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SHORT COMMUNICATION

Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy?

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Summary Reduced heart rate variability (HRV) may predispose to sudden unexpected death in epilepsy (SUDEP). We ascertained whether HRV predicts SUDEP in chronic epilepsy using a case—control design and investigated parameters of inter-ictal HRV in 14 patients (7 had died from SUDEP). No HRV parameter was associated with SUDEP. Thus, although altered HRV might be involved in SUDEP, HRV parameters are not clear-cut predictors for SUDEP.

Introduction

Heart rate variability (HRV) is the beat-to-beat variability of successive heartbeats and is modulated by a balanced parasympathetic—sympathetic autonomic activity (Stein and Kleiger, 1999). Impaired HRV is known to be associated with an increased risk of sudden cardiac death in an apparently healthy population (Stein and Kleiger, 1999). Previous studies have demonstrated decreased HRV in chronic epilepsy patients and have suggested that this may play a role in the pathophysiology of SUDEP (Tomson et al., 1998; Ronkainen et al., 2005). Possible mechanisms include an impaired autonomic function with augmented sympathetic tone (Diehl et al., 1997; Hilz et al., 2002). We ascertained inter-ictal HRV in a matched-pair case—control design to identify a potential predictive role of HRV for SUDEP in medically refractory epilepsy patients.

Methods

Patients with medically refractory focal epilepsy who underwent standard pre-surgical assessment at the National Hospital for Neurology and Neurosurgery between 1996 and 2004 and who later died of SUDEP were included. Living medically refractory focal epilepsy patients were matched as controls for admission date of video-EEG telemetry, age and gender. At the last follow up all control patients were still alive. This assessment was part of a continuing mortal-

Abbreviations: AED, antiepileptic drug; FLE, frontal lobe epilepsy; HF, high frequency; HRV, heart rate variability; LF, low frequency; RMSSD, root mean square of successive differences; SD, standard deviation; SDNN, standard deviation of the RR intervals; SUDEP, sudden unexpected death in epilepsy; TLE, temporal lobe epilepsy; VLF, very low frequency.

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ity audit and was approved as such by the Joint Ethics Committee of NHNN and the Institute of Neurology. Video-EEG telemetry was performed using conventional scalp EEG recordings (10—20 system) or intracranial recordings (1 patient) at a sampling rate of 200 Hz. ECG was recorded from 2 channels with a modified lead I (adhesive electrodes placed below the clavicles of either side). Peri-ictal data of 12 patients (no. 1—12, Supplementary Online Material) were included in a previous project (Surges et al., in press). HRV was analysed blinded to the outcome in a 1-h interval (by C.H.) with an in-house written software using Matlab (The MathWorks, Natick, MA, USA). As HRV was previously shown to be different in chronic TLE and control patients with most important differences during night around 4 am and during the afternoon (Ronkainen et al., 2005), HRV was determined during 1-h intervals between 4—5 am and 4—5 pm of the last recording day. Occasional ECG artefacts were removed prior to analysis. RR intervals were determined semi-automatically using the first derivative of the voltage signal and resulting data were visually inspected to ensure accuracy of the algorithm. RR intervals, the standard deviation of the RR intervals (SDNN, in ms) and their root mean square of successive differences (RMSSD, in ms) were calculated. The power spectrum of the RR-interval time series was obtained by a fast Fourier transform after re-sampling (7200 samples). The cumulative power was determined in three frequency bands: very low frequency (VLF, 0.005—0.04 Hz), low frequency (LF, 0.04—0.15 Hz), and high frequency (HF, 0.15—0.4 Hz). LF is primarily a measure of sympathetic activity, whilst HF is primarily a measure of parasympathetic activity. Sympathovagal balance was estimated by calculating LF/HF ratio. Statistics were performed using conditional logistic regression analysis with STATA software (StataCorp LP, TX 77845, USA). *P*-Values < 0.05 were regarded as statistically significant. The inter-individual variability of HRV parameters is relatively large (Tomson et al., 1998; Ronkainen et al., 2005). Therefore, we assumed that a clear-cut clinical predictor for SUDEP should differ at least by two standard deviations (SD) of the means. Then, with an α of 0.05, we would require at least 6 people in each group to have a 90% chance of detecting this difference. Data values are expressed as mean ± SD.

Results

A total of 7 SUDEP and 7 living control patients were assessed (Table 1). Mean age/epilepsy duration were 34.0 ± 7.0 years/23.9 ± 6.8 years in controls and 35.0 ± 7.7 years/23.9 ± 7.5 years in SUDEP patients.

Most patients were on more than one antiepileptic drug (AED). AED treatment was reduced in 11 patients during telemetry, but re-instituted to usual doses at least 12—48 h prior to HRV assessment (supplementary table). No statistically significant differences were found in the studied HRV parameters (Table 2).

Table 1 Clinical characteristics.

Patient	Age/sex/epilepsy duration	Etiology/epilepsy
1/S	32/F/10	Left TLE with hippocampal sclerosis
2/C	29/F/22	Cryptogenic left FLE
3/S	33/F/25	Right TLE epilepsy with postischemic lesion
4/C	32/F/11	Right TLE with diffuse post-radiation and resection (medulloblastoma) defect
5/S	36/M/26	Left FLE with gangliocytoma/hamartoma
6/C	32/M/29	Left TLE with hippocampal sclerosis
7/S	21/M/19	Cryptogenic left FLE
8/C	25/M/20	Right TLE with hippocampal sclerosis
9/S	44/M/26	Right FLE with posttraumatic lesions
10/C	43/M/26	Cryptogenic left FLE
11/S	43/M/34	Left TLE with hippocampal sclerosis
12/C	44/M/30	Bilateral TLE with bilateral hippocampal sclerosis
13/S	36/F/27	Cryptogenic TLE (probably left)
14/C	33/F/29	Left TLE with dysembryoplastic neuroepithelial tumor

S, SUDEP patient; C, control patient.

Table 2 HRV parameters.

	RR (ms)	SDNN (ms)	RMSSD (ms)	Total power (ms^2)	VLF (ms^2)	LF (ms^2)	HF (ms^2)	LF/HF ratio
4—5 am								
Control	994 ± 153	70 ± 25	49 ± 26	3233 ± 1872	1545 ± 816	941 ± 513	747 ± 724	2.31 ± 1.46
SUDEP	936 ± 140	74 ± 40	51 ± 32	3846 ± 2596	1983 ± 1478	1277 ± 802	586 ± 507	2.71 ± 0.81
P-Value	0.51	0.83	0.92	0.67	0.59	0.44	0.66	0.50
4—5 pm								
Control	799 ± 137	59 ± 17	46 ± 23	2318 ± 1132	905 ± 421	913 ± 456	500 ± 449	2.78 ± 1.66
SUDEP	823 ± 71	67 ± 16	38 ± 12	2319 ± 1186	1245 ± 498	777 ± 595	297 ± 178	2.81 ± 1.17
P-Value	0.72	0.45	0.53	0.99	0.31	0.70	0.38	0.97

Mean ± SD.