

## **Intensity of autonomic disturbance following tonic-clonic seizures is correlated with post-ictal generalized EEG suppression**

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**RATIONALE:** Sudden unexpected death in epilepsy (SUDEP) poses a poorly understood, but considerable risk to patients with uncontrolled epilepsy. Recent work demonstrated that SUDEP risk may increase in direct proportion to the duration of post-ictal generalized electroencephalographic (EEG) suppression (Lhatoo SD et al. *Ann Neurol* 2010;68:787-796). Here, we examined the profile of autonomic alterations after epileptic seizures with a novel wrist-worn electrodermal activity (EDA) biosensor and explored the relationship between the seizure intensity, quantified as the degree of autonomic imbalance and post-ictal EEG suppression.

**METHODS:** We continuously recorded EDA of pediatric patients with epilepsy admitted to the long-term video/EEG/ECG monitoring unit at Children's Hospital Boston with custom designed wrist-worn EDA sensors. Video and EEG recordings were examined by two board-certified clinical neurophysiologists to determine seizure type, ictal EEG localization, EEG seizure onset and offset, and duration of post-ictal generalized EEG suppression. Post-ictal generalized EEG suppression was defined as the immediate post-ictal generalized decrease of EEG signals below 10  $\mu$ V in amplitude, not including muscle, movement, breathing, electrode or other artifacts. The amplitude of the EDA response was determined as the difference between the response peak and pre-ictal baseline. The vagal-mediated high frequency spectral component (HF) of heart rate variability was computed by integrating the spectral powers between 0.15 and 0.4 Hz. The impact on vagal function was measured as the maximal percentage change in HF power during the post-ictal period compared to the pre-ictal baseline.

**RESULTS:** We included 11 patients with refractory epilepsy in this study, all of which were candidates for epilepsy surgery. A total of 34 seizures comprising 22 complex partial and 12 secondarily generalized tonic-clonic seizures were included. We observed that the post-ictal period was characterized by a surge in sympathetic EDA and heart rate coinciding with persistent suppression of vagal-mediated HF power. The impact of autonomic dysregulation was more pronounced after tonic-clonic seizures compared to complex partial seizures. The amplitude of EDA response was strongly and positively correlated with the duration of EEG suppression ( $r = 0.81$ ,  $p = 0.003$ ). In contrast, the maximal percentage change in HF power was strongly and negatively correlated ( $r = -0.87$ ,  $p = 0.002$ ) with the duration of EEG suppression (i.e. a greater reduction of HF power was associated with a longer post-ictal EEG suppression).

**CONCLUSION:** We found that the magnitude of both sympathetic activation and parasympathetic suppression increased approximately linearly with duration of EEG suppression after tonic-clonic seizures. These results highlight a critical window of post-ictal autonomic dysregulation that may be relevant in the pathogenesis of SUDEP and hint at the possibility for assessment of SUDEP risk by autonomic biomarkers.