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Heart rate variability in patients with untreated epilepsy

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Summary

Background: Several studies have reported reduced heart rate variability (HRV) in patients with chronic epilepsy under treatment with antiepileptic drugs. This impairment in cardiac autonomic control might be of relevance in relation to the risk of sudden unexpected death in patients with chronic refractory epilepsy. Little information is, however, available on HRV in untreated patients with newly diagnosed epilepsy.
Methods: We used spectral analysis to assess HRV based on 24 h ambulatory EKG recordings in 22 consecutive untreated patients with epilepsy (15 with localization-related, 4 with generalized idiopathic and 3 with undetermined epilepsy). The HRV in these patients was compared with 22 age and sex matched healthy controls.
Results: When analysing the full 24 h recordings, there were no significant difference between the patients and the controls in any of the analyzed measures of HRV: standard deviation of RR-intervals ($P = 0.191$), total power ($P = 0.170$), very low frequency power ($P = 0.329$), low frequency power (LF) ($P = 0.161$), high frequency power (HF) ($P = 0.186$) and the LF/HF ratio ($P = 0.472$). The results were very similar for daytime and nighttime recordings.
Conclusion: Our results suggest that there is no major effect of epilepsy as such on HRV in patients with untreated epilepsy. It should be emphasized that this study assessed newly diagnosed patients and that the results may not be applicable to patients with chronic epilepsy.

Introduction

Impairment of autonomic cardiac control has been discussed as a possible contributing mechanism for sudden unexpected death in epilepsy (SUDEP).[1,2]

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Autonomic cardiac control can be assessed clinically by analysis of heart rate variability (HRV) based on EKG recordings.[3,4] HRV is of special interest in the context of SUDEP since a reduced HRV has been shown to predict mortality and more specifically sudden death in other conditions than epilepsy, e.g. congestive heart failure, diabetic neuropathy, after acute myocardial infarction and stroke[5–9] and is according to preliminary observations possibly also a marker for an increased risk of SUDEP.[10] Several studies have reported reduced HRV in patients with newly diagnosed epilepsy[11] or with chronic epilepsy under treatment with antiepileptic drugs.[12–16] These studies were, however, not designed to distinguish between the effects of epilepsy as such from those of the ongoing drug treatment.

The contribution of the epilepsy per se to the impaired autonomic cardiac control remains to be evaluated.[17,18] In particular data on HRV in untreated newly diagnosed epilepsy patients is scarce. To date there is only one published report comparing HRV in untreated epilepsy with normal controls. This study from Turkey reported increased sympathetic control of HRV in highly selected young patients with unspecified generalized tonic–clonic seizures compared with healthy controls,[19] but further studies of more representative and better characterized epilepsy patients are needed. The aim of this study was to investigate HRV in patients with untreated epilepsy and to assess the effect of epilepsy per se.

Patients and methods

Patients

Adult patients with newly diagnosed epilepsy attending the Department of Neurology at the Karolinska Hospital in Stockholm, Sweden, were eligible for inclusion in the study. Only patients without antiepileptic drugs (AEDs) were included. Patients with a history of heart failure, coronary heart disease, diabetes, uraemia or any other known disease that might affect the autonomic nervous system were excluded, as were patients with brain tumours and those for which immediate treatment with AEDs was considered necessary. Patients using medication known to affect the heart rate or blood pressure were excluded.

Controls

For each patient one healthy control subject was selected matched for age and sex. The controls were selected from a bank of previously recorded healthy volunteers.

Methods

The patients with epilepsy and their controls had an ambulatory 24 h digital EKG recording during which they were free to practice their normal daily activities. They were asked to keep a seizure-diary during the recordings.

QRS-complexes were classified by automatic analysis of the digitally recorded EKG signal. The consecutive RR-intervals and the corresponding classification code were exported to an ASCII text file. For the frequency domain analysis 5 min epochs of data were analysed by custom made software. The time series of RR-intervals were re-sampled at a frequency of two samples/s (2 Hz). Gaps in the time series due to non-normal RR-intervals (QRS-labelled by the Aspect System classification as noise or ectopic beats) were filled with values calculated by linear interpolation between the adjacent normal RR-intervals. The computer program checked for misclassified drop beats deviating more than three S.D.s from the mean normal RR-interval of each epoch. Epochs with more than 4% of non-normal RR-intervals were excluded from further analysis. At least 50% of a 24 h recording had to be analyzable for a tape to be included, in accordance with issued guidance.[4] All together a maximum of 288 epochs were thus analyzed per patient, representing both active and resting periods. The frequency domain of the time series of RR-intervals was analyzed with an auto regression method.[20] The mean RR-interval of each time series was subtracted and then detrended by applying linear regression. The power spectrum of the frequency domains was divided into four different frequency bands: total power (TP) 0.0033–0.40 Hz (ms^2); very low frequency power (VLF), 0.0033–0.04 Hz (ms^2); low frequency power (LF), 0.04–0.15 Hz (ms^2); high frequency power (HF), 0.15–0.40 Hz (ms^2). From the power, we calculated the LF/HF ratio as an index of the balance between sympathetic and parasympathetic influences on HR.[21] HF reflects respiratory sinus arrhythmia and is mainly related to parasympathetic activity.[21–23] LF oscillations are associated with baroreflexor control of sympathetic activity[21,22,24] but parasympathetic activity might also influence LF.[25]

