BRIEF COMMUNICATION

Heart rate variability analysis indicates preictal parasympathetic overdrive preceding seizure-induced cardiac dysrhythmias leading to sudden unexpected death in a patient with epilepsy

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Summary

Evidence for seizure-induced cardiac dysrhythmia leading to sudden unexpected death in epilepsy (SUDEP) has been elusive. We present a patient with focal cortical dysplasia who has had epilepsy for 19 years and was undergoing presurgical evaluation. The patient did not have any cardiologic antecedents. During long-term video–electroencephalography (EEG) monitoring, following a cluster of secondarily generalized tonic–clonic seizures (GTCS), the patient had prolonged postictal generalized EEG suppression, asystole, followed by arrhythmia, and the patient died despite cardiopulmonary resuscitation. Analysis of heart rate variability showed a marked increase in the parasympathetic activity during the period preceding the fatal seizures, compared with values measured 1 day and 7 months before, and also higher than the preictal values in a group of 10 patients with GTCS without SUDEP. The duration of the QTc interval was short (335–358 msec). This unfortunate case documented during video-EEG monitoring indicates that autonomic imbalance and seizure-induced cardiac dysrhythmias contribute to the pathomechanisms leading to SUDEP in patients at risk (short QT interval).

KEY WORDS: Heart rate variability, Short QT, Sudden unexpected death in epilepsy, Video-EEG.

Sudden unexpected death in epilepsy (SUDEP) refers to the death of a seemingly healthy patient with epilepsy, with or without evidence of a seizure.[1] Generalized tonic–clonic seizures (GTCS) constitute the major risk factor for SUDEP.[2]

The pathomechanism of SUDEP is not yet fully elucidated. The few reported cases of SUDEP occurring during video–electroencephalography (EEG) monitoring provide valuable information on the mechanisms leading to death. The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS) was a worldwide attempt to collect cases of SUDEP that have occurred during video-EEG monitoring.[3] Monitoring data available for 10 patients showed a consistent pattern with rapid breathing after secondary GTCS, followed within 3 min by fatal cardiorespiratory dysfunction. Although from a theoretical point of view, the most plausible mechanism seemed to be seizure-induced hypoventilation or cardiac dysrhythmia, so far most of the evidence lends support to the predominant role of central hypoventilation related to postictal generalized EEG suppression (PGES).[1,3–5]

Only two reported cases suggested that seizure-induced cardiac dysrhythmia could lead to SUDEP. However, in one of these cases the patient had a prior myocardial infarction

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and was having chest pain during the fatal cluster of seizures.[6] The other case was a near-SUDEP, with successful cardiopulmonary resuscitation (CPR) in a patient with seizure-induced ventricular fibrillation.[7]

Measures of heart rate variability (HRV) reflect sympathetic and parasympathetic activity. A meta-analysis of 39 studies that evaluated HRV in patients with epilepsy confirmed the hypothesis of sympathovagal imbalance in epilepsy, as shown by lower values of parasympathetic activity when compared to controls,[8] and it was suggested that this might play a role in the mechanism of SUDEP. However, a case-controlled study of seven patients who died from SUDEP and seven controls failed to show that altered HRV was involved in SUDEP.[9] Nevertheless HRV in the period immediately preceding SUDEP has not been investigated yet.

We describe herein a previously unreported patient who developed cardiac dysrhythmias following a cluster of GTCS during video-EEG monitoring and who died despite CPR. We analyzed the evolution of the HRV in this patient, including also the period immediately preceding the cluster of seizures leading to SUDEP, and we compared it with a group of patients with GTCS.

Methods

Case of SUDEP

A 25-year-old right-handed man with therapy-resistant focal epilepsy was undergoing presurgical evaluation. The patient had complex partial seizures rarely evolving to secondarily generalized convulsive seizures, since the age of 6 years. Magnetic resonance imaging (MRI; 3 Tesla [3T], according to the epilepsy surgery protocol) did not reveal any structural abnormality. Interictal EEG showed epileptiform discharges in the left frontotemporal region. The antiepileptic medication (oxcarbazepine, topiramate, and lacosamide) was slowly tapered under continuous surveillance, 1 week prior to admission to the epilepsy monitoring unit (EMU). The family history was negative for epilepsy and for sudden unexpected death. The patient was otherwise healthy and did not have any cardiologic antecedents.

