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Bitemporal seizure spread and its effect on autonomic dysfunction

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ABSTRACT

Objective: Autonomic dysregulation is a possible pathomechanism of sudden unexpected death in epilepsy (SUDEP). Cardiac arrhythmias and autonomic symptoms are most commonly associated with seizures arising from the temporal lobes. The aim of this study was to investigate whether simultaneous seizure activity in both temporal lobes affects the autonomic nervous system differently from seizure activity in one temporal lobe as assessed by heart rate variability (HRV).
Methods: Electrocardiography (ECG) and intracranial electroencephalography (iEEG) data from 13 patients with refractory temporal lobe epilepsy who had seizures that propagated electrically from one temporal lobe to the other during video-EEG–ECG monitoring were retrospectively reviewed. The time domain, frequency domain, and nonlinear parameters of HRV were evaluated by analyzing 4-minute-long ECG epochs, sampling from baseline, preictal and postictal periods as well as epochs constituting unitemporal and bitemporal ictal activity.
Results: Heart rate was significantly higher during bitemporal ictal activity compared with all other time points. The time domain and nonlinear parameters of HRV were significantly decreased during bitemporal activity compared with baseline, and multiple components of HRV (standard deviation of RR intervals (SDNN), coefficient of variation (CV), root mean square of successive differences (RMSSD), and standard deviation of short-term variability (SD1)) were significantly lower during bitemporal activity compared with unitemporal activity. Frequency domain analysis showed no significant differences.
Conclusion: This study shows that bitemporal seizure activity significantly increases heart rate and decreases HRV, indicating increased autonomic imbalance with a shift towards sympathetic predominance, and this may increase the risk of SUDEP.

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1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is a fatal complication of epilepsy and is the most common cause of epilepsy-related death, accounting for between 7.5 and 17% of all epilepsy-related deaths [1] and up to 50% of all deaths in refractory epilepsy [2]. It is defined as the sudden and unexpected, nontraumatic, and nondrowning death of a person with epilepsy, without a toxicological or anatomical cause of death detected during the postmortem examination [3]. The event is typically unwitnessed, which makes determining the precise course of perimortem events difficult. This, in addition to the fact that by definition the postmortem examination does not reveal a cause of death, has made it difficult to ascertain specific risk factors and elucidate the pathophysiological mechanisms of SUDEP. Proposed theories include respiratory arrest, cerebral shutdown, and cardiac arrest, although these mechanisms are not necessarily mutually exclusive.

The cardiorespiratory system is tightly regulated by the autonomic nervous system, and normal autonomic homeostasis is maintained by balancing parasympathetic and sympathetic activity. Autonomic disturbances are frequently reported during seizures [4–6], and in the few case reports of patients who have suffered from SUDEP and where autonomic nervous activity has been measured, there are consistent findings of autonomic imbalance [6,7]. Overall, autonomic dysfunction and an imbalance between the parasympathetic and sympathetic nervous systems are likely to play a significant role in the production of electrocardiography (ECG) abnormalities and respiratory abnormalities seen during epileptic seizures and, thus, may play a substantial role in SUDEP [8].

Autonomic activity and autonomic dysfunction can be measured using heart rate variability (HRV). The continuous modulation of sympathetic and parasympathetic innervations results in variations in heart rate (HR), and HRV analysis assesses cardiac autonomic regulation through quantification of sinus rhythm variability [9]. A number of

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different studies have demonstrated that patients with chronic epilepsy have a reduced HRV and that seizures can further modulate the autonomic nervous system [10,11]. However, most of these studies have been performed in the interictal state, and the few periictal HRV studies have largely used scalp electrodes for the electroencephalography (EEG) recordings. In this study, data were collected from patients undergoing intracranial depth electrode presurgical evaluation, providing far greater temporal and spatial resolution in establishing the start and end of epileptiform activity compared with scalp electrodes.

The temporal lobes are important components of the central autonomic network [12], and seizures arising in the temporal lobes are most commonly associated with cardiac abnormalities [13]. Furthermore, seizures that spread bilaterally have been shown to increase the chance of a change in cardiac rhythm [14,15]. The aim of the current study was to test whether bitemporal ictal activity affects autonomic imbalance, assessed by HRV, in a way that is different from unitemporal ictal activity.

2. Methods

2.1. Patients

This was a retrospective study of ECG and intracranial EEG data collected during standard clinical procedures. The medical records of patients with epilepsy who had been admitted to the Telemetry Unit at the National Hospital for Neurology and Neurosurgery between February 1996 and April 2014 for intracranial depth electrode presurgical evaluation were reviewed. Inclusion criteria for the study were as follows: the patient must have had bitemporal depth electrode implantation, and they must have experienced a partial seizure that started in either the right or left temporal lobe and subsequently spread bitemporally. As this is a retrospective study, the bitemporal depth electrode implantation was not controlled, and the depth electrodes were positioned based on each patient's clinical indication. To allow reliable detection of temporal lobe seizures, only patients who had at least four 6-contact orthogonal depth electrodes implanted into both the right and left amygdala and the hippocampus were included. The most mesial depth electrode contacts detected epileptiform activity in the amygdala, hippocampus and parahippocampal gyrus while the more lateral contacts detected activity in the lateral neocortex. A table detailing the precise electrode placement protocol for each patient is shown in S1. Partial seizures with bitemporal ictal activity that subsequently developed into bilateral tonic–clonic seizures were excluded to reduce the effect of different seizure types on seizure-related modulations in HRV [16].