In the time domain, the mean of the standard deviations of all normal RR-intervals for all 5 min segments of a 24 h EKG recording (SDRR) was calculated. All analyses were first made for the full 24 h period. Separate analyses were thereafter made for nighttime (00:00 a.m. to 05:00 a.m.) and daytime (07:30 a.m. to 09:30 p.m.), respectively.

A non-paired *t*-test was used to compare HRV data between patients and controls. Significance

was assumed for P-values < 0.05. Stata 7.0 software was used for data analysis (Stata Corporation, USA).

The study was approved by the institutional review board and all patients and healthy subjects gave their informed consent.

Results

We enrolled 24 consecutive adult patients with newly diagnosed epilepsy. Two patients with concomitant diseases known to affect the autonomic nervous system or a history of cardiac diseases were excluded. In total 22 patients (13 female/9 male) were thus included in the study. Patient characteristics are summarized in Table 1. The median age was 33 years (18—76), and the median time from their first seizure to enrolment in the study 27 months (2 days to 20 years). Fifteen of the patients had localization-related, four generalized idiopathic and three undetermined epilepsy.

Twenty-two patients with newly diagnosed epilepsy, without AED, and 22 healthy controls were thus examined. All patients had been seizure free at least 24 h before the EKG recording and none reported seizures during the recording. There was no significant difference in any of the HRV measures between the patients and their controls whether the whole 24 h registration periods were compared or nighttime and daytime recordings were analyzed separately (Table 2).

Table 1 Characteristics at the time of EKG recording of the 22 untreated patients with epilepsy

Patient no.	Sex/age (years)	Seizure types[a]	Epilepsy types[b]	Duration[c]	Neuroradiology	EEG
1	F/31	CPS	LC	4 y	Normal (MRI)	Normal
2	F/27	CPS	LC	3 y	Normal (MRI)	Epileptiform activity, bilateral
3	F/63	CPS	LS	3 y	Dural fistula left occipital lobe (CT)	Non-epileptiform abnormal activity, left frontotemporal
4	F/37	GTCS + SPS	LS	10 y	Normal (MRI)	Normal
5	M/72	CPS	LC	3 m	Normal (CT)	Non-epileptiform abnormal activity, left temporal
6	F/69	GTCS	U	1.5 m	Normal (CT)	Non-epileptiform abnormal activity, bilateral
7	M/76	CPS	LS	4 d	Hypodensity left temporal lobe (CT)	Non-epileptiform abnormal activity, left frontotemporal
8	M/27	GTCS + CPS	LC	5 y	Normal (MRI)	Epileptiform activity, left frontotemporal
9	M/32	GTCS + CPS	LS	10 y	Unspecific white object left (MRI)	Normal
10	M/34	GTCS	LS	2 d	Cavernoma right temporal lobe (MRI)	Non-epileptiform abnormal activity, left temporal
11	F/56	GTCS	LC	11 m	Normal (CT)	Normal
12	M/43	GTCS	LC	1 y	Normal (MRI)	Normal
13	F/72	GTCS	U	5 y	Normal (CT)	Normal
14	F/33	GTCS + SPS	LS	5 m	Hypodensity right occipital lobe (CT)	Epileptiform activity, right parietal
15	F/24	CPS	LC	5 y	Normal (MRI)	Normal
16	M/26	CPS	LS	1.5 y	Cavernoma of the left insula (MRI)	Non-epileptiform abnormal activity, bilateral
17	F/18	Absence	GI	4 y	Normal (MRI)	Epileptiform activity, bilateral
18	M/23	GTCS + Absence	GI	2 m	Normal (CT)	Not completed
19	F/32	GTCS + Myoclon	GI	6 m	Normal (CT)	Normal
20	F/37	GTCS	U	17 y	Normal (CT)	Normal
21	F/19	CPS	LC	7 m	Normal (MRI)	Non-epileptiform abnormal activity, left frontotemporal
22	M/33	GTCS	GI	20 y	Normal (MRI)	Epileptiform activity, bilateral

[a] GTCS: generalized tonic—clonic seizures, CPS: complex partial seizures, SPS: simple partial seizures.
[b] LS: localization-related symptomatic, LC: localization-related cryptogenic, GI: generalized idiopathic, U: undetermined.
[c] Time from first seizure of the patient to enrolment in study years/months/days.

