



Peri-Ictal Cardiac and Respiratory Disturbances in Epilepsy: Incidental Finding or Culprit of SUDEP?

Enhanced QT Shortening and Persistent Tachycardia After Generalized Seizures.

Surges R, Scott CA, Walker MC. *Neurology* 2010;74:421–426.

OBJECTIVE: Generalized tonic-clonic seizures (GTCS) are a major risk factor for sudden unexpected death in epilepsy (SUDEP). We investigated whether ictal/postictal cardiac features were dependent on seizure type within individual patients. **METHODS:** ECG data from patients with medically refractory temporal lobe epilepsy (TLE) undergoing pre-surgical investigation who had both complex partial seizures and secondarily GTCS during video-EEG telemetry were retrospectively reviewed. Peri-ictal heart rate (HR), corrected QT interval (QTc), HR variability, and cardiac rhythm were assessed. **RESULTS:** Twenty-five patients were included in this study. Secondarily GTCS led to higher ictal HR, persistent postictal tachycardia, and decreased postictal HR variability. Moreover, abnormal shortening of QTc occurred in 17 patients mainly during the early postictal phase and significantly more often in secondarily GTCS. Abnormal QTc prolongation occurred in 3 patients with no significant association with GTCS. Benign cardiac arrhythmias occurred in 14 patients and were independent of seizure type. **CONCLUSIONS:** Our data suggest a substantial disturbance of autonomic function following secondarily generalized tonic-clonic seizures (GTCS) in patients with medically refractory temporal lobe epilepsy. The observed alterations could potentially facilitate sudden cardiac death and might contribute to the association of sudden unexpected death in epilepsy with GTCS.

Lengthening of Corrected QT During Epileptic Seizures.

Brotherstone R, Blackhall B, McLellan A. *Epilepsia* 2010;51:221–232.

PURPOSE: To measure the corrected QT cardiac repolarization time before and during epileptic seizures. **METHODS:** Thirty-nine video-EEG/ECG/SAO₂ (electroencephalography/electrocardiography/oxygen saturation) telemetry patients were included in this prospective study. Epileptic seizures were identified both clinically and electrographically. RR intervals and associated QT intervals were measured 5 min prior to the onset of the identified seizure. Consecutive RR and associated QT intervals were then measured from the seizure onset until the seizure had ended and the EEG had resumed its pre-seizure trace. Averaged RR and QT intervals over nine consecutive beats were applied to Bazett's, Hodges's, Fridericia's, and Framingham's formulas to compare the corrected QT values before and during the seizures. **RESULTS:** A total of 156 seizures had corrected QT analysis performed. Nine generalized tonic-clonic seizures (5 patients), 34 absences (6 patients), 12 tonic seizures (6 patients), 27 temporal lobe seizures (14 patients), 58 frontal lobe seizures (4 patients), and 16 subclinical seizures (4 patients). All formulae reported a statistically significant difference in corrected QT ($p < 0.001$) during total seizure data compared to total pre-seizure values. According to Bazett's formula, 21 seizures (nine patients) transiently increased their corrected QT beyond normal limits, with a maximum corrected QT of 512 ms during a right temporal lobe seizure. **CONCLUSION:** Significant lengthening of corrected QT cardiac repolarization time occurred during some epileptic seizures in this study. Prolonged corrected QT may have a role in sudden unexplained death in epilepsy (SUDEP).

Ictal Hypoventilation Contributes to Cardiac Arrhythmia and SUDEP: Report on Two Deaths in Video-EEG-Monitored Patients.

Bateman LM, Spitz M, Seyal M. *Epilepsia* 2010;51:916–920. Sudden unexplained death in epilepsy (SUDEP) is a common cause of death in patients with epilepsy, with cardiorespiratory dysfunction and a primary cessation of cerebral function proposed as causes. We report two cases of SUDEP in patients with intractable temporal lobe epilepsy undergoing video-EEG (electroencephalography) telemetry at two centers. Both had secondarily generalized convulsions. EEG, electrocardiography (ECG), and respiratory changes in these two patients are reported herein. Ictal/postictal hypoventilation may contribute to SUDEP with the resulting hypoxemia and acidosis leading to failure of recovery of cortical function and eventual cardiac failure.



Commentary

Sudden unexpected death in epilepsy (SUDEP) is the most frequent cause of death in epilepsy. Its incidence has been found to range from 0.35 to 1 to 2 per 1,000 person-years in chronic epilepsy under adequate control and increases up to 3 to 9 per 1,000 person-years in treatment-resistant epilepsy (1). Although the actual causes are yet to be identified, multiple pathogenic mechanisms are believed to be operant in SUDEP, with cardiac and respiratory disturbances suspected to play a leading role.

Seizure-related disturbances of cardiac rate, rhythm, and conduction have been identified in patients with epilepsy (PWE), with ictal and postictal tachycardia being the most frequent (reported in more than 90% of seizures). Although the prevalence of cardiac abnormalities in population-based studies of PWE was found to be comparable (5.3%) to that of the general population (2), frequent cardiac abnormalities have been identified in patients with treatment-resistant epilepsy, and, in particular, they have been associated with generalized tonic-clonic (GTC) seizures and longer seizure duration (1). For example, in one prospective study of 51 PWE, one or more cardiac abnormalities were identified in 39%; in 14% they were considered to be severe, including atrial fibrillation, junctional escape rhythm, and ST-segment elevation (3). Although significantly less frequent, seizure-related bradycardia and asystole have been also identified with prevalence rates ranging from 0.27 to 0.4 percent in two large case series (4, 5).

