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Seizures and Cardiac Dysrhythmias: And the Beat (Sometimes) Goes On

Serious Cardiac Arrhythmias Detected by Subcutaneous Long-Term Cardiac Monitors in Patients With Drug-Resistant Epilepsy

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Background and Objectives: Epilepsy is associated with an increased risk of cardiovascular disease and premature mortality, including sudden unexpected death in epilepsy (SUDEP). Serious cardiac arrythmias might go undetected in routine epilepsy and cardiac investigations. Methods: This prospective cohort study aimed to detect cardiac arrhythmias in patients with chronic drug-resistant epilepsy ($\geq$5 years duration) using subcutaneous cardiac monitors for a minimum follow-up duration of 12 months. Participants with known cardiovascular disease or those with abnormal 12-lead ECGs were excluded. The device was programmed to automatically record episodes of tachycardia $\geq$140 beats per minute (bpm), bradycardia 40 bpm for $\geq$3 seconds, or asystole $\geq$3 seconds. Findings: Thirty-one patients underwent subcutaneous cardiac monitoring for a median recording duration of 2.2 years (range 0.5-4.2). During this time, 28 patients (90.3%) had episodes of sustained ($\geq$30 seconds) sinus tachycardia, 8/31 (25.8%) had sinus bradycardia, and 3 (9.7%) had asystole. Three patients (9.7%) had serious cardiac arrhythmias requiring additional cardiac interventions. Among them, 2 patients had prolonged sinus arrest and ventricular asystole ($>$6 seconds), leading to pacemaker insertion in one, and another patient with epileptic encephalopathy had multiple episodes of recurrent nonsustained polymorphic ventricular tachycardia and bundle branch conduction abnormalities. The time to first detection of a clinically significant cardiac arrhythmia ranged between 1.2 and 26.9 months following cardiac monitor insertion. Discussion: Implantable cardiac monitors detected a high incidence of clinically significant cardiac arrhythmias in patients with chronic drug-resistant epilepsy, which may contribute to the incidence of premature mortality, including SUDEP.

Commentary

Cardiac rhythm disturbances can coexist in patients with epilepsy due to a myriad of reasons which include comorbid cardiovascular disease, seizure-induced elevation of catecholamines following generalized seizures,[1] or in the setting of channelopathies that express the affected ion channel in both heart and brain.[2] These dysrhythmias can occur during an ictal event,[3] interictal state or postictally,[4] and have been postulated to increase the risk of sudden unexpected death in epilepsy (SUDEP). Video-EEG recordings of SUDEP cases indicate that postictal arrhythmias are highly specific markers of fatal seizures.[5]

The incidence of serious arrhythmias (bradycardic or asystolic events) in patients monitored in video-EEG units is reported to be 0.4%.[3,6] What about in the outpatient setting when patients are monitored with ambulatory electrocardiogram (ECG)? van der Lende et al[7] studied a group of 49 patients with drug-resistant epilepsy, half of which experienced generalized seizures, with an implantable loop recorder (ILR) capturing over 16 000 seizures and with ECG recordings made during 4679 seizures. Clinically relevant arrhythmias were defined as asystole ($\geq$6 seconds with syncope or $\geq$10 seconds regardless of symptoms), ventricular tachycardia ($\geq$180 beats per minute [bpm])/fibrillation or bradycardia [$\leq$40 bpm]). Patients with ictal systole (focal seizures with sudden flaccid falls), structural cardiac disease, abnormal baseline ECG, and use of beta-blockers were excluded from the study. The authors report no clinically relevant arrhythmias during a 2-year period of follow-up. Intriguingly, tilt table exams, performed in all patients prior to ILR, were positive in nearly 50% of the patients.

Similar results are reported by Serdyuk et al[8] in a cohort of 193 patients with drug-resistant epilepsy monitored with an ILR with a median follow-up of 36 months. Most of the patients had extratemporal epilepsy (74%) and were taking sodium channel modulators (72%). The incidence of ictal sinus tachycardia was 66.8% and of sinus bradycardia 6.7%; 2.6%

experienced SUDEP. Three patients required pacemaker implantation due to cardiac pauses of >6 seconds. The authors note a high rate of false-positive arrhythmia detection for auto-triggered events because of muscular artifacts during seizures, thereby compromising the device memory.