Table 2 Heart rate variability in the 22 patients with untreated epilepsy vs. age and sex matched controls

	Age and sex matched controls, 24 h ($n = 22$)		Untreated with epilepsy vs. controls, 24 h ($n = 22$)			Age and sex matched controls, nighttime ($n = 22$)		Untreated with epilepsy vs. controls, nighttime ($n = 22$)			Age and sex matched controls, daytime ($n = 22$)		Untreated with epilepsy vs. controls, daytime ($n = 22$)		
	Mean	95% CI	Mean	95% CI	*P*-value	Mean	95% CI	Mean	95% CI	*P*-value	Mean	95% CI	Mean	95% CI	*P*-value
SDRR	76.8	62.1–91.7	65.0	53.8–76.2	0.19	78.3	62.7–93.9	66.9	53.6–80.1	0.25	73	59.2–86.8	62.5	51.8–73.3	0.22
TP	5083	2787–7378	3327	2073–4581	0.17	5667	3185–8150	4051	2349–5754	0.27	4252	2404–6100	2794	1692–3895	0.17
VLF	1491	1041–1940	1214	841–1586	0.33	1609	1099–2119	1358	942–1773	0.43	1290	887–1694	1079	704–1454	0.43
LF	2132	1112–3153	1326	740–1911	0.16	2160	1161–3159	1516	622–2409	0.32	1880	1096–2664	1193	686–1700	0.13
HF	1460	490–2429	787	411–1163	0.19	1899	778–3021	1178	577–1778	0.24	1082	190–1973	521	265–778	0.22
LF/HF	2.77	2.26–3.28	2.52	2.02–3.02	0.47	1.83	1.32–2.33	1.77	1.37–2.17	0.85	3.30	2.61–3.99	3.16	2.57–3.74	0.75

Analyses of the full 24 h period, nighttime (00:00 a.m. to 05:00 a.m.) and daytime (07:30 a.m. to 09:30 p.m.) (*t*-test). SDRR, standard deviation of RR-intervals (ms); TP, total power (ms^2); VLF, very low freq. power (ms^2); LF, low frequency power (ms^2); HF, high frequency power (ms^2); LF/HF, low frequency power/high frequency power.

Discussion

In this study on 22 patients with untreated epilepsy we could not demonstrate any statistically significant difference in any of the analysed parameters, SDRR, TP, VLF, LF, HF or LF/HF compared to age and sex matched healthy controls. We cannot exclude that the lack of significance was due to the small number of patients and limited statistical power (52% power for a difference in LF with a $P < 0.05$ level). It is also possible that the broad range of epilepsy and the heterogeneity of seizure types may have affected our results.

However, our patients reflect the normal spectrum of patients with adult epilepsy and they were well classified using seizure-semiology, EEG and neuroradiology.

A Turkish study has recently reported reduced HF, increased LF and consequently an increased LF/HF ratio in 42 young men (military recruits) with newly diagnosed generalized tonic–clonic seizures compared with healthy controls.[19] These patients, however, cannot be considered representative of new onset epilepsy in general. The mean frequency of generalized tonic–clonic seizures among these patients was 8 attacks/year for an average of 5.6 years before diagnosis. Consequently, they had suffered a high number of major seizures before they were included in the study. Furthermore, the study failed to classify the type of seizures, partial or generalized, and epilepsy, partly since the patients were not subjected to an EEG examination.

In our present study, we could not confirm the findings from the study of Evrengul et al.[19] In contrast, HRV measures in our patients with newly diagnosed epilepsy were not different in any respect from the results obtained in the age and sex matched healthy controls but the trends in our study suggests lower LF and LF/HF ratio rather than the opposite as in the study of Evrengul et al.[19]. In addition to dissimilarities in patient selection and characterization, there are methodological differences that can contribute to the divergent outcomes of the two studies. In order to qualify for inclusion in the Turkish study, patients had to stay in hospital until they had a seizure recorded on a video-surveillance in the hospital department. The patients had thus been hospitalized for 42 ± 11 (mean $\pm$ S.D.) days before the EKG recordings. Although it seems unlikely, it is unclear if the controls had been subjected to the same procedure. In our study, the procedures for assessment of HRV were the same for patients and controls, an ambulatory 24 h EKG recording.

