Suppressed circadian heart rate dynamics in temporal lobe epilepsy

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Objectives: To measure interictal circadian rhythm of heart rate (HR) variability in patients with temporal lobe epilepsy (TLE) using a 24 hour ECG recording.

Methods: Various conventional and dynamic fractal measures of HR variability were analysed in 17 patients with refractory TLE, 20 patients with well controlled TLE, and 37 healthy age and sex matched control subjects.

Results: The SD of all RR intervals ($p < 0.01$), the measured power spectral components of HR variability (low frequency power ($p < 0.01$), high frequency power ($p < 0.05$)), and the SD₁ ($p < 0.05$) and SD₂ ($p < 0.01$) Poincaré two dimensional vector analysis measurements were suppressed in the patients. This suppression was observed during both day and night time; however, it was more pronounced at night, and nocturnal increase in HR variability usually seen in the normal population could not be detected in the patients. The HR variability measures did not correlate with the duration of epilepsy, the age of the patients, or with the anti-epileptic drugs used.

Conclusion: TLE was associated with reduced HR variability, which was more pronounced during night than day, and the nocturnal increase in HR variability was abolished in patients with TLE. The alteration in autonomic regulation of HR variability was similar in patients with both refractory and well controlled TLE.

Epileptic seizures may be associated with autonomic dysregulation manifesting, for example, as blood pressure (BP) and heart rate (HR) changes.^{1–2} Moreover, there is increasing evidence of inter-ictal autonomic nervous system dysfunction in patients with temporal lobe epilepsy (TLE).^{3–7} An association of the occurrence of autonomic dysfunction with life threatening arrhythmias in patients with epilepsy and even with sudden unexpected death in epilepsy (SUDEP) has been suggested,^{8–9} but the clinical significance of autonomic dysfunction in patients with epilepsy is still poorly outlined.

SUDEP is a widely recognised phenomenon, but its basic mechanism remains unclear. Previous studies have defined a number of risk factors that are associated with SUDEP,^{3–10–11} but otherwise healthy, compliant patients may also die unexpectedly.^{12–13} Hypoventilation and cardiac changes occurring during or immediately after a seizure have also been connected with SUDEP.^{14–15} Furthermore, some studies imply that SUDEP usually occurs during sleep,^{16–17} suggesting that circadian rhythms may contribute to its pathogenesis.

Circadian rhythms are endogenously mediated 24 hour cycles of behavioural or physiological activity, but the interactions that occur between the mammalian circadian clock, acute seizures, and chronic epilepsy have so far not been characterised. Earlier studies observed a decreased circadian HR fluctuation in several cardiovascular and neurological diseases,^{18–22} and after an acute myocardial infarct it seems to be related to lethal cardiac arrhythmic events.²³ The circadian rhythms of autonomic cardiovascular functions have not been previously evaluated in TLE, although it is known that patients with epilepsy often have nocturnal seizures.

The hypothesis of the present study was that HR variability is lower in patients with TLE during the night than during the day, reflecting a suppression of circadian dynamics. This study was designed to assess the circadian rhythm of HR variability in patients with TLE using a 24 hour ECG recording.

MATERIALS AND METHODS

Patients and controls

This was a post hoc re-analysis of data from a previously published study.²⁴ Seven patients were excluded from the re-analysis owing to technical problems. The study was carried out in the Department of Neurology, University Hospital of Oulu, Finland, with the approval of the local ethics committee. All the patients and control subjects gave their informed consent before their inclusion in the study.

