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Novel Seizure Biomarkers in Continuous Electrocardiograms from Pediatric Epilepsy Patients

***Abstract*— There is growing evidence that seizures are accompanied by multi-system changes, not only in the brain but also in organs and systems under its control. Non-EEG measurements from these systems could be leveraged to improve seizure prediction, which is difficult but critical to the success of next-generation epilepsy therapies. Clinical electrophysiology studies during presurgical patient evaluations routinely collect continuous EEG but also ECG data that span multiple days. Prior work has reported electrocardiographic changes but has primarily focused on ventricular activity and brief peri-ictal intervals. Using novel data-driven classification and separation of the ECG high-dimensional signal space, this study investigated seizure-related changes in both ventricular and atrial activity. Measures of complexity as well as heart rate and R-R interval length were analyzed over time in continuous ECGs from 22 pediatric patients with pharmacoresistant seizures and no diagnosed cardiovascular anomalies. Fifteen patients (>68%) had significant changes in atrial or ventricular activity (or both) in intervals containing seizures. Thus, for a substantial number of patients, cardiac markers may be specifically modulated by seizures and could be leveraged to improve and personalize seizure prediction.**

***Clinical Relevance*— Electrocardiographic changes during seizure evolution in children with medically refractory epilepsy remain relatively unexplored. Using continuous single-lead ECG recordings (median = 93.3 h) from 22 pediatric patients with medically refractory epilepsy, seizure-related changes in atrial signal complexity and/or ventricular parameters (including heart rate and R-R interval length) were identified. These may represent novel non-EEG, markers of seizure evolution that could be used to ultimately improve next-generation targeted therapies.**

I. Introduction

Epilepsy affects more than 1% of the US population. About 30-40% of patients with the disorder do not respond to medications and suffer from debilitating and sometimes life-threatening seizures. Almost 200,000 children in the US have medically refractory seizures and have a substantially higher risk of morbidity and mortality (4-5 times higher) than the general pediatric population [1]. Uncontrollable seizures can adversely affect development and may lead to physical and cognitive deficits across the lifespan. Children with pharmacoresistant seizures, who are not good candidates for epilepsy surgery, currently have very limited treatment options. As promising next-generation therapies (including neurostimulation and targeted drug delivery) evolve, their options may increase. However, these novel therapies critically depend on early detection of seizure-related activity in the brain for seizure prevention.

The success of spatio-temporally targeted interventions in epilepsy, a disorder that is characterized by aberrant electrodynamic changes in the brain that may occur hours prior to seizure onset, depends on the ability to detect these changes before they spread to large areas of the brain. When focal pathological neural activity is detected early, targeted neurostimulation may prevent seizure occurrence. However, seizure detection and prediction remain difficult problems [2-5]. This is in part due to the heterogeneity of the disorder but also the limitations of many prediction algorithms that have been developed based on either short scalp EEGs that do not capture the variability of a functioning brain's neural activity or invasive EEGs that are significantly less noisy than scalp signals and sample highly focal areas of the brain. In the last few years, additional physiological measurements have received increasing attention, including electrodermal activity, accelerometer data, electromyographic signals and cardiac activity measured by the ECG [6-9].

Although seizure biomarker discovery from non-EEG data is of significant interest, similar issues of sensitivity and specificity as with the EEG have limited the estimation of robust measures that can be used for seizure detection and prediction. This highlights the complexity of the disorder, heterogeneity of patient physiology, and potential need to integrate markers from different modalities. In addition, irrespective of modality, continuous signals that capture the entire range of variability of the measured system (e.g., neural, cardiovascular, neuromuscular) are critically needed in the evaluation of seizure biomarkers.

In the last few years, there has been increased interest in the epileptic heart [10 (review), 11] and seizure-related electrocardiographic changes (e.g., bradycardia or tachycardia) [12-15]. Beyond changes in heart rate, morphological changes in the ECG have also been reported, but the majority of prior work has focused on the QRS+T wave complex and its features. In contrast, atrial activity remains relatively unexplored, with the exception of sudden unexpected death in epilepsy (SUDEP) [16]. Continuous cardiac recordings (1-2 ECG electrodes) are available in most noninvasive and invasive neurophysiological studies that are part of a patient's presurgical evaluation. These signals provide a unique opportunity to identify and systematically evaluate electrophysiological seizure markers in the presence of significant inter- and intra-ECG variability. If sensitive and specific, these markers may then be used to improve seizure prediction, either individually or integrated with EEG and other measures. To date there are very limited prior investigators of the continuous ECG in epilepsy [17].

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This paper presents the estimation and initial evaluation for seizure specificity of ventricular and atrial measures identified in 22 pediatric epilepsy patients, using a *data-driven* algorithm to separate atrial and ventricular signal contributions in single-channel continuous ECG. Existing algorithms based on Independent Component Analysis (ICA) are not adequate for 1-2 lead ECG [18-19], while those based on signal templates may be model-based [20-21]. Continuous ECGs spanning multiple days are significantly contaminated by artifacts (respiration- and/or movement-related) and vary dynamically as a function of physiological state (sleep, arousal, wakefulness, physical activity). All sources of signal variance need to be accounted for and separation should ideally be data-driven. The developed method uses classification to estimate a template of the QRS+T waveform adaptively over time, which is matched to true complexes (confirmed via signal similarity) and subtracted from the ECG to obtain the atrial signals.

Following signal separation, waveform distances and heart rate from ventricular signals and measures of complexity (entropy and fractal dimension) from atrial signals were estimated. Temporal parameter changes were identified over the duration of the recordings using changepoint detection. Individual measures were compared in intervals with and without seizures to assess specificity to seizure evolution.

II. Materials and Methods

All analyses were conducted in the Harvard Medical School High-Performance Cluster using the software Matlab (release R2019a, Mathworks, Inc). Data were collected at the Comprehensive Epilepsy Center at Boston Children's Hospital using a clinical EEG/ECG system (Natus, Inc).

A. Patient Characteristics

All analyzed patients had been diagnosed with medically refractory focal epilepsy and were undergoing continuous noninvasive EEG/ECG monitoring as part of their presurgical evaluation. A total of 22 children (12 boys and 10 girls, median age = 10.2 years, interquartile range (IQR) = 6.2 years) were studied. Their number of seizures varied from 2 to 48 (median = 7, IQR = 8). Recordings spanned 17.7 - 227.4 h (median = 93.3 h, IQR = 54.1 h). All seizures were focal, with a distribution of foci that is representative of the pediatric epilepsy patient population.

B. ECG Signal Characteristics and Preprocessing

ECGs were recorded continuously using two leads (left and right) and were sampled at 1024 samples/s. In several patients, only one of the two leads recorded data of adequate quality for analysis. A 3rd order elliptical stopband filter (1 Hz bandwidth, 20 dB attenuation in the stopband, 0.5 dB ripple in the passband) was used to suppress the 60 Hz powerline noise and its harmonics. Signals were filtered in both directions to eliminate potential phase distortions associated with the filter's non-zero phase. Respiration may affect the RR interval at frequencies <1 Hz [22]. Given this and other potential low-frequency artifacts in ECG, signals were also highpass filtered (using a cutoff of 2 Hz) using the same type of IIR (but highpass) filter.

C. Algorithm for Ventricular and Atrial Signal Separation

The organization of the developed ECG separation algorithm is schematically summarized in Figure 1.

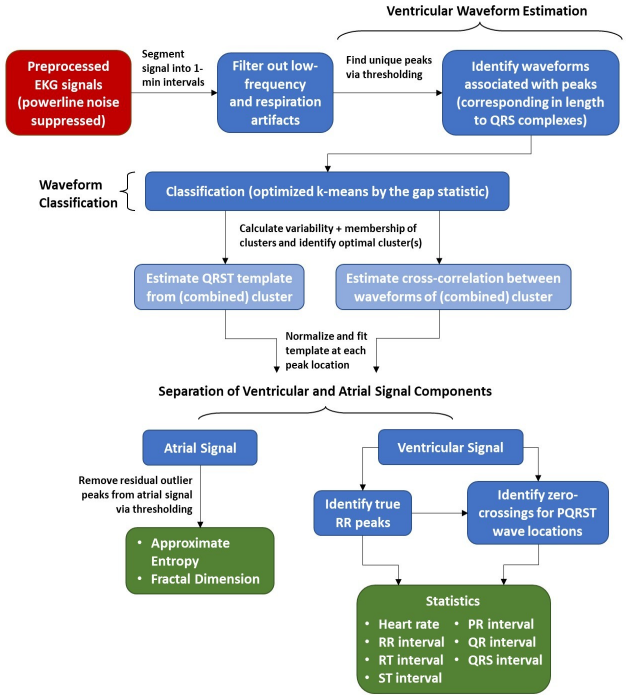

Figure 1. Analysis flow for ventricular and atrial signal separation via classification, pattern matching and estimation of respective parameters.

R-peak detection: A 1-min analysis window was used. Extreme outlying positive and negative amplitudes were estimated from normalized, zero-mean signals as thresholds for peak detection. Waveforms were identified from unique peaks by segmenting signals 0.05 s to the left to 0.39 s to the right of each peak (typical length of the QRS+T complex).

Classification: The gap statistic [23] was first estimated from the identified waveforms, to identify an upper bound for the number of k-means clusters. Optimizing the classification algorithm was beyond the scope of this study. However, k-means was selected because it is a simple and unsupervised method. Given potentially significant heterogeneity of ECGs from epilepsy patients who are having their AEDs gradually withdrawn, supervised classification that relies on training data may have a number of challenges related to the choice of these data. The robustness of the classification was increased through additional steps. A lower bound was imposed on the number of signals in a cluster, assuming that in segments containing primarily true QRS+T wave complexes the number of waveforms should approximately correspond to an age-appropriate heart rate. Also, if an optimal number of clusters could not be estimated, the segment was assumed to contain noise and/or artifacts.

Template estimation: Assuming that segments with good quality data contained primarily QRS+T wave complexes, the cluster with the highest membership (and in most cases the lowest inter-waveform variance) was used to estimate the template. In cases where the cluster

with the smallest variance did not have the highest membership, the two clusters were combined as long as the former met a lower bound for the number of waveforms. The QRST template was then estimated from this cluster as the median of its signals. In addition, the median cross-correlation between these signals was also estimated as a threshold of similarity to be used in matching the template to the data.

Separation of atrial and ventricular activity and parameter estimation: The normalized QRS+T template was adaptively matched to each peak and subtracted from the ECG signal to obtain the atrial and ventricular components. Following this separation, multiple parameters were estimated from the two signals, including approximate entropy and Higuchi Fractal Dimension (measures of signal complexity and regularity [24-25]) from the atrial signal, and R-R intervals, heart rate, QRS length, P-R, R-Q, R-T, S-T wave intervals from the ventricular signal. Ventricular measures were estimated following the elimination of artifactual peaks in the ECG based on their dissimilarity (assessed via cross-correlation) with the estimated QRS+T waveform template. Although not an exhaustive set, anomalies in ventricular activity have been previously reported in patients with epilepsy [10]. In contrast, the type of atrial measures analyzed in this study have not been previously reported in this population.

Changepoint detection and comparison of seizure and non-seizure intervals: Significant fluctuations of each estimated measure's temporal pattern across the entire duration of the recordings were estimated via changepoint detection [26], with the mean as the relevant statistic. The upper bound for the number of changepoints was varied in the estimation from 20 to 60. The significance of differences between intervals with vs without seizures was assessed via nonparametric statistical comparisons.

III. Results

The present investigation focused on 4 measures estimated from ECGs in 22 analyzed patients: approximate entropy, fractal dimension, R-R interval length and heart rate (its reciprocal). Only a few patients had two ECG leads with data of adequate quality for analysis. Thus, results are based on signals from the sole or best of the two leads. Fifteen patients (68.2%) had significant changes, in one or more measures, in intervals containing seizures, irrespective of the upper bound of changepoints used in the detection. Not all measures varied significantly between intervals containing seizures and those without. Table 1 summarizes the median variability of all 4 measures in intervals containing seizures compared to those that did not, for patients with statistically significant seizure-specific changes. Out of the remaining 7 patients, 2 had marginal differences between intervals with vs without seizures ($0.5<p<0.1$) and 5 had no significant changes in any of the 4 measures. There was no statistical difference in median number of seizures between those with vs without cardiac changes (median = 7 seizures for both).

TABLE I. Median approximate entropy, fractal dimension, heart rate, R-R length in intervals with vs without seizures for patients with significant differences between the two.

Pt #	*Approx. Entropy*		*Fractal Dim.*		*Heart Rate*		*RR Interval*	
	SZ	*Non-SZ*	*SZ*	*Non-SZ*	*SZ*	*Non-SZ*	*SZ*	*Non-SZ*
1	0.7	0.9	1.5	1.5	77.2	89.7	0.8	0.7
					p = 0.02			
2	1.2	1.1	1.5	1.5	72.3	63.2	0.8	0.9
					p = 0.02			
3	0.8	1.0	1.5	1.5	122.6	109.4	0.5	0.5
					p = 0.02			
4	1.3	0.8	1.5	1.5	104.8	104.7	0.6	0.6
	p < 0.01							
5	0.7	0.7	1.3	1.3	87.3	80.5	0.7	0.7
					p = 0.01			
7	1.2	1.0	1.6	1.5	91.9	78.7	0.7	0.8
	p = 0.03				**p < 0.01**			
8	0.8	1.0	1.5	1.5	93.3	61.9	0.6	1.0
					p < 0.01			
10	0.6	0.8	1.3	1.4	94.9	90.8	0.6	0.7
			p = 0.01					
13	0.8	0.6	1.5	1.3	115.7	111.0	0.5	0.5
			p = 0.01					
15	0.6	0.8	1.3	1.3	129.8	110.8	0.5	0.5
					p = 0.01			
16	1.0	0.9	1.6	1.5	109.8	69.6	0.5	0.9
			p = 0.01		**p < 0.01**			
17	1.0	0.9	1.5	1.3	98.1	86.3	0.6	0.7
			p = 0.01					
20	1.2	1.0	1.6	1.5	105.4	110.9	0.6	0.5
			p < 0.01					
21	0.7	1.0	1.4	1.4	85.4	71.5	0.7	0.8
	p = 0.01							
22	0.7	0.9	1.3	1.3	95.6	86.9	0.6	0.7
	p = 0.03				**p = 0.04**			

Nine patients had significant seizure-specific changes in atrial complexity (entropy or fractal dimension) and 9 had significant changes in heart rate/R-R interval (3 had both atrial and ventricular changes). In 7 of 9 patients, intervals (between changepoints) containing seizures had *higher atrial complexity* (*lower regularity*). Eight of 9 patients had statistically *higher heart rate* in intervals containing seizures (independently of sleep vs wakefulness) compared to non-seizure intervals (one had lower heart rate). Figures 2 and 3 show temporal patterns of cardiac measures in 2 patients, with significant seizure-related increase in heart rate and atrial fractal dimension, respectively. Seizure times and means between changepoints are superimposed.

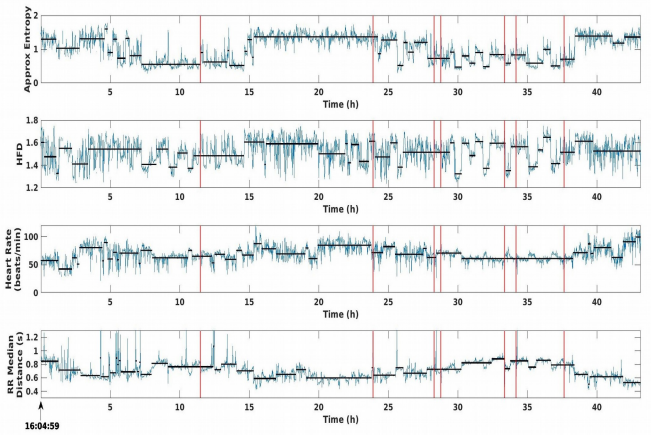

Figure 2. Temporal patterns (over ~43 h) of atrial and ventricular measures and 7 superimposed seizures (red lines) for a patient with significant seizure-related R-R changes. Intervals between changepoints are also shown (black lines).

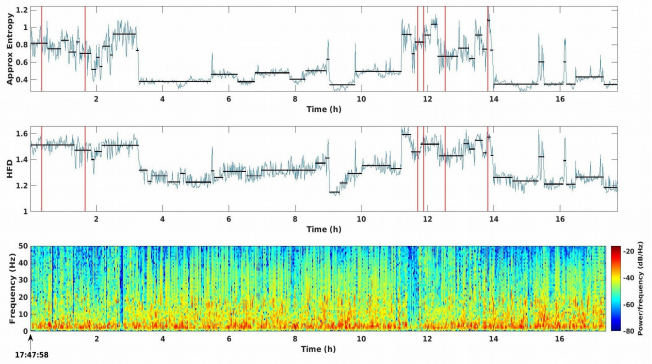

Figure 3. Temporal patterns of atrial complexity and spectral content for a patient with 6 seizures and statistically higher, seizure-related, atrial fractal dimension over ~18 h.

IV. Conclusion

A data-driven classification-based approach has been developed to facilitate the investigation of seizure-related changes separately in atrial and ventricular activity during continuous ECG monitoring of children with intractable epilepsy. Novel measures of atrial complexity but also traditional ventricular activity measures were estimated from a relatively small cohort of 22 patients and no diagnosed cardiovascular anomalies. Overall, significantly increased atrial signal complexity (lower regularity; 7 of 9 patients with atrial changes) and/or significantly increased heart rate (8 of 9 patients with ventricular changes) were identified in almost 70% of patients in peri-ictal intervals. Although these parameters are representative and not exhaustive measures of cardiac activity and ECG morphology, initial findings suggest that measurable electrocardiographic changes occur frequently in patients during seizure evolution, in some cases hours before ictal onset. These changes could be leveraged to improve the field's fundamental understanding of the impact of seizures on the autonomic system and how they modulate cardiac activity. Given the heterogeneity of epilepsy in children, these results need to be validated in a large cohort. Finally, additional ventricular parameters (e.g., the T-wave alternans, which has been previously reported in epilepsy studies [10]) and atrial signal measures also need to be investigated and compared for seizure sensitivity/specificity.

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