In conclusion, we could not demonstrate any significant difference in HRV measures between our patients with untreated newly diagnosed

epilepsy and matched healthy controls. This observation needs to be interpreted with some caution because of the limited number of included patients and the non-significant apparent trend towards lower HRV measures among the patients (Table 2). Our results, however, suggest that there is no major effect of the epilepsy as such on HRV in patients with newly diagnosed epilepsy. It should be emphasized that this study assessed newly diagnosed patients and that the results may not be applicable to patients with chronic epilepsy. Further studies are needed to assess the effect of epilepsy per se in patients with untreated epilepsy; such a study should be performed on larger patient groups in patients with well classified epilepsy with age and sex matched healthy controls.

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References

1. Ryvlin P, Montavont A, Kahane P. Sudden unexpected death in epilepsy: from mechanisms to prevention. *Curr Opin Neurol* 2006;**19**(2):194—9.
2. Lathers CM, Schraeder PL. Autonomic dysfunction in epilepsy: characterization of autonomic cardiac neural discharge associated with pentylenetetrazol-induced epileptogenic activity. *Epilepsia* 1982;**23**(6):633—47.
3. Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. *Swiss Med Wkly* 2004;**134**(35—36):514—22.
4. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;**93**(5):1043—65.
5. Bigger Jr JT, Fleiss JL, Rolnitzky LM, Steinman RC. Stability over time of heart period variability in patients with previous myocardial infarction and ventricular arrhythmias. The CAPS and ESVEM investigators. *Am J Cardiol* 1992;**69**(8):718—23.
6. Binder T, Frey B, Porenta G, Heinz G, Wutte M, Kreiner G, et al. Prognostic value of heart rate variability in patients awaiting cardiac transplantation. *Pacing Clin Electrophysiol* 1992;**15**(11 Pt 2):2215—20.
7. Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987;**59**(4):256—62.
8. Takase B, Kurita A, Noritake M, Uehata A, Maruyama T, Nagayoshi H, et al. Heart rate variability in patients with diabetes mellitus, ischemic heart disease, and congestive heart failure. *J Electrocardiol* 1992;**25**(2):79—88.
9. Bigger Jr JT, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. *J Am Coll Cardiol* 1993;**21**(3):729—36.
10. Eppinger N, Shaumann R, Jokeit H, Buettner U, Kraemer G. Reduced heart rate variability (HRV) in victims of sudden death in epilepsy (SUDEP). *Epilepsia* 2004;**45**(Suppl. 3):p65.
11. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. *Epilepsy Res* 2003;**57**(1):69—75.
12. Frysinger RC, Engel J, Harper RM. Interictal heart rate patterns in partial seizure disorders. *Neurology* 1993;**43**(10):2136—9.
13. Massetani R, Strata G, Galli R, Gori S, Gneri C, Limbruno U, et al. Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability. *Epilepsia* 1997;**38**(3):363—9.
14. Isojarvi JI, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllyla VV. Interictal cardiovascular autonomic responses in patients with epilepsy. *Epilepsia* 1998;**39**(4):420—6.
15. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. *Epilepsy Res* 1998;**30**(1):77—83.
16. Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllyla VV, Isojarvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia* 2000;**41**(1):42—7.
17. Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllyla VV, Isojarvi JI. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2002;**72**(1):26—30.
18. Ansakorpi H, Korpelainen JT, Tanskanen P, Huikuri HV, Koivula A, Tolonen U, et al. Cardiovascular regulation and hippocampal sclerosis. *Epilepsia* 2004;**45**(8):933—9.
19. Evrengul H, Tanriverdi H, Dursunoglu D, Kaftan A, Kuru O, Unlu U, et al. Time and frequency domain analyses of heart rate variability in patients with epilepsy. *Epilepsy Res* 2005;**63**(2—3):131—9.
20. Burg J. Maximum entropy spectral analysis. *37th Meeting of the Society of Exploration Geophysicists*. 1967.
21. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;**213**(4504):220—2.
22. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;**248**(1 Pt 2):H151—3.
23. Katona PG, Jih F. Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. *J Appl Physiol* 1975;**39**(5):801—5.
24. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986;**59**(2):178—93.
25. Saul JP, Rea RF, Eckberg DL, Berger RD, Cohen RJ. Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *Am J Physiol* 1990;**258**(3 Pt 2):H713—21.