In the EMU the patient had a cluster of two secondarily generalized tonic–clonic seizures, starting with tonic elevation of the right arm, version toward right side, followed by bilateral tonic and later clonic convulsions. The patient was in a supine position and there was no airway obstruction. Ten seconds before the clinical start, buildup of rhythmic ictal EEG activity (8–10 Hz) was observed in the left frontal-centrotemporal region. The first seizure lasted 70 s, and was followed by a PGES of 83 s. Ten minutes after termination of the first seizure, a second seizure started, with electroclinical features similar the first seizure. Before the start of the second seizure the patient regained consciousness. The duration of the second seizure was 79 s and the duration of the PGES (Data S1) was unusually long (174 s). Immediately after the seizure the patient became tachycardic (120–150 bpm) with premature ventricular complexes (PVCs) for 29 s (Data S2A), and then he became bradycardic (56–68 beats per minute [bpm]) for 32 s, with escape rhythm (Data S2B). This was followed by asystole for 9 s (Data S2C), 23 s bradycardic period with slow atrial fibrillation intermixed with PVCs (Data S2D), and by 28 s period of asystole/ventricular fibrillation (Data S2E). Respiratory arrest was noticed by the medical staff, and CPR was started immediately. Spontaneous breathing restarted along with electrocardiography (ECG), 34 s after CPR was started. However, the patient developed supraventricular tachycardia with 240 bpm (Data S2F) and was transferred to the intensive care unit. During transport the patient developed ventricular arrhythmia. The patient died despite advanced CPR. The autopsy found focal cortical dysplasia in the left temporal lobe, but it did not reveal a cause of death.

Patients with GTCS

Data from 11 GTCS from 10 consecutive patients (7 male; age 12–63 years, median 30.5 years) with at least 30 min preictal uninterrupted video-EEG and artifact-free ECG signal were analyzed. The clinical and demographic data are detailed in Data S3. One patient with idiopathic generalized epilepsy had primary GTCS; all other patients had secondarily GTCS. Eight patients were tapered off medication before the monitoring. At the last follow-up, all control patients were still alive. Postictal periods of 10 minutes with artifact-free ECG were available for nine GTCS from six patients.

Analysis of heart rate variability

ECG recordings were obtained using lead I with a 256 Hz sampling rate. A detailed description of the analysis method is presented in Data S4. Briefly, the following time-domain parameters were calculated: HR (heart rate), RMSSD (root mean square differences of successive RR intervals), SDNN (standard deviation of the RR intervals), NN50 (the number of pairs of successive beat-to-beat intervals that differ by >50 msec), and pNN (percent of NN50). Cardiac vagal index (CVI) and cardiac sympathetic index (CSI) were calculated using the geometric Lorenz-plot method[10] and the CVI/CSI ratio was determined. In addition, frequency-domain parameters were calculated: low frequency (LF) power (0.04–0.15 Hz), high frequency (HF) power (0.15–0.4 Hz), and LF/HF ratio.

Parasympathetic activity is expressed in RMSSD, pNN, CVI, and HF power, whereas the LF power is believed to be a mixture of sympathetic and parasympathetic activity.

HRV in the preictal (30 min) period of the first of the two consecutive GTCS was calculated for the case of SUDEP and compared with 30 min interictal periods of the patient,

1 day and 7 months before the SUDEP. In addition, the preictal and postictal HRV of the case of SUDEP was compared with the preictal and postictal HRV of the other patients with GTCS. We calculated the mean corrected QT interval (QTc) according to Fridericia's formula.[11]

Results

The case of SUDEP had longer PGES duration (174 s) than the other patients with GTCS (0–113 s; Data S3). The case of SUDEP had pronounced increase in the parasympathetic activity (HF power, RMSSD, CVI, CVI/CSI-ratio, pNN) from 7 months before to 1 day before SUDEP and an even further increase in the last 30-min period preceding the cluster of seizures leading to SUDEP (Fig. 1 and Data S5).

