Decreased heart rate and enhanced sinus arrhythmia during interictal sleep demonstrate autonomic imbalance in generalized epilepsy

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Introduction
- Epilepsy is known to impact autonomic function during seizures (ictal periods), but less is understood about autonomic function in interictal periods, especially during sleep, when sudden unexpected death in epilepsy (SUDEP) is most likely to occur.
- We hypothesized that epilepsy affects the activity of the autonomic nervous system even in the absence of seizures, which should manifest as differences in heart rate variability (HRV) and cardiac cycle.
- Measures of HRV include mean heart rate (HR) and the high-frequency modulation of HR due to breathing, known as respiratory sinus arrhythmia (RSA). Both of these metrics offer insight into the balance between sympathetic and parasympathetic tone.
- Thus, we analyzed and compared HRV and electrocardiogram (ECG) waveforms as non-invasive measures of the autonomic tone from both neurologically normal and epileptic children/adolescents, in order to assess differences in sympathetic-parasympathetic balance during sleep (in the absence of any epileptiform activity).

Methods
Data & Subject Cohort: ECG recordings along with height, weight, and blood pressure (BP) data from 116 children and adolescents during stage 2 sleep were obtained (courtesy of University Hospitals, Cleveland, OH). Cohorts consisted of 25 neurologically normal control subjects and 91 patients with generalized epilepsy. ECG data from 12 subjects who were not initially epileptic, but were later diagnosed with epilepsy, were analyzed separately.

HRV Analyses: The instantaneous HR and its power spectral density (PSD) were computed. The PSD was high-pass filtered above 0.1 Hz to isolate the RSA peak.

Adjustment of HRV Parameters: Some parameters were adjusted for age, body mass index (BMI), and gender as the residuals of a linear fit to those three covariates.

Receiver-Operating Characteristic (ROC) Curves: HRV parameters were used as classification metrics for epilepsy, and the sensitivity and specificity of these parameters were determined and used to plot the ROC curve as well as the optimal threshold for classification.

Results. 1) Increased HRV in Epilepsy

Figure 1: HRV in representative control (blue) and epilepsy (red) subjects.

A. Raw ECG traces across 30 s; decreased HR is apparent in epilepsy.
B. Instantaneous HR; lower baseline and increased variability are visible in epilepsy.
C. PSD of HR over 30 minutes, filtered above 0.1 Hz; high-frequency modulation of HR (RSA peak around 0.3 Hz) is enhanced in epilepsy.

2) Enhanced RSA and Decreased HR in Epilepsy

Figure 2: Analysis of HRV across all control (○) and epilepsy (■) subjects.
A. RSA is enhanced in epilepsy.
B. Frequency of RSA, a measure of the respiratory frequency, is not different in epilepsy.
C. Mean HR is decreased in epilepsy. In conjunction with enhanced RSA, this points to increased parasympathetic activity during interictal periods in epilepsy.

3) HRV as a Biomarker for Epilepsy

Figure 3: Sensitivity and specificity of HRV parameters for epilepsy, and comparison of BPs.

A. ROC curves for RSA, mean HR, and RSA/HR ratio, with optimal thresholds marked.
B. Sensitivity, specificity, and accuracy for above parameters; all three are decent biomarkers.
C. Control vs. epilepsy: RSA and HR are negatively correlated, consistent with their being mediated by parasympathetic activity.
D. Sensitivity and specificity for above parameters in the control (Control) and epilepsy (Epilepsy) groups, suggesting that sympathetic tone is normal during interictal periods in epilepsy.

4) Lengthened Ventricular Diastole in Epilepsy

Figure 4: ECG waveform analyses of control (blue, ○) and epilepsy (red, ■) subjects.

A. Mean-subtracted, cycle-triggered average ECG traces. Physiologically relevant cardiac intervals appear to be different in epilepsy. Could this be due to dromotrophic (cardiac conduction) or inotropic (cardiac electrical activity) effects, in addition to the chronotropic (cardiac rhythm) ones already observed in Figure 2?
B. The QT interval (normalized to the RR interval, and reported as a percentage) is not significantly different after adjustment for age, BMI, and gender.
C. However, the PR/RR interval, a measure of the atrial systole, is significantly shorter in epilepsy, indicating that epilepsy is associated with dromotrophic effects in addition to chronotropic ones.
D. This relative shortening occurs at the expense of a longer relative ventricular diastole, i.e. the TP/RR interval is significantly longer in epilepsy (even after adjustment for age, BMI, & gender).
E. The adjusted TP/RR parameter correlates positively with RSA and negatively with adjusted HR, suggesting that these three parameters are mechanistically linked.

Conclusions and Future Work
- The three main findings highlighted here (enhanced RSA, decreased HR, and lengthened ventricular diastole) are readily explained by increased parasympathetic tone, leading to enhanced cholinergic neuromodulation of the cardiac cycle.
- Out of a separate cohort of 12 individuals not initially diagnosed with epilepsy but who developed it at a later time, 10 (83%) had significantly enhanced RSA and 7 (58%) had decreased HR even before diagnosis. This suggests that increased parasympathetic tone may be a leading factor in the etiology of epilepsy.
- HRV measures such as mean HR, power of RSA, and the RSA/HR ratio may prove useful as non-invasive, prognostic biomarkers for generalized epilepsy.
- Future studies might investigate the use of parasympathetic modulators as alternative treatments for epilepsy, which has been previously overlooked.

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Poster and related paper from our lab available at: http://www.case.edu/med/galanlab/publications.html