There were 37 TLE patients, who had been seen in the outpatient clinic, included in the study. The study group consisted of 17 patients with refractory TLE who continued to have seizures (mean (SD) seizures/month 20.3 (38.2)), despite the appropriate use of anti-epileptic drugs (AEDs), and who were not suitable candidates for epilepsy surgery or other newer epilepsy therapies. Of the 20 patients with well controlled TLE, 16 had become seizure free after starting AED treatment, and four had fewer than two seizures per year. Patients with any other disease (such as diabetes mellitus, alcoholism, or cardiopulmonary disease), manifestations of other central or peripheral nervous system disorders, or medication (other than AEDs) known to affect the autonomic nervous system were excluded from the study. Women who were pregnant or lactating were also excluded. Various cerebral lesions are known to decrease HR variability, therefore, to exclude symptomatic epilepsy, magnetic resonance imaging of the brain was performed on all the patients, except three patients with well controlled TLE who suffered from claustrophobia, on whom computed tomography of the brain was performed. Three patients had left hippocampal sclerosis, and two had right hippocampal sclerosis. All the other patients had normal imaging of the brain. The excluded

Abbreviations: AED, anti-epileptic drug; ApEn, approximate entropy; BP, blood pressure; HF, high frequency; HR, heart rate; LF, low frequency; SUDEP, sudden unexpected death in epilepsy; TLE, temporal lobe epilepsy; VLF, very low frequency

patients were more often men than women and, as a result, the present study included more women than men.

Patients were carefully interviewed and clinically examined. Their epilepsy and seizure types were classified according to the recommendations of the International League Against Epilepsy.^{25–26} All patients had TLE. Thirteen patients with refractory and 16 with well controlled TLE had secondarily generalised seizures. Three patients with refractory and two patients with well controlled TLE had complex partial seizures, while one with refractory and two with well controlled TLE had simple partial seizures.

Results of laboratory tests (liver and renal functions, serum electrolytes, and basic haematological indices) were normal. Serum AED levels within the therapeutic range in all patients. Blood samples for the laboratory tests were taken in the morning before the 24 hour ECG recording.

An interictal EEG recording was obtained from all the patients. Normal EEG or general slowing was seen in 15 patients. Left temporal focal slow waves, or irritation, or both were detected in 15 patients, and right temporal focal abnormalities were seen in seven.

The control group consisted of 37 healthy age and sex matched subjects selected from healthy individuals participating in a study comparing the characteristics of hypertensive and normotensive subjects, who were randomly selected by personal social security codes from the general population of the local community. All were carefully examined and had no medication or other disease affecting the autonomic nervous system in their medical history. The demographic data of the patients and controls are given in table 1.

Methods

A two channel, 24 hour ambulatory ECG recording (Del Mar CardioCorder, model 456A; Del Mar Medical, Irvine, CA, USA) was performed once on all the patients and controls. During recording, patients and controls were allowed to perform their daily activities. They also kept a diary to document seizures and abnormal events during the recording.

The ECG data was sampled digitally and transferred from an Oxford Medilog scanner (Oxford Instruments, Oxford, UK) to a microcomputer for analysis of HR variability. All the RR interval time series were first edited automatically, then careful manual editing was performed by visual inspection of

the RR intervals. For detecting artefacts and premature beats, and deleting the filling gaps, each RR interval time series was passed through a filter using previously described methods.²⁷

In the final analysis, the 24 hour HR variability data was divided into segments of 3600 seconds, and only segments with over 85% sinus beats were included in the analysis. The mean values of the night hours (from 1200 to 0600) and the day hours (from 0900 to 2100) were calculated. The mean duration of all RR intervals and the standard deviation of all the RR intervals (SDNN) were computed as time domain measures. The SDNN primarily reflects a low fluctuation in HR behaviour, possibly reflecting peripheral vascular resistance and thermoregulation.²⁸

An autoregressive model was used to estimate the power spectrum densities of HR variability.²⁹ Linear trends were abolished from the RR interval data segments of 512 samples to make the data more stationary. The power spectra were quantified by measuring the area in three frequency bands: 0.005–0.04 Hz (very low frequency; VLF), 0.04–0.15 Hz (low frequency; LF) and 0.15–0.4 Hz (high frequency; HF). The VLF component was excluded from the circadian analysis because its spectral analysis requires a minimum of 12–16 hours of HR data.³⁰ The HF fluctuation of the RR interval mainly reflects the cardiovagal modulation and the inspiratory inhibition of vagal tone, whereas the LF band is thought to reflect sympathetic excitation,³¹ sympathovagal balance,³² and arterial pressure oscillations.³³

