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The relationship between seizure onset zone and ictal tachycardia: An intracranial EEG study

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HIGHLIGHTS

- There is not a strict hemispheric lateralization on the cortical control of sympathetic function during seizures.
- Evolution of seizures over larger areas of brain and in particular spread to the contralateral hemisphere, define the degree and rate at which ictal tachycardia occurs.
- Development of ictal tachycardia early in a seizure is a common and reproducible occurrence in the same individual and may be used as a biomarker in the development of automatic seizure detection systems.

ABSTRACT

Objectives: Seizures are often accompanied by ictal tachycardia, which, when pronounced, is one of the cardiac arrhythmias associated with sudden unexpected death in epilepsy (SUDEP). We examined the relationship between the lateralization and localization of seizure onset and development of ictal tachycardia.
Methods: We identified patients who underwent bi-hemispheric intracranial EEG recording over a period of 18 months. Two to four consecutive seizures were reviewed for each patient.
Results: Fifty-seizures from 19 consecutive patients were analyzed. Forty seizures (80%) developed tachycardia (>20% increase from baseline), but laterality at seizure onset did not predict its occurrence ($p = 0.168$).
Bi-laterality at ictal onset was associated with early ictal tachycardia (<10 s) ($p = 0.0208$).
Seizures out of sleep developed tachycardia faster (mean 19.7 s vs. 68.2 s, $p = 0.0067$), but the state of alertness was not predictive of the development of tachycardia within 10 s of seizure onset.
Temporal and/or orbito-frontal lobe involvement was associated with tachycardia when compared to any other lobar combinations at ictal onset ($p = 0.0073$).
Conclusion: Laterality at seizure onset does not predict the occurrence of ictal tachycardia. Involvement of the temporal and orbito-frontal cortex, spread to the contralateral hemisphere and state of alertness, may define the degree and rate of autonomic changes.
Significance: Our results help clarify the autonomic control during seizures and offer potential use for future studies in SUDEP risk and automatic seizure detection.

1. Introduction

Autonomic discharges observed during seizures may lead to both cardiac and respiratory changes. Ictal sinus tachycardia is the most commonly observed electrocardiographic change and

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maximal ictal heart rate has been shown to be significantly higher in those who later died of sudden unexpected death in epilepsy (SUDEP) (Nei et al., 2004), a significant cause of death that may account for up to 17% of deaths among patients with epilepsy (Jehi and Najm, 2008; Nei and Hays, 2010). Prior studies have evaluated the influence of hemispheric laterality and/or lobar involvement at seizure onset on the degree and direction of these changes with conflicting results.

Stimulation studies (Oppenheimer et al., 1992) and analysis of spontaneously occurring seizures have suggested an association between right hemispheric onset and development of marked ictal tachycardia (Leutmezer et al., 2003; Mayer et al., 2004) versus left hemispheric onsets associated with ictal bradycardia (Almansori et al., 2006). Other studies have demonstrated that the hemisphere involved at seizure onset does not reliably predict the development of ictal tachycardia (Garcia et al., 2001; Moseley et al., 2011; Opherk et al., 2002; Rugg-Gunn et al., 2004; Wilder-Smith and Lim, 2001).

Cerebral regions regarded responsible for autonomic control include the insula, the anterior cingulate and the ventromedial prefrontal cortex (Jehi and Najm, 2008; Shorvon and Tomson, 2011). There is evidence that ictal tachycardia occurs more frequently in temporal lobe epilepsy (TLE) (Moseley et al., 2011) and some investigators have argued that among temporal lobe seizures, those originating in the mesial temporal structures are more likely to manifest with ictal tachycardia (Garcia et al., 2001; Leutmezer et al., 2003). On the other hand, a study by Opherk showed that the region of onset did not influence the ictal HR significantly (Opherk et al., 2002).

The type of seizure (simple partial seizures (SPS), complex partial seizures (CPS), generalized and tonic seizures) has also been evaluated in the development of ictal tachycardia with some studies supporting no significant association (Keilson et al., 1989; Rugg-Gunn et al., 2004) and others demonstrating a higher prevalence of tachycardia among generalized seizures (Moseley et al., 2011; Nei et al., 2000; Opherk et al., 2002).