A total of 40 patients were identified as fitting the inclusion criteria; however, access to the data of 15 of the patients (between 2001 and 2007) was unavailable, and therefore, 25 patients (10 male, 15 female; mean age = 33 years, age range: 19–53 years) were selected for analysis.

2.2. Video-EEG–ECG monitoring

All patients were continuously monitored in the Telemetry Unit via the use of video-EEG–ECG recording systems (Nicolet Biomedical; Viasys Healthcare, Inc., Conshohocken, PA) allowing synchronous recordings of brain activity, heart activity, and clinical symptoms. There was no formal respiratory monitoring; however, upon video review, any obvious changes in respiratory pattern or signs of respiratory distress were documented. The 25 patients were monitored for a total of 4417.5 h (mean = 176.7 h, standard deviation (SD) = 73.9 h). A modified lead 1 ECG was used to generate simple ECG signals. All ECG data with a sampling rate of less than 200 Hz were excluded from the HRV analysis to ensure reliable results were obtained during the HRV analysis [9]. The patients were informed to push an event button if they felt a seizure warning, and clinical physiologists, specialist nurses, and doctors from the epilepsy department determined the exact timings of electroclinical seizure onset and offset.

2.3. Study design

Data from February 1996 to March 2000 were reviewed using EEG review v2.1, whereas the data from between September 2008 and April 2014 were reviewed using CareFusion NicVue v2.9.3. For each seizure, three 4-minute (240-s) ECG epochs were selected at the following time points: a baseline epoch beginning 3 h before seizure onset and at least 3 h after a previous seizure, a preictal epoch beginning 4 min before seizure onset, and a postictal epoch beginning immediately after seizure offset. The four-minute epoch duration was chosen in compliance with the recommendations that for frequency domain HRV analysis, the epoch duration should be approximately 10 times the wavelength of the lowest frequency band of interest, which in this case was the 0.04-Hz band of the low frequency component [9]. In addition, an ECG epoch constituting the full length of unitemporal seizure (UtS) activity and a separate ECG epoch constituting the entire bitemporal seizure activity were also selected for HRV analysis. Seizures were excluded if either the duration of the UtS activity or the bitemporal seizure activity was less than 30 s, thereby providing more reliable data for HRV analysis [17,18] (mean UtS duration = 68 s, SD = 35; mean bitemporal seizure duration = 79 s, SD = 24).

As the data used in this study were collected during standard clinical presurgical intracranial depth electrode evaluation, patient movement was not restricted leading to potential ECG artifacts. Therefore, seizures were excluded from the analysis if there were no artifact-free ECG epochs available, if there was a discontinuation of the recording for any reason, e.g., removal of electrodes during a seizure, or if the R-peak amplitude was too small to make reliable R peak detection possible.

2.4. HRV analysis

Each artifact-free ECG epoch was exported as a text file and subsequently analyzed using Kubios HRV version 2.1 (Tarvainen & Niskanen, Biosignal Analysis and Medical Imaging Group (BSAMIG), Department of Applied Physics, University of Eastern Finland, Kuopio, Finland).

The HRV analysis was divided into three broad categories; *time domain*, *frequency domain*, and *nonlinear analysis*. For the *time domain analysis*, the following parameters were calculated for all the exported ECG epochs: mean heart rate ($\overline{HR}$), standard deviation of RR intervals (SDNN), and the root mean square of successive differences (RMSSD). It has been suggested that differing HRs can affect SDNN [19]; therefore, in order to control for this potential bias and exclude the effect of HR on HRV, the coefficient of variation (CV) was analyzed, where CV = SDNN / RR and is expressed as a percentage.

For the *frequency domain analysis*, high-frequency (HF, 0.15–0.4 Hz) and low-frequency (LF, 0.04–0.15 Hz) band analysis was performed, and a ratio of LF/HF was also calculated. The HF band is thought to be of parasympathetic origin and is closely linked to respiratory sinus arrhythmia whereas the LF band is thought to represent both sympathetic and parasympathetic activity [9]. The frequency domain analysis was only calculated for the baseline, preictal, and postictal epochs because of the unreliable results that would be obtained from analyzing the ECG epochs from the unitemporal and bitemporal seizure states, which were unlikely to last for the necessary four-minute duration.

In addition to time domain and frequency domain analysis, *nonlinear analysis* of HRV was calculated and included standard deviation of both short-term RR interval variability (SD1) and long-term RR interval variability (SD2). Both approximate entropy (ApEn) and sample entropy (SampEn) were also calculated to complete the nonlinear measures for each ECG epoch.

2.5. Statistics

Statistical analysis was performed using IBM SPSS Statistics 21, and all graphs were drawn using GraphPad Prism 7. A significance

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