In addition to spectral analysis, the SD of continuous long term RR interval variability (SD₂) and the instantaneous beat to beat RR interval variability (SD₁) were assessed using quantitative two dimensional vector analysis (Poincaré).^{34–35} SD₁ describes the magnitude of the beat to beat variability reflecting vagal modulation of the HR variability and has a relatively strong correlation with the HF spectral component, and SD₂ describes the long term RR interval fluctuation and reflects the magnitude of the LF spectral component. One advantage of the Poincaré method over spectral analysis techniques is that it is not sensitive to stationary irregularities and trends in RR intervals, therefore being more suitable for HR variability analyses using ambulatory ECG recordings.³⁵

Approximate entropy (ApEn) and fractal correlation were used to measure non-linear HR variability. ApEn is a measure that quantifies the regularity of time series data.²⁷ It measures the logarithmic likelihood that runs of patterns (beat to beat difference of RR interval length) are close in the next incremental comparisons. A time series containing many repetitive patterns has a relatively small ApEn, whereas more random data produce higher ApEn values.

The detrended fluctuation analysis technique was used to quantify the fractal correlation properties of HR. The fractal property was defined for the short term (<11 beats, α) correlation of RR interval data (short term scaling exponents).³⁶ Night to day ratios were calculated for the time domain, frequency domain, and fractal measures of HR variability by dividing the night by the day values.

Statistical analysis

The data were analysed using the SPSS software (version 10.0; SPSS Inc. Chicago, IL, USA). Statistical analysis was performed using the Mann-Whitney two sample test to compare the values of the controls and those of the patients, and to compare the day and night values. Spearman's correlation coefficients were used to estimate the correlation of the HR variability during night and day with the duration of TLE and the age of the patients. In all cases $p < 0.05$ was considered significant. The Mann-Whitney two sample test was used to analyse the association of HR variability with the laterality of the seizure focus.

Table 1 Demographics of the study patients and controls			
Variable	Patients with TLE		Controls (n = 37)
	Refractory (n = 17)	Well controlled (n = 20)	
Age (years, mean (SD))	32.1 (7.2)	32.2 (6.6)	32.2 (8.3)
Men/women	4/13	9/11	13/24
Duration of TLE (years, mean (SD))	22.7 (10.0)	14.2 (10.1)	–
Seizure characteristics			
Seizure free (no. of patients)	–	11	–
Seizure per month (mean (SD))	20.3 (38.2)	0.03 (0.07)	–
Antiepileptic medication			
Monotherapy			
Carbamazepine	–	10	–
Oxcarbazepine	4	7	–
Phenytoin	–	1	–
Lamotrigine	–	1	–
Polytherapy			
CBZ with other AED(s)	7	1	–
OXC with other AED(s)	6	–	–

AED, anti-epileptic drug; CBZ, carbamazepine; OXC, oxcarbazepine.

RESULTS

The mean values for the various measures of HR variability for the 24 hour ECG recordings of the patients with refractory and well controlled TLE and the controls are presented in table 2. The night and day values are presented separately. During the night, the SDNN ($p = 0.001$), the spectral components LF ($p = 0.001$) and HF ($p = 0.004$), the SD_1 ($p = 0.001$) and SD_2 ($p = 0.001$) Poincaré components and the short term fractal property component α ($p = 0.01$) of the patients were significantly lower than those of the controls (table 2). Similarly, during the day, SDNN ($p = 0.001$), the spectral components LF ($p = 0.001$) and HF ($p = 0.036$) and the SD_1 ($p = 0.022$) and SD_2 ($p = 0.001$) Poincaré components were decreased in the patients compared with the controls. ApEn showed no differences in any group during either the night or day. The mean RR interval value showed no difference between study groups.