The case of SUDEP had higher preictal CVI/CSI ratio, HF power, and RMSSD than the other patients with GTCS (Fig. 2 and Data S6). The CVI/CSI ratio was 3.2 times higher than the median of the control seizures. The absolute HF power was 7 times higher than the median of the control seizures, 1.4 times higher than the control seizure with highest HF power (Fig. 2 and Data S5), and also higher than the previously published data.[9,12]

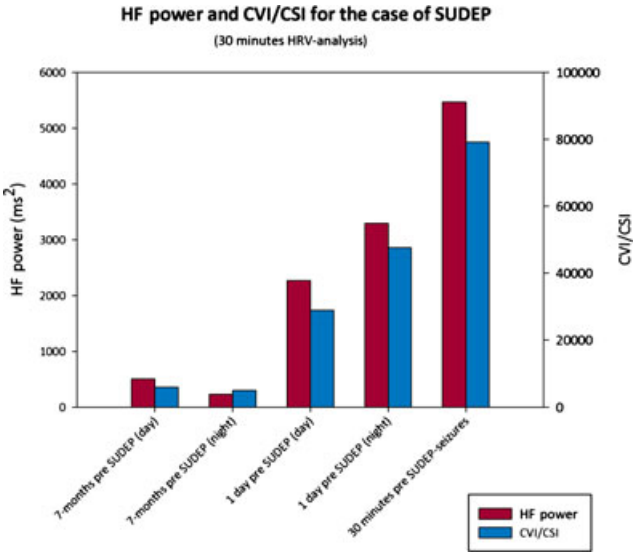

Figure 1.
High-frequency (HF) power and ratio between cardiac vagal index (CVI) and cardiac sympathetic index (CSI) for the SUDEP case during interictal periods of 30 min, 7 months before SUDEP (daytime and night), 1 day before SUDEP (daytime and night), and during the 30 min preictal period preceding the cluster of seizures leading to SUDEP.
Epilepsia © ILAE