Persistent heart rate elevation (HRE), abnormalities of cardiac repolarization, and decrease of heart-rate variability (HRV) have been associated with sudden death in *non-epilepsy* populations. In one of the studies selected for this commentary, Surges et al. found higher ictal HRE, persistent postictal tachycardia, decreased HRV, and abnormal repolarization demonstrated by abnormal shortening or prolongation of corrected QT (QTc) intervals in GTC seizures of 25 patients with treatment-resistant temporal lobe epilepsy (TLE). Changes of QTc intervals were investigated by Brotherstone et al. in a study of 39 patients also selected for this commentary, which revealed abnormal QTc prolongations in clinical and electrographic partial seizures of temporal lobe origin and in GTC seizures.

In studies of PWE whose death was attributed to SUDEP, an association was found with ictal HRE, but less conclusive data exist with respect to abnormal QTc prolongations. Indeed, in a retrospective study of 21 patients with refractory partial epilepsy who had undergone a video-EEG monitoring study and whose death was considered to have resulted from definite ($n = 6$) or probable ($n = 15$) SUDEP, the ictal maximal heart rate (HR) was significantly higher in seizures of these patients compared with those of a control group ($n = 43$) matched for type and severity of seizure disorder (mean: 149 beats/min vs 126 beats/min; $p < 0.001$) (6). Of note, greater increases in HR were associated with seizures arising from sleep than from wakefulness (78 beats/min increase vs 47 beats/min; $p < 0.001$) in SUDEP but not in the control group (52 beats/min vs 43 beats/min; $p = 0.27$). In this study, however, there was no significant difference in the frequency of ictal cardiac repolarization and rhythm abnormalities in SUDEP patients (56%) and controls (39%, $p = 0.39$). Unfortunately, changes in HRV were not investigated.

The association between abnormal QTc and SUDEP was investigated in another study of 11 patients with treatment-resistant epilepsy who later died of SUDEP (7). Mean QTc intervals were calculated for the period immediately preceding, concurrent with, and following interictal epileptiform discharges in study patients and 11 PWE matched for age, sex, and severity of seizure disorder. There was a significant prolongation of the mean QTc interval concurrent with epileptiform discharges in SUDEP patients only ($p = 0.02$). Yet, such QTc prolongation exceeded currently accepted upper limits in one case only and by a small margin.

Cardiac abnormalities may be facilitated or compounded by comorbidities that are frequent in PWE. For example, decreased HRV has been identified as a potential pathogenic mechanism mediating cardiac arrhythmias in patients with primary depressive and anxiety disorders (8). Furthermore, primary depressive disorders have been also associated with an increased risk of sudden death. Thus, whether comorbid depression and anxiety disorders play an additional role in SUDEP is a thought-provoking question that deserves further investigation.

As stated previously, seizure-related respiratory disturbances have been identified as the other set of variables playing a significant pathogenic role in SUDEP. In fact, it is possible that cardiac disturbances may contribute to a fatal outcome when coupled with seizure-related apnea or hypoventilation. This hypothesis is supported by a recent report of two patients that died of SUDEP while undergoing a video-EEG. These cases were reviewed in the third paper selected for this commentary. A documented ictal and postictal hypoxemia was complicated by acidosis in both patients, which led to bradyarrhythmias and ultimately recurrent periods of asystole in one. Furthermore, significant ictal and persistent postictal hypercarbia was documented in convulsive and nonconvulsive seizures in one-third of 33 patients with treatment-resistant partial epilepsy (9). Of note, clinically significant oxygen desaturation was recorded in one-third of seizures and was associated with longer seizure duration but surprisingly was not restricted to GTC seizures.

Based on these data, two questions need to be addressed: 1) Should seizure-related cardiac and respiratory variables be measured systematically in every patient undergoing a video-EEG? 2) Would such data lead to practical preventive measures or would they only cause unnecessary fear in patients and family members? Identification of seizure-related bradyarrhythmias or asystole is a potential benefit, as it might prompt the implant of a pacemaker. Yet, such benefit remains theoretical, as the value of implanting such a device was questioned in a study of patients who were implanted with a pacemaker after having been found to have an ictal asystole during video-EEG, as no recurrent asystole or bradycardia sufficient to trigger the pacemaker occurred during a mean follow-up period of 5 years (10). Also, identification of ictal hypoxemia may lead to the use of selective serotonin reuptake inhibitors, which in one open retrospective study appeared to lower the severity of ictal hypoxemia in complex partial but not in GTC seizures (11). Yet, these findings need to be replicated in double-blind placebo-controlled studies. On the other hand, no video-EEG should be conducted without continuous EKG and oxygen saturation monitoring.



Clearly, serious seizure-related cardiac and respiratory variables are identified in a significant number of patients with treatment-resistant epilepsy, but their real pathogenic role in SUDEP remains elusive. The only way to solve this complex problem is with a prospective, very large multicenter study sponsored by a governmental agency (e.g., National Institutes of Health) in which abnormalities of peri-ictal cardiac and respiratory variables recorded during video-EEG are compared between patients who go on to die of SUDEP and age- and sex-matched controls.

by *Andres M. Kanner, MD*

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