The SDNN, the spectral components LF and HF, and the SD_1 and SD_2 Poincaré components were lower ($p < 0.05$) in the well controlled and refractory patients with TLE than in the controls when compared separately. There were no differences in any HR variability measurements ($p > 0.05$), apart from ApEn in the night ($p = 0.026$), between the patients with refractory and those with well controlled TLE when compared with each other.

Fig 1 shows the suppression of the circadian fluctuation of the HF and LF spectral components in TLE patients compared with the healthy controls. The LF value of the patients was decreased throughout the 24 hour recording time. Similarly, the HF value was significantly lower in the patients than in the controls during the day, but the difference was more pronounced during the night. The nocturnal increase in HF and LF spectral components that was seen in the controls could not be detected in the patients.

The mean night to day ratios of the SDNN (fig 2), SD_1 , and SD_2 Poincaré components were lower in the patients (median, interquartile range: SDNN 0.80, 0.68 to 1.07, $p = 0.014$; SD_1 1.16, 0.98 to 1.44, $p = 0.030$; SD_2 0.78, 0.62 to 0.92, $p = 0.007$) than in the controls (SDNN 1.07, 0.90 to 1.17; SD_1 1.48, 1.07 to 1.70; SD_2 0.98, 0.74 to 0.97). There were no differences in the mean night to day ratios in the spectral components LF and HF, ApEn, and the short term

Figure 1 The 24 hour circadian fluctuation of low-frequency (A) and high frequency (B) components of HR variability (medians) in patients with TLE (circles) and in healthy controls (squares). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for comparison between patients and controls, Mann-Whitney two sample test.

fractal property component α ($p > 0.05$) between patients and controls. Furthermore, none of the night to day ratios of the HR variability measures were different between the patients with refractory and those with well controlled TLE ($p > 0.05$).

None of the patients or controls had cardiac arrhythmias or other clinically significant ECG abnormalities during the recording. Six of the patients with refractory TLE reported having a partial seizure during the 24 hour ECG recording. Analysis of HR variability of these patients showed no

Table 2 The night time and daytime values for the time domain, frequency domain, and fractal measures of HR variability in patients with temporal lobe epilepsy and in the controls

	Night				Day			
	Patients with TLE				Patients with TLE			
Patients with TLE	Refractory (n = 17)	Well controlled (n = 20)	All patients (n = 37)	Controls (n = 37)	Refractory (n = 17)	Well controlled (n = 20)	All patients (n = 37)	Controls (n = 37)
RR interval (ms)	1000 (926 to 1072)	976 (893 to 1127)	987 (909 to 1073)	1006 (935 to 1133)	764 (700 to 857)	780 (732 to 847)	778 (714 to 847)	793 (716 to 836)
SDNN (ms)	63 (59 to 90)†	75 (66 to 87)†	71 (61 to 87)†	110 (82 to 142)	81 (72 to 99)†	86 (72 to 111)*	82 (73 to 100)†	105 (92 to 129)
LF (ms × ms)	559 (432 to 1000)‡	977 (606 to 1363)†	749 (528 to 1149)‡	2378 (1235 to 3196)	668 (542 to 985)†	1043 (697 to 1325)*	810 (584 to 1236)‡	1544 (959 to 2202)
HF (ms × ms)	474 (301 to 1238)*	716 (346 to 944)*	524 (328 to 1008)†	1292 (627 to 3000)	265 (175 to 530)*	373 (258 to 774)	336 (204 to 587)*	527 (227 to 1324)
SD_1	26 (20 to 40)*	32 (23 to 34)†	30 (21 to 35)†	41 (31 to 68)	20 (19 to 30)*	25 (23 to 34)	24 (20 to 31)*	31 (21 to 48)
SD_2	86 (80 to 121)‡	105 (79 to 117)†	95 (80 to 118)‡	145 (112 to 183)	109 (100 to 134)†	120 (104 to 148)*	119 (104 to 135)†	143 (126 to 176)
α	1.04 (0.86 to 1.23)	0.90 (0.73 to 1.18)	0.99 (0.81 to 1.19)†	1.03 (0.83 to 1.21)	1.26 (1.17 to 1.31)	1.23 (1.16 to 1.36)	1.26 (1.17 to 1.32)	1.25 (1.08 to 1.39)
ApEn	1.39 (1.27 to 1.50)	1.26 (1.11 to 1.38)	1.31 (1.16 to 1.45)	1.29 (1.12 to 1.47)	1.10 (1.03 to 1.20)	1.16 (1.08 to 1.25)	1.13 (1.06 to 1.22)	1.13 (0.97 to 1.25)

