597

Data expressed as mean ± S.E.

Anthropometric and heart rate variables

Fig. 1 demonstrates anthropometric and heart rate variables in patients with FLE and controls. Between-group differences in RR and HF power ($P < 0.05$) but not age, height, weight, BMI, LF, LF%, HU and LU were significant ($P > 0.05$). As a group, the patients had a significantly lower mean heart rate interval (687.76 ms *vs.* 780.15 ms; $P = 0.008$) and HF power (5.22 ln[ms^2] *vs.* 5.96 ln[ms^2]; $P = 0.043$).

In Table 2, we divided patients into carbamazepine (CBZ) using group and non-CBZ using group. The CBZ using group had a significantly higher mean heart rate interval (747.5 ms *vs.* 659.65 ms; $P = 0.037$) comparing to non-CBZ using group. There was no significant between-group difference in other heart rate variables and anthropometric characteristics.

In Table 3, we divided patients into polytherapy group and monotherapy group. There was no significant difference in anthropometric and heart rate variables between poly- and mono-therapy groups.

Discussion

Autonomic dysregulation and SUDEP have been described not only in TLE but also other forms of epilepsy.[3,13] We believe that HRV could be used to indicate the risk of SUDEP and guide the treatment of epileptic patients. Our study confirms that FLE with repetitive seizures causes change in interictal cardiac autonomic function. Faster heart rates or lower heart rate intervals in our patients with FLE were found to correspond to lower parasympathetic regulation rather than higher sympathetic drive. Although it has been believed for the last 10 years that increased sympathetic activity accounts for cardiac tachyarrthymia and SUDEP in TLE,[7] a recent study found decreased parasympathetic drive in addition to increased sympathetic drive in some patients.[4]

Since increased sympathetic drive is believed to underlie SUDEP, most researchers have favored treatments directed towards reducing sympathetic activity.[14,15] In one study, increasing parasympathetic or vagal activity was shown to protect against sudden death by suppressing atrial or ventricular fibrillation.[16] Taken together with our report, these reports suggest that risk of SUDEP probably could be higher in patients with FLE and is likely due to lower parasympathetic drive. When we calculated the HU for further correction of parasympathetic index from the possible effect of decreased RR in algorithm, a lower HU without significance ($P = 0.138$) was noted in FLE group when compared with controls. However, the concomitant decrease of parasympathetic regulation and heart rate interval is a known phenomenon in current physiology and the HF is still thought to represent parasympathetic index by most researchers.[11]

In this study, our results were limited by a relatively small sample size and lack of uniformity. Some patients were included who (1) were receiving CBZ which has been reported to affect autonomic regulation in epileptic patients[15] (2) suffered different seizure types arising from different locations within the frontal lobe. All of these factors could conceivably affect the results. In subgroup analyses of our patients, CBZ using group *vs.* non-CBZ using group or polytherapy group *vs.* monotherapy group did not have any significant between-group differences in sympathetic or parasympathetic indices. We might conduct more studies to clarify the confounding effects of AEDs on HRV of epileptic patients in the future.

GTC was the most common seizure type in our patients with FLE. Eighteen patients (72%) were reported with GTC but 6 of them (24%) suffered CPS with secondarily generalized tonic–clonic seizures. Three (12%) had GT and 1 (4%) of the patients had absence besides GTC. GTC is known as the seizure type most often found to cause autonomic dysregulation and increase risk of SUDEP.[2,13] The frontal lobe have extensive neural link[9] and the spread of seizure activities from frontal lobe foci[10] to other brain regions and autonomic centers can result in dysregulation of ANS. Which offers a possible explanation for both the higher incidence of GTC and impaired HRV in our patients.

HRV varies widely in healthy subjects,[11] possibly due to effects of circadian rhythms,[17] gender,[12] age,[12] weight[18] and body mass index.[19] In this study, all interictal heart rates were recorded during the daytime to avoid major circadian effects, and anthropometric factors known to affect HRV were excluded by careful selection of controls. Since there were no significant between-group differences in these circadian and anthropometric characteristics, we believe our study more accurately reflects the effect of frontal lobe epilepsy on HRV.

A 24-h ECG recording provides information on circadian changes of HRV in a patient and is considered to be a standard procedure. However, 5-min ECG recordings have the advantage that they can be performed repetitively in a ward, clinic, hospice, or even the patient's home to minimize the effects on ANS regulation resulting from the stress from the study itself. The digitized data file of a 5-min recording is relatively small and can even be transmitted over the Internet for a remote analysis. This technology is especially valuable in patients who are uncooperative or unwilling to undergo 24-h monitoring of ECG with analysis of HRV.[20] It is highly assessable and a positive result can suggest a further 24-h recording of ECG with analysis of circadian changes of HRV.

Conclusions

Our data indicate that patients with frontal lobe epilepsy have shorter interictal heart rate intervals and faster heart rates, which

we postulate might be due to lower parasympathetic or vagal regulation of autonomic cardiac activity. This suggests that the mechanism of decreased HRV in patients with FLE is probably different from that in patients with TLE. However, future work on autonomic regulation in a larger number of subjects with FLE may help elucidate the pathophysiological details for autonomic dysregulation in frontal lobe epilepsy.

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