Ictal tachycardia tends to occur early after seizure onset and often precedes the clinical and even the electrographic changes observed on scalp EEG (Blumhardt et al., 1986; Sevcencu and Struijk, 2010; Zijlmans et al., 2002). It also frequently occurs in a stereotypical pattern within an individual, making tracking of HR activity a potential non-invasive marker to be included in seizure warning systems or even in "on demand" electrical stimulation therapies (Sevcencu and Struijk, 2010).

In this retrospective study, we used bi-hemispheric intracranial EEG (ICEEG) recording that allows for precise spatial and temporal localization of seizure onset and spread to examine the development of ictal tachycardia in patients with refractory epilepsy. We defined ictal tachycardia as a 20% increase in heart rate (HR) from baseline.

2. Methods

The New York University Comprehensive Epilepsy Center electroencephalography (EEG) reports were reviewed to identify patients who had undergone bi-hemispheric intracranial EEG recordings for epilepsy surgery over an 18-month period. Children below 12 years of age, patients with prior brain resection, patients experiencing status epilepticus, and those who had previous cerebral radiation therapy, were excluded.

All patients underwent 128-channel ICEEG recordings. A standard pre-cordial single-channel electrocardiogram (ECG) was recorded continuously on the EEG in all cases.

Three consecutive, electrographically similar seizures with interpretable EKG at seizure onset and over the preceding 90 s (baseline) were reviewed for each patient. For two patients only two seizures met criteria for inclusion. For patients with fewer than three similar seizures, seizures of an additional seizure type were included, if available; this allowed for three or four seizures per patient analyzed.

Following identification of the included seizures, the ICEEG and EKG data were extracted and analyzed separately. Instantaneous HR was automatically calculated using the R-R interval derived by NicOne (Natus, Madison, WI) software. The raw EKG tracing was visually reviewed to verify accuracy of the calculated HR. We defined significant tachycardia as a 20% increase in HR compared to baseline HR. Early ictal tachycardia was defined as development of significant tachycardia within 10 s from seizure onset (Galimberti et al., 1996). The baseline was calculated as the mean HR over the 90 s preceding the electrographic seizure onset.

Upon review of the electrographic seizures on the ICEEG recording, the ictal localization was categorized as frontal (F), orbitofrontal (O-F), temporal (T; including mesial temporal when depth electrodes were available), parietal (P) and occipital (O) regions for each second of each seizure.

For the included seizures, the video recording was also reviewed in order to determine the type of seizure (SPS, CPS +/− secondary generalization, tonic, subclinical) and onset out of the awake or asleep state.

Age, gender, magnetic resonance imaging (MRI) findings, and results of the pathologic analysis of resected tissue when available were also collected (Table 1).

Correlations were examined using Pearson's chi-square and Fischer's exact test for categorical data and unpaired *t*-test and Kruskal–Wallis one-way analysis of variance for continuous data.

P values < 0.05 were considered statistically significant.

This study was approved by the Internal Review Board of New York University School of Medicine.

3. Results

Nineteen consecutive patients (6 men and 13 women – mean age 29.7, range 15–51) were identified. All eligible patients had focal onset treatment resistant epilepsy (documented failure of at least 3 anti-epileptic drugs (AEDs)). On admission patients were on a varying number of AEDs (range 1–5, median 3) that were gradually tapered to capture seizures.

Fifty-nine seizures were reviewed. Nine seizures were excluded from analysis because the EKG was not interpretable throughout the electrographic seizure and no tachycardia developed during the interpretable portion of the EKG tracing. It was, therefore, impossible to determine if tachycardia developed later in those seizures (Supplementary Table S1).

3.1. Hemispheric lateralization at ictal onset

Laterality at ictal onset did not predict the occurrence of ictal tachycardia (Chi-square 3.568, 2, $p = 0.168$) (Fig. 1).

Forty seizures (80%) were associated with significant (>20% increase in HR) tachycardia. Twelve seizures had bilateral and 28 seizures had unilateral ictal onset. Among those with unilateral ictal onset, 13 (46%) developed tachycardia only upon spread to the contralateral hemisphere. Ten seizures (6 patients) had interpretable EKG throughout the electrographic seizure and did not develop a significant increase in HR.

Time to development of significant tachycardia varied between 3 and 243 s (mean 37.8 s, median 16.5 s) and did not depend on laterality at seizure onset (Kruskal Wallis $p = 0.248$). Bilateral ictal activity at seizure onset was associated with early ictal tachycardia (<10 s) (Chi-square 7.747, 2, $p = 0.0208$) (Fig. 2).