Night = 0000–0600; day = 0900–2100. SDNN, SD of all RR intervals; LF, low frequency; HF, high frequency; SD_1 , beat to beat variability measure from Poincaré; SD_2 , long term variability measure from Poincaré; α , short term fractal correlation parameter; ApEn, approximate entropy. Values are presented as medians (interquartile range). † $p < 0.05$, ‡ $p < 0.01$, ‡ $p < 0.001$ compared with controls, Mann-Whitney U test.

Figure 2 The graph shows the night to day ratio of the SD of all RR intervals (SDNN) in patients with temporal lobe epilepsy ($n=37$; $p<0.05$) and in healthy controls ($n=37$). Values are presented as medians (the horizontal bar) with the interquartile range (end of the boxes). Vertical capped bars show the minimum and the maximum values. Filled circles present the range of the outliers.

differences compared with the analysis of HR variability of patients without seizures.

Altered circadian HR variability during the night or day did not correlate significantly with the duration of TLE, the AEDs used, or the age of the patients. There was also no correlation with altered circadian HR variability and the side of the seizure focus ($p>0.05$).

DISCUSSION

HR variability was decreased, and physiological circadian fluctuation almost abolished, in patients with TLE. In particular, the LF and HF power spectral components and the SD_1 and SD_2 measures of Poincaré analysis were lower in the patients than in the healthy controls. The altered rhythm of circadian HR variability did not correlate with the duration of TLE or the age of the patients.

Previous studies have reported diminished interictal HR variability in TLE patients using conventional short and long term ECG recordings,^{3–7} but the clinical significance of the findings has remained unclear. The findings of the previous analysis of HR variability in the present patients suggest that in TLE, diminished HR variability is due to the epileptic process itself, rather than to any specific AED regimen,²⁴ but contrary reports have been published.^{3, 10} There are no previous reports focusing on the circadian rhythm of HR variability in epilepsy. In the present study, the decreased circadian HR variability did not correlate with the duration of TLE or the age of the patients, nor was it associated with any specific AED regimen. However, all patients were taking AEDs that block voltage dependent sodium channels, and, therefore, it was difficult to assess the effects of different types of AEDs on cardiovascular autonomic regulation. Moreover, the changes were seen in both patients with refractory and those with well controlled TLE. Therefore it seems that cardiovascular dysregulation is associated with TLE itself regardless of its duration or severity.

In general, low HR variability is often associated with sudden arrhythmic death,^{37, 38} but recent studies have suggested that low HR variability also predicts non-arrhythmic cardiac events.^{39, 40} However, different study designs and patient populations make it difficult to compare the results of the different studies. Reduction of circadian HR fluctuation has been reported in various cardiovascular and neurological diseases, including stroke,¹⁸ diabetes mellitus,¹⁹ coronary artery disease,²⁰ hypertension,²¹ and recently Parkinson's disease.²² After an acute myocardial infarct, suppressed circadian fluctuation seems to be related to lethal arrhythmic

events.²³ In a recent study, abnormal long term HR dynamics predicted post-stroke mortality.⁴¹ Furthermore, a previous study with a random sample of 325 subjects followed up for 10 years showed that an altered short term fractal scaling exponent of HR dynamics indicated an increased risk for cardiac mortality, particularly sudden cardiac death.⁴²