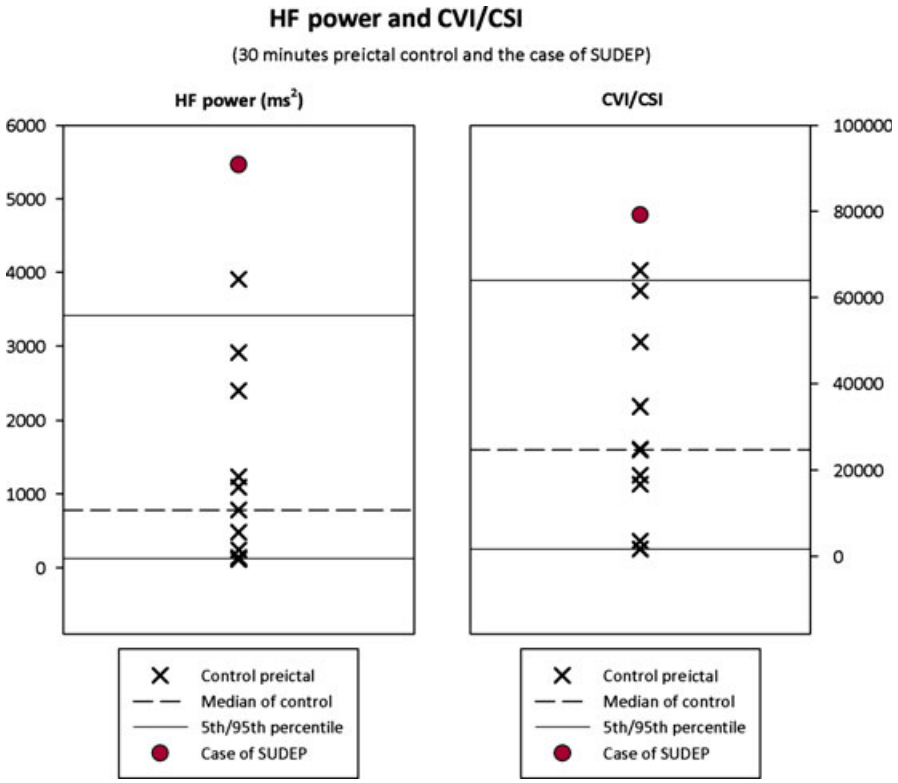

Figure 2.
High-frequency (HF) power and ratio between cardiac vagal index (CVI) and cardiac sympathetic index (CSI) in the 30 min preictal periods from the case of SUDEP and the other patients with GTCS.
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The other HRV parameters and the postictal analysis did not distinguish between the case of SUDEP and the other patients with GTCS. The corrected QT interval (QTc) of the case of SUDEP was between 335 and 358 msec (Data S7), which is shorter than the lower limit of normal (370 msec) and also shorter than the group of the other patients with GTCS (392–485 msec) (Data S3). Analysis of the ECG data showed that the case of SUDEP had long periods with supraventricular tachycardia, without any complaints, and unrelated to physical activity or seizure. The short QT syndrome can be associated with supraventricular tachyarrhythmias; therefore, this finding further supports that the patient could have had this syndrome.

Discussion

Tachyarrhythmias induced by seizures have been hypothesized to cause SUDEP, but compelling evidence has been lacking so far.[13] This patient died following a cluster of seizures in the EMU, and the history and findings suggest that autonomic imbalance and cardiac dysrhythmias are part of the pathomechanisms leading to SUDEP.

The patient had a short QT interval (also in the interictal period) and periods with supraventricular tachycardia, but in the absence of complaints, this case did not fulfill the criteria for short QT syndrome (had no cardiologic antecedents; family history was negative). Malignant tachyarrhythmias are facilitated by abnormal cardiac repolarization. Shortening of the QT interval is an indicator of abnormal cardiac repolarization, and it is an established risk factor for sudden cardiac death (SCD). The patient with SUDEP developed cardiac arrest but also supraventricular arrhythmias, which are common in short QT syndrome. Genetic defects in ion channels associated with SCD (*KCNH2* and *SCN5A*) have also been found associated with SUDEP.[14] This case of SUDEP suggests that short QT interval might be an additional risk factor for SUDEP, and advocates for measuring this before admitting patients to the EMU and before tapering the antiepileptic medication.

HRV analysis showed increased parasympathetic activity in the case of SUDEP, during the interictal periods, and further increases in the preictal period. The parasympathetic overdrive, in addition to the abnormal cardiac repolarization, probably contributed to pathogenesis of the cardiac dysrhythmias in the postictal period. It was hypothesized that the acute autonomic changes that may occur in "voodoo death" (also known as "scared-to-death" syndrome) including parasympathetic hyperactivity may also play a role in SUDEP.[15] This case of SUDEP occurred after a cluster of seizures. Therefore, it is possible that malignant dysrhythmia was triggered by the prolonged/repeated ictal activity. The magnitude of postictal sympathetic activation and parasympathetic suppression increases with duration of PGES.[16] However, in this case of SUDEP the postictal HRV changes did not distinguish between the SUDEP case and the controls.

To the best of our knowledge, this is the first publication on the periictal HRV analysis of a seizure leading to SUDEP. According to the recently proposed unified SUDEP definition and classification,[17] our case can be categorized as "SUDEP Plus," because of the short QT interval. Because only a few SUDEP cases could be analyzed in detail, one cannot precisely estimate the percentage of SUDEP cases in which a preexisting condition (vulnerability) could have contributed to the fatal outcome following an epileptic seizure.

In addition to providing further insight into the pathomechanism of SUDEP, these findings are possibly important for preventing SUDEP in selected patients at risk. Portable devices implementing an algorithm that detects parasympathetic hyperactivity could trigger an alarm during the preictal phase.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. EEG recording in the period immediately following the end of the second seizure.

Data S2. ECG during the period following the second seizure.

Data S3. Data on the control patients—with GTCS but without SUDEP.

Data S4. Heart rate variability methods and control seizure selection.

Data S5. Heart rate variability (HRV) data during preictal, postictal, and interictal period of SUDEP case and preictal and postictal period of the other patients with GTCS.

Data S6. Preictal RMSSD for the SUDEP case and the controls.

Data S7. Corrected QT intervals for the patient with SUDEP.