In the current study by Sivathamboo et al[9] report on the incidence of serious cardiac arrhythmias, defined as warranting additional cardiologist assessment or intervention, in a prospective observational study of 31 adult patients with refractory epilepsy. The primary endpoint was detection of serious arrhythmias, and the secondary endpoint was the time to the first detection of a serious event. The cohort consisted of a mixed group of adult patients (mean age of 41 years) with half of the group experiencing focal to bilateral tonic–clonic seizures. Two-thirds of the group had lesional focal epilepsy and 40% had temporal lobe ictal onsets. The majority (87%) were treated with anti-seizure medication polytherapy, including a sodium channel modulator in 90%. Patients with structural heart disease, a history or risk factors for cardiac conduction abnormalities or sleep apnea were excluded. Patients underwent monitoring via an ILR that was programmed to detect tachycardia (≥140 bpm), bradycardia (≤40 bpm), and asystole of ≥3 seconds. Patients and their caretakers were instructed to record events using the external activator and keep a seizure diary. An attempt to correlate an arrhythmia with seizure activity, either in the ictal or postictal state, was made but the authors acknowledge that ascertainment was not always reliable. ECG recordings were reviewed every 3 months by a cardiologist. Mean duration of follow-up was 2.2 year. A total of 3437 ECGs were reviewed.

Nonclinically significant cardiac conduction abnormalities were frequent (45%) and independent of seizures. In 90% of patients at least 1 type of arrhythmia was detected, the most common being sustained sinus tachycardia. Sinus bradycardia occurred in 8 patients, 7 with focal epilepsy, and independent of seizure activity. In 3 patients, this progressed to asystole. These were referred for subsequent cardiology management; one patient was found to have an episode of sinus bradycardia that progressed to >10 seconds with ventricular asystole and a syncopal event, 1 month after implantation; a permanent pacemaker was subsequently implanted. The second patient was found to have episodes of sinus arrest with ventricular asystole 26 months following device implantation for which he was referred for implantation of a pacemaker. In the third patient with severe epileptic encephalopathy, multiple types of cardiac episodes were captured including polymorphic ventricular and sinus tachycardia occurring in the pre-ictal or postictal states. The authors conclude that patients with chronic drug-resistant epilepsy exhibit a high incidence of clinically significant cardiac arrhythmias which may contribute to premature mortality.

Strengths of the study include the prospective design, long sampling duration, and inclusion of a mixed group of patients with different seizure types. Limitations include the lack of a control group, limited ILR memory storage space, low specificity for detection of arrhythmias due to seizure-related artifacts, and the unreliability of seizure diaries to help distinguish ictal from interictal arrhythmias.

Questions that are raised by these results include: Can the high incidence of cardiac conduction abnormalities be explained by the higher proportion of patients treated with sodium channel modulators? If so, does the risk differ among the subtypes of sodium channel modulators? What is the incidence in patients with less severe epilepsy; what about in those with poor treatment adherence? Does the laterality and/or location of the seizure focus influence the risk? What is the incidence with subclinical seizures? To answer the latter will require monitoring with an ILR and continuous EEG, including intracranial electrodes in patients with deep epileptogenic foci-conditions, steps that may be unrealistic in the context clinical research. Do we have reliable seizure detection wearables that can supplement seizure diaries? Large cohorts of patients will be required to answer these questions.

If the incidence of serious arrhythmias is indeed as high as reported by Sivathamboo et al,[9] should we recommend long-term monitoring with IRL for all patients with drug-resistant epilepsy? It could be that early detection and treatment of serious arrhythmias may prevent premature mortality and potentially SUDEP. This becomes especially important for subgroups of patients with drug-resistant epilepsy, such as those with sodium channelopathies and/or concomitant heart disease. These are all important and complex questions that require future research and a careful analysis of risks both at the individual and population levels.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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