Circadian rhythms are endogenously mediated biological rhythms with a cyclic period of about 24 hours. The suprachiasmatic nucleus of the hypothalamus is thought to be the major component of the mammalian circadian timing system controlling the circadian changes.⁴³ The insular cortex, on the other hand, is considered to be the most important cortical area controlling the cardiovascular regulation and has wide connections to other cortical and subcortical cardiovascular autonomic controlling centres.^{44, 45} In TLE, seizures arise from the mesial temporal structures—that is, the amygdala and hippocampus, or neocortical regions, and damage in those areas may result in abnormalities manifested by the attenuation of circadian rhythms. The design of the present study did not allow the drawing of any conclusion about the possible association of damage to specific temporal lobe structures with the observed changes in autonomic cardiovascular control.

SUDEP is more common in refractory epilepsy, but otherwise healthy, compliant patients may also die unexpectedly.^{12, 13} Moreover, SUDEP has been noted to be prevalent both in idiopathic generalised epilepsy and in TLE. We included both refractory and well controlled patients in the present study. However, only TLE patients were included to make the study population more homogenous and to allow a meaningful comparison between the patients with epilepsy and the controls.

A large body of data has defined different risk factors for SUDEP, including low AED serum concentration, a high number of AEDs taken concomitantly, male sex, a long duration of epilepsy, and number of epileptic seizures per year,^{3, 10, 11, 17} but its basic mechanism is not yet understood. Some studies have suggested that SUDEP is caused by cardiovascular autonomic dysfunction, which exposes the patient to arrhythmias, sinus arrest, and neurogenic pulmonary oedema.^{9, 46, 47} Abnormalities of nocturnal HR variability are particularly interesting, because SUDEP has been observed to occur usually during sleep.^{11, 13, 16, 17} Previous studies suggest^{20, 48} that suppressed nocturnal vagal activity is an unfavourable phenomenon, particularly in coronary artery disease, leading to unopposed sympathetic activity and an imbalance between the sympathetic and parasympathetic cardiovascular autonomic regulatory systems.

Interestingly, the present study showed that suppression of HR variability in TLE is most pronounced at night, suggesting a night time parasympathetic dysfunction for patients with epilepsy. None of the above risk factors was associated with significant difference in HR variability in this study. This suggests that impaired circadian HR variability is one of the risk factors for, but not the direct cause of SUDEP. Consistent with this, a recent study suggested that nocturnal suppression of HR variability in patients with epilepsy may contribute to the risk of SUDEP during the night.⁴⁹ The present observation that suppressed circadian HR variability was also present in patients with well controlled TLE is in accordance with the concept that healthy, compliant patients with epilepsy may also die unexpectedly. Additional prospective studies are needed to evaluate the association between SUDEP and the impaired circadian HR variability in TLE and in other types of epilepsies.

Earlier studies have suggested that carbamazepine may decrease HR variability.^{3, 6, 7, 10} Recently, it was demonstrated in a prospective study that carbamazepine may suppress both parasympathetic and sympathetic functions in newly

diagnosed epilepsy.⁵⁰ Interestingly, in that study the circadian HR fluctuation appeared to be already decreased before carbamazepine treatment, and after starting carbamazepine the HR variability suppression was more pronounced both in day time and night time. This suggests that epilepsy itself may be associated with circadian cardiovascular dysregulation. In the present study, we did not find any association between the AED medication used and the diminished circadian cardiovascular regulation. However, the number of patients in the present study was small, and all patients were taking voltage dependent sodium channel blocker with or without other AEDs. Therefore, the effect of different types of AEDs on suppressed circadian HR variability is difficult to assess in the present study.

In conclusion, TLE is associated with diminished HR variability. This diminution is more pronounced during the night than during the day, reflecting depressed physiological circadian HR fluctuation. In fact, the nocturnal increase in HR variability usually seen in the normal population could not be detected in patients with TLE. There were no differences in HR variability between patients with well controlled and those with refractory TLE. Therefore, the reduction in HR variability and in its circadian fluctuation seems to be associated with TLE itself, not with the duration or